Synthetic BIOLOGICS

CDI has a (Prevention) Perception Problem:

Lessons from the On-going Development of SYN-004 (ribaxamase)

Forward-Looking Statements

This presentation includes forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995, as amended, on Synthetic Biologics' current expectations and projections about future events. In some cases forward-looking statements can be identified by terminology such as "may," "should," "potential," "continue," "expects," "anticipates," "intends," "plans," "believes," "estimates," "indicates," and similar expressions. These statements are based upon management's current beliefs, expectations and assumptions and are subject to a number of risks and uncertainties, many of which are difficult to predict and include statements regarding our timeline for our SYN-004 (ribaxamase) and SYN-010 clinical trials and reporting of data, the size of the market, benefits to be derived from use of SYN-004 (ribaxamase) and SYN-010, our anticipated patent portfolio, and our execution of our growth strategy. The forward-looking statements are subject to risks and uncertainties that could cause actual results to differ materially from those set forth or implied by any forward-looking statements. Important factors that could cause actual results to differ materially from those reflected in Synthetic Biologics' forward-looking statements include, among others, our product candidates demonstrating safety and effectiveness, as well as results that are consistent with prior results, our ability to initiate clinical trials and if initiated, our ability to complete them on time and achieve the desired results and benefits, our clinical trials continuing enrollment as expected, our ability to obtain regulatory approval for our commercialization of product candidates or to comply with ongoing regulatory requirements, regulatory limitations relating to our ability to promote or commercialize our product candidates for the specific indications, acceptance of our product candidates in the marketplace and the successful development, marketing or sale of our products, developments by competitors that render our products obsolete or non-competitive, our ability to maintain our license agreements, the continued maintenance and growth of our patent estate, our ability to become or remain profitable, our ability to establish and maintain collaborations, our ability to obtain or maintain the capital or grants necessary to fund our research and development activities, a loss of any of our key scientists or management personnel, and other factors described in Synthetic Biologics' annual report on Form 10-K for the year ended December 31, 2016, subsequent quarterly reports on Form 10-Qs and any other filings we make with the SEC. The information in this presentation is provided only as of the date presented, and Synthetic Biologics undertakes no obligation to update any forward-looking statements contained in this presentation on account of new information, future events, or otherwise, except as required by law.

The Gut Microbiome and Disease Prevention

- The gut microbiome is a collection of ~39 trillion microbes in our GI tract (predominantly the colon)[1]
- A healthy gut microbiome protects the body from disease
  - Antibiotics are the primary source of microbiome damage
- Protecting the gut microbiome can prevent disease
  - Preclude emergence of pathogens and MDROs
  - Prevent detrimental changes to microbial metabolome
  - Preserve healthy gut barrier function
- Conceptually simple
  - Validated in part by the success of antimicrobial stewardship programs[2,3,4]

[1]Sender (2016) *Cell* **164:**337-40. [2]King (2017) *Int J Qual Health Care* **29:**785-91. [3]Dingle (2017) *Lancet Infect Dis* **17:**411-21. [4]Karp (2018) *J Antimicrob Chemother* Oct 25. doi: 10.1093/jac/dky408. **MDRO** = multidrug resistant organism

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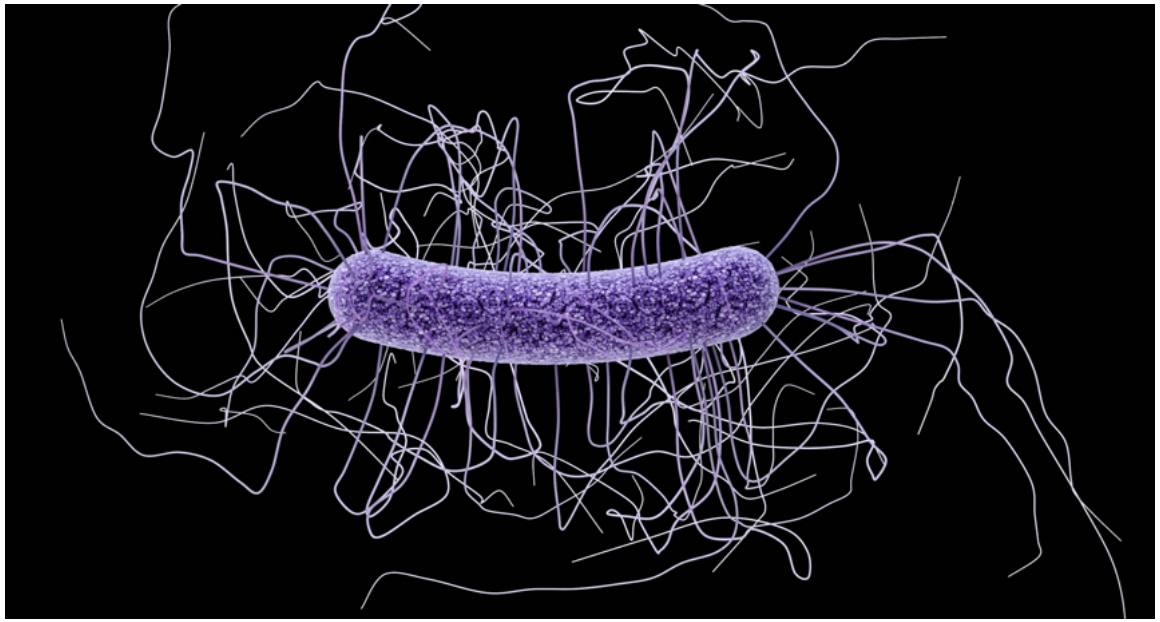
Clostridium difficile Infection

The definitive gut microbiome disease

- *C. difficile* exists as toxigenic and non-toxigenic species in the colon
  - Up to 17.5% of healthy adults[1,2] and 26% of hospitalized adults[3-5] can have asymptomatic *C. difficile* colonization
    - Readily transmitted by contact with spores
- *C. difficile* infection (**CDI**) is due to secretion of an enterotoxin (toxin A; TcdA) and a cytotoxin (toxin B; TcdB)
  - Toxins can cause diarrhea and inflammation
    - Serious CDI complications include pseudomembranous colitis, toxic megacolon, colon perforation, sepsis and death



A major cause of CDI is disruption to the gut microbiome by antibiotics

[1]Furuya-Kanamori (2015) *BMC Infect Dis* **15**:516. [2]Schäffler (2018) **9:**646. [3]Donskey (2015) *Infect Dis Clin N Am* **29:** 13–28. [4]Dubberke (2018) *Infect Control Hosp Epidemiol* **39:**1330–3. [5]McDonald (2018) *Clin Infect Dis* **66**:987-994

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Clostridium difficile Infection is Costly

Epidemiological and economic burden of CDI in the USA from a modeling approach[1]

606,058

CDI patients in the USA in 2014

>1 in 5

experience at least one CDI recurrence

~7

extra days spent in the hospital by CDI patients[2]

$5.4B

added cost to healthcare and community in 2014

44,500

CDI-attributable deaths (7%)

[1]Desai (2016) *BMC Infect Dis* (2016) **16:**303. Overnight stays in the hospital contributed 78% of the total direct and indirect costs of CDI cases in healthcare facilities and 52% of costs for CDI cases originating in the community. [2]van Kleef (2014) *J Hosp Infect* **88**:213-7

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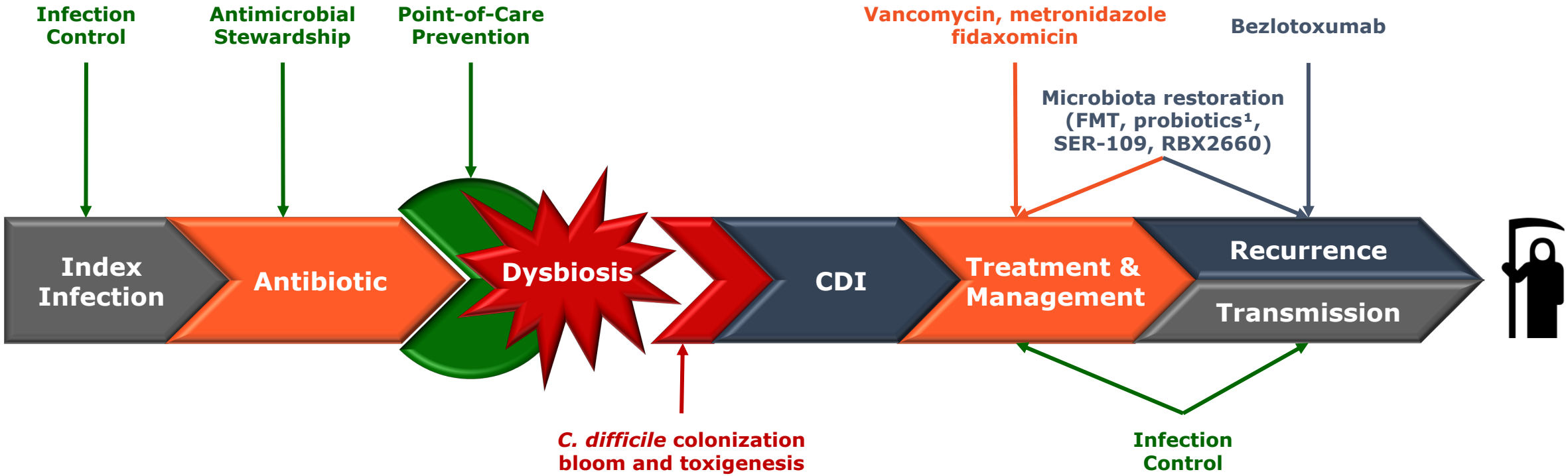
Protecting the Gut Microbiome from Antibiotics

Targeted strategy to prevent *Clostridium difficile* infection (CDI)



[1]Very mixed clinical results (see Goldenberg (2017) *Cochrane Database Syst Rev.* **12:**CD006095. doi: 10.1002/14651858) and current IDSA-SHEA guidelines indicate "there are insufficient data at this time to recommend administration of probiotics for primary prevention of CDI outside of clinical trials" (see McDonald (2018) *Clin Infect Dis* **66**:987-994).

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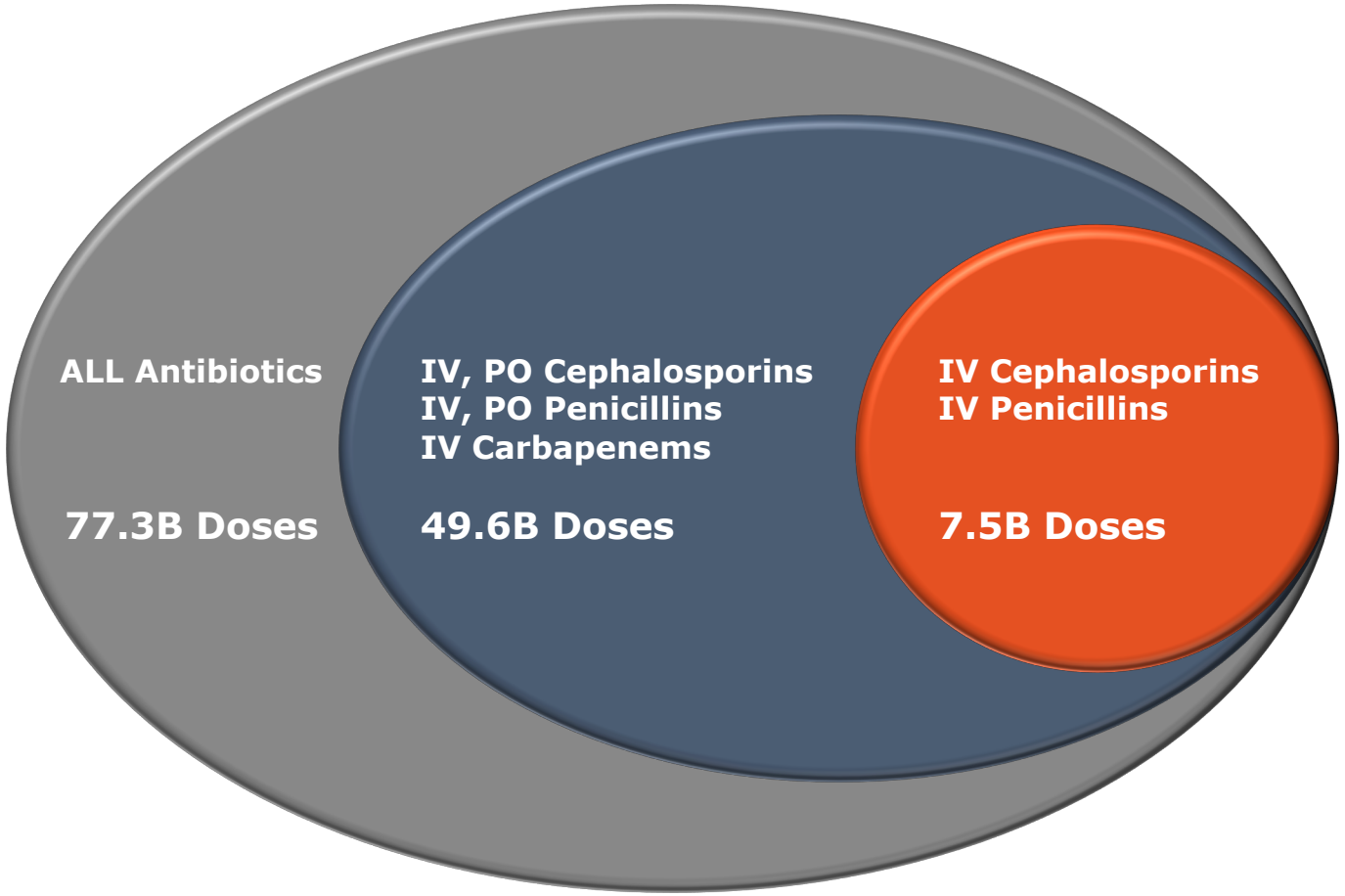
Billions of Opportunities to Damage the Microbiome

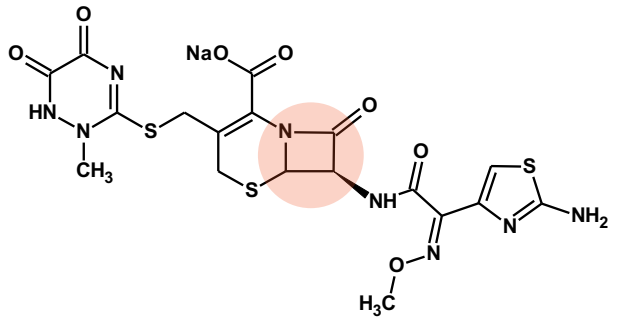
Antibiotic use worldwide[1]



β-Lactam Antibiotics

Some of the worst gut microbiome offenders

~64% of the World's antibiotics
~57% of US antibiotics
100's of millions of patients



[1]Data extracted from IMS Health 2017; doses in standard units. Macrolides, fluoroquinolones and tetracyclines make up the majority of the remaining non-β-lactam antibiotics

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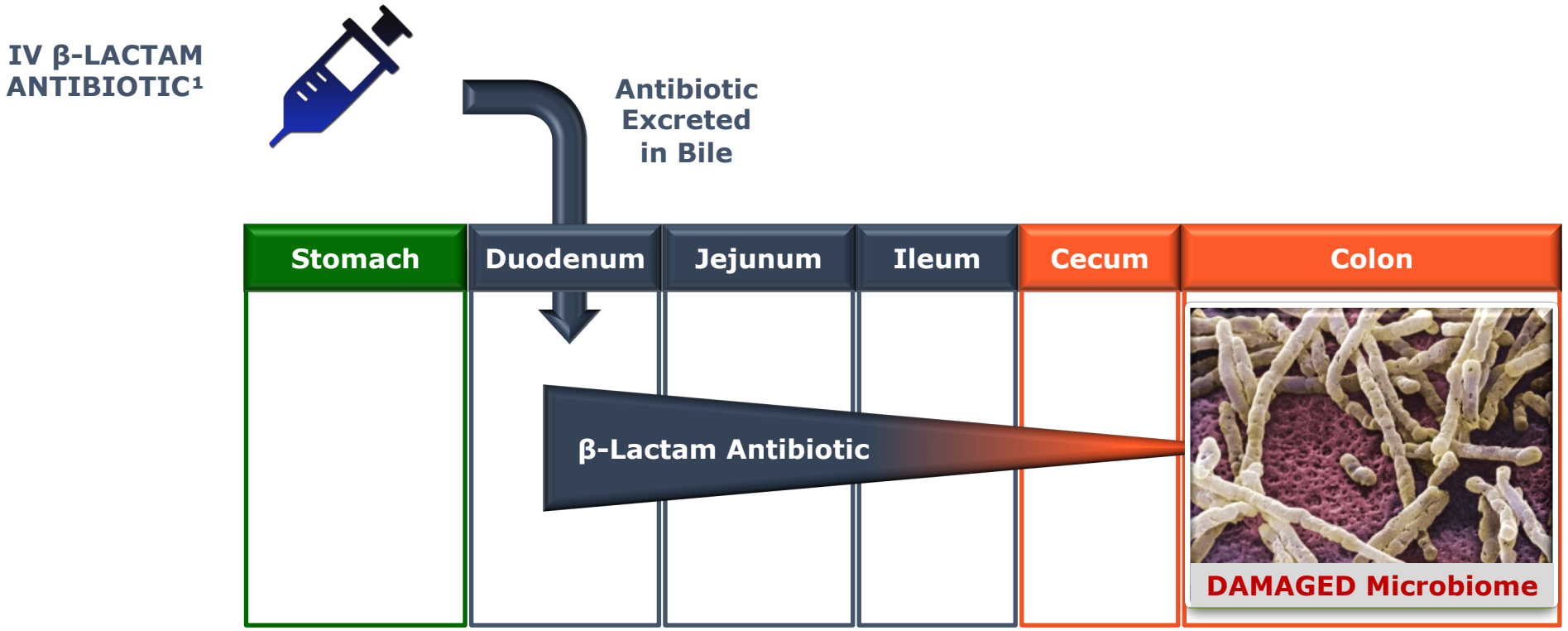
SYN-004 (ribaxamase) to Protect the Gut Microbiome

β-lactam antibiotic excreted into the GI tract damages the microbiome



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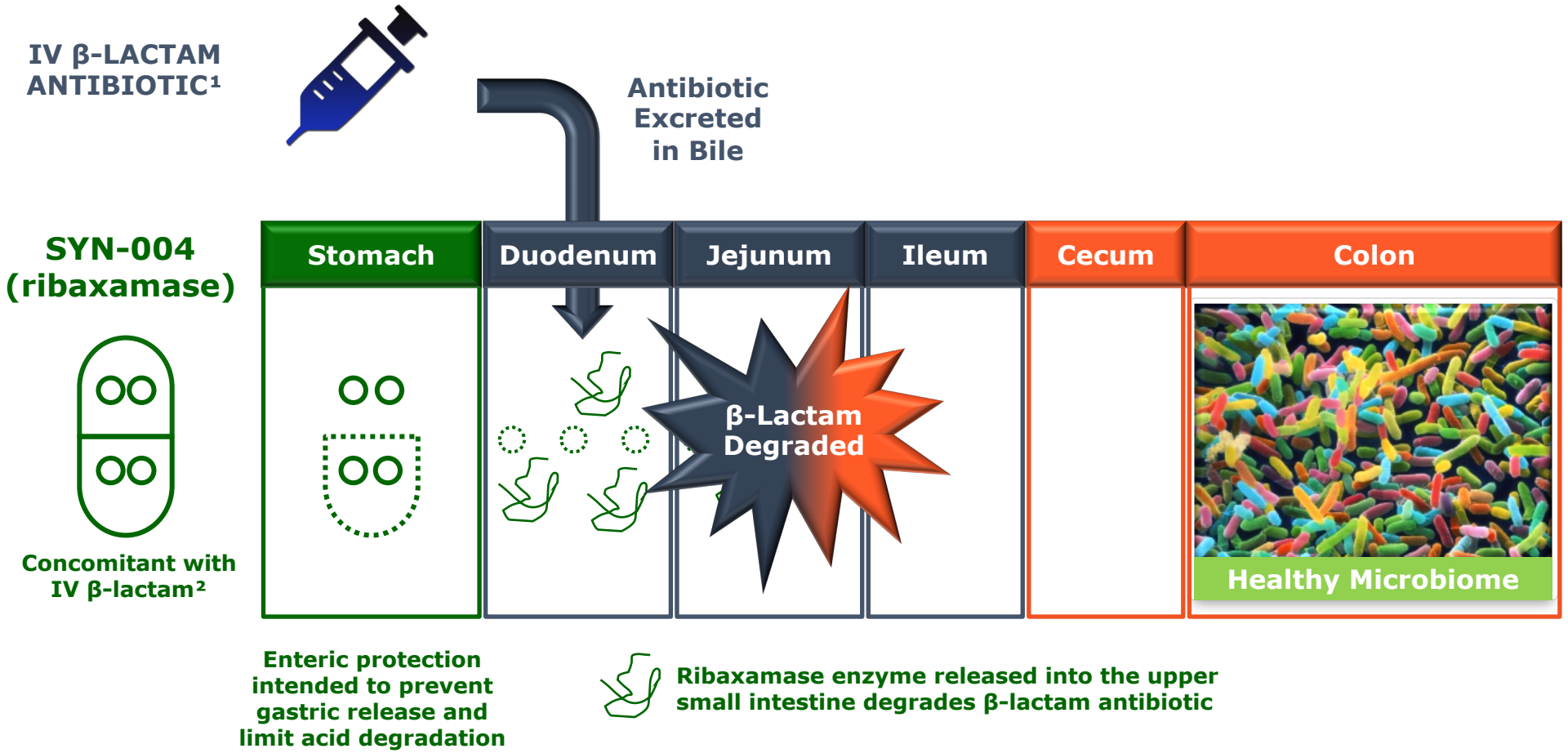
SYN-004 (ribaxamase) to Protect the Gut Microbiome

Degrading β-lactam antibiotic excreted into the GI tract



[1]SYN-004 (ribaxamase) degrades penicillins and cephalosporins; a separate preclinical stage product (SYN-006) degrades carbapenems
[2]Administered concomitantly with IV β-lactam antibiotic throughout the course of IV antibiotic therapy

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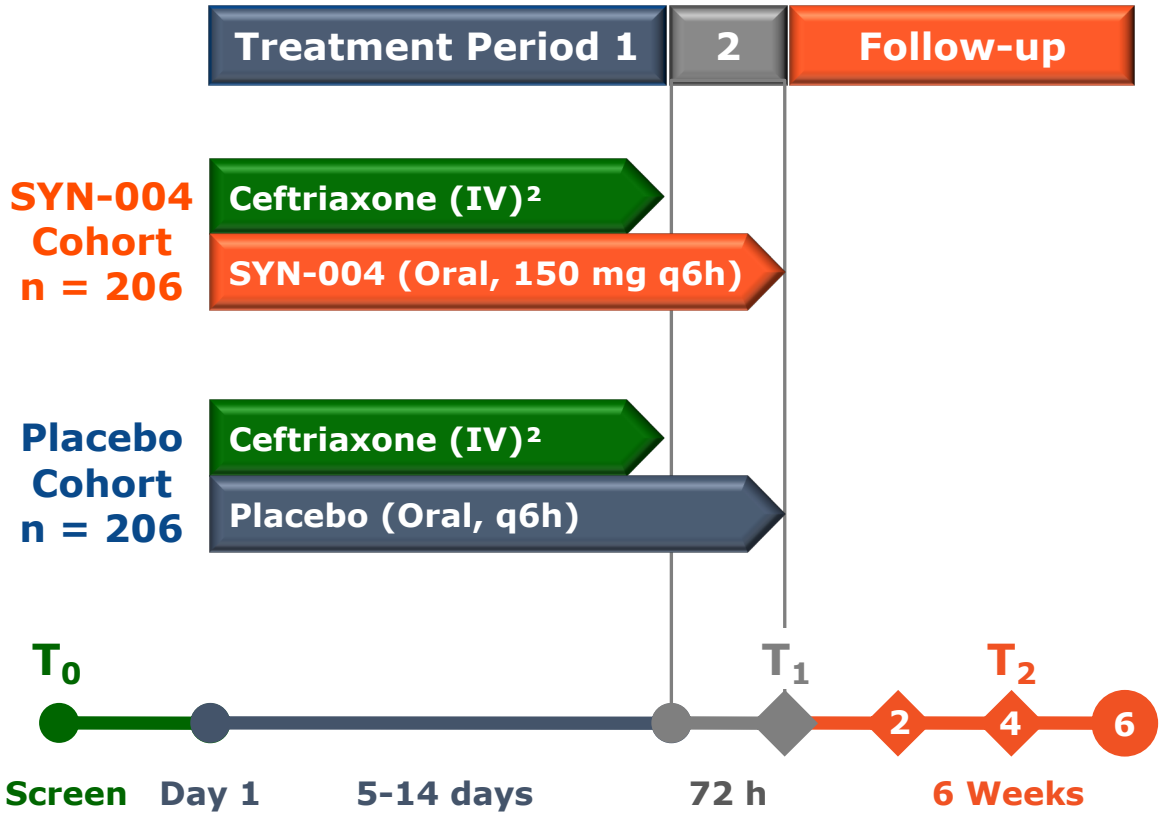
SYN-004 (ribaxamase) Phase 2b Clinical Trial

Protected the microbiome, prevented CDI, reduced emergence of VRE



- Patients admitted for treatment of LRTI at 54 sites (Europe, North America)[1]
- **Reduced CDI incidence**
  - Placebo (7) **3.4%**
  - SYN-004 (2) **1.0%**[2]
- **Suppressed emergence of MDROs**
  - **Reduced VRE** colonization by 43.9%[3]
  - **Reduced** expression of multiple AMR genes
- **Preserved the microbiome**
  - **Reduced** ceftriaxone-mediated loss of microbial diversity in stool samples

[1]Kokai-Kun (2017) *Gastroenterology* **152 (Suppl 1):**S1309
[2]P=0.045 vs Placebo. [3]P=0.0002 vs Placebo. P-values are based on one-sided z-test (Chi-square) for the comparison of SYN-004 to Placebo.
LRTI = clinical diagnosis of moderate to severe lower respiratory tract infection. **VRE** = vancomycin resistant enterococci

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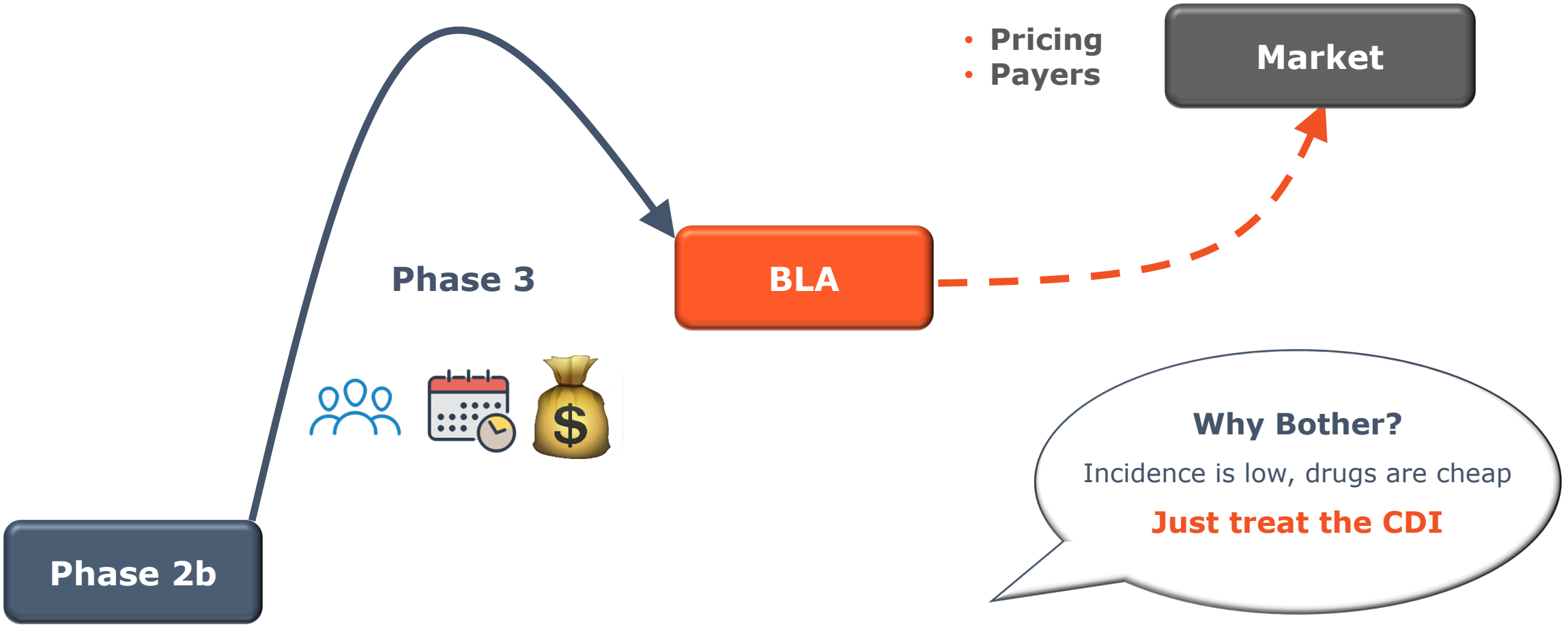
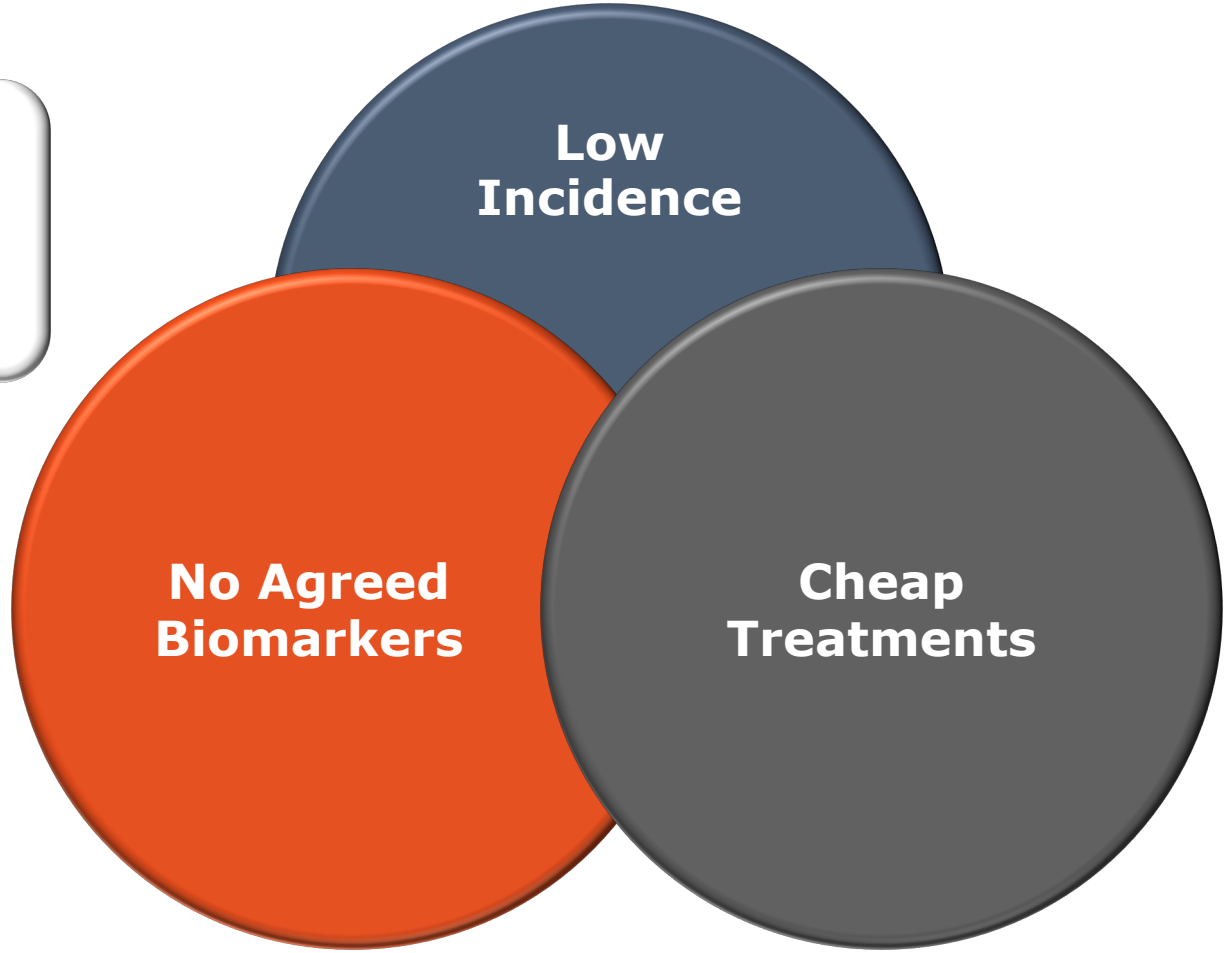
We Began Evaluating the Path Forward…



3 Key Challenges in Developing CDI Preventatives

Clinical Trial Size, Cost



Market Access

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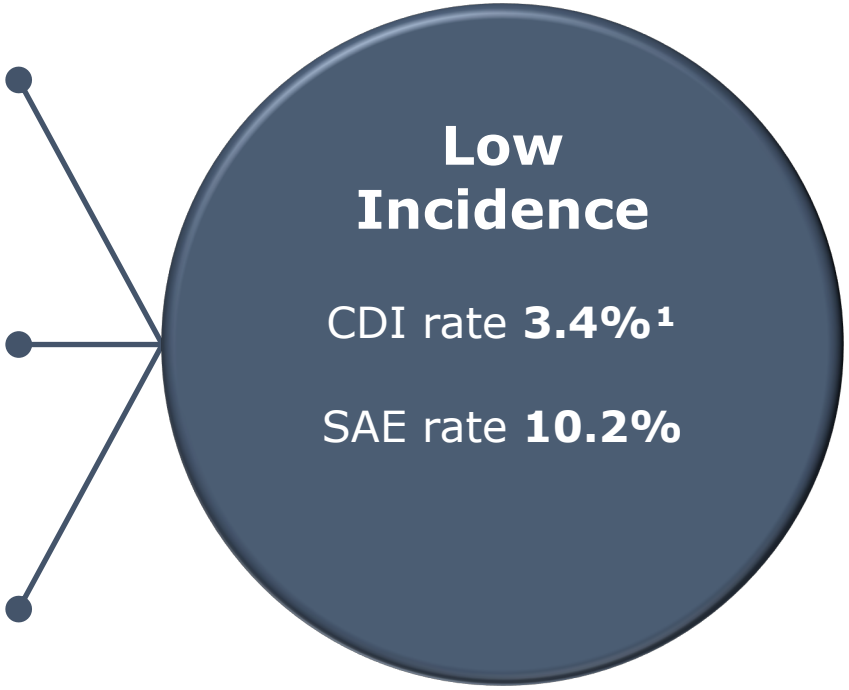
1. Prevention Trials >> Intervention Trials

SYN-004 may be prescribed to a **broad range** of patients

Most patients **won't** get CDI (with or without SYN-004)

Potential **efficacy** can be diluted by underlying ID patient comorbidities



Demonstrating CDI reduction in a prevention trial means dosing a lot of patients

[1]Incidence and SAE data are from the Placebo group of the SYN-004 (ribaxamase) Phase 2b clinical trial (patients with lower respiratory tract infections treated with IV ceftriaxone)

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Designing a Phase 3 CDI Prevention Trial

Antibiotic Types

SYN-004 Timing

Index Infections

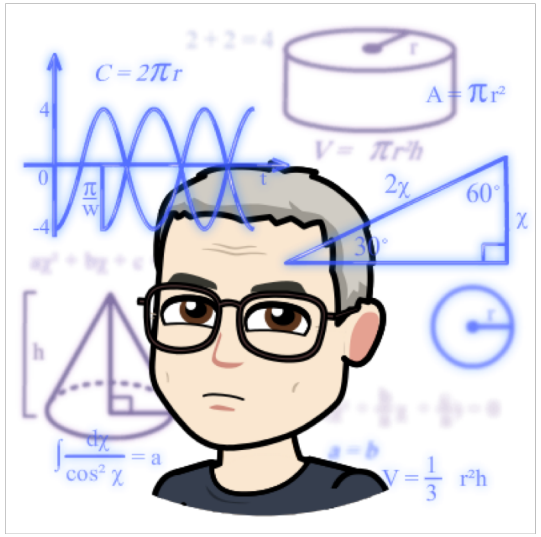
Dosing Days

Prior Antibiotics

Comorbidities

Demographics

HCF Exposure



Conmeds

Prior CDI

CDI Rates

CDI Assay

Study Sites

Compliance

HCF: Healthcare facility

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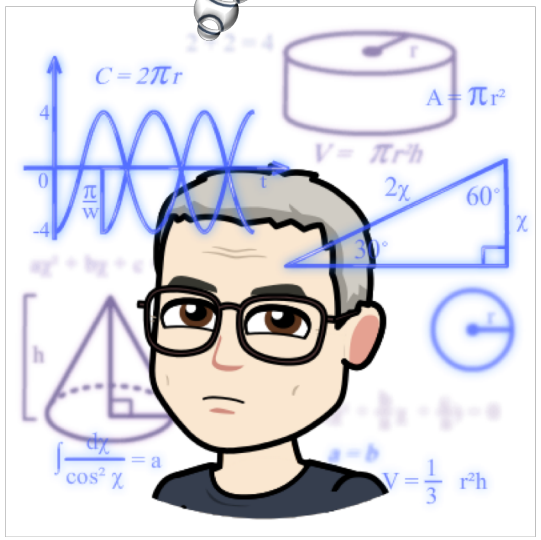
Designing a Phase 3 CDI Prevention Trial

Can we simplify the trial with a biomarker endpoint?



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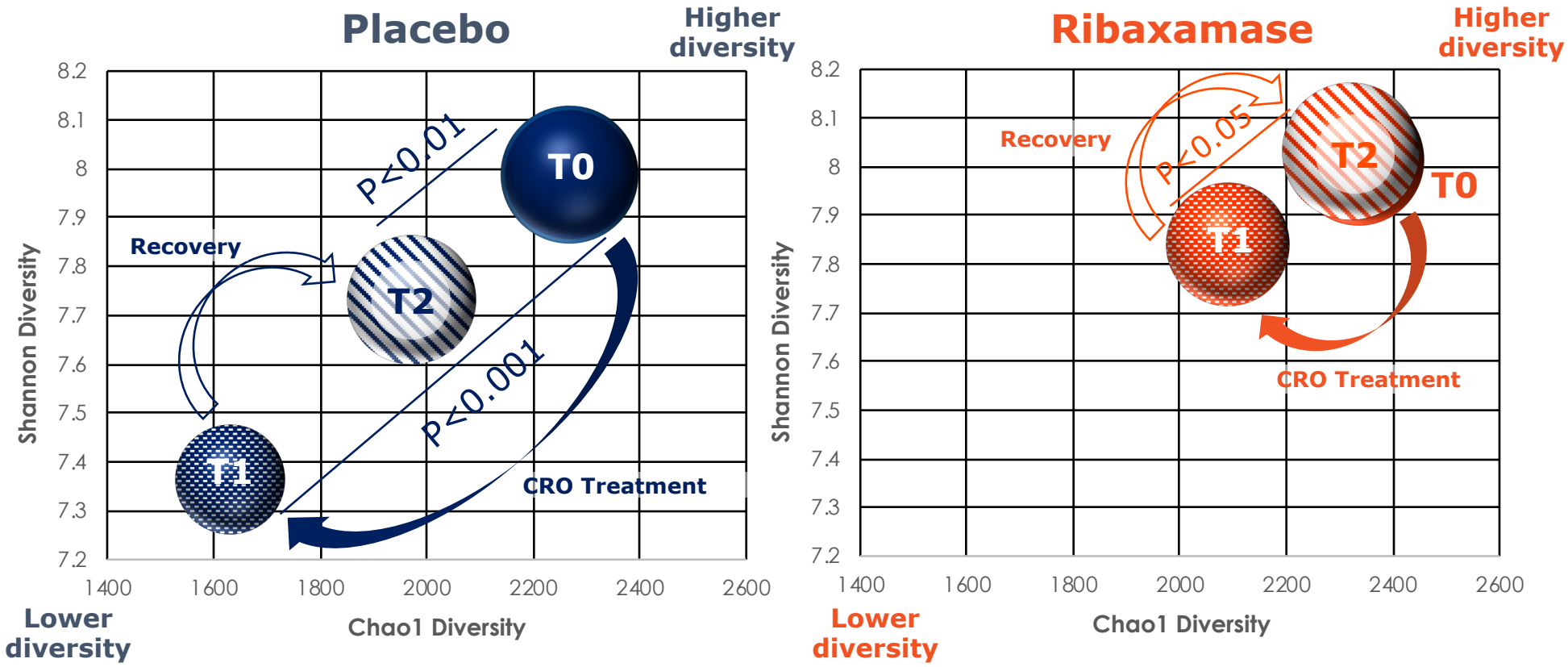
SYN-004 (ribaxamase) Protected Microbial Diversity



Compared to T0, patients receiving ribaxamase demonstrated **significantly better maintenance and recovery** of microbial diversity at T1 and T2 versus Placebo

[1]Shannon Index and Chao1 represent α-diversity, a measure of the microbial community composition within a sample.
[2]Size of each ball is relative to the standard error of the sample group

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2. Microbiome Endpoints Can’t Help (Yet)

No Agreed Biomarkers

Dysbiosis is **not** an approvable endpoint

- **Higher** incidence of dysbiosis endpoint should enable smaller clinical trials
- Having dysbiosis **doesn’t** always mean the patient will get sick
- Can’t **reliably** predict CDI occurrence using pretreatment *C. diff* colonization

Image: Don’t Argue trimmed wood cigar box lid, Canadian Museum of Civilization #CNC 2001.185.37, Tony Hyman Collection

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C. difficile Colonization vs CDI

PARAMETER	*C. difficile* Colonized Pretreatment		Not Colonized Pretreatment		
	Placebo	SYN-004	Placebo	SYN-004	
Baseline (n)	5	3	198	202	
Colonization (n) during Period 1-2	2	0	14	7†	Hospital Onset
CDI (n) during Period 1-2	0	0	4	1	
CDI/New Colonization	**--**	**--**	**29%**	**14%**	
New Colonization (n), Follow-up	0	0	4	4	Community Onset HCFA
CDI (n) during Follow-Up	0	0	3	1	
CDI/New Colonization	**--**	**--**	**75%**	**25%**	
Total New Colonization on Study	0	0	18	11‡	
Total CDI on Study	0	0	7	2*	
CDI/New Colonization	**--**	**--**	**39%**	**18%**	

Lost *C. diff* NO CDI

*P=0.0454, †P=0.0586, ‡P=0.0880 vs Placebo. P-values are based on one-sided z-test (Chi-square) for the comparison of percentages of patients in each group with CDI or *C. difficile* colonization at indicated time point. **HCFA** = healthcare facility associated

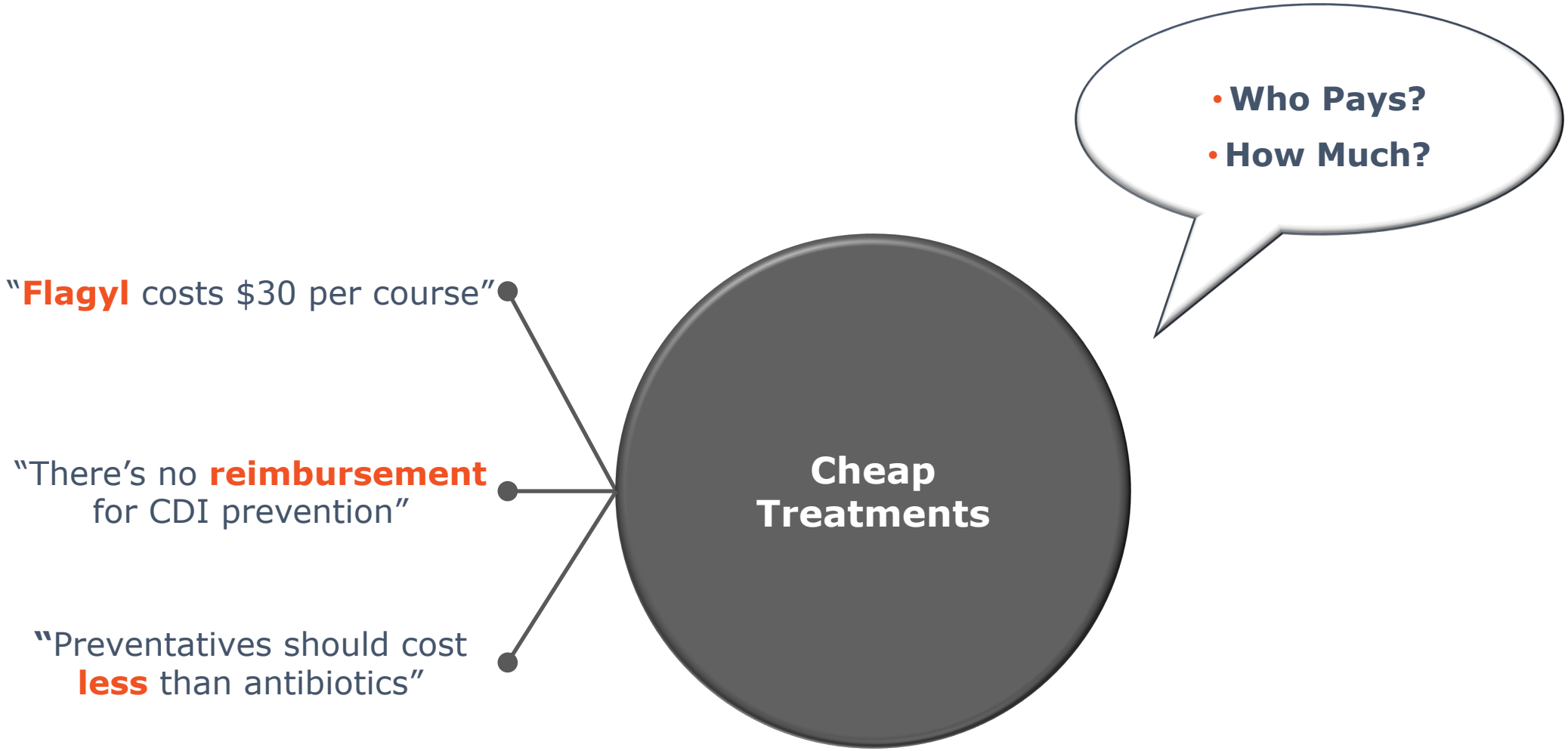
SYN-004 (ribaxamase) Phase 3 Proposal

Lots of variables means large numbers

- On-going discussions with the FDA
- We proposed one large, global, multi-center, randomized controlled clinical trial
  - Primary efficacy endpoint **reduction of CDI incidence** in SYN-004 vs Placebo
  - Co-primary safety endpoint **relative risk of mortality** in SYN-004 vs Placebo
- Evaluate a **broad range** of patients who are receiving IV β-lactam antibiotics
  - Enroll patients at high risk for CDI (e.g. age, prior antibiotic, HCF/LTCF exposure)
  - Evaluate multiple β-lactam antibiotics (e.g. ceftriaxone, piperacillin/tazobactam)
  - Evaluate different index infections (e.g. LRTI, UTI, intraabdominal)
- Enroll up to **4,000** patients to balance different parameters between groups
  - Trial intended to be self-replicating

CDI: *Clostridium difficile* infection. **LRTI:** lower respiratory tract infection. **UTI:** urinary tract infection.

3. When You Look to Fund a 4,000 Patient Trial



Who Pays? The Notorious DRG

- Q: If an HAI occurs who bears the cost? The hospital or the plan?
  - "Well when you're talking about a hospital acquired infection, you're talking about a patient who's already in the hospital for another reason and their stay is extended because of the hospital acquired infection. **That's all going to be incorporated into the DRG**, so there's not going to be any additional cost to the managed care company."

    – Commercial Insurer - 1.55 Million Lives - 80% Commercial[1]
  - "So, for instance, you'd mentioned about the possibility of a new medication for hospital acquired infections. Our opening position would be that **that's just a part of the DRG** and you will probably have **shorter hospital stays** because of that

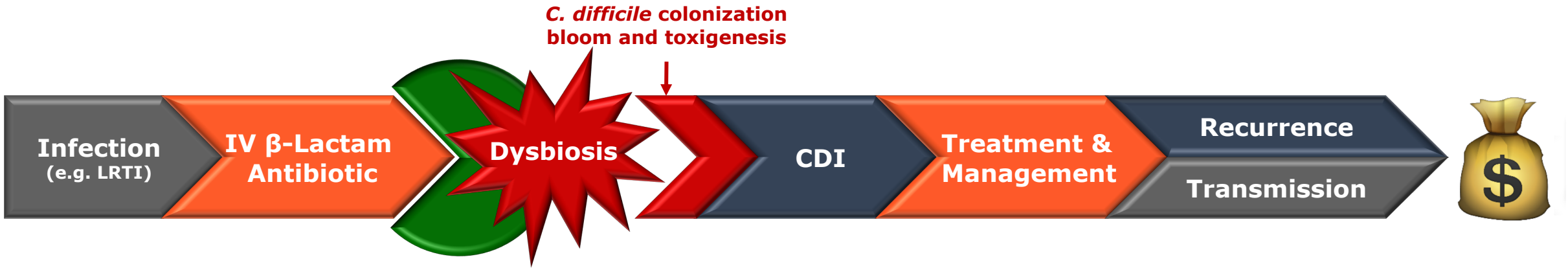
    – Commercial Insurer - 9 Million Lives - 60% Commercial[1]

By relying on DRGs, Medicare and Payers shift the cost of HAIs onto hospitals

[1]Interviews conducted pursuant to market access study contracted by Synthetic Biologics, March 2018
DRG = diagnosis related group; medically-adjusted lump sum DRG payments are intended to cover the cost of all items and services furnished to the patient during their entire hospital stay.
HAI = hospital acquire infection; Medicare imposes reimbursement penalties on hospitals with the worst HAI scores (HACRP; Section 3008 Affordable Care Act)

How Much? Valuing Point-of-Care CDI Prevention

Simplified prevention cost-savings model based on SYN-004 Phase 2b results



Patients (n)	**1,000**	**--**	**34 (3.4%)**	**10**	**+$810,000***
Cost	**DRG**	**--**	**$510,000[1]**	**$300,000[2,3]**	
Patients (n)	**1,000**	**1,000**	**10 (1.0%)**	**3**	**+$240,000***
Cost	**DRG**	**<$570 per patient Net cost saving**	**$150,000**	**$90,000**	

*Not including penalties, legal liabilities, mortality

[1]Published direct and indirect costs of CDI are variable; current example uses $15,000 per patient for incident CDI and $30,000 per patient for recurrent CDI see Shah (2016) *J Hospital Infect* **93:**286-9, Zhang (2016) *BMC Infect Dis* **16:**447, Kwon (2015) *Infect Dis Clin N Am* **29:**123–34, Gabriel (2014) *J Hospital Infect* **88:**12-21. [2]CDI recurrence (20-40%) from McFarland (2002) *Am J Gastroenterol* **97:**1769-75, Durovic (2017) *Infect Control Hosp Epidemiol* **38:**891-6. [3]Hospital transmission rate of CDI (1-2%) from Durham (2016) *Emerg Infect Dis* **22:**608-16 and Widmer (2017) *Clin Infect Dis* **64:**393-400.

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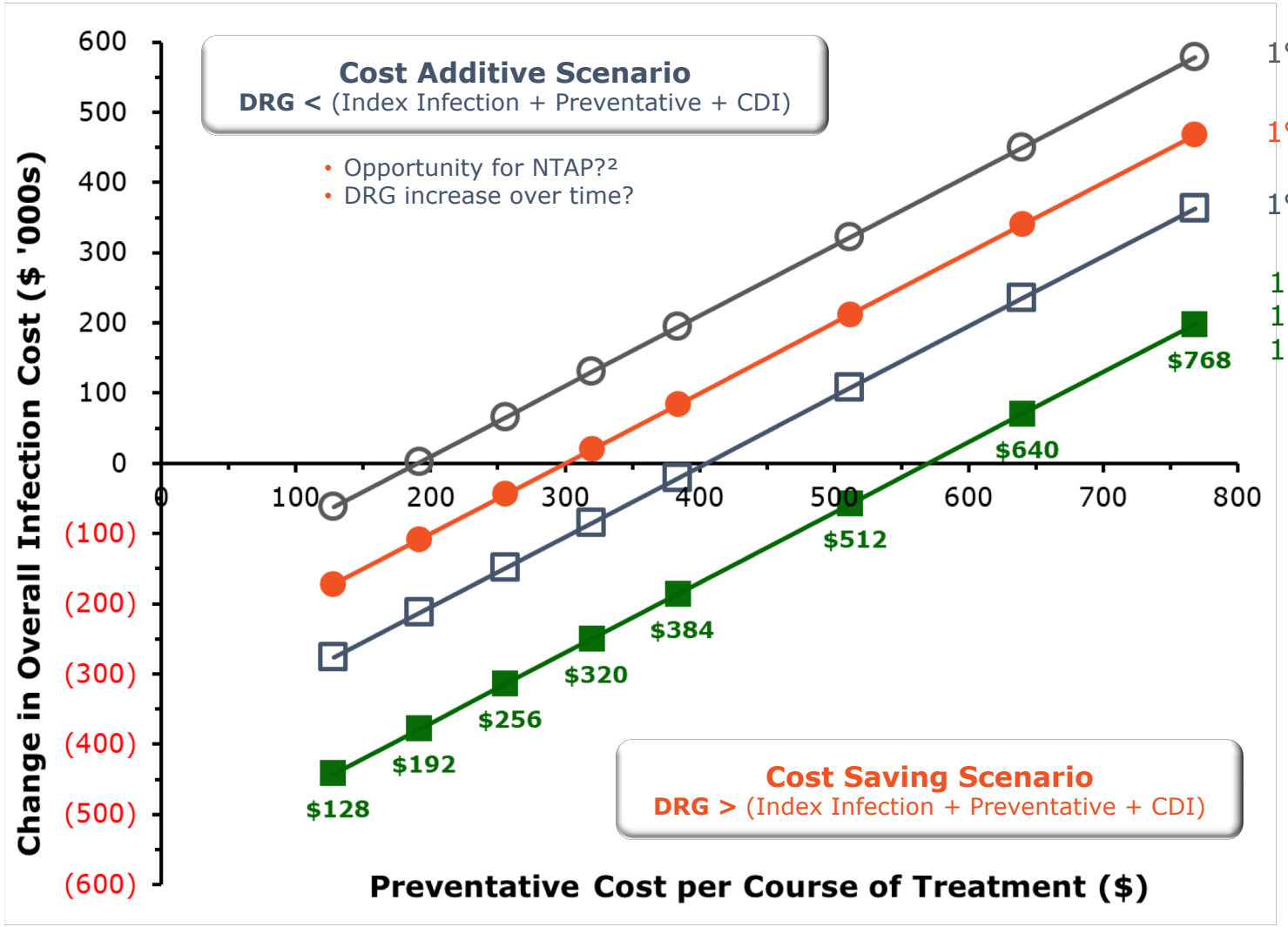
Factors Affecting Preventative Cost:Benefit



1° CDI cost = $5,000/patient

1° CDI rate = 1.7%

1° CDI preventative effect = 50% reduction

1° CDI rate = 3.4%[1]
1° CDI preventative effect = 71% reduction
1° CDI cost = $15,000/patient

Cost Neutral Scenario
DRG = (Index Infection + Preventative + CDI)

By way of comparison…
Drug price for a course of **vancomycin**
125 mg t.i.d. x 14 days = $270-$570
(www.goodrx.com accessed 02Nov2018)

[1]Cost sensitivity example based on simplified model in previous slide using CDI incidence and preventative effect size are from SYN-004 Phase 2b clinical trial
[2]Medicare New Technology Add-on Payment (**NTAP**) can provide additional payment for new therapies that can demonstrate significant clinical benefit

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In Conclusion

- During SYN-004 (ribaxamase) development we have encountered a bizarre CDI "prevention perception problem" that is entirely financial
  - Incidence is low, treatments are cheap, **just treat the CDI**
- This short-sighted approach is a function of clinical development costs and uncertain market access and ignores the comprehensive disease burden
  - The need for targeted, effective CDI prevention remains acute for patients, clinicians, healthcare facilities and the community
- With continued advocacy, education and strong science we should be able to eradiate these perceptions
  - "Let's say with some condition there's a drug or some surgery and everybody seems to be doing it, then that will end up in the DRG if it changes the cost significantly (over time)"
    – Commercial Insurer - 0.9 Million Lives - 100% Commercial[1]

[1]Interviews conducted pursuant to market access study contracted by Synthetic Biologics, March 2018.

Thank You

- *But beyond just the money, it's also the morbidity and mortality that we were talking about before, right? And that, I think, from a clinician's standpoint,* ***our job is to heal people*** *and to help them make it so that—so you can take care of things in the right way."*
  - Chief Medical Officer - 396 Bed Community Hospital[1]

[1]Interviews conducted pursuant to market access study contracted by Synthetic Biologics, March 2018.