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ECONOMIC INCENTIVES FOR THE DEVELOPMENT OF RAPID POINT-OF-CARE (POC) DIAGNOSTIC DEVICES FOR *C. DIFFICILE*, CARBAPENEM-RESISTANT ENTEROBACTERIACEAE (CRE), AND *NEISSERIA GONORRHOEAE*

FINAL REPORT

Submitted to:
Hui-Hsing Wong, M.D., J.D.
U.S. Department of Health and Human Services
Office of the Assistant Secretary of Planning and Evaluation
200 Constitution Ave., SW
Washington, DC 20201

Submitted by:
Aylin Sertkaya
Daniel Ertis
Nyssa Ackerley
Calvin Franz
Eastern Research Group, Inc.
110 Hartwell Avenue
Lexington, MA 02421
www.erg.com

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DISCLAIMER

This report was prepared by ERG, under contract to the Office of the Assistant Secretary for Planning and Evaluation (ASPE). The findings and conclusions of this report are those of the author(s) and do not necessarily represent the views of ASPE, Centers for Disease Control and Prevention (CDC), Food and Drug Administration (FDA) or U.S. Department of Health and Human Services (HHS).

LIST OF ACRONYMS

ASPE	Office of the Assistant Secretary for Planning and Evaluation
C. difficile	*Clostridioides (Clostridium) difficile*
CDC	Centers for Disease Control and Prevention
CDI	*Clostridioides (Clostridium) difficile* infection
CLIA	Clinical Laboratory Improvement Amendments
CMS	Centers for Medicare and Medicaid Services
CRE	Carbapenem-resistant Enterobacteriaceae
ENPV	Expected net present value
ERG	Eastern Research Group, Inc.
FDA	Food and Drug Administration
Gonorrhea	*Neisseria gonorrhoeae* infection, also NGI
HHS	U.S. Department of Health and Human Services
HRQoL	Health-related quality of life
N. gonorrhoeae	*Neisseria gonorrhoeae*
NGI	*Neisseria gonorrhoeae* infection, also gonorrhea
NPV	Net present value
POC	Point of care
PYS	Peak-year sales
QALY	Quality adjusted life year
VSL	Value of a statistical life
VSLY	Value of a statistical life year

EXECUTIVE SUMMARY

Antibacterial resistance is responsible for excess morbidity, mortality, and medical costs around the globe. Estimates vary widely, but the economic cost of antibacterial resistance in the United States could be as high as $20 billion and $35 billion a year in excess direct healthcare costs and lost productivity costs, respectively (CDC, 2013). The most recent report by the Centers for Disease Control and Prevention (CDC) on U.S. antibiotic resistance threats identifies three microorganisms as urgent threats: *Clostridioides (Clostridium) difficile (C. difficile* hereinafter), carbapenem-resistant Enterobacteriaceae (CRE), and drug-resistant *Neisseria gonorrhoeae* (*N. gonorrhoeae* hereinafter) (CDC, 2013). These bacteria add substantial cost to the strained U.S. healthcare system, often resulting in "prolonged and/or costlier treatments, extended hospital stays, additional doctor visits and healthcare use, and…greater disability and death compared with infections that are easily treatable with antibiotics" (CDC, 2013). These bacteria proliferate due to a variety of interrelated reasons including poor antibiotic stewardship, inconsistent infection control practices, continued transmission despite treatment, and novel mechanisms of resistance. To help combat the spread of these bacteria, the CDC (2013) recommends four core actions:

1. Preventing infections and preventing the spread of resistance.
2. Tracking resistant bacteria.
3. Improving the use of today's antibiotics.
4. Promoting the development of new antibiotics and developing new diagnostic tests for resistant bacteria.

This study helps address the fourth core action by assessing the impact of different incentives on the development of new rapid point-of-care (POC) diagnostic devices, which take a short time (e.g., 30 minutes or less) to yield results for physicians to make treatment decisions at the bedside (National Institutes of Health, 2018). Although diagnostic tests have long played a central role in the clinical management of infectious diseases, recent research shows that traditional laboratory tests, which can take up to a week to identify infection-causing bacteria, may not be as clinically useful as their rapid counterparts in several key respects. Patients tested with rapid diagnostics tend to get appropriate treatment sooner, spend less time in healthcare facilities, and have less severe health outcomes (Barbut, et al., 2014). Moreover, rapid POC devices would allow clinicians to isolate patients and enact infection control procedures quickly in inpatient settings as well as prevent community spread in outpatient settings. Further, for certain types of infections, they could allow more rapid tailoring of treatments to the antibiotic susceptibilities of individual infections (Tuite, et al., 2017). Despite these benefits, many of the diagnostic tools available for identifying *C. difficile*, CRE, and *N. gonorrhoeae* continue to be costly, not particularly fast, or otherwise limited in scope (e.g., no susceptibility or bacterial strain identification).

Drawing on the analytical decision-tree model framework developed by Sertkaya et al. (2014), this study assesses the private and social impacts of developing hypothetical rapid POC diagnostics for the detection of *C. difficile*, CRE, and *N. gonorrhoeae*. The study also considers the level of incentive needed to reach a private value equivalent to that of a rapid POC device with $100 million in peak-year sales. We evaluate four categories of incentives that encompass strategies proposed in the policy literature:

- Tax incentives.
- Modifications to the clinical study process and FDA review standards.
- Private grants, awards, and prizes given during the R&D phase, clinical phase, and FDA application phase of development.
- Centers for Medicare and Medicaid Services (CMS) reimbursement level changes.

For *C. difficile*, CRE, and *N. gonorrhoeae* infections under baseline market scenarios, we find that the expected net present value (ENPV) for a hypothetical rapid POC device ranges from -$19.0 million to $289.1 million (see Table E - 1). The observed wide range of results is primarily attributable to differences in market size among the infection types. Theoretically, negative ENPVs indicate that, at baseline, if the device company were to push forward with development, it could expect development costs to exceed revenues. In perfectly functioning markets, one would not expect a diagnostic manufacturer to proceed with rapid POC development under many of the baseline scenarios (especially CRE for which all baseline ENPVs are negative).

Table E - 1. ENPV of Developing Rapid POC Diagnostics for *C. difficile*, CRE, and *N. gonorrhoeae* Infections

Infection	Scenario	ENPV (in $ Million)
C. difficile	Low Price, Large Market	-$13.8
	Low Price, Small Market	-$19.0
	High Price, Large Market	$121.5
	High Price, Small Market	-$17.2
CRE	Low Price, Large Market	-$18.4
	Low Price, Small Market	-$18.9
	High Price, Large Market	-$1.8
	High Price, Small Market	-$14.4
N. gonorrhoeae	Low Price, Large Market	-$7.4
	Low Price, Small Market	-$17.1
	High Price, Large Market	$289.1
	High Price, Small Market	$33.8

To evaluate the extent to which these private returns align with the societal impact of the infections, we estimate the societal willingness to pay (WTP) to avoid mortality and morbidity associated with *C. difficile*, CRE, and *N. gonorrhoeae* infections (hereinafter referred to as CDI, CRE infection, and NGI) (see Table E - 2). As with private returns, we find that there is wide variation in the estimated societal WTP across the different infection types. As shown in Table E - 2, the total social annual burden of CDI, CRE infection, and NGI in the United States is $178 billion in 2016 dollars. CDI, with a social burden of $166 billion, represents close to 95 percent of the total annual burden of all three infections. Of the $166 billion in social burden associated with CDI, over 97 percent is due to mortality. The ENPV framework's sensitivity to mortality explains why, although there are more cases of NGI each year than CDI and CRE infection combined, NGI (which is not associated with increased mortality) represents less than 1 percent of the total annual burden of all three infections. Despite the high degree of variability in social burden among the infection types, even the infection with the lowest annual social burden—NGI, $1.3 billion—has a social value far greater than the estimated private ENPV.

The gap between the private and public returns to rapid POC device development suggests that incentives are desirable to stimulate the development of diagnostics to detect the three infections considered in this analysis. However, given the degree of uncertainty associated with different model parameters and the limited scope of this project, it is difficult to ascertain the necessary levels of such incentives. The size of the social benefit from developing new rapid POC devices is also highly uncertain and based on the improvement in outcomes from a hypothetical new diagnostic. It is also important to note that the impact of rapid POC devices on health outcomes is inextricably linked with other infection control practices, such as antimicrobial stewardship, patient isolation, hand hygiene, and environmental cleaning and disinfection for CDIs and CRE infections (Slayton, et al., 2015).

Table E - 2. Value of Lost Morbidity and Mortality in the United States from *C. difficile,* CRE, and *N. gonorrhoeae* Infections in 2016

Parameter	Value [a]			
	CDI	CRE Infection	NGI	Total
Total Number of Cases per Year (in 2016)	**468,567**	**9,620**	**826,703**	**1,304,890**
Burden of Mortality (in $ 2016 Billion) [b]	$161.7	$10.7	$0.0	**$172.4**
Burden of Morbidity (in $ 2016 Billion) [c]	$4.3	$0.01	$1.3	**$5.6**
Total Burden (in $ 2016 Billion)	**$166.0**	**$10.7**	**$1.3**	**$178.0**

[a] Figures may not add up due to rounding.
[b] The figure is the product of number of deaths and the value of a statistical life (VSL) estimated at $9.78 million in $ 2016.
[c[The figure is the product of total loss in quality-adjusted life years (QALYs) and the value of a statistical life year (VSLY) estimated at $497,800 in $ 2016. The total loss in QALYs across all infections is estimated at 11,184 by taking into account the health-related quality of life (HRQoL) and duration of illness for all clinical manifestations of each type of infection.

1 INTRODUCTION

New rapid point-of-care (POC) diagnostic devices that can yield results for physicians to make treatment decisions at the bedside (National Institutes of Health, 2018) have an important role in the fight against communicable infections and growing antibacterial resistance. Given the potentially sizable benefits of these devices, governments have been considering several policy incentives to foster their development. While many approaches have been proposed, the path for policymakers to succeed in accelerating rapid POC device development is not well established. Sertkaya, et al. (2014) worked to fill that void by developing an analytical framework to evaluate the economic value (private and social) of developing rapid diagnostic tools. The analytical framework allowed the authors to systematically examine the effects of policy alternatives on the expected net present value (ENPV), a key metric manufacturers consider when deciding whether to proceed with development of a new rapid POC device for detecting MRSA. This study updates and expands on that work by updating the ENPV model's key assumptions and applying the revised framework to three new microorganisms: *Clostridioides (Clostridium) difficile* (*C. difficile*), carbapenem-resistant Enterobacteriaceae (CRE), and drug resistant *Neisseria gonorrhoeae* (*N. gonorrhoeae*). The Centers for Disease Control and Prevention (CDC) considers each of these microorganisms an "immediate public health threat that requires urgent and aggressive action" (CDC, 2013).

1.1 *C. Difficile* Infection (CDI)

1.1.1 Background

C. difficile is a Gram-positive, spore-forming bacterium typically spread through the fecal-oral route (Surawicz, et al., 2013). In healthy individuals, "intestinal microbiota—also known as gut flora—confers *C. difficile* colonization resistance" keeping *C. difficile* from germinating and colonizing the gastrointestinal tract. In other words, the presence of *C. difficile* spores alone does not cause CDI. When antibiotic intake disturbs intestinal microbiota, the gastrointestinal tract becomes "a permissible environment for *C. difficile* spores to germinate and for vegetative organisms to colonize the [GI tract] and release toxins responsible for inducing CDI symptoms" (Kociolek & Gerding, 2016). Estimates from studies suggest that asymptomatic colonization may be as high as 15 percent in healthy adults and as high as 51 percent in the elderly in long term care facilities, chronic care, or nursing homes (Bartsch, et al., 2012; Furuya-Kanamori, et al., 2015). According to a prevalence survey of 183 acute care U.S. hospitals, *C. difficile* (12.1 percent) was the most common single organism causing healthcare-associated infections (Magill, et al., 2014).

Due to increased healthcare utilization (especially antimicrobial exposure) and higher comorbidity, people of advanced age are more likely to get CDI. The incidence among individuals 65 years of age and older is five times that of younger people (Hunter, et al., 2016). Moreover, Lessa, et al. (2015) found that over one quarter of healthcare-associated CDI cases present with symptoms while in nursing homes. Overall, based on the CDC's Emerging Infections Program, there were 453,000 incident cases of CDI in the U.S. in 2011 (Lessa, et al., 2015), which is around 470,000 in 2016 when adjusted for population growth.

Most cases of CDI are mild to moderate, typically resulting in diarrhea and abdominal cramping. In more severe cases, colitis or pseudomembranous colitis can occur. In the most severe, complicated cases, patients may experience ileus, hypotension, shock or sepsis, toxic megacolon, and abdominal perforation. In such cases, patients often require intensive care transfer or hospital admission, and,

depending on the CDI-related complication, colectomy (Kociolek & Gerding, 2016; Kwon, et al., 2015; Surawicz, et al., 2013). Regardless of CDI severity, approximately one in five individuals experience CDI recurrence (Fekety, et al., 1997). As Kwon, et al. (2015) note, concomitant with the increase in morbidity related to CDI, is an increase in mortality. Described fully in Section A.2.5.1 of the Technical Appendix, we estimate there were approximately 16,500 CDI-attributable deaths in 2016.

Although most *C. difficile* infections are mild to moderate with patients responding well to traditional antibiotic therapies (metronidazole, vancomycin, or a combination of the two), researchers are increasingly concerned with "the emergence of epidemic strains with novel virulence factors and antibiotic resistance, such as BI/NAP1/027" (Kociolek & Gerding, 2016). Moreover, metronidazole and vancomycin suppress the intestinal microbiota—known as dysbiosis—which is thought to increase the likelihood of CDI recurrence (Kociolek & Gerding, 2016). As such, clinicians are increasingly treating CDI patients with more expensive and newer antibiotics, such as fidaxomicin, or fecal microbiota transplantation (FMT) to counteract the microbiota disruptions associated with traditional antibiotic therapies (Kociolek & Gerding, 2016). FMT, which consists of "transferring minimally processed, uncharacterized fecal material from a healthy donor to a recipient," is associated with efficacy rates of 81 percent to 90 percent for patients with recurrent CDI (Khanna, et al., 2016). While FMT is promising, large randomized controlled trials to assess efficacy and potential adverse events have not yet been conducted (Kociolek & Gerding, 2016). Other interventions for treating and preventing CDI include non-FMT probiotic preparations, anti-*C. difficile* whey protein concentrates, intravenous immunoglobulin (IVIG) products that neutralize *C. difficile* toxins, and injectable and oral vaccines (Kociolek & Gerding, 2016).

1.1.2 Current *C. difficile* Diagnostics on the Market

Table 1 summarizes the *C. difficile* test methods that are currently on the market. These diagnostics are used with stool samples and have varying degrees of cost-effectiveness. Although this report focuses on the development of rapid POC *C. difficile* diagnostics for both colonization and infection (to optimize infection control practices and reduce transmission), there is also a need to develop *C. difficile* diagnostics that better delineate patients who are colonized versus those who will benefit from therapy. Recently, concern has arisen over potential low positive predictive value for clinical CDI using nucleic acid amplification tests (NAAT) alone, despite their high analytic positive- and negative-predictive value for the presence of toxin-encoding *C. difficile* (McDonald, et al., 2018). This is highly dependent upon the pre-test probability for CDI in the tested population. Moreover, a recent report demonstrates the significant overlap, both in terms of measurable toxin using an ultrasensitive assay and organism load using NAAT, between patients who are *C. difficile*-colonized vs. infected (Pollock, et al., 2018). Thus, it appears likely that both under treatment (i.e., missed diagnosis especially in settings where toxin enzyme immunoassays [EIAs] are used alone) and over treatment (i.e., especially in settings where NAATs are being used alone) may be occurring. Although now recommended, it is unknown whether tests such as EIA and NAAT, used in combination will improve clinical outcomes (McDonald, et al., 2018).

1.1.3 Cost of CDI

CDI has a substantial economic impact on the health care system. The primary driver of CDI-related costs is expensive hospital stays that include accommodation in emergency and special care units and extensive use of pharmacy, laboratory, and imaging services (O'Brien, et al., 2007). Moreover, for many patients, CDI treatment and recovery involves transfer to long-term care facilities, follow-up

testing, and/or home health care (Dubberke & Olsen, 2012). From the hospital perspective, there may be lost opportunity to generate revenue as CDI patients require private rooms and tend to have longer lengths of stay than the average patient, and *C. difficile* transmission within hospitals can perpetuate CDI-associated costs (Kwon, et al., 2015). As many of these costs are difficult to quantify, the literature tends to focus on CDI-attributable direct medical costs in hospitalized patients. Table 2 summarizes studies reporting CDI-attributable costs in hospitalized patients, adjusted for inflation to 2016 US dollars.

The wide range of hospital costs attributable to CDI observed in Kwon, Olsen, & Dubberke, (2015), $1.3 billion to $6.3 billion, is due to differences in study populations (some studies include surgical patients, others do not; some studies include ventilated patients, others do not, etc.) and a lack of standardized method for calculating attributable costs. As mentioned above, these costs represent only a portion of the true economic impact of CDI. They fail to consider indirect costs borne by hospitals, CDI-attributable costs in ambulatory settings, productivity losses for patients, and costs borne by third-party payers, which Slayton, et al. (2015) cite as being at least $547 million annually.

Table 1. Summary of *C. difficile* Test Methods from 2010 – 2018

Method	Ease of use	Time to detection (days)	Cost	Performance Characteristics (%)		Comment(s)
				Sensitivity	Specificity	
Generic methods						
Toxigenic culture	Complex	5–7	Variable	N/A	N/A	Not standardized
Enzyme immunoassay Tox A, B	Easy	<1	Moderate	60–81	91–99.4	Poor positive predictive value also noted
CCNA (cell culture neutralization assay)	Complex	2–3	Variable	67–86	97–100	Not standardized
Glutamate dehydrogenase (GDH)	Easy	<1	Moderate	71–100	76–98	Must also do toxin test; high negative predictive value
NAATs (nucleic acid amplification tests)	Moderate to complex	<1	Expensive	77–100	93–100	Cost-effectiveness data desirable
Brand name immunoassays and NAATs						
Xpert *C. difficile* assay (Cepheid, Sunnyvale, CA)						
Quik Chek (Alere, Waltham, MA)						
Illumigene *C. difficile* assay (Meridian Bioscience, Cincinnati, OH)						
Tox A/B Quik Chek (Wampole/TechLab, Blacksburg, VA)						
C Diff Quik Chek EIA (Wampole/TechLab, Blacksburg, VA)						
ProGastro Cd assay (Prodesse, Waukesha, WI)						
BD GeneOhm Cdiff assay (BD Diagnostics, San Diego, CA)						
Vidas *C. difficile* GDH (Biomerieux SA, Marcy-l'Étoile, France)						
Immunocard *C. difficile* GDH (Meridian Bioscience Inc., Cincinnati, OH)						
Premier *C. difficile* GDH (Meridian Bioscience Inc., Cincinnati, OH)						
C. difficile Toxin A + B Fecal Antigen Detection Microwell Elisa Kit (IVD Research Inc., Carlsbad, CA)						
XPECT *Clostridium difficile* Toxin A/B (Remel, Inc., San Diego, CA)						
OSOM C. difficile Toxin A/B Test (Sekisui Diagnostics, LLC, Lexington, MA)						

N/A = Not applicable

Source: Barbut et al. (2014); Carroll & Loeffelholz (2011); Larson et al. (2010); U.S. Food and Drug Administration, (2018)

Table 2. Hospital Costs Attributable to CDI—Adapted from Kwon, Olsen, & Dubberke, (2015)

Study	Cost per Case in 2012 USD [a]	Cost per Case in 2016 USD [b]	Cost per Annum in 2012 USD [c]	Cost per Annum in 2016 USD [b, c]
Dubberke et al. (2008)	$3,427	$3,536	$1,242,321,770	$1,281,940,750
Song et al. (2008)	$16,242	$16,760	$5,887,887,420	$6,075,658,493
O'Brien et al. (2007)	$16,307	$16,827	$5,911,450,570	$6,099,973,097
Stewart and Hollenbeak (2011)	$9,960	$10,278	$3,610,599,600	$3,725,745,511

[a] Kwon, Olsen, & Dubberke (2015) adjusted all study-specific cost estimates to 2012 USD.
[b] Inflated using Consumer Price Index-All Urban Consumers Table CUUR0000SA0 (Bureau of Labor Statistics, 2016).
[c] Extrapolation based on the total number of discharges (362,510) from 2012 HCUP data (Kwon, et al., 2015).

1.2 CRE Infection

1.2.1 Background

Enterobacteriaceae are a family of Gram-negative bacteria that have been shown to cause 84 to 87 percent of urinary tract infections, 42 to 61 percent of biliary tract infections, 72 to 89 percent of gram-negative bacteremia, and other diseases such as intra-abdominal infections and pneumonia. This family of bacteria—which includes *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter* species, and others—is concerning both for its prevalence and its increasing association with antibiotic resistance (Thaden, et al., 2017). Although these bacteria have displayed multiple antibiotic resistances since the early 1980s, they have historically been susceptible to carbapenems, members of the β-lactam class of antibiotics. Beginning in the early 2000s, however, *Enterobacteriaceae* began to develop resistance to carbapenems, often considered the antimicrobial "last line of defense" for this infection (Tischendorf, et al., 2016). Although Carbapenem-resistant *Enterobacteriaceae* (CRE) are isolated relatively infrequently—annual CRE infection incidence is estimated at 2.93 cases per 100,000 population—they have been identified in 48 states, the District of Columbia, and Puerto Rico (Logan & Weinstein, 2017; Guh, et al., 2015). Moreover, invasive CRE infections are associated with mortality rates from 24 to 70 percent, depending on the patient population and treatment variables (Thaden, et al., 2017). According to CDC's Emerging Infections Program, there were 9,300 incident cases of CRE infection in the U.S. in 2011 (CDC, 2013).

CRE transmission occurs primarily in healthcare settings via patients who are carriers. CRE move from the contaminated hands of healthcare workers or contaminated fomites to patients who then acquire the bacteria through the fecal-oral route. Following ingestion, CRE colonization of the digestive tract depends on several factors, including "patient characteristics that resist colonization such as gastric acidity and the composition of the gut flora" (Temkin, et al., 2014). As with *C. difficile* colonization, recent antibiotic use is a risk factor for CRE colonization as disruption of normal intestinal microbiota allow the CRE to multiply. Upon colonization, infection occurs when the CRE from the digestive tract serves as a source of infection to another site, such as the bloodstream, lungs, or urinary tract. Among hospitalized patients, the probability of progressing from CRE carriage to CRE infection is between 7.6 percent and 16.5 percent; depending on risk factors, such as immune status, the presence of indwelling devices, antibiotic exposure, mechanical ventilation, prolonged hospitalization, and more (Temkin, et al., 2014; Tischendorf, et al., 2016; Logan & Weinstein, 2017). A recent active surveillance study of seven U.S. metropolitan areas during 2012-2013 found that over half of all CRE infection cases involve people 65 and older and that 80 percent of all cases involve people 50 and older (Guh, et al., 2015).

As mentioned above, CRE may cause a variety of infections including bloodstream, urinary tract, intra-abdominal, pulmonary (ventilator-associated or not), and skin and soft tissue (including surgical site) (Vardakas, et al., 2015; Temkin, et al., 2014). These infections are clinically indistinguishable from those caused by carbapenem-susceptible *Enterobacteriaceae*. However, patients with CRE infections are more likely to have worse outcomes due to more severe underlying illness and longer hospitalization. When studies control for these potentially confounding factors, the mortality rate among CRE-infected patients still tends to be substantially higher than that of patients with carbapenem-susceptible infections. The higher mortality rate is not because CRE are *a priori* more virulent, but because "adequate treatment is delayed or unavailable, and because available treatment options are less efficacious compared with agents used to treat susceptible organisms" (Temkin, et al., 2014). Described fully in Section 0 of the Technical Appendix, we estimate there were 1,097 CRE-attributable deaths in 2016.

"Antibiotic options for treating CRE infections are limited and depend on the source and severity of the infection, the antibiotic susceptibility profile of the bacterium, and the side effect profiles of the agents being considered" (Thaden, et al., 2017). Moreover, "comparative treatment outcomes data remain sparse; involve the use of older antibiotic treatments; and are largely limited to case reports, case series, and retrospective, single-center observational studies. As such, they provide only modest guidance on the optimal treatment of patients with infections due to CRE" (Martirosov & Lodise, 2016). Current treatment options for CRE infections include the following antimicrobials: ceftazidime-avibactam, tigecycline, polymyxins (colistin, polymyxin B), fosfomycin, and aminoglycosides (gentamicin, amikacin, tobramycin). Although these antimicrobials have *in vitro* activity against CRE, "there are ongoing reports of resistance to these agents when they are used for CRE infections, especially as monotherapy…prompt[ing] most clinicians to employ combination therapy" (Martirosov & Lodise, 2016). Failure rates for these antimicrobials are still unacceptably high, ranging from 38.7 to 49 percent for monotherapy and 25 to 27.4 percent for combination therapy (Martirosov & Lodise, 2016). Emerging treatments for CRE infections include plazomicin, meropenem-vaborbactam, eravacycline, Ceftazidime-avibactam, and imipenem-relebactam (Thaden, et al., 2017).

1.2.2 Current CRE Diagnostics on the Market

Although a variety of CRE tests are currently available, accurate and timely detection of CRE infection is difficult because *Enterobacteriaceae* may not be susceptible to carbapenems via a variety of mechanisms (Lutgring & Limbago, 2016). For example, some *Enterobacteriaceae* species have intrinsic resistance to carbapenems, others produce enzymes "that confer carbapenem resistance when combined with chromosomal porin mutations that prevent accumulation of β-lactam agents in the bacteria," and others contain mobile genetic elements that produce carbapenemase directly (Lutgring & Limbago, 2016).

Detecting these various elements is important both epidemiologically (carbapenemase-producing CRE are considered the most substantial risk to public health) and clinically (some new antibiotics may have activity against some carbapenemases but not others) (Lutgring & Limbago, 2016).

Table 3 summarizes the carbapenemase-producing CRE tests that are currently on the market.

Table 3. Carbapenemase-producing CRE Detection Methods—Adapted from Lutgring & Limbago (2016)

Test method	Accuracy [a]	Turnaround Time [b]	Information Provided	Limitation(s)	Accessibility [c]
Broth microdilution MBL screen	High	Next day	Detection of MBL	Detects only MBL	Low-moderate (LDT)
Gradient MIC strip (including the Etest KPC and Etest MBL)	Moderate	Next day	Detection of KPC or an MBL	Detects only KPC or MBL; poor specificity when AmpC present	Moderate (commercial RUO)
Multidisc mechanism testing	High	Next day	Detection of KPC, an MBL, or OXA-48	None known	Moderate (commercial RUO, LDT)
Modified Hodge test	Moderate	Next day	Detection of carbapenemase activity	Poor sensitivity for NDM producers; poor specificity when AmpC Present	High (CLSI-endorsed method)
Carba NP test (including the Rosco Rapid Carb screen [d], Blue-Carba test [d], and Rapidec Carba NP test)	Moderate	Same day	Detection of carbapenemase activity	Poor sensitivity for OXA-48 producers; poor sensitivity for mucoid isolates	Moderate (CLSI-endorsed method)
Carbapenemase inactivation method	High	Next day	Detection of carbapenemase activity	None known	High (LDT)
MALDI-TOF MS	High	Same day	Detection of carbapenemase activity	None known	Low-moderate (LDT)
PCR, real-time PCR (including LDT, Xpert Carba-R test, hyperplex SuperBug ID [d], and Check-Direct CPE assay [d])	High	Same day	Detection of specific carbapenemase genes	Unable to detect novel carbapenemases	Low-moderate (CLSI-endorsed method, LDT, commercial RUO)
Microarray (including Verigene, BioFire, and Check-Points)	High	Same day	Detection of specific carbapenemase genes	Unable to detect novel carbapenemase	Low-moderate (FDA approved, commercial RUO)
Whole-genome sequencing	High	Several days	Detection of carbapenem resistance mechanisms	Unable to detect novel carbapenemase	Low (LDT)

[a] Accuracy: high, >90% sensitivity and specificity; moderate, 70 to 90% sensitivity and specificity; low, <70% sensitivity and specificity.
[b] Turnaround time, time to results from pure culture of isolate.
[c] Accessibility: High, all clinical microbiology laboratories could perform this test; moderate, advanced clinical microbiology laboratories could perform this test; low, reference laboratories and/or state or public health laboratories could perform this test.
[d] Not available in the United States.
LDT = laboratory-developed test
RUO = research use only
CLSI = Clinical and Laboratory Standards Institute

1.2.3 Cost of CRE Infection

According to a recent study by Bartsch, et al. (2017), the median cost of a CRE infection ranges from $22,484 to $66,031 for hospitals, $10,440 to $31,621 for third-party payers, and $37,778 to $83,512 for society.[1] Corroborating these ranges, Almario et al. (2015) found the cost of hospital admission for CRE sepsis to be $32,915 in 2015 dollars. Based on an infection incidence of 2.93 per 100,000 population (9,418 infections), the total cost of CRE infections ranges from $217 to $334 million for hospitals, $129 to 172 million for third-party payers, and $303 to 1,593 million for the society as a whole.

1.3 *N. gonorrhoeae* Infection (NGI)

1.3.1 Background

Gonorrhea, caused by infection with the *Neisseria gonorrhoeae* bacterium (also referred to as NGI here), is the second most commonly reported notifiable disease in the U.S. (CDC, 2017). Gonorrhea is transmitted through sexual contact with an infected partner and can also be spread from mother to baby during childbirth. *N. gonorrhoeae* infects the mucous membranes of the reproductive tract, including the cervix, uterus, and fallopian tubes in women, and the urethra in women and men. Less frequently, *N. gonorrhoeae* can infect the mucous membranes of the mouth, throat, eyes, and rectum. The primary symptoms of NGI in men are painful or difficult urination (dysuria) and urethral discharge. NGI symptoms in women include dysuria, increased vaginal discharge, and vaginal bleeding between periods, but these symptoms are often mild, nonspecific, and mistaken for other conditions (CDC, 2016a). Asymptomatic urethral NGI is uncommon in men (less than 10 percent of cases), but women with NGI are asymptomatic more than 50 percent of the time. Asymptomatic NGI is concerning both epidemiologically (patients may unwittingly spread the infection to a partner) and clinically (genital NGI that is undetected or not appropriately treated might ascend to the upper genital tract and result in severe reproductive complications). For men, the most common complication from untreated NGI is epididymitis and, for women, severe complications include pelvic inflammatory disease, chronic pelvic pain, tubal factor infertility, and ectopic pregnancy (Unemo & Shafer, 2014; Regnier & Huels, 2014). Gonorrhea is not associated with increased mortality, though if the infection spreads to the blood, it is considered potentially life threatening. In men who have sex with men (MSM), infection with NGI is associated with a greater risk of HIV infection (Bernstein, et al., 2010; Vaughan, et al., 2015).

In 2016, a total of 468,514 cases of gonorrhea were reported in the U.S., yielding a rate of 145.87 cases per 100,000 population. This represents an increase of 18.5 percent from 2015 and an increase of 48.6 percent from 2009 (CDC, 2017). Cases of gonorrhea documented and reported to the CDC, however, likely represent only half of all new gonococcal infections in the U.S. (Satterwhite, et al., 2013). As such, the CDC estimates that approximately 820,000 cases of NGI occur in the U.S. each year (CDC, 2016a). Rates of reported NGI cases are highest among adolescents and young adults. Among females, NGI rates are highest among those aged 20-24 years (595.5 cases per 100,000 females) and 15-

[1] The social costs include productivity losses due to absenteeism and mortality. Bartsch, et al. (2017) calculate productivity losses for mortality as the net present value of missed lifetime earnings based on an estimate of yearly annual wage and years of life lost assuming that patients with CRE infection are 60 years or older and a discount rate of 3 percent.

19 years (482.1 cases per 100,000 females). Among males, the rate was highest among those aged 20-24 years (616.8 cases per 100,000 males) and 25-29 years (545.1 cases per 100,000 males) (CDC, 2017).

Gonorrhea can be cured with proper treatment, which consists of dual therapy of 250 mg ceftriaxone as a single intramuscular dose plus 1 g azithromycin orally (Kirkcaldy, et al., 2017; CDC, 2016a). *N. gonorrhoeae*, however, is noted for its "extraordinary capacity to alter its genetic material," and has acquired or developed mechanisms of resistance to previous generations of antimicrobials, including sulfonamides, penicillins, earlier cephalosporins, tetracyclines, macrolides, and fluoroquinolones (Unemo & Shafer, 2014). Increasing resistance to ceftriaxone and azithromycin (CDC, 2017), combined with a "severely depleted" pipeline for gonorrhea treatment (Alirol, et al., 2017) has researchers concerned about managing the spread of gonorrhea in the future (Kirkcaldy, et al., 2017).

1.3.2 Current NG Diagnostics on the Market

Current detection methods for NGI include microscopy of stained smears, culture, and nucleic acid amplification tests (NAATs). The following list of advantages and disadvantages of each test method is adapted from Unemo & Shafer (2014).

- *Microscopy of stained smears*—Primary **advantages** are price, relatively quick results, and high sensitivity and specificity for the diagnosis of NGI in symptomatic men with urethral discharge. Primary **disadvantage** is that negative results do not exclude infection for cervical, pharyngeal, or rectal gonorrhea, or for asymptomatic patients due to the low sensitivity of the method. Additionally, the method does not provide data on antimicrobial resistance.

- *Culture, the historical "gold standard"*—Primary **advantages** are high sensitivity (particularly in urethral specimens from men with urethral discharge) and up to 100 percent specificity (if appropriate species-verifying assays are applied) and is the only established method that enables complete antimicrobial resistance testing. Primary **disadvantages** are time to results and that to obtain high sensitivity and specificity, medical staff must strictly optimize the conditions for sample collection, transport, and storage and the culture methodology, as *N. gonorrhoeae* are exceedingly sensitive to external environmental factors. Additionally, culture is laborious when testing small batches of isolates and not ideal for routine antimicrobial resistance testing.

- *NAATs*—Primary **advantages** include sensitivity superior to those of all other diagnostic methods (including in specimens from the cervix and non-genital anatomic sites), easier specimen collection (noninvasive, self-collected samples, such as urine, can effectively be used), transportation, and storage. NAATs are also rapid, allow automation, and enable simultaneous detection of several pathogens. Primary **disadvantages** include lack of antimicrobial resistance detection (NAATs must be paired with cultures to detect antimicrobial susceptibility, and limited sensitivity and specificity of molecular assays for susceptibility to some antimicrobials) and potential cross-reaction with commensal *Neisseria* species resulting in false-positive reports. As of 2018, FDA-cleared NAAT assay platforms for the detection of *N. gonorrhoeae* include Abbott RealTime m2000 CT/NG (Abbott Molecular), Amplicor and cobas CT/NG (Roche Molecular Diagnostics), Aptima (Hologic/Gen-Probe), BD ProbeTec ET and Qx (Becton Dickinson), and Xpert CT/NG Assay (Cepheid).

1.3.3 Cost of NGI

Healthcare costs for NGI vary substantially based on the severity of the infection. Uncomplicated cases of NGI that do not progress beyond the lower genital tract typically clear up quickly following treatment and incur several hundred dollars in testing and treatment costs. When infection persists and/or progresses to the upper genital tract, however, costs increase substantially. As shown in Table 4, the most severe health outcomes associated with NGI, pelvic inflammatory disease, chronic pelvic pain, and ectopic pregnancy, can cost up to 40 times as much as an uncomplicated infection.

Table 4. NGI-attributable Costs and Productivity Losses

Outcome	Cost Estimate (2016 $) [a]	Source
Health Costs (per episode)		
Men (uncomplicated)	$233	Regnier and Huels (2014)
Men (epididymitis)	$440	Regnier and Huels (2014)
Women (uncomplicated)	$224	Regnier and Huels (2014)
Women (pelvic inflammatory disease) [b]	$4,504	Regnier and Huels (2014)
Women (chronic pelvic pain)	$8,639	Aledort et al. (2005)
Women (ectopic pregnancy)	$9,298	Aledort et al. (2005)
Women (infertility)	$1,725	Aledort et al. (2005)
Productivity loss (per individual)		
Untreated men	$51	Regnier and Huels (2014)
Untreated women	$257	Regnier and Huels (2014)
Treated men/women [c]	$265	Regnier and Huels (2014)

[a] For consistency, we inflated all dollar amounts to represent 2016 dollars using Consumer Price Index-All Urban Consumers Table CUUR0000SA0 (Bureau of Labor Statistics, 2016). It is also possible to use the medical care component of the consumer price index as the inflator. To the extent that medical care inflation may have exceeded overall inflation, our 2016-dollar values may be underestimated.
[b] Estimate represents the lifetime medical cost of the consequences of one case of PID, including infertility, ectopic pregnancy, and chronic pelvic pain.
[c] Productivity loss for treated men and women is higher than untreated men and women because they miss work to seek medical care.

2 STUDY OBJECTIVE

The objective of this study is to examine the private and social returns for developing rapid POC diagnostic devices for the detection of *C. difficile*, CRE, and *N. gonorrhoeae* infections using the approach in Sertkaya, et al. (2014). The present study examines the following incentives: tax incentives, modifications to the clinical study process, modifications to the FDA review standards, research and development (R&D) phase awards, clinical phase awards, FDA application phase awards, and Centers for Medicare and Medicaid Services (CMS) reimbursement level changes.

3 METHODOLOGY

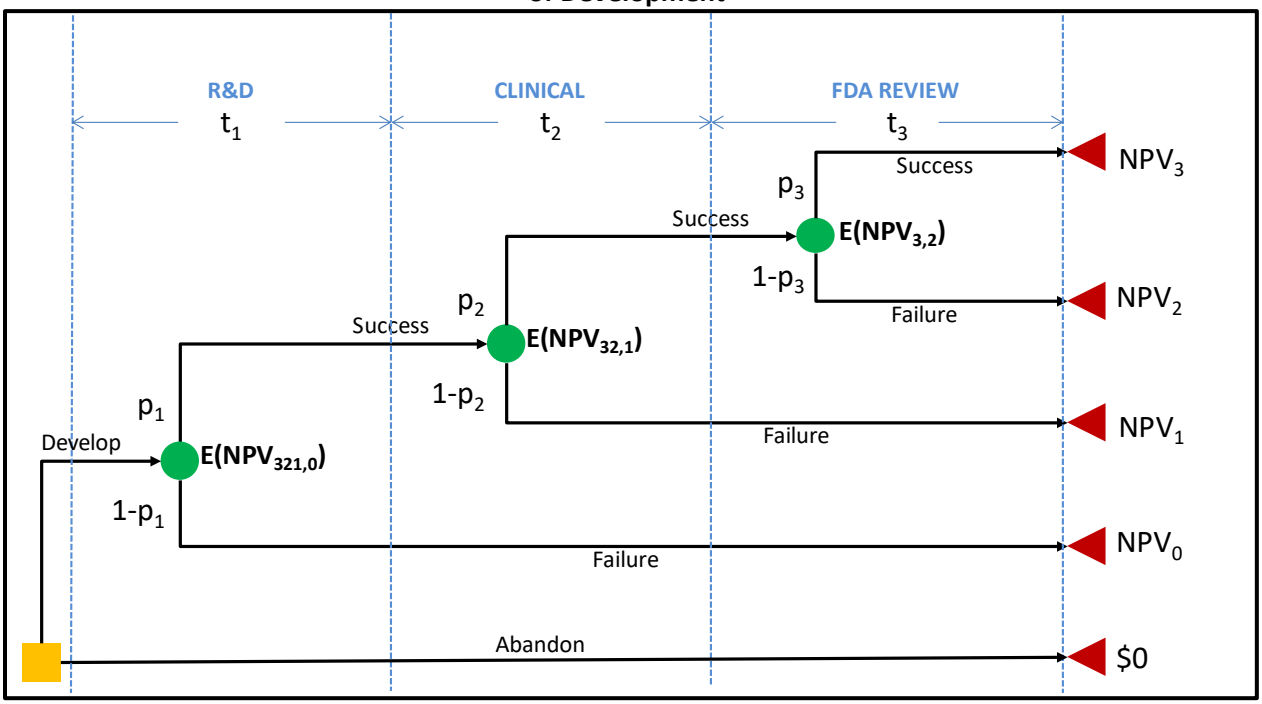
We use an analytic model to evaluate the value of private and social returns to rapid POC diagnostic devices for the detection of *C. difficile,* CRE, and *N. gonorrhoeae* infections. Our model parameters are primarily based on published studies, interviews with diagnostic device manufacturers, and occasionally supplemented with expert opinion. Further, we rely on economic analysis guidelines published by the U.S. Department of Health and Human Services (U.S. Department of Health and Human

Services ASPE, 2016) in monetizing our estimates of mortality and morbidity. The Technical Appendix discusses our key model parameters in further detail.

3.1 Modeling Private Returns (Private ENPV)

Our analysis is based on the ENPV framework developed in Sertkaya, et al. (2014). The ENPV approach in Sertkaya, et al. (2014) models a company's evaluation of medical product development from pre-clinical research through FDA approval as a decision tree (Figure 1).

Figure 1. Decision Tree Depicting ENPV of Developing a New Hypothetical Rapid POC Device by Stage of Development



In the model, the net present value (NPV) that the company would earn at each of the end nodes (i.e., red triangles) is given by

$$NPV = \sum[(R_i - C_i) \div (1 + r)^i] \qquad \text{for } i = 0,\ldots, T$$

where, r is the real opportunity cost of capital that captures the time value effect; T is the total product life including development time; i represents the development stage (e.g., pre-clinical, Phase 1, Phase 2, etc.), and; R and C are the revenues and costs at each stage, respectively. Given that the uppermost branch represents the case where the product completes all development stages and successfully reaches the market, it is the only scenario where the company earns a positive NPV. By contrast, if the company pushed forward with development but the product failed at some point, it would incur the costs of the clinical study and other supply chain related activities without earning any revenues. Therefore, all other outcome nodes in the figure represent negative NPVs.

The returns at each chance node (i.e., green circles) are calculated from right to left across the tree by multiplying the NPVs associated with each outcome by the probabilities of that outcome

occurring. These values thus represent the expected NPVs. For example, the ENPV at the start of the FDA review phase, $E(NPV_{3.2})$, in Figure 1 is computed as:

$$E(NPV_{3,2}) = p_3 \times NPV_3 + (1 - p_3) \times NPV_2$$

where p and (1 - p) are the success and failure probabilities, respectively. This value, $E(NPV_{3,2})$, can then be used to do the same calculation for the chance node at Phase 3, and so forth until the value at the first chance node can be calculated. The value, $E(NPV_{321,0})$, represents the ENPV to the company of moving forward with product development at the time when the decision is made to continue or abandon the new device concept. It includes all revenues and all pre-clinical and clinical research, and supply chain activity related costs for the product that successfully makes it to market as well as those that fail at some stage. At each node, the company can re-evaluate the ENPV and make the decision whether to continue with development. The private ENPV framework is readily adaptable to analyzing the impact of different types of policy tools, including changes in reimbursement, for rapid POCs designed to detect *C. difficile*, CRE, and *N. gonorrhoeae* infections.

3.2 Modeling Social Returns (Social NPV)

Similar to the private returns discussed above, we again use the methodology employed in Sertkaya, et al. (2014) for evaluating social returns for each of the three types of bacterial infections the rapid POC devices are designed to detect. The basic steps involved in estimating social returns, i.e., the WTP to avoid morbidity and mortality associated with each infection, include the following:

Step 1 – Estimate the WTP to Avoid Morbidity and Mortality for an Individual. We estimate the burden of experiencing an infection to the individual from each type of bacteria under consideration. We primarily consider two potential cases for each illness:

- Morbidity – the individual becomes sick, then returns to full health; and
- Mortality – the individual dies as a result of the disease.

To measure the value of avoiding morbidity, we use Quality-Adjusted Life Years (QALYs). QALYs measure the equivalent number of years of life in perfect health lost as a result of the illness, and are widely considered to provide some measure of a patient's lost "utility" or preference due to illness. The QALY loss associated with an illness is the product of health-related quality of life (HRQoL) lost and the duration of the illness. The HRQoL is bounded by 0 and 1 where 1 means perfect health and zero is death. We estimate QALYs lost as a result of illness i for a given patient in perfect health as:

$$\text{Lost QALYs per Patient} = (1 - HRQoL_i) \times (ID_i \div 365)$$

where $HRQoL_i$ is the HRQoL weight associated for illness i as available from the Tufts University Cost-effectiveness Analysis Registry and ID_i is duration of illness i in days. Since a HRQoL of one represents one full year in perfect health, the above equation adjusts the effect of the illness on the individual's well-being by accounting for the duration of that illness.

In accordance with HHS guidance (2016), we assume that the average patient is 40 years old. In the case of death, the QALY weight is zero, so the loss of QALYs for a single patient for a single year of life would be 1.0, and the period over which the QALYs were lost would be the years of life lost.

Step 2 – Estimate the WTP to Avoid Morbidity and Mortality for Society as a Whole (i.e., Annual Societal Burden). To calculate societal WTP to avoid these infections, we estimate the total number of illnesses and deaths associated with each of type of infection in the U.S. per year. The total number of cases per year are derived from the literature and conversations with experts from CDC. We derive rates for different health outcomes (e.g., death, surgical intervention requiring hospitalization, pelvic inflammatory disease, etc.) for each type of infection from the clinical literature and consultation with CDC experts.

Step 3 – Monetize Societal WTP to Avoid Morbidity and Mortality. We apply the value of a statistical life (VSL) to the estimated number of deaths to monetize the burden of mortality. We monetize our estimates of QALYs lost by using the value of a statistical life year (VSLY). We recognize that this approach is clearly a mere approximation of WTP and has been criticized in the past for using a constant estimate of VSL instead of allowing VSL to vary over a person's life span. Although still controversial, we argue that in the absence of direct, valid estimates of WTP, this approach provides a usable alternative.

Step 4 – Calculate the Net Present Value (NPV) of the Societal WTP to Avoid Morbidity and Mortality for the Projected Useful Life of the New Rapid POC Diagnostic Device. Using the annual monetized societal WTP to avoid disease computed in Step 3, we estimate the burden over the useful life of the device by adjusting for population growth and using a 3 percent social discount rate.

4 FINDINGS

4.1 Private Returns

Using the ENPV framework outlined in Section 3.1 above, we analyzed cost, time, and probability of success parameters at each stage of the rapid POC diagnostic device development process, from pre-clinical research through FDA review. Framework parameters were adjusted for CDI-, CRE infection-, and NGI-specific considerations, and, for each infection type as described in Section A.1 of Appendix A. In computing private returns, we considered four price and market-size scenario combinations (see Table 5).

The low-price scenarios assume a platform-free diagnostic with an average expected price per test of $1.50, similar to a rapid strep test. The high-price scenarios assume a platform-based diagnostic with an average expected price per test of $39.66, similar to sophisticated assay-based tests. The small- and large-market scenarios, described fully in Section A.1.14 of Appendix A, evaluate the economic performance of the diagnostics when different assumptions are made about screening-eligible patient populations.

Table 5. Price and Market Size Parameters, by Type of Infection

Infection	Scenario	Average Expected Price per Test (in $)	Average Number of Tests per Patient	Number of Tests per Annum (in thousands)
C. difficile	Low Price, Large Market	$1.50	1	17,168
	Low Price, Small Market			563
	High Price, Large Market	$39.66		17,168
	High Price, Small Market			563
CRE	Low Price, Large Market	$1.50		2,106
	Low Price, Small Market			1,406
	High Price, Large Market	$39.66		2,106
	High Price, Small Market			1,406
N. gonorrhoeae	Low Price, Large Market	$1.50		37,636
	Low Price, Small Market			16,078
	High Price, Large Market	$39.66		37,636
	High Price, Small Market			16,078

Using the values noted in Table 5 above along with assumptions about the rate of market uptake for these diagnostics (see Section A.1.13 of Appendix A), the baseline net present value that would be obtained should the diagnostic successfully reaches the market (i.e., the value of $NPV_{3,b}$ in Figure 1) ranges from $1.0 million to $2.1 billion for CDI, $2.6 million to $254.0 million for CRE infection, and $29.5 million to $4.5 billion for NGI (see Table 6).

Table 6. Annual Revenues by Year and Net Present Value ($NPV_{3,b}$) Upon Successful Product Launch (in 2016 $ Million)

Infection	Scenario	Revenues by Year									$NPV_{3,b}$
		1	2	3	4 [a]	5	6	7	8	9	[b]
C. difficile	Low Price, Large Market	$5.9	$11.4	$16.1	$18.5	$16.6	$17.0	$17.2	$17.3	$17.5	$78.3
	Low Price, Small Market	$0.1	$0.1	$0.2	$0.2	$0.2	$0.2	$0.2	$0.2	$0.2	$1.0
	High Price, Large Market	$155.4	$300.7	$425.2	$490.1	$439.2	$448.9	$454.3	$458.3	$461.9	$2,070.8
	High Price, Small Market	$2.0	$4.0	$5.6	$6.5	$5.8	$5.9	$6.0	$6.0	$6.1	$27.3
CRE	Low Price, Large Market	$0.7	$1.4	$2.0	$2.3	$2.0	$2.1	$2.1	$2.1	$2.1	$9.6
	Low Price, Small Market	$0.2	$0.4	$0.5	$0.6	$0.5	$0.6	$0.6	$0.6	$0.6	$2.6
	High Price, Large Market	$19.1	$36.9	$52.2	$60.1	$53.9	$55.1	$55.7	$56.2	$56.7	$254.0
	High Price, Small Market	$5.1	$9.9	$14.0	$16.1	$14.4	$14.8	$14.9	$15.1	$15.2	$68.1
N. gonorrhoeae	Low Price, Large Market	$12.9	$24.9	$35.3	$40.6	$36.4	$37.2	$37.7	$38.0	$38.3	$171.7
	Low Price, Small Market	$2.2	$4.3	$6.0	$7.0	$6.2	$6.4	$6.5	$6.5	$6.6	$29.5
	High Price, Large Market	$340.7	$659.3	$932.2	$1,074.4	$962.8	$984.0	$995.8	$1,004.7	$1,012.5	$4,539.7
	High Price, Small Market	$58.4	$113.1	$159.9	$184.3	$165.2	$168.8	$170.9	$172.4	$173.7	$778.9

[a] The year in which revenues from the sale of the diagnostic are at their maximum (i.e., peak-year sales value).
[b] The figure corresponds to the net present value of total revenues the developer would receive over the lifetime of the diagnostic (9 years) upon successful product launch where the discount rate is 3 percent.

4.1.1 Baseline ENPV

Based on the model parameters and assumptions described in Appendix A and the methodology summarized in Section 3.1, Table 7 shows the baseline ENPVs, $ENPV_b$, for developing new rapid POC diagnostics for the detection of *C. difficile*, CRE, and *N. gonorrhoeae* infections given the stream of revenues, $NPV_{3,b}$ (see Table 6) that these manufacturers would realize under each scenario.

From the table, the baseline ENPV ranges from -$19.0 million to $121.5 million for CDI, -$18.9 million to -$1.8 million for CRE infection, and -$17.1 million to as high as $289.1 million for NGI depending on test price and market size. Negative ENPVs indicate that, at baseline, if the device company were to push forward with development, it could expect development costs to exceed revenues. In perfectly functioning markets, one would not expect a diagnostic manufacturer to proceed with rapid POC development under many of the baseline scenarios (especially CRE infection for which all baseline ENPVs are negative.

Table 7. Baseline ENPV ($ENPV_b$) of Developing Rapid POC Diagnostics for *C. difficile*, CRE, and *N. gonorrhoeae* Infections

Infection	Scenario	$ENPV_b$ (in 2016 $ Million)
C. difficile	Low Price, Large Market	-$13.8
	Low Price, Small Market	-$19.0
	High Price, Large Market	$121.5
	High Price, Small Market	-$17.2
CRE	Low Price, Large Market	-$18.4
	Low Price, Small Market	-$18.9
	High Price, Large Market	-$1.8
	High Price, Small Market	-$14.4
N. gonorrhoeae	Low Price, Large Market	-$7.4
	Low Price, Small Market	-$17.1
	High Price, Large Market	$289.1
	High Price, Small Market	$33.8

4.1.2 Threshold ENPV Needed for Development

As described in Section A.1.11, a device development project becomes desirable when expected annual revenues at peak-year (i.e., year 4 in our model) are around $100 million according to the industry experts interviewed for this study. With the exception of the high-price-large-market scenario for CDI and both high-price scenarios for NGI, the annual revenues at year 4 are lower than $100 million at baseline (see Table 6). Thus, under nine out of the twelve infection-scenario combinations considered, the returns to developing a rapid POC diagnostic are insufficient for moving forward with product development at the time when the decision is made to continue or abandon the new device concept.

To evaluate the threshold ENPV, $ENPV_t$, needed to tip the scales toward device development for the nine infection-scenario combinations under which the returns are insufficient for developing the diagnostic, we adjusted the peak-year (i.e., year 4) annual revenues to $100 million in our analytical model. This is equivalent to shifting the annual revenue curve up to the point where year 4 revenues are $100 million.

Table 8 shows the net present value that would be obtained should the diagnostic successfully reach the market when peak-year sales are at $100 million, i.e., $NPV_{3,PYS=\$100M}$ for the nine applicable infection-scenario combinations. From the table, the net present value upon successful market entry when peak-year sales are at $100 million ranges from $520.8 million to $542.8 million for CDI, $470.6 million to $542.4 million for CRE infection, and $494.1 million to $534.7 million for NGI.

Because experts interviewed noted that peak-year sales requirement could range from a low of $10 million for a large manufacturer with an existing platform to a high of $1 billion for a venture-backed small startup, we also considered peak-year sales of $75 million, $50 million, and $25 million for sensitivity analysis purposes. Tables comparable to Table 8 that depict annual revenues and corresponding net present value figures for these additional peak-year sales assumptions are omitted for brevity.

Table 8. Annual Revenues by Year and Net Present Value Upon Successful Product Launch where Year 4 Revenues = $100 Million ($NPV_{3,PYS=\$100M}$) (in 2016 $ Million)

Infection	Scenario	Revenues by Year with Year 4 Revenues = $100 Million									$NPV_{3,PYS=\$100M}$ [b]
		1	2	3	4 [a]	5	6	7	8	9	
C. difficile	Low Price, Large Market	$87.3	$92.8	$97.5	$100.0	$98.1	$98.4	$98.6	$98.8	$98.9	$520.8
	Low Price, Small Market	$99.8	$99.9	$100.0	$100.0	$100.0	$100.0	$100.0	$100.0	$100.0	$542.8
	High Price, Large Market	N/A									
	High Price, Small Market	$95.6	$97.5	$99.1	$100.0	$99.3	$99.5	$99.5	$99.6	$99.6	$535.3
CRE	Low Price, Large Market	$98.4	$99.1	$99.7	$100.0	$99.8	$99.8	$99.8	$99.9	$99.9	$540.4
	Low Price, Small Market	$99.6	$99.8	$99.9	$100.0	$99.9	$99.9	$100.0	$100.0	$100.0	$542.4
	High Price, Large Market	$58.9	$76.8	$92.0	$100.0	$93.8	$94.9	$95.6	$96.1	$96.5	$470.6
	High Price, Small Market	$89.0	$93.8	$97.9	$100.0	$98.3	$98.6	$98.8	$99.0	$99.1	$523.7
N. gonorrhoeae	Low Price, Large Market	$72.2	$84.3	$94.6	$100.0	$95.8	$96.6	$97.0	$97.4	$97.7	$494.1
	Low Price, Small Market	$95.2	$97.3	$99.1	$100.0	$99.3	$99.4	$99.5	$99.5	$99.6	$534.7
	High Price, Large Market	N/A									
	High Price, Small Market	N/A									

PYS = Peak-year sales
N/A = Not applicable as estimated year 4 sales at baseline exceed $100 million.
[a] The year in which revenues from the sale of the diagnostic are at their maximum (i.e., peak-year sales value). The figure is set to $100 million.
[b] The figure corresponds to the net present value of total revenues the developer would receive over the lifetime of the diagnostic (9 years) upon successful product launch when year 4 revenues are equal to $100 million and the discount rate is 3 percent.

Next, we computed the threshold ENPVs under each of the peak-year sales assumptions, i.e., $ENPV_{t,PYS=i}$ where i = $100 million, $75 million, $50 million, and $25 million, using the formulas noted in Section 3.1. Table 9 depicts the threshold ENPVs needed for development under the different peak-year sales assumptions for each of the applicable infection-scenario combinations.

From the table, the threshold ENPVs when peak-year sales assumption is $100 million range from $16.0 million to $18.0 million for CDI, $13.0 million to $18.0 million for CRE infection, and $14.0 million to $17.0 million for NGI. When the peak-year sales assumption is $25 million, the threshold ENPVs are significantly lower and negative in value ranging from -$11.0 million to -$10.0 million for CDI and CRE infection and -$11.0 million for NGI. Additionally, at $25 million peak-year sales, seven of the twelve infection-scenario combinations have baseline peak-year sales values greater than $25 million.

Table 9. Threshold ENPVs Under Different Peak-year Sales Requirements (in 2016 $ Million)

Infection	Scenario	Threshold ENPV			
		PYS = $100 M	PYS = $75 M	PYS = $50 M	PYS = $25 M
C. difficile	Low Price, Large Market	$16.0	$7.0	-$2.0	-$11.0
	Low Price, Small Market	$18.0	$9.0	-$1.0	-$10.0
	High Price, Large Market	N/A	N/A	N/A	N/A
	High Price, Small Market	$17.0	$8.0	-$1.0	-$10.0
CRE	Low Price, Large Market	$18.0	$8.0	-$1.0	-$10.0
	Low Price, Small Market	$18.0	$9.0	-$1.0	-$10.0
	High Price, Large Market	$13.0	$4.0	N/A	N/A
	High Price, Small Market	$16.0	$7.0	-$2.0	-$11.0
N. gonorrhoeae	Low Price, Large Market	$14.0	$5.0	-$4.0	N/A
	Low Price, Small Market	$17.0	$8.0	-$1.0	-$10.0
	High Price, Large Market	N/A	N/A	N/A	N/A
	High Price, Small Market	N/A	N/A	N/A	N/A

PYS = Peak-year sales

N/A = Not applicable as the baseline year 4 (i.e., the peak year in our model) revenues are greater than the specified peak-year sales value.

As noted previously, if baseline ENPV is lower than the threshold ENPV needed for development, then this implies that the developer is unlikely to undertake the rapid POC development project in the absence of any incentives.

In Table 10, we compare the baseline ENPV to threshold ENPV for each of the applicable infection-scenario combinations under the four different peak-year sales assumptions modeled. Values in parentheses represent the difference between the threshold ENPV—the ENPV that would be necessary to begin device development—and baseline ENPV (= $ENPV_{t,PYS=i} - ENPV_b$ where i = $100 million, $75 million, $50 million, and $25 million) for each of the applicable infection-scenario combinations.

As can be observed from Table 10, the magnitude of the difference between threshold and baseline ENPV varies directly with the peak-year sales value. Higher peak-year sales requirements result in higher threshold values and vice versa across all applicable infection-scenario combinations.

Table 10. Baseline and Threshold ENPV of Developing Rapid POC Diagnostics for *C. difficile*, CRE, and *N. gonorrhoeae* Infections (in 2016 $ Million)

Infection	Scenario	Baseline ENPV	Threshold ENPV (Difference) [a]			
			PYS = $100 M	PYS = $75 M	PYS = $50 M	PYS = $25 M
C. difficile	Low Price, Large Market	-$13.8	$16.0 ($29.8)	$7.0 ($20.8)	-$2.0 ($11.8)	-$11.0 ($2.8)
	Low Price, Small Market	-$19.0	$18.0 ($37.0)	$9.0 ($28.0)	-$1.0 ($18.0)	-$10.0 ($9.0)
	High Price, Large Market	$121.5	N/A	N/A	N/A	N/A
	High Price, Small Market	-$17.2	$17.0 ($34.2)	$8.0 ($25.2)	-$1.0 ($16.2)	-$10.0 ($7.2)
CRE	Low Price, Large Market	-$18.4	$18.0 ($36.4)	$8.0 ($26.4)	-$1.0 ($17.4)	-$10.0 ($8.4)
	Low Price, Small Market	-$18.9	$18.0 ($36.9)	$9.0 ($27.9)	-$1.0 ($17.9)	-$10.0 ($8.9)
	High Price, Large Market	-$1.8	$13.0 ($14.8)	$4.0 ($5.8)	N/A	N/A
	High Price, Small Market	-$14.4	$16.0 ($30.4)	$7.0 ($21.4)	-$2.0 ($12.4)	-$11.0 ($3.4)
N. gonorrhoeae	Low Price, Large Market	-$7.4	$14.0 ($21.4)	$5.0 ($12.4)	-$4.0 ($3.4)	N/A
	Low Price, Small Market	-$17.1	$17.0 ($34.1)	$8.0 ($25.1)	-$1.0 ($16.1)	-$10.0 ($7.1)
	High Price, Large Market	$289.1	N/A	N/A	N/A	N/A
	High Price, Small Market	$33.8	N/A	N/A	N/A	N/A

PYS = Peak-year sales

N/A = Not applicable as the baseline year 4 (i.e., the peak year in our model) revenues are greater than the specified peak-year sales value yielding a baseline ENPV value that is greater than threshold ENPV needed for development.

[a] The figures in parentheses correspond to the difference between threshold ENPV and baseline ENPV values. If the difference is positive, it implies that the device company is unlikely to develop the device on its own without any exogenous incentives.

4.2 Social Returns

Using the ENPV framework outlined in Section 3.2 above, we estimated the societal WTP to avoid mortality and morbidity associated with CDI, CRE infection, and NGI. Framework parameters were adjusted for CDI-, CRE infection-, and NGI-specific health outcomes, which are described in Sections A.2.5.1, 0, and 0 below. As shown in Table 11 below, the total social annual burden of CDI, CRE infection, and NGI is the U.S. in 2016 dollars is $178 billion. CDI, with a social burden of $166 billion, represents close to 95 percent of the total annual burden of all three infections. Of the $166 billion in social burden associated with CDI, over 97 percent is due to mortality. The ENPV framework's sensitivity to mortality explains why, although there are more cases of NGI each year than CDI and CRE infection combined, NGI (which is not associated with mortality) represents less than 1 percent of the total annual burden of all three infections.

Table 11. Value of Lost Morbidity and Mortality in the United States from *C. difficile*, CRE, and *N. gonorrhoeae* Infections in 2016

Parameter			Value*			
			CDI	CRE Infection	NGI	Total
Total Number of Cases per Year (in 2016)		Initial	468,567	9,620	826,703	**1,304,890**
		Recurrent	90,091	N/A	N/A	**90,091**
Number of Deaths	Initial	First year	7,720	1,097	0	**8,817**
		1-year post surgery†	1,917	N/A	N/A	**1,917**
		2-year post surgery†	1,514			**1,514**
		5-year post surgery†	1,589			**1,589**
		7-year post surgery†	1,822			**1,822**
		11-year post surgery†	1,970			**1,970**
	Recurrent		0			**0**
VSL per Patient (in $ 2016)			$9,779,000			
Burden of Mortality (in $ 2016 Billion)			$161.7	$10.7	$0	**$172.4**
Number of Patients that Survive	Initial	First year	460,847	8,522	826,703	**1,287,260**
		1-year post surgery	1,975	N/A	N/A	**1,975**
		2-year post surgery	1,607			**1,607**
		5-year post surgery	1,843			**1,843**
		7-year post surgery	2,240			**2,240**
		11-year post surgery	2,727			**2,727**
	Recurrent		90,091			**90,091**
Lost QALYs			8,604	20	2,560	**11,184**
VSLY (in $ 2016)			$497,800			
Burden of Morbidity (in $ 2016 Billion)			$4.3	$0.01	$1.3	**$5.57**
Total Burden (in $ 2016 Billion)			**$166.0**	**$10.7**	**$1.3**	**$178.0**

N/A = Not applicable
VSL = Value of a Statistical Life
VSLY = Value of a Statistical Life Year
QALY = Quality-Adjusted Life Year
* Figures may not add up due to rounding.
† Deaths in future years are discounted at 3 percent.

4.3 Comparative Analysis Results

It is difficult to project the number of *C. difficile*, CRE, and *N. gonorrhoeae* infections that would be avoided due to reduced transmission rates afforded by purely hypothetical rapid POC diagnostics *a priori*. However, it is possible to calculate the number of incident cases that would need to be avoided so that that the value of social returns is equivalent to the difference between the threshold ENPV needed for manufacturers to begin clinical research and the baseline ENPV, for each type of infection. This type of information is the type of evidence that may be relevant to justify incentives for development of rapid POC devices. Using a decision tree framework similar to the one depicted in Figure 1, where the uppermost end node is positive and represents the total societal WTP to avoid morbidity and mortality associated with the given infection over the rapid POC diagnostic device's lifetime and the remaining end nodes are zero, we first calculate the societal WTP at the decision node. Next, by setting this societal WTP to the difference between the threshold ENPV and baseline ENPV (see values in parentheses in Table 10), we back-calculate the number of incident cases that would need to be avoided for each of the applicable infection-scenario combinations under the four different peak-year sales values considered. Table 12 shows the number of avoided cases per year needed to justify providing economic incentives sufficient to bridge the gap between threshold ENPV and baseline ENPV across the different infection types studied.

Table 12. Number of Avoided Cases per Year Needed to Equate Baseline ENPV to Threshold ENPV Needed for Development

Infection	Scenario	Baseline ENPV [a]	Threshold ENPV [a]				Number of Avoided Cases per Year Needed			
			PYS = $100 M	PYS = $75 M	PYS = $50 M	PYS = $25 M	PYS = $100 M	PYS = $75 M	PYS = $50 M	PYS = $25 M
C. difficile	Low Price, Large Market	-$13.8	$16.0	$7.0	-$2.0	-$11.0	50.0	34.9	19.7	4.6
	Low Price, Small Market	-$19.0	$18.0	$9.0	-$1.0	-$10.0	62.1	47.0	30.2	15.1
	High Price, Large Market	$121.5	N/A	N/A	N/A	N/A	0.0	0.0	0.0	0.0
	High Price, Small Market	-$17.2	$17.0	$8.0	-$1.0	-$10.0	57.5	42.4	27.2	12.1
CRE	Low Price, Large Market	-$18.4	$18.0	$8.0	-$1.0	-$10.0	19.4	14.1	9.3	4.5
	Low Price, Small Market	-$18.9	$18.0	$9.0	-$1.0	-$10.0	19.7	14.9	9.5	4.7
	High Price, Large Market	-$1.8	$13.0	$4.0	N/A	N/A	7.9	3.1	0.0	0.0
	High Price, Small Market	-$14.4	$16.0	$7.0	-$2.0	-$11.0	16.2	11.4	6.6	1.8
N. gonorrhoeae	Low Price, Large Market	-$7.4	$14.0	$5.0	-$4.0	N/A	8,051.7	4,667.4	1,283.1	0.0
	Low Price, Small Market	-$17.1	$17.0	$8.0	-$1.0	-$10.0	12,811.2	9,426.9	6,042.6	2,658.3
	High Price, Large Market	$289.1	N/A	N/A	N/A	N/A	0.0	0.0	0.0	0.0
	High Price, Small Market	$33.8	N/A	N/A	N/A	N/A	0.0	0.0	0.0	0.0

N/A = Not applicable as baseline ENPV is greater than threshold ENPV obviating the need for incentives.

In Table 12, the difference between threshold ENPV and baseline ENPV is expressed in number of avoided cases of infection per year needed to justify the economic incentive amount needed (rightmost columns). For example, under the low-price, large-market scenario for a rapid POC device to detect CDI has a baseline ENPV of -$13.8 million. The threshold ENPV for the device if peak-year sales requirement is $100 million is $16 million. The difference between the threshold and baseline ENPV under this infection-scenario combination is $29.8 million (= $16 million - -$13.8 million). In other words, for this manufacturer to undertake development, the value of the economic incentive needs to be at least $29.8 million. From the same table, "society" should be willing to pay $29.8 million if the device can avoid 50 cases of CDI per year.

If the baseline ENPV is greater than or equal to the threshold ENPV under a modeled peak-year sales assumption (cells denoted as "N/A" in Table 12), then no avoided cases are "needed" to meet the ENPV threshold as the company would develop the device regardless of any exogenous incentives.

4.4 Incentive Analysis Results

As seen in the comparative analysis in Section 4.3, there are many scenarios in which the baseline ENPV for a rapid POC diagnostic is less than the ENPV threshold a developer would require to begin production. In such cases (for example, the CRE high price, large market scenario in which the baseline ENPV is -$1.8 million and the PYS $100 million ENPV is about $14.8 million higher), we perform incentive analyses to evaluate which interventions could be used to bring baseline peak-year sales up to the thresholds necessary to stimulate development (see Table 13).

Several important trends are visible in Table 13. First, a hypothetical rapid POC diagnostic for the detection of CRE would require an economic incentive in almost every scenario. The only exceptions are high price, large market scenarios in which the peak-year sales threshold is set to $50 million or $25 million. Of the three infection types considered in this analysis, CRE infection is the most reliant on economic incentives to reach the development tipping point. Second, low-price scenarios would require economic incentives at all peak-year sales thresholds except for $25 million, and all CDI and CRE infection small market scenarios would require economic incentives, regardless of peak-year sales levels. This suggests that, without incentives, rapid POC diagnostic developers are unlikely to begin research and development in low price and/or small market scenarios. On the other hand, hypothetical *C. difficile* and NG rapid diagnostics show private returns above the development threshold in high price, large market scenarios.

Table 13. Economic Incentive Analysis Overview

Infection	Scenario	Economic Incentives Needed (Yes/No)?			
		PYS = $100 M	PYS = $75 M	PYS = $50 M	PYS = $25 M
C. Difficile	Low Price, Large Market	Yes	Yes	Yes	Yes
	Low Price, Small Market	Yes	Yes	Yes	Yes
	High Price, Large Market	No	No	No	No
	High Price, Small Market	Yes	Yes	Yes	Yes
CRE	Low Price, Large Market	Yes	Yes	Yes	Yes
	Low Price, Small Market	Yes	Yes	Yes	Yes
	High Price, Large Market	Yes	Yes	No	No
	High Price, Small Market	Yes	Yes	Yes	Yes
N. gonorrhoeae	Low Price, Large Market	Yes	Yes	Yes	No
	Low Price, Small Market	Yes	Yes	Yes	Yes
	High Price, Large Market	No	No	No	No
	High Price, Small Market	No	No	No	No

PYS = Peak-year sales

For each of the "yes" infection-scenario combinations in Table 13, we evaluated the impacts of the following economic incentives on ENPV:

- *Tax incentives*—Tax incentives for rapid POC diagnostic R&D can take many forms, including (but not limited to) tax credits, tax allowances, tax deferrals, accelerated depreciation, and favorable "patent box" tax rates (i.e., reduced tax rate for income derived from patents). Each of these types of incentives are expected to impact the real opportunity cost of capital in our model. Thus, we evaluate these incentives by changing the real opportunity cost of capital parameter (see Section A.1.1) in the analytical model.

- *Modifications to the clinical study process and FDA review standards*—These incentives encompass several ideas intended to streamline the clinical study and device review processes for rapid POC diagnostics to shorten the timelines and, in turn, reduce the costs associated with developing these diagnostics. Easing development and approval requirements could reduce development costs by shortening the time to market for these products, thereby increasing the potential returns to developers. We evaluate these incentives by changing the clinical study duration or FDA application review time parameters in the analytical model.

- *R&D phase, clinical phase, and FDA application phase cash prize awards*—Privately- and publicly-funded prize incentives and product development partnerships (PDPs) for medical innovation have flourished in recent years. Prize incentives directly reduce R&D costs and risks or increase revenues. They can take a variety of forms, including milestone monetary prizes, best entry tournaments, elective systems (e.g., the optional reward scheme), and others. In this study, we model this category of incentives as payments of lump-sum amounts upon successful completion of a phase. We evaluate these incentives by considering infusions of capital at various stages in the diagnostic development process.

- *Modifications to Centers for Medicare and Medicaid Services (CMS) reimbursement levels*—The margin between CMS reimbursement levels and test prices has a direct impact on the private returns of a diagnostic device. For example, a $10 test that has a CMS reimbursement level of $20 can potentially generate twice the return of a similar test that

has a reimbursement level of $15 as it gives the manufacturer the ability to charge a higher price. We evaluate this incentive by modifying the CMS reimbursement levels in our analytical model.

Similar to the threshold analysis in Section 4.3, in which we calculate how many cases of CDI, CRE infection, and NGI would need to be avoided to equate the incentive needed to the societal WTP, we evaluate the various economic incentives described above by changing the variable of interest in the analytical model until the peak-year sales threshold for development is reached.

4.4.1 Tax Incentives

Table 14 provides the results of the tax incentive analysis. Cells with numeric estimates indicate scenarios in which baseline peak-year sales were below the device development threshold, but changing the real opportunity cost of capital (ROCC) parameter in the analytical model results in meeting the peak-year sales threshold.[2]

Table 14. Tax Incentive Analysis

Infection	Scenario	Tax Incentives Needed?			
		PYS = $100 M	PYS = $75 M	PYS = $50 M	PYS = $25 M
C. difficile	Low Price, Large Market	No Solution	No Solution	No Solution	5.4%
	Low Price, Small Market	No Solution	No Solution	No Solution	No Solution
	High Price, Large Market	N/A	N/A	N/A	N/A
	High Price, Small Market	No Solution	No Solution	No Solution	No Solution
CRE	Low Price, Large Market	No Solution	No Solution	No Solution	No Solution
	Low Price, Small Market	No Solution	No Solution	No Solution	No Solution
	High Price, Large Market	5.1%	8.4%	N/A	N/A
	High Price, Small Market	No Solution	No Solution	No Solution	No Solution
N. gonorrhoeae	Low Price, Large Market	0.8%	3.6%	8.3%	N/A
	Low Price, Small Market	No Solution	No Solution	No Solution	No Solution
	High Price, Large Market	N/A	N/A	N/A	N/A
	High Price, Small Market	N/A	N/A	N/A	N/A

PYS = Peak-year sales
N/A = Not applicable

ROCC in the analytical model is set to 11.5 percent by default, and the cells with the reported percentage reflect the adjusted ROCC necessary to meet the given peak-year sales values. Cells with "N/A" indicate cases where the peak-year sales needed for device development is satisfied by baseline conditions and no tax incentive is necessary. The cells denoted as "no solution" indicate scenarios in which baseline peak-year sales were below the device development threshold and changing the ROCC parameter is insufficient for meeting the development threshold ENPV. As Table 14 illustrates, tax incentives provide the necessary boost to the development threshold in 18 percent of eligible scenarios

[2] The real opportunity cost of capital represents the rate of return (net of inflation) that the developer would otherwise be able to earn at the same risk level as the investment in the new rapid POC diagnostic that has been selected. The value of ROCC varies significantly by sponsor-specific factors, such as product portfolio and size of company, as well as other exogenous factors, such as economic and regulatory climate for device development projects.

(of the 33 scenarios where an economic incentive is needed, changes to ROCC are sufficient in only 6 of them). Further, tax incentives are only indicated in large market scenarios.

4.4.2 Modifications to the Clinical Study Process and FDA Review Standards

Table 15 provides the results of the clinical study process and FDA review standards analysis. The cells denoted as "N/A" indicate cases where the peak-year sales needed for device development is satisfied by baseline conditions and no changes to the clinical study process or FDA review standards are necessary. The cells denoted as "no solution" indicate scenarios in which baseline peak-year sales were below the device development threshold and changing the clinical study duration and the FDA application review time parameters was insufficient for meeting the development threshold ENPV. As Table 15 illustrates, there were no scenarios in which modifying clinical study time or FDA review time resulted in meeting peak-year sales development thresholds.

Table 15. Clinical Study Process and FDA Review Standards Analysis

Infection	Scenario	Clinical Study Process or FDA Review Standard Modifications Needed?			
		PYS = $100 M	PYS = $75 M	PYS = $50 M	PYS = $25 M
C. Difficile	Low Price, Large Market	No Solution	No Solution	No Solution	No Solution
	Low Price, Small Market	No Solution	No Solution	No Solution	No Solution
	High Price, Large Market	N/A	N/A	N/A	N/A
	High Price, Small Market	No Solution	No Solution	No Solution	No Solution
CRE	Low Price, Large Market	No Solution	No Solution	No Solution	No Solution
	Low Price, Small Market	No Solution	No Solution	No Solution	No Solution
	High Price, Large Market	No Solution	No Solution	N/A	N/A
	High Price, Small Market	No Solution	No Solution	No Solution	No Solution
N. gonorrhoeae	Low Price, Large Market	No Solution	No Solution	No Solution	N/A
	Low Price, Small Market	No Solution	No Solution	No Solution	No Solution
	High Price, Large Market	N/A	N/A	N/A	N/A
	High Price, Small Market	N/A	N/A	N/A	N/A

PYS = Peak-year sales
N/A = Not applicable

4.4.3 R&D Phase, Clinical Phase, and FDA Application Phase Cash Prize Awards

Table 16 provides the results of an analysis where incentives of cash prize awards are given for one product at different phases of development. Cells with dollar amounts indicate scenarios in which baseline peak-year sales were below the device development threshold but adding a cash prize into the scenario results in meeting the peak-year sales value. The dollar amounts are the award amounts necessary to meet the threshold ENPV for each scenario. Cells denoted as "N/A" indicate cases where the threshold ENPV needed for device development is satisfied by baseline conditions and no incentive is necessary. As Table 16 illustrates, cash awards can be used in any scenario to meet development threshold ENPVs. However, the requisite award amounts vary considerably from scenario to scenario. For example, in the case of a high price, large market CRE diagnostic at $75 million peak-year sales requirement, an R&D phase award of $17.1 million would be sufficient to meet the development threshold ENPV. On the other hand, the award would need to be about 12 times larger ($203.9 million) in the low price, small market $75 million peak-year sales requirement CRE infection scenario. As Table 16 indicates, the later in the development process an award is given, the greater it needs to be to incentivize new product development.

Table 16. R&D Phase, Clinical Phase, and FDA Application Phase Award Analysis

Infection	Scenario	Phase	R&D, Clinical, or FDA Application Phase Awards Needed?			
			PYS = $100 M	PYS = $75 M	PYS = $50 M	PYS = $25 M
C. difficile	Low Price, Large Market	R&D	$93.4	$64.7	$36.1	$7.4
		Clinical	$146.8	$101.7	$56.7	$11.6
		FDA	$223.3	$154.8	$86.3	$17.7
	Low Price, Small Market	R&D	$114.4	$64.7	$57.1	$28.4
		Clinical	$179.8	$134.7	$89.7	$44.6
		FDA	$273.5	$204.9	$136.4	$67.9
	High Price, Large Market	R&D	N/A	N/A	N/A	N/A
		Clinical	N/A	N/A	N/A	N/A
		FDA	N/A	N/A	N/A	N/A
	High Price, Small Market	R&D	$107.3	$78.6	$49.9	$21.3
		Clinical	$168.6	$123.5	$78.5	$33.4
		FDA	$256.5	$187.9	$119.4	$50.9
CRE	Low Price, Large Market	R&D	$112.1	$83.4	$54.7	$26.1
		Clinical	$176.1	$131.1	$86.0	$41.0
		FDA	$267.9	$199.4	$130.8	$62.3
	Low Price, Small Market	R&D	$114.0	$85.3	$56.6	$28.0
		Clinical	$179.1	$134.1	$89.0	$44.0
		FDA	$272.5	$203.9	$135.4	$66.9
	High Price, Large Market	R&D	$45.7	$17.1	N/A	N/A
		Clinical	$71.9	$26.8	N/A	N/A
		FDA	$109.3	$40.8	N/A	N/A
	High Price, Small Market	R&D	$96.2	$67.5	$38.8	$10.2
		Clinical	$151.2	$106.1	$61.1	$16.0
		FDA	$230.0	$161.4	$92.9	$24.3
N. *gonorrhoeae*	Low Price, Large Market	R&D	$68.1	$39.4	$10.7	N/A
		Clinical	$107.0	$61.9	$16.9	N/A
		FDA	$162.7	$94.2	$25.7	N/A
	Low Price, Small Market	R&D	$106.7	$78.0	$49.3	$20.7
		Clinical	$167.6	$122.6	$77.5	$32.5
		FDA	$255.0	$186.5	$118.0	$49.4
	High Price, Large Market	R&D	N/A	N/A	N/A	N/A
		Clinical	N/A	N/A	N/A	N/A
		FDA	N/A	N/A	N/A	N/A
	High Price, Small Market	R&D	N/A	N/A	N/A	N/A
		Clinical	N/A	N/A	N/A	N/A
		FDA	N/A	N/A	N/A	N/A

[a] Peak-year sales

4.4.4 CMS Reimbursement Incentives

Table 17 provides the results of the CMS reimbursement analysis. Cells with percentage estimates indicate scenarios in which baseline peak-year sales were below the device development threshold but changing the CMS reimbursement level for the diagnostic results in meeting the peak-year sales threshold. The percentages are the percent change necessary to meet the threshold ENPV for each scenario. Cells with "N/A" indicate cases where the threshold ENPV needed for device development is satisfied by baseline conditions and no change in CMS reimbursement level is necessary. As Table 17 illustrates, increases in CMS reimbursement level can be used in every applicable scenario to

meet development threshold ENPVs. However, the requisite increases in reimbursement levels vary considerably from scenario to scenario. For example, in the case of a low price, large market $50 million PYS NGI diagnostic, an increased reimbursement of 29.6 percent would be sufficient to meet the development threshold ENPV. On the other hand, some scenarios, such as low price, small market CDI would need CMS reimbursement levels to increase by over 10,000 percent for the diagnostic to reach development thresholds at any level of peak-year sales requirement.

Table 17. CMS Reimbursement Level Analysis

Infection	Scenario	CMS Reimbursement Level Change Needed?			
		PYS = $100 M	PYS = $75 M	PYS = $50 M	PYS = $25 M
C. difficile	Low Price, Large Market	564.9%	391.5%	218.2%	44.8%
	Low Price, Small Market	52,547.9%	39,378.8%	26,209.7%	13,040.6%
	High Price, Large Market	N/A	N/A	N/A	N/A
	High Price, Small Market	1,863.8%	1,365.7%	867.6%	369.5%
CRE	Low Price, Large Market	5,524.1%	4,110.9%	2697.8%	1,284.6%
	Low Price, Small Market	20,953.2%	15,682.8%	10,412.3%	5,141.9%
	High Price, Large Market	85.3%	31.8%	N/A	N/A
	High Price, Small Market	668.8%	469.5%	270.1%	70.8%
N. gonorrhoeae	Low Price, Large Market	187.8%	108.7%	29.6%	N/A
	Low Price, Small Market	1,715.1%	1,254.2%	793.3%	332.4%
	High Price, Large Market	N/A	N/A	N/A	N/A
	High Price, Small Market	N/A	N/A	N/A	N/A

PYS = Peak-year sales
N/A = Not applicable

5 CONCLUSIONS

The CDC's most recent report on U.S. antibiotic resistance threats identifies three microorganisms as urgent threats: *C. difficile*, CRE, and drug-resistant *N. gonorrhoeae* (CDC, 2013). These bacteria cost the healthcare system billions of dollars each year and can have severe impacts on those who become infected. Although the development of new antimicrobial drugs to combat these bacteria is important, medical journals are replete with studies showing that substantial benefits can be achieved using the existing antibiotic portfolio when patients carrying or infected by these bacteria are identified rapidly. Patients tested with rapid diagnostics tend to get appropriate treatment sooner, spend less time in healthcare facilities, and have less severe health outcomes (Barbut, et al., 2014). Moreover, rapid POC devices allow clinicians to isolate patients and enact infection control procedures quickly as well as tailor treatments to the antibiotic susceptibilities of individual infections (Tuite, et al., 2017).

In this study, we assessed the expected private returns of developing rapid POC devices for identifying *C. difficile*, CRE, and *N. gonorrhoeae* infections. Based on the model parameters and assumptions described in the Technical Appendix, the ENPV for manufacturers of new rapid POC diagnostics fall in the following ranges depending on test price and market size:

- CDI: -$19.0 million to $121.5 million;
- CRE infection: -$18.9 million to -$1.8 million; and
- NGI: $-17.1 million to $289.1 million.

Given the degree of uncertainty associated with different model parameters, we urge caution when interpreting projected returns for these theoretical rapid diagnostics. However, the model does highlight certain regularities, such as substantially lower expected private returns for a CRE infection diagnostic than for CDI or NGI. To complement our private returns analysis, we also evaluated the annual societal burden of *C. difficile*, CRE, and *N. gonorrhoeae* infections using WTP to avoid the mortality and morbidity associated with these infections as our metric. The potential societal WTP to avoid these infections, i.e., the social return of developing rapid POC diagnostics for the three infections, are as follows:

- CDI: $166.0 billion ($161.7 billion from mortality, $4.3 billion from morbidity);
- CRE infection: $10.7 billion ($10.7 billion from mortality, $0.01 billion from morbidity); and
- NGI: $1.3 billion ($0 from mortality, $1.3 billion from morbidity).

As all three infections have market scenarios in which private returns are not sufficient to develop rapid POC devices, we evaluated several economic incentives that could potentially spur development. Assuming $100 million in peak-year sales would be required to begin device development, tax incentives—analyzed by lowering the real opportunity cost of capital (ROCC) parameter in the analytical model from a baseline of 11.5 percent—were sufficient for reaching development thresholds only for CRE infection and NGI in the following scenarios:

- CRE infection: high price, large market (new ROCC of 5.1 percent)
- NGI: low price, large market (new ROCC of 0.8 percent)

In other scenarios, tax incentives were insufficient for reaching development thresholds or, due to high baseline ENPVs, no incentives were needed at all.[3] We also assessed the impacts of modifying the clinical study duration and FDA application review time parameters in the analytical framework. However, there were no scenarios in which modifying clinical study time or FDA review time resulted in meeting peak-year sales development thresholds. Another incentive we considered was cash prizes that could be awarded in various stages of the diagnostic development process (research and development, clinical, or FDA review). Assuming $100 million in peak-year sales would be required to begin device development, the following awards would be needed to hit development thresholds across various market scenarios[4]:

- R&D phase
  - CDI: $93.4 million to $114.4 million
  - CRE infection: $45.7 million to $114.0 million
  - NGI: $68.1 million to $106.7 million

[3] At the $100 million peak-year sales requirement, no incentives are needed for CDI when a high price and large market are assumed. The same is true of NGI when a high price is assumed (regardless of market size).
[4] As with the tax incentive analysis, at the $100 million peak-year sales requirement, no incentives are needed for CDI when a high price and large market are assumed. The same is true of NGI when a high price is assumed (regardless of market size).

- Clinical study phase
  - CDI: $146.8 million to $179.8 million
  - CRE infection: $71.9 million to $179.1 million
  - NGI: $107.0 million to $167.6 million
- FDA review/approval phase
  - CDI: $223.3 million to $273.5 million
  - CRE infection: $109.3 million to $272.5 million
  - NGI: $162.7 million to $255.0 million

We also considered the impact of changes to CMS reimbursement levels on device development thresholds. Assuming $100 million in peak-year sales would be required to begin development, the following increases in CMS reimbursement level would be needed to hit development thresholds across various market scenarios[5]:

- CDI: 564.9 percent to 52,547.9 percent;
- CRE infection: 85.3 percent to 20,953.2 percent; and
- NGI: 187.8 percent to 1,715.1 percent.

As with our private returns analysis, we urge caution when drawing conclusions from our incentive analysis given the degree of uncertainty associated with different model parameters. Also, these incentives were analyzed independently so we cannot draw conclusions about the amount of incentives necessary if combinations of incentives were implemented. Certain patterns that emerge, however, are relevant for designing policies to incentivize development of antibacterial rapid POC devices. We note that the magnitude of the award needed for device companies to begin pre-clinical development increases the further along the decision tree the development milestone occurs. This is primarily due to discounting; whereby future revenues contribute increasingly less to net present value the further out they are. We also note that solely relying on shortening the clinical study process or FDA application review times would not be sufficient to entice device developers to begin research and development, and that changes to CMS reimbursement levels would need to be substantial if they were to single-handedly spur device development. Though outside the scope of this project, it is possible that a combination of incentives could be used to make rapid POC diagnostic development more enticing under a wider range of market scenarios.

As with any analytical framework that forecasts future revenues, we rely on assumptions about consumer behavior and market dynamics that cannot be known with certainty ahead of time. For example, to assess device revenue streams under different economic conditions, we evaluate a "large market" scenario and a "small market" scenario. The large market scenario assumes a market share of 75 percent at peak-year sales and a pricing and reimbursement structure similar to rapid strep tests that are currently on the market. Alternatively, the small market scenario assumes a 25 percent market share at peak-year sales and a pricing and reimbursement structure similar to that of platform-based

[5] As with the award incentive analysis, at the $100 million peak-year sales requirement, no incentives are needed for CDI when a high price and large market are assumed. The same is true of NGI when a high price is assumed (regardless of market size).

diagnostics that use interchangeable cartridges. In reality, market share, test prices, and CMS reimbursement levels will depend on actual device specifications as well as exogenous factors, such as physician willingness to adopt new technologies, hospital and healthcare clinic screening guidelines, and the speed with which competitors enter the market. Although we have tried to capture these dynamics in our analytical framework and therefore the results presented above, uncertainty surrounding these factors is a limitation of our study.

Additionally, in our social burden analysis, we were unable to quantify certain health outcomes, particularly with respect to gonorrhea. For example, among women with gonorrhea who progress to pelvic inflammatory disease (PID), some experience chronic pelvic pain, ectopic pregnancy, and tubal factor infertility. These health outcomes are excluded from our morbidity and mortality calculations for various reasons. We exclude ectopic pregnancy and tubal factor infertility because there is substantial ambiguity when modeling pregnancy-related health outcomes—not all women become pregnant, not all women *want* to become pregnant, etc., making it impossible to know what percentage of the population with gonorrhea would experience quality of life reductions from pregnancy-related outcomes. We exclude chronic pelvic pain from our analysis because there are insufficient data on the typical duration and characteristics of associated symptoms. Due to these exclusions and others (e.g., excluding healthcare costs borne by third-party payers, such as Medicare and private insurance companies), we potentially underestimated the benefits of rapid POC diagnostics for detecting gonorrhea, CDI, and CRE infection. Moreover, even in cases where we do quantify health outcomes, we had to make assumptions about topics for which there is no consensus in the medical and health economics literature, such as what qualifies as severe *C. difficile* infection and how to calculate CRE-attributable mortality.

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APPENDIX A: TECHNICAL APPENDIX

This technical appendix presents the assumptions and parameters of the economic model developed for hypothetical rapid point-of-care (POC) diagnostics capable of detecting *C. difficile*, Carbapenem-resistant Enterobacteriaceae (CRE), or *N. gonorrhoeae* infections, referred to as CDI, CRE infection[6], and NGI models hereinafter. We model two types of hypothetical rapid POCs; one assumes a brand-new technology like that of the strep test which provides highly accurate rapid results; the other assumes that the diagnostic would feature a new platform and a new cartridge like the technologies for the existing POCs for these infections currently in the market. We further assume that both types would qualify for a waiver from the Clinical Laboratory Improvement Amendments (CLIA).[7]

A.1 PRIVATE EXPECTED NET PRESENT VALUE (ENPV) MODEL PARAMETERS AND ASSUMPTIONS

Table A - 1 below presents the estimates for the private ENPV parameters and assumptions used in the CDI, CRE infection, and NGI models. The following sections discuss the basis for these estimates in further detail.

A.1.1. Real Opportunity Cost of Capital (ROCC)

The real opportunity cost of capital (ROCC) represents the rate of return (net of inflation) that the developer would otherwise be able to earn at the same risk level as the investment in the new rapid POC diagnostic that has been selected. The value of ROCC varies significantly by sponsor-specific factors, such as product portfolio and size of company, as well as other exogenous factors, such as economic and regulatory climate for device development projects.

According to a study by Harrington (2012), the estimated ROCC for the medical device sector ranges from a low of 9.6 percent to a high of 13.7 percent (Table A - 2). In the model, we use 11.5 percent as the average real opportunity cost of capital.

[6] CRE is different from the other analytes as it is not synonymous with an infection per se but a phenotype that can exist for many infections.

[7] Under CLIA, FDA categorizes *in vitro* diagnostic tests by their degree of complexity: waived, moderate complexity, and high complexity. Tests that are waived by regulation under 42 CFR 493.15(c), or cleared or approved for home use or for over-the-counter use, are automatically categorized as waived following clearance or approval. Additionally, the developer of a test designated as "moderate complexity" may submit an application to FDA to request the categorization to be changed to "waived" (U.S. Food and Drug Administration, 2018).

Table A - 1. Private ENPV Model Parameters and Assumptions

Parameter	Industry Average					
Real Opportunity Cost of Capital	11.5%					
R&D Cost	$9,000,000					
Clinical Study Cost	$4,800,000					
FDA 510(k) + CLIA Waiver Application Preparation and Review Cost	$625,000					
Phase Durations						
R&D Time (in Months) [a]	42					
Clinical Study Time (in Months) [b]	24					
FDA 510(k) + CLIA Waiver Application Preparation & Review Time (in Months)	10.5					
Phase Success Probabilities						
R&D Success Probability	48%					
Clinical Study Success Probability	80%					
FDA 510(k) Application + CLIA Waiver Success Probability	73%					
Supply Chain Activity Costs [e]	$16,000,000					
Total Product Life (in Months)	102					
Product Launch Success Probability [c]	50%					
Time to Second/Competitive Entrant upon FDA Approval (in Months)	36					
% Reduction in Revenues due to Second/Competitive Entrant	15%					
Development Threshold for Peak-year Sales	$100,000,000					
	Low Price			**High Price**		
Technology Adoption						
Time to Reach 50% of Peak-year Sales after Launch (in Months)	15			15		
Estimated Steepness of the Technology Adoption Curve	0.1			0.1		
Expected Market Share at Peak-Year Sales	75%			25%		
Share of Total Revenues from Platform Sales	0%			17%		
Reimbursement Level per Test	$16.33			$47.80		
Average Expected Price per Test	$1.50			$39.66		
Average Number of Tests per Patient	1			1		
Market Size in Number of Tests per Annum (in Thousands)	**CDI**	**CRE Infection**	**NGI**	**CDI**	**CRE Infection**	**NGI**
	17,168	2,106	37,636	563	1,406	16,078

[a] Time from inception to clinical study.

[b] Incorporates CLIA waiver testing.

[c] Percent of new product launches that end up being commercially successful.

Table A - 2. Real Opportunity Cost of Capital (ROCC) Estimates from Harrington (2012)

Estimation Method	Time	Estimate	95% Confidence Bound
CAPM [a]	2001 – 2005	9.6%	8.5% – 10.8%
	2006 – 2008	11.2%	9.9% – 12.5%
FF [b]	2001 – 2005	11.3%	9.4% – 13.3%
	2006 – 2008	13.7%	12.0% – 15.4%
Overall [c]		**11.5%**	**8.5% – 15.4%**

[a] CAPM = Capital asset pricing model

[b] FF = Fama & French empirically driven three-risk factor model

[c] The figure is the average of all reported point estimates. The 95 percent confidence bound corresponds to the lowest and highest bounds among those reported.

A.1.2. R&D Costs

R&D costs for a new rapid POC diagnostic are based on the development of a new platform (i.e., instrumentation) and the development of the diagnostic (i.e., assay or cartridge) itself. A major factor influencing R&D costs is the existence of a predicate device. Given that there currently are FDA-approved *C. difficile*, CRE, and *N. gonorrhoeae* tests in the market, we assume that the new rapid POC diagnostic for detecting *C. difficile*, CRE, or *N. gonorrhoeae* will likely have a predicate device which will allow the manufacturer to pursue FDA clearance through the 510(k) route. While the precise sequence of steps may vary from case to case, the R&D costs associated with bringing a device to market generally include: development of engineering drawings (in house or outsourced), process and workflow validation, defining the final materials list (including trial and error with injection-molded plastic components), device bench testing, and development of design controls. Additionally, manufacturers incur research expenses to establish both that a clinical need for a new device exists and what marketing characteristics (sensitivity, specificity, time to results, and specimen type [sputum, stool, etc.]) they should target.

Making the engineering steps more difficult (and therefore costly) is the need to "design out" complexity for CLIA waiver and POC use.[8] CLIA-waived devices cannot have any complex user steps or generate results requiring substantial interpretation, as such, there is considerable chemical and mechanical engineering burden to automate processes that could otherwise be performed in a laboratory (for example, manufacturers must automate a method for DNA extraction and amplification, integrate an algorithm for identifying toxigenic genes, and present test results on a user-friendly touch screen). Taking this challenge into account, we estimate the total R&D cost for a rapid POC device for detecting *C. difficile,* CRE, or *N. gonorrhoeae* infection at $9.0 million, $5.85 million of which is represented by new platform R&D[9] and $3.15 million of which is represented by new assay/diagnostic R&D. We assume that the R&D costs for a truly novel technology like a strep test which would not include a platform, would be comparable at $9.0 million.

A.1.3. Clinical Research Costs

Depending upon the characteristics of the diagnostic, manufacturers might be required to perform one or more clinical studies to obtain data for a 510(k) application and a CLIA waiver. While

[8] We note that CLIA waiver and POC are not synonymous; not all POC devices are CLIA-waived.

[9] Many assays have a general platform where multiple assays can be run independently as disposable cartridges. This spreads the 'platform' development over multiple 'products.' However, in this analysis, we are trying to capture the full development costs of a novel system which is why we use the full platform development costs.

only a small fraction of 510(k) device applications require clinical studies, they are the norm for most microbiology *in vitro* diagnostic devices. Subsequently, sponsors have conducted clinical studies for most of the FDA-cleared rapid diagnostics for bacterial diseases in support of their 510(k) applications. Thus, we assume that the manufacturer of a new *C. difficile,* CRE, or *N. gonorrhoeae* rapid POC diagnostic will need to conduct testing with clinical specimens to demonstrate substantial equivalence to a predicate device. Key drivers of clinical study costs include the number of patients, specimen collection kits used, sample collection and processing (both on-site and at reference labs), clinical research organization (CRO) fees, and site selection and coordination (which may need geographic variation: Northeast, Midwest, West Coast, etc.). Moreover, manufacturers must develop software for storing and analyzing clinical study data.[10]

Based on discussions with industry experts and our research, the clinical study costs could range from a low of $500,000 to as high as $10.0 million for some diagnostics that require 1,000 – 1,500 patients and collection of multiple specimens and inclusion of symptomatic as well as asymptomatic patients. Given the wide range, we use a point estimate of $4.8 million for conducting a clinical study for a rapid POC diagnostic for *C. difficile,* CRE, or *N. gonorrhoeae*.[11]

A.1.4. FDA 510(k) and CLIA Waiver Submission Costs

Upon completion of clinical research, the manufacturer of the new diagnostic needs to prepare a package for submission to FDA. Additionally, under the Medical Device User Fee Act (MDUFA), device sponsors must pay a fee for entering the FDA review process. The 2016 FDA fee for 510(k) submissions was $5,228. A lower fee ($2,614 in 2016) is used for small businesses. The costs for preparing this regulatory submission (i.e., 510(k) clearance package) could be highly variable depending on device characteristics and whether the manufacturer uses in house or outsourced regulatory affairs support. We estimate that this cost ranges from $250,000 to $1.0 million based on discussions with industry. Combined, we estimate the costs for submitting a 510(k) application to FDA with clinical data at $625,000.

A.1.5. Phase Durations

Based on discussions with industry experts, the time it takes to bring a new rapid POC device to market could range from 3 to 5 years if it does not require the development of a new platform, to around 6 to 7 years if a new platform is necessary along with the test. The timeline for venture capital backed startups might be even longer due to funding constraints. For the model, we assume that it takes 5.71 years (68.5 months) to get to the point of submitting a 510(k) application to FDA, with 3.5 years (42 months) spent on concurrent platform and diagnostic R&D, 2 years (24 months) spent on clinical research, and 2.5 months spent preparing the 510(k) and CLIA waiver application. Further, we estimate it takes approximately 8 months for a complete review of the submitted application depending

[10] While there are off-the-shelf (OTS) software solutions for storing and analyzing clinical study data, these may be too expensive for small startups. We did not allocate costs for this specific activity in the model; this is meant to be descriptive of the spectrum of costs involved in developing a device.

[11] Clinical research costs for a CRE device could potentially be higher due to low prevalence of CRE infection making patient recruitment more difficult.

on whether the sponsor elects for a concurrent or stepwise 510(k) and CLIA waiver review.[12,13] Summing the phase durations described above, it takes 76.5 months (just under 6.5 years) to bring a new rapid POC diagnostic and platform to market in our model.

A.1.6. Phase Success Probabilities

Over the course of bringing a rapid POC device to market, most failures tend to occur at the early R&D phase. During this period, manufacturers perform medical market/health economics research and attempt to expand a core competency (such as a superior method for extracting DNA) into a commercially viable diagnostic. They then integrate that diagnostic into a CLIA-waived test for POC use. Although balancing analytical constraints with marketing targets (sensitivity, specificity, etc.) poses some difficulty, industry experts agreed that engineering challenges (especially designing and integrating a CLIA-waivable platform) would be the most difficult. Based on input from industry experts, we assume an R&D success probability point estimate of 48 percent with a lower bound of 10 percent and an upper bound of 95 percent.

Industry experts interviewed for the study indicated that devices making it through the R&D phase are likely to generate sufficient data in clinical studies for a favorable decision, especially if there is a guidance document outlining the type of diagnostic FDA is looking for. Additionally, for common healthcare-associated infections, several factors make clinical studies easier: there is a large supply of subjects, the pathogen is not seasonal (like the flu), the biology of the pathogen is well-understood, and there are many reference devices already on the market.[14] Based on this input, we assume a clinical study success probability point estimate of 80 percent.

To estimate the FDA application success probability for a new rapid POC device, we consider both the 510(k)-success probability and the CLIA waiver success probability. As described above, by the time a device reaches the clinical stage, it has a very high chance of success in making it to market. Thus, for the 510(k)-application stage, we assume a success probability point estimate of 96 percent. Experts noted, however, that obtaining a CLIA waiver is much more difficult. A CLIA waiver applicant must provide "flex studies" showing that untrained personnel can successfully use the diagnostic and, just as important, not misuse the POC diagnostic and generate an erroneous result. That is, CLIA-waived devices must perform as well as laboratory-based methods while remaining insensitive to a wide range of environmental and usage variations. Industry provided numerous examples of variations that, when unaccounted for in the clinical study or the "flex studies," can result in an unfavorable CLIA waiver decision. For instance:

[12] Based on conversations with industry, the concurrent approach takes around 7 months and the stepwise approach takes around 9 months (3 months for 510(k) review and 6 months for CLIA waiver review). Thus, a successful concurrent review would allow the CLIA-waived device to reach the market approximately 2 months faster than the stepwise approach. For a point estimate in the model, we average the duration of the two approaches since the decision to submit a concurrent or stepwise application will vary from manufacturer-to-manufacturer.

[13] The duration is dependent on how complete the application is. The average time to decision is shorter for 510(k) reviews, as there are mandated review times under MDUFA, with the FDA review time being less than 90 days and a dual 510(k)/CLIA application being 180 days. The estimated duration of 8 months (240 days) accounts for those cases where it may take some time for an application to be considered "complete" for FDA review.

[14] Clinical research phase duration may be longer for CRE given its low prevalence.

- If the diagnostic requires three drops of a reagent, it must be able to accommodate two to four drops in case the technician loses count.
- Cartridges need to work forwards and backwards or only fit in the platform one direction.
- Cartridge packaging must clearly describe how to tear it open (and must be easy to tear so that technicians are not tempted to take off their gloves).
- Devices must have an alarm that goes off if the technician tries to put in a cartridge that has already been used.
- Devices must have a mechanism that confirms and documents that the sample matches the proper patient.

Considering the rigorous requirements for demonstrating that a diagnostic uses a CLIA-waivable methodology, we assume a CLIA waiver success probability point estimate of 50 percent. Averaging this with the 510(k)-success probability estimate described above, we arrive at an FDA application success probability point estimate of 73 percent.

A.1.7. Costs of Supply Chain Activities

Rapid POC diagnostic developers need to undertake a variety of additional activities concurrently with clinical development, including manufacturing a sample of devices using validated processes for use in clinical studies and other demonstrations and acquisition of GMP-compliant capabilities. Scaling up manufacturing processes is a crucial step for efficiently getting to market as soon as possible after receiving approval from FDA. Industry experts note that the costs associated with this phase can be robust. Whereas companies might produce 100-200 devices during the early development stages, scaling up for product launch might entail manufacturing hundreds of platforms and potentially hundreds of thousands of assays/cartridges. Based on conversations with rapid POC diagnostic manufacturers, we estimate supply chain activity costs can range from $15.0 million to $17.0 million, with a likely point estimate of $16.0 million. We further assume in the model that these costs are evenly distributed across the average 6.5 years it takes to bring a device to market.

A.1.8. Total Product Life

Based on interviews with industry experts, we use an estimate of 8.5 years (i.e., 102 months) to characterize the average life cycle of a new rapid POC diagnostic upon FDA approval. Though the span of time over which a rapid POC diagnostic is used may extend beyond this 8.5-year period, expected revenues from sales in years beyond 8.5 contribute very little to private ENPV as it is anticipated that patient and clinical needs will have evolved and/or that the next generation of the device will be on the market.

A.1.9. Product Launch Success Probability

Based on interviews with industry experts, only about half of new product launches end up being commercially successful. Although some manufacturers describe difficulties with reimbursement and pricing of new diagnostics, the primary challenge to market success is hospital/clinician uptake. Before a hospital or clinic purchases a new rapid POC diagnostic device they must consider:

- The cost of the test relative to first line antibiotic therapies,
- Clinician dogma regarding empirical treatment,
- The proximity of pathology labs,

- Current and upcoming CDC guidance on infectious disease screening and reporting requirements, and
- Other metrics such as whether the diagnostic generates data that align with infectious disease incentive programs.

Given these challenges, we use a 50 percent likely point estimate for new rapid POC diagnostic product launch success probability.

A.1.10. Timing for Competitor Entry and Expected Percentage Reduction in Revenues due to Competition

The market for rapid POC diagnostics is competitive, especially for healthcare-associated infections that have the potential to impact sizeable populations, such as *C. difficile*. Unlike antibacterial drugs, rapid POC diagnostics do not have marketing exclusivity protections that would prevent other device manufacturers from market entry for a specified time. Thus, we assume that other manufacturers of rapid POC diagnostics for *C. difficile*, CRE, and *N. gonorrhoeae* will enter the market over time reducing revenues to the developer. Industry experts indicated, however, that the time to a competitive entrant could be highly variable. If there is strong uptake of the new rapid POC device, other manufacturers will begin developing (or proceed with developing) their own diagnostic immediately; on the other hand—as described in Section A.1.8 above—many new diagnostics do not achieve commercial success, thus delaying competitor interest in developing a rival product. Weighing these considerations, we assume a competitor would enter the market approximately 3 years (i.e., 36 months) after the first mover. In the model, this represents our estimate for the average time to experiencing a reduction in market share for the initial manufacturer.

The reduction in revenues associated with a competitive entrant are also highly variable. Key factors include the size of the next entrant (startup vs. established manufacturer), the pricing/marketing approach of the next entrant (are they trying to compete with the first mover or displace them altogether?), and the ability of the first mover to cultivate brand loyalty. Based on input from industry experts, we assume a reduction in revenues due to increased competition of 15 percent in the model.

A.1.11. Development Threshold for Peak-year Sales

Discussions with industry experts indicate that the decision to develop a device depends on multiple factors, including company size (large vs. small venture-backed startup), whether the development involves a brand-new platform and, most importantly, expected returns. According to some, the expected valuation for the device needs to be at least $50 million whereas for others the return-on-investment (ROI) needs to be 10 times or more.[15] In terms of annual sales, a device development project becomes desirable when expected annual revenues at peak-year sales are around $100 million, though they could range from a low of $10 million for a large manufacturer with an existing platform to a high of $1 billion for a venture-backed small startup. Based on our discussions, we estimate the development threshold for peak-year revenues from sales at $100 million in the model.

[15] Some companies might be willing to accept lower ROI in exchange for greater market share.

A.1.12. Reimbursement Level per Test

Reimbursement levels play a substantial role in procurement decisions for healthcare organizations as the profit margin for a diagnostic is driven by the difference between the price of the test and the level of CMS reimbursement. The CPT codes used in submitting reimbursement requests for diagnostic devices designed to detect *C. difficile*, CRE, and *N. gonorrhoeae* infections are 87493, 87798, and 87591, respectively. The Medicare fee-for-service national limit for reimbursement for these codes as of January 2016 is $47.80[16,17] (Centers for Medicare and Medicaid Services, 2015).

Based on Babady, et al. (2010), the price of a Cepheid Xpert *C. difficile* Epi assay, which is a rapid PCR-based assay with a turn-around time of less than one hour, to a healthcare organization was $36.00 in 2010. Accounting for inflation, this translates to $39.66 in 2016. Banach, et al. (2014) report the cost of surveillance testing for CRE at a New York City hospital at $8.53 per specimen in 2011. Accounting for inflation, this translates to $9.18 in 2016. According to STDCheck.com, STD testing which includes a panel of 10 tests for pathogens including chlamydia, syphilis, and gonorrhea is $198, for an average price per test of $19.80. There is, however, variability in how much hospitals pay for these types of diagnostic tests based on their purchasing contracts and the Group Purchasing Organization(s) they work with.

For the platform-cartridge type rapid POC device, we use the the test price of $39.66 for all three infections and a CMS reimbursement rate of $47.80 in the model. To model a truly innovative rapid POC comparable to a strep test in terms of ease of use and speed, we assume that the price and the CMS reimbursement level for such a test also needs to be comparable to that of strep test, at $1.50 and $16.33, respectively (Centers for Medicare and Medicaid Services, 2015).

A.1.13. Technology Adoption

We model the adoption of a new rapid POC diagnostic use in healthcare settings as an S-shaped logistic curve involving an exponential, transitional, and plateau phase, a commonly used function for characterizing tecnological diffusion over time (see Figure A - 1). More specifically:

$$A_t = M_{Peak\text{-}year} \div \{1 + \exp[-s \times (t - t_{Peak\text{-}year})]\}$$

where

A_t = Adoption rate in percentage at time t

$M_{Peak\text{-}year}$ = Expected market share at peak-year sales in percentage

s = Estimated steepness of the technology curve

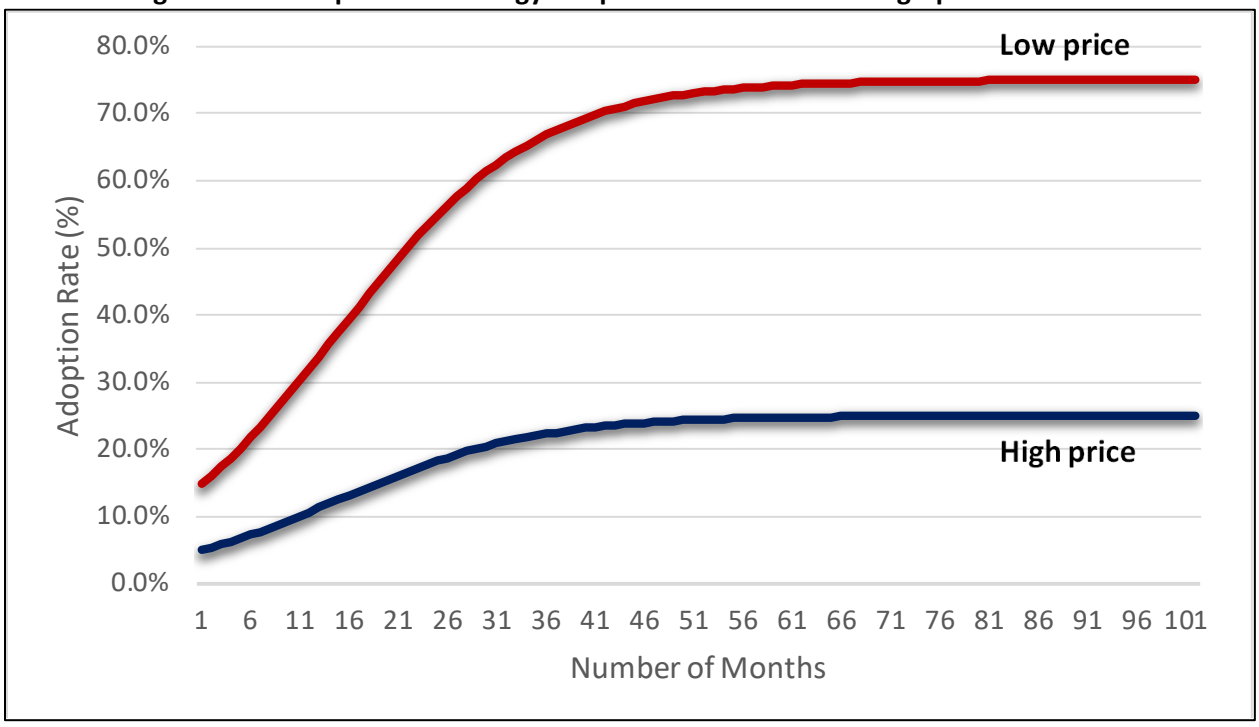
$t_{Peak\text{-}year}$ = Estimated time to reach 50 percent of peak-year sales in months

[16] This price represents the reimbursement level for a diagnostic with one indication. Industry experts noted, however, that some rapid POC diagnostics might have multiple targets. In such cases, the level of Medicare reimbursement could scale linearly. For example, the reimbursement limit for an assay with five targets would be ($47.80*5) = $239.00.

[17] Commercial payment rates will vary by laboratory contracts.

We assume that the estimated steepness of the technology curve and the time to reach 50 percent of peak-year sales are invariant between the two high- and low-price scenarios with values of 0.1 and 15 months, respectively. However, we judge that the expected market share at peak-year sales under the low-price scenarios will likely be higher than that under high-price scenarios given the convenience and the assumed price point for the strep-like test. Thus, we assume that the expected market share for at peak-year sales is 75 percent for low-price scenarios and 25 percent for high-price scenarios in the model.

Figure A - 1. Shape of Technology Adoption Under Low- and High-price Scenarios



A.1.14. Market Size Estimates

When making market size estimates, we assume that the hypothetical rapid POC devices would qualify for a CLIA waiver. As opposed to nonwaived diagnostics that can only be used in laboratories or sites that meet CLIA quality standards, have been inspected, and have a CLIA certificate. CLIA-*waived* diagnostics can be used in diverse settings such as ambulatory clinics, nursing homes, long-term care facilities, and intensive care units. Given these differences, the market for CLIA-waived diagnostics is much larger than for nonwaived tests.

A.1.14.1 CDI Market Size

We considered two alternative market sizes for a *C. difficile* rapid POC test (large and a small market one). Under the large market scenario, we assumed everyone 65 or older admitted to a hospital and those patients that visit a physician's office with acute diarrhea would be screened with the rapid POC test for CDI if the price of the test is comparable to that of a strep test (around $1.50). There is no publicly available data on the number of hospital admissions by age cohort. Thus, we used the number of hospital discharges for Medicare beneficiaries 65 years or older as a proxy in the analysis. The number of hospital discharges for Medicare beneficiaries in 2013 is reported at 8,920,517 (Centers for

Medicare and Medicaid Services, 2017), which is 9,050,862 when adjusted for population growth from 2013 to 2016. The number of physician's office visits due to acute diarrhea is 8.0 million in 2013 (Lever, et al., 2013), which is 8,116,895 when adjusted for population growth from 2013 to 2016. This results in a *C. difficile* rapid POC diagnostic market size of 17,167,757 under the large market scenario (Table A - 3).

Table A - 3. *C. difficile* rapid POC Diagnostic Market Size under Large-market Scenario – Screening for All Hospital Inpatient Admissions and Physician's Office Visits due to Acute Diarrhea

Parameter	Value	Source/Comments
Number of Hospital Inpatient Discharges for Medicare Beneficiaries 65 and Older in 2013	8,920,517	Centers for Medicare and Medicaid Services (2017)
% Population Growth, 2013 to 2016	1.5%	U.S. Census Bureau (2015)
Expected Number of Hospital Inpatient Discharges for Medicare Beneficiaries 65 and Older in 2016	9,050,862	Product of hospital inpatient admissions and population growth from 2013 to 2016
Number of Physician Office Visits due to Acute Diarrhea in 2013	8,000,000	Lever et al. (2013)
% Population Growth, 2013 to 2016	1.5%	U.S. Census Bureau (2015)
Expected Number of Physician Office Visits due to Acute Diarrhea in 2016	8,116,895	Product of physician's office visits and population growth from 2013 to 2016
Total CDI Market	17,167,757	Sum of hospital inpatient admissions for 65+ patients and physician's office visits

For an alternate scenario (small-market scenario), we assumed that testing would be done only for those nursing home patients transferred to hospitals for admission (estimated at 351,708 in 2016) and for those nursing home residents who develop diarrhea (estimated at 211,025 in 2016). This results in a CDI rapid diagnostic market size of 562,732 (Table A - 4).

Table A - 4. *C. difficile* rapid POC Diagnostic Market under Small-market Scenario – Nursing Home Residents Transferred to Hospitals and Those That Develop Diarrhea

Parameter	Value	Source/Comments
Number of Nursing Home Residents in 2014	1,400,000	CDC (2016b)
% Population Growth, 2014 to 2016	0.5%	U.S. Census Bureau (2015)
Expected Number of Nursing Home Residents in 2016	1,406,830	Product of number of nursing home residents and population growth from 2014 to 2016
Percent of Nursing Home Residents Transferred to Hospitals for Admission per Year	25%	HHS Office of Inspector General (2013)
Expected Number of Nursing Home Residents Transferred to Hospitals for Admission per Year	351,708	Product of number of nursing home residents and transfers to hospitals [a]
Percent of Nursing Home Residents that Develop Diarrhea	15%	Meyer (2016)
Expected Number of Nursing Home Residents that Develop Diarrhea	211,025	Product of number of nursing home residents and percent that develop diarrhea
Total CDI market	562,732	Sum of hospital transfers and number that develop diarrhea

[a] These represent the hospitalizations as defined by CMS for the Medicare and Medicaid population.

A.1.14.2 CRE Infection Market Size

As shown in Table A - 5 and further described below, we estimate the market size for a rapid POC diagnostic at 2,106,055 units per year. The figure includes patients hospitalized from long-term care facilities (LTCFs) and high-risk patients transferred from one hospital to another for whom active screening would be cost effective.

Table A - 5. Market Size Estimate for a Rapid POC Diagnostic Device for Detecting CRE Infection

Cohort	Number of Rapid POC CRE Diagnostic Tests per Year	Calculation
LTCF-to-Hospital Transfers	699,971	See Table A - 6
ICU-to-ICU Transfers	270,544	See Table A - 7
ER-to-ER Transfers	1,135,540	See Table A - 7
Total	**2,106,055**	

Given the advanced age of those typically exposed to CRE (median age 66), the "high prevalence of prior hospitalizations or indwelling devices," and the association with "discharge to long-term care settings" (Guh, et al., 2015), we use the U.S. LTCF population as the starting point for our market size estimate. Data on the U.S. LTCF population come from CDC's (2016b) "Long-Term Care Providers and Services Users in the United States: Data From the National Study of Long-Term Care Providers" which reports 1,369,700 nursing homes residents and 1,340,700 hospice care recipients for a combined 2,710,400 LTCF patients in the U.S. in 2014.[18] Inflating this estimate for population growth from 2014 to 2016, we get an LTCF population of 2,723,623.

As described above, our market size estimate is intended to capture high-risk populations for whom CRE screening might be cost-effective. From a CDC surveillance and infection control perspective, one approach to controlling CRE regionally is to screen patients upon hospital admission, regardless of what prompted their transfer to the hospital. Multiplying the 2,723,623 LTCF patients described above by the LTCF hospitalization rate of 25.7 percent reported in Tanuseputro, et al. (2015) results in an estimated 699,971 annual transfers from LTCFs to hospitals (Table A - 6).

Table A - 6. Market Size Estimate for a Rapid POC Diagnostic Device for Detecting CRE Infection Among LTCF-to-Hospital Transfers in the U.S.

Parameter	Value	Source/Comments
In-scope LTCF Population, 2016 [a]	2,710,400	CDC (2016b)
% Population Growth, 2014 to 2016	0.5%	U.S. Census Bureau (2015)
In-scope LTCF Population, 2016	2,723,623	Product of in-scope LTCF population and % population growth from 2014 to 2016
% LTCF Residents Hospitalized	25.7%	Tanuseputro, et al. (2015)
Estimated LTCF-to-Hospital Market Size	699,971	Product of in-scope LTCF population and LTCF hospitalization rate

[a] CDC (2016b) provides data on other long-term care populations such as residents of residential care communities and users of home health agencies. Per conversations with CDC, however, these populations are effectively community dwellers and are not considered to be at increased risk for CRE carriage. As such, ERG has limited the LTCF population to those in nursing homes and those receiving hospice care.

[18] CDC (2016b) provides data on other long-term care populations such as residents of residential care communities and users of home health agencies. Per conversations with CDC, however, these populations are effectively community dwellers and are not considered to be at increased risk for CRE carriage. As such, ERG has limited the LTCF population to those in nursing homes and those receiving hospice care.

We believe screening for CRE infection when patients are transferred from hospital-to-hospital would also be cost-effective if the originating hospital had a CRE infection episode within the past year. Thus, we made the simplifying assumption that if a competitively-priced rapid POC diagnostic were available, receiving hospitals would use it to screen all incoming transfers. As such, our market size analysis estimates the annual number of hospital-to-hospital transfers in the U.S. As shown in Table A - 7 and further described below, we estimate the market size for a rapid POC diagnostic used on patients transferred between ICUs at 270,544 units per year and the market size for a rapid POC diagnostic used on patients transferred between ERs at 1,135,540 units per year.

Table A - 7. Market Size Estimate for a Rapid POC Diagnostic Device for Detecting CRE Infection Among Hospital ICU-to-Hospital ICU Transfers in the U.S.

Parameter	Value	Source/Comments
Hospital-to-Hospital: ICU		
ICU Stays – 29 Surveillance States, 2011	4,600,000	Barrett et al. (2014)
ICU Stays – Total U.S., 2011	7,931,034	ICU stays from 29 surveillance states increased proportionally to account for the other 21 states
% Population Growth, 2011 to 2016	3.4%	U.S. Census Bureau (2015)
Projected ICU Stays, 2016	8,203,579	Product of U.S. ICU stays and % population growth from 2011 to 2016
ICU-to-ICU Transfer Rate, %	3.3%	Average of transfer rates reported in Zimmerman et al. (2006) and Iwashyna, et al. (2009)
ICU Transfer Market Size	270,544	Product of U.S. ICU stays and the ICU-to-ICU transfer rate
Hospital-to-Hospital: ER		
Annual ER Visits in the U.S., 2011	136,296,000	CDC (2011)
% Population Growth, 2011 to 2016	3.4%	U.S. Census Bureau (2015)
Projected ER Visits, 2016	140,979,717	Product of U.S. ICU stays and % population growth from 2011 to 2016
ER-to-ER/ER-to-Inpatient Transfer Rate, % [a]	0.8%	Kindermann et al. (2015); ASPE and CDC expert judgment
ER Transfer Market Size	1,135,540	Product of U.S. ER visits and the ER-to-ER/ER-to-inpatient transfer rate

[a] Among the 50 highest transfer rate disease categories reported in Kindermann et al. (2015), 24 were judged to be more relevant for the elderly population (renal failure, infective arthritis, etc.). The number of transfer events for these 24 categories is 35,220 which translates to a transfer rate of 0.8 percent (35,220 transfer events among 4,372,640 total ER events).

The most robust data on hospital-to-hospital transfers were available for patients moved from intensive care units (ICUs) and emergency rooms (ERs). Thus, we focus our analysis on those two populations. The starting point for our ICU transfer estimate was the Agency for Healthcare Research and Quality's (AHRQ) Healthcare Cost and Utilization Project (HCUP) statistical brief on the "utilization of intensive care services" (Barrett, et al., 2014). This report, based on HCUP's State Inpatient Databases (SID) from 29 states, found that in 2011 there were 4.6 million adult hospital stays that involved ICU use. As the HCUP SID data were chosen to cover "a broad cross-section of U.S. hospitals" (Barrett, et al., 2014), we can scale this number up proportionally to account for ICU stays in the 21 other states, giving us a U.S. total of 7,931,034 in 2011. Adjusting this number for population growth, we get an estimated 8,203,579 ICU stays in 2016. Multiplying this number by the average ICU-to-ICU transfer rate identified

in our literature review (3.3 transfers per 100 ICU stays),[19] we get an estimated market size of 270,544 CRE rapid POC tests.

The starting point for our ER transfer estimate was CDC's (2011) National Hospital Ambulatory Medical Care Survey, which reported 136,296,000 ER visits in the U.S. in 2011. Adjusting this number for population growth, we get an estimated 140,979,717 ER visits in 2016. Multiplying this figure by the rate of 0.8 inter-hospital transfers per 100 applicable ER events reported in Kindermann et al. (2015),[20] we get an estimated market size of 1,135,540 CRE rapid POC tests.

For modeling purposes, we assume that the total market size under low-price scenarios is 2,106,055 which includes the in-scope LTCF population, ICU-to-ICU, and ER-to-ER transfers. For high-price scenarios, we estimate the market size at 1,406,083 which excludes the LTCF population.

A.1.14.3 NGI Market Size

As shown in Table A - 8 and further described below, we estimate the market size for a rapid POC diagnostic at 37,635,769 units per year. However, we note that this estimate does not take into the consideration that multiple tests might be required for men who have sex with men (MSM) and women with rectal or pharyngeal exposure.

Table A - 8. NG Rapid POC Diagnostic Market Size

Cohort	Number of NG Rapid POC Diagnostic Tests per Year
Sexually active women	23,618.060
Pregnant women	3,936,475
MSM	2,442,120
Persons with HIV	938,557
Partners of those diagnosed with gonorrhea	397,809
Sexually active women with recurrent UTI	5,942,747
Individuals taking HIV PrEP	360,000
Total	**37,635,769**

We used CDC's (2016c) screening recommendations as a starting point for estimating the market size for an NG rapid POC diagnostic. This population includes sexually active women under 25 (and older if at increased risk), pregnant women under 25 (and older if at increased risk), MSM, and persons with HIV (CDC, 2016a). Based on conversations with CDC and ASPE, we also included partners of those diagnosed with gonorrhea, sexually active women with recurrent UTI, and individuals taking HIV pre-exposure prophylaxis (PrEP). It is possible that some groups—especially partners of those diagnosed with gonorrhea—may not be mutually exclusive of the other groups. In such cases, one patient might count toward the test total in more than one NGI group. Although we have tried to avoid such double counting, some patients would presumably fall into multiple categories and/or have had

[19] Iwashyna, et al. (2009) report a transfer rate of 4.5 transfers per 100 ICU stays and from Zimmerman et al. (2006) we can derive a transfer rate of 2.1 transfers per 100 ICU stays. Unfortunately, Iwashyna et al. (2009) do not provide their underlying data, so we use an unweighted average of the two studies' rates (3.3 transfers per 100 ICU stays).

[20] See footnote to Table A - 7.

the test performed more than once per year. Table A - 8 presents a summary of the market size estimate, and the sections below describe our calculations for each population.[21]

For modeling purposes, we assume that the total market size under low-price scenarios is 37,635,769 which includes all the cohorts outlined in Table A - 8. For high-price scenarios, we estimate the market size at 16,078,485 which excludes annual screens for sexually active women (excluding 2,060,776 that are considered high-risk).

Sexually Active Women

CDC (2016c) recommends gonorrhea screening for sexually active women under 25 years of age and, if at increased risk, sexually active women age 25 years and older (see Table A - 9). We made the simplifying assumption that if a competitively-priced rapid POC diagnostic were available, gynecologists would use it when conducting annual exams on women under 25, regardless of sexual history. Assuming women between the ages of 15 and 24 (inclusive) have annual gynecology exams, this represents 21,382,495 tests in 2015 (American Community Survey, 2016). Inflating this figure for projected population growth in 2016, we get 21,557,284 tests (U.S. Census Bureau, 2015).

Table A - 9. Sexually Active Women Market Size for an NG Rapid POC Diagnostic

Cohort	Number of Individuals	Average Number of NG Rapid POC Diagnostic Tests per Person	Total Number of NG Rapid POC Diagnostic Tests
Sexually Active Women under 25 [a]			
15 to 19 years	10,311,036	1	10,311,036
20 to 24 years	11,071,459		11,071,459
Total in 2015	21,382,495		21,382,495
Sexually Active Women above 24 at High Risk [a, b]			
25 to 29 years	176,834	5	884,172
30 to 34 years	140,217		701,084
35 to 39 years	61,207		306,035
40 to 44 years	30,555		152,776
Total in 2015	408,813		2,044,067
Grand Total in 2015	21,791,308	N/A	23,426,562
Percent Population Growth 2015 to 2016 [c]		0.82%	
Grand Total in 2016	21,969,439	N/A	23,618,060

N/A = Not Applicable
[a] American Community Survey (2016); [b] CDC (2012); [c] U.S. Census Bureau (2015)

For sexually active women over 25, we estimated the share at increased risk for gonorrhea using the percent of women between the ages of 25 and 44 (inclusive) who report having had five or more

[21] Although there is overlap between some of these populations ERG's market size estimate is intended to capture the number of tests given annually, not the number of people screened. For example, a sexually active 23-year-old woman might be screened once during her annual checkup and once again six months later if she presents with recurrent UTI. Since two diagnostics were used within a year, we would want both tests reflected in our annual market size estimate.

opposite-sex partners in the past year (CDC, 2012).[22] Multiplying this rate (approximately 0.95 percent) by the number of women in the U.S. between the ages of 25 and 44 in 2015—42,224,270 (American Community Survey, 2016)—results in an estimated 408,813 women between the ages of 25 and 44 who had five or more opposite-sex partners in the past year. Increasing this estimate by a factor of five to account for repeat NG screening after each partner results in a market size estimate of 2,044,067 for sexually active women over 25 at increased risk for contracting gonorrhea. Inflating this figure for projected population growth in 2016, we get 2,060,776 tests (U.S. Census Bureau, 2015).

Pregnant Women

CDC (2016c) recommends gonorrhea screening for pregnant women under 25 years of age and older women if at increased risk. We made the simplifying assumption that if a competitively-priced rapid POC diagnostic were available, obstetricians would use it during first trimester screening regardless of age or risk factors. To estimate the number of pregnant women in the U.S., we adjusted the number of births reported by CDC (2015a) to account for twins, triplets, quadruplets, and higher-order multiples. In 2014, CDC (2015a) reported births of 3,848,214 singletons, 135,336 twins, 4,233 triplets, 246 quadruplets, and 47 quintuplets and higher-order multiples. Dividing the number of reported twins by two, the number of triplets by three, etc. and adding those quotients to the reported number of singletons, we arrived at a U.S. estimate of 3,917,364 pregnant women.[23] Assuming all pregnant women are screened during the first trimester, we estimate pregnant women represent 3,979,276 NG diagnostics when adjusted for population growth from 2014 to 2016 (U.S. Census Bureau, 2015) (Table A - 10).

Table A - 10. Pregnant Women Market Size for an NG Rapid POC Diagnostic

Type of Birth	Number of Births	Total Number of NG Rapid POC Diagnostic Tests
Singletons [a]	3,848,214	3,848,214
Twins [a]	135,336	67,668
Triplets [a]	4,233	1,411
Quadruplets [a]	246	62
Quintuplets + higher-order multiples [a]	47	9
Total Births in 2014 [a]	3,988,076	3,917,364
Percent Population Growth 2014 to 2016 [b]	0.49%	
Total Births in 2016	4,007,533	3,979,276

[a] CDC (2015a); adjusted for twins, triplets, and other multiples
[b] U.S. Census Bureau (2015)

[22] CDC has changed its definition of elevated risk warranting screening to include women 25 years or older who have a new sex partner, more than one sex partner, a sex partner with concurrent partners, or a sex partner who has a sexually transmitted infection (CDC, 2016c). However, we lack an estimate of the number of women who meet CDC's new elevated risk definition for use in estimating this population. To the extent that the number of women who meet the new CDC elevated risk criteria differs from those who report having had five or more opposite-sex partners in the past year (see Table A - 9), our estimate of the sexually active women may be an over- or under-estimate.

[23] ERG divided the number of reported quintuplets and higher-order multiples (47) by five since details about the higher-order multiples were not reported in the national data.

Men Who Have Sex with Men (MSM)

CDC (2016c) recommends annual gonorrhea screening for sexually active MSM. To estimate the number of MSM in the U.S., we combined CDC's (2015a) estimate of gay men in the U.S. (2,046,000) with CDC's estimate of bisexual men in the U.S. (559,000) for an estimated 2,605,000 MSM in 2015. Inflating to account for population growth in 2016, we get an estimate of 2,626,294 MSM (U.S. Census Bureau, 2015). We subtracted 184,174 from this total to account for married gay couples that we are using as a proxy for low risk.[24] This results in an estimated NG diagnostic market of 2,442,120 non-married MSM in 2016 (see Table A - 11)

Table A - 11. MSM Market Size for an NG Rapid POC Diagnostic

Cohort	Total Number of NG Rapid POC Diagnostic Tests
Gay Men [a]	2,046,000
Bisexual Men [a]	559,000
Total Gay and Bisexual Men [a]	2,605,000
Percent Population Growth 2015 to 2016 [b]	0.82%
Total Gay and Bisexual Men in 2016	2,626,294
Male Same-Sex Joint Filers [c]	(183,280)
Percent Population Growth 2014 to 2016 [b]	0.49%
Total Male Same-Sex Joint Filers in 2016	(184,174)
Total At-Risk MSM in 2016 [d]	2,442,120

[a] CDC (2015b)
[b] U.S. Census Bureau (2014)
[c] Fisher et al. (2016); see footnote 24
[d] At-Risk MSM = (Total Gay and Bisexual Men) – (Total Male Same-Sex Joint Filers)

Persons with HIV

CDC (2016c) recommends annual gonorrhea screening for sexually active individuals with HIV. CDC (2016d) reports that as of 2013, an estimated 1.1 million people were living with HIV in the U.S. Of these, CDC reports that 166,000 are undiagnosed. Subtracting undiagnosed cases from 1.1 million and inflating the result to account for population growth from 2014 to 2016 gives an estimate of 938,557 status-aware people living with HIV (U.S. Census Bureau, 2015).

Partners of Those Diagnosed with Gonorrhea

In consultation with CDC and ASPE, we assumed that partners of those diagnosed with gonorrhea would be screened for infection. According to CDC surveillance (2016f; 2016e), in the U.S. in 2015, there were 173,514 reported cases of gonorrhea among women and 221,070 reported cases among men. Assuming each reported case results in one notified partner and inflating the case counts for projected population growth from 2015 to 2016 (U.S. Census Bureau, 2015), we estimate an NG diagnostic market of 397,809 for partners of those diagnosed with gonorrhea.

[24] The U.S. Treasury Department (Fisher, et al., 2016) reported 183,280 same-sex joint filers in 2014. ERG assumes 50 percent are men. 50 percent of 183,280 couples*2 = 183,280 individuals. Inflating this number for population growth from 2014 to 2016 gives an estimate of 186,422 individuals (U.S. Census Bureau, 2014).

Sexually Active Women with Recurrent UTI

In consultation with ASPE, we assumed that clinicians would screen sexually active women with recurrent UTI for gonorrhea. The first step in developing this estimate was to determine the annual number of outpatient visits for UTI among women. Data are limited on outpatient visits for specific diagnoses, limiting our scope to emergency department visits and physician office visits.

CDC (2010a) reports 1,124,000 emergency department visits for UTI among women age 15-64 and an additional 391,000 visits for women 65 and over. Summing these and inflating for population growth from 2007 to 2016 gives an estimate of 1,629,492 annual emergency department visits (U.S. Census Bureau, 2015). CDC (2010b) also reports 38,298,000 annual visits to physician offices for diseases of the genitourinary system, but does not break this estimate down by sex. To estimate the share represented by women, we used the more granular emergency department visit data. As mentioned above, there are an estimated 1,629,492 annual emergency department visits among women due to UTI (CDC, 2010a). In contrast, CDC (2010a) reports a population-growth adjusted 168,143 annual emergency department visits among men due to "other urinary dysfunctions" (U.S. Census Bureau, 2014), giving a female to male emergency department visit split of 90.9 percent to 9.4 percent. Assuming these proportions hold for physician office visits, we estimate there are 37,339,339 annual physician office visits by female patients for UTI after adjusting for population growth from 2007 to 2016.

Combining the emergency department and physician office visits we arrive at an estimated 38,968,831 annual outpatient visits by women for UTI. We then adjusted this number for age and UTI recurrence. Although CDC (2015c) surveillance has found cases of gonorrhea across all age groups, we assume women 50 and over would not be screened for *N. gonorrhoeae* even if they presented with recurrent UTI. Our decision to exclude women over 50 is based on our understanding that post-menopausal women are not at increased risk for gonorrhea and Rowe and Juthani-Mehta's (2013) finding that, for women over 50, UTI incidence is not as strongly correlated with sexual activity as it is with younger women. To adjust our emergency department and physician office visit estimate for age, we used Kobayashi et al.'s (2016) finding that 61 percent of all ambulatory care visits for uncomplicated UTI in women are for patients age 18 to 49. Applying this percentage to our preliminary estimate of 38,968,831, we get 23,770,987 annual outpatient visits for UTI in women aged 18 to 49. The final step is adjusting this number for UTI recurrence. Eells et al. (2014) note "after an initial UTI, approximately 20 to 30 percent of women with a UTI will have a second UTI within 6 months." Multiplying 23,770,987 by the midpoint of Eells's range (25 percent), we get an estimated NG diagnostic market of 5,942,747 annual cases of recurrent UTI treated in outpatient settings among women age 18-49 (see Table A - 12).

Table A - 12. Sexually Active Women with Recurrent UTI Market Size for an NG Rapid POC Diagnostic

Cohort	Total Number of NG Rapid POC Diagnostic Tests
Emergency Department Visits for UTI	
Women Age 15-64 [a]	1,124,000
Women Age 65+ [a]	391,000
Total Women Age 15+	1,515,000
Percent Population Growth 2007 to 2016 [b]	7.6%
Total Emergency Department Visits by Women 15+ for UTI in 2016	1,629,492
Physician Office Visits for Diseases of the Genitourinary System	
Men and Women [c]	38,298,000
Share of Physician Office Visits for Diseases of the Genitourinary System by Women [a]	90.6%
Physician Office Visits by Women for Diseases of the Genitourinary System [a, c]	34,715,781
Percent Population Growth 2007 to 2016 [b]	7.6%
Total Physician Office Visits by Women for Diseases of the Genitourinary System in 2016	37,339,339
Outpatient (ER + Physician Office) Visits by Women for UTI and Genitourinary Disease in 2016	38,968,831
Share of Women Treated for Uncomplicated UTI in Outpatient Settings by Women 18 to 49 [d]	61.0%
Outpatient Visits for UTI and Genitourinary Disease Among Women Age 18 to 49	23,770,987
Share of Women Who Experience a Second UTI Within 6 Months of an Initial UTI [e]	25%
Total Sexually Active Women Who Will Experience a Recurrent UTI	5,942,747

[a] CDC (2010a)
[b] U.S. Census Bureau (2015)
[c] CDC (2010b)
[d] Kobayashi et al. (2016)
[e] Eells et al. (2014)

Individuals Taking HIV Pre-exposure Prophylaxis

In consultation with CDC, we assumed that individuals taking HIV PrEP would be screened for gonorrhea four times per year.[25] We could not find an official estimate of the number of people taking PrEP in the U.S.; however, Mincer (2016) indicated that 90,000 people were taking the drug in the U.S. in mid-2016. Multiplying 90,000 by four to account for multiple screenings throughout the year, we estimate an NG diagnostic market of 360,000 for individuals taking HIV PrEP in 2016. Even though Mincer (2016) does not provide a breakdown, we acknowledge that most of the 90,000 are likely to be in the MSM population reported in Table A – 11 above leading to double-counting. However, because some might be testing a lot more frequently than modeled, there also is the possibility of under-counting in our model. Therefore, it is possible that the potential over-estimation of market size due to the overlap between MSM and HIV PreP population estimates is offset by under-estimation of number of tests performed on these two populations.

[25] CDC's (2016c) overview of PrEP notes "people who use PrEP must commit to taking the drug every day and seeing their health care provider for follow-up every 3 months."

A.2 SOCIAL BURDEN OF ILLNESS PARAMETERS AND ASSUMPTIONS

Table A - 13 below presents the assumptions and parameters used in estimating the social burden of illness for CDI, CRE infection, and NGI in the U.S. The following sections discuss the basis for these estimates in further detail.

Table A - 13. Social Burden of Illness Parameters and Assumptions

Parameter			CDI	CRE Infection	NGI
Real Annual Social Rate of Discount			3%		
VSL per Patient (in $ 2016)			$9,779,005		
VSLY (in $ 2016)			$497,848		
Total Number of Cases per Year (in 2016)	Initial		468,567	9,620	826,703
	Recurrent		90,091	N/A	N/A
Health Outcomes					
Number of Patients that Die	Initial	First year	7,720	1,097	0
		1-year post surgery†	1,917	N/A	N/A
		2-year post surgery†	1,514		
		5-year post surgery†	1,589		
		7-year post surgery†	1,822		
		11-year post surgery†	1,970		
	Recurrent		0	N/A	N/A
Lost QALYs for Patients that Survive			8,604	20	2,560

N/A = Not applicable
VSL = Value of a Statistical Life
VSLY = Value of a Statistical Life Year
QALY = Quality-Adjusted Life Year
† Deaths in future years are discounted at 3 percent.

A.2.1. Real Annual Social Rate of Discount

Circular A-4 from the Office of Management and Budget (OMB) provides guidelines for regulatory analysis.. It suggests using discount rates of 3 and 7 percent regulatory analysis with 3 percent representing the "social rate of time preference". In accordance with this guidance, we use a 3 percent discount rate.

A.2.2. Value of a Statistical Life (VSL) in 2016

In accordance with the HHS guidance (2016) for regulatory impact analysis, we use value of a statistical life (VSL) to value the burden of mortality. For analyses conducted in 2014 dollars, the HHS guidance recommends the use of a central VSL estimate of $9.3 million. Since the year of analysis in our model is 2016, we adjusted this value to account for inflation and changes in real income since 2013 (Table A - 14).

Table A - 14. Value of a Statistical Life (VSL) in 2016

Parameter	Value	Source/Comment
VSL in 2014 (in 2014 $)	$9,300,000	HHS Guidance, 2016
VSL in 2016 (in 2016 $)	$9,307,071	Calculation
VSL in 2016 (in 2016 $) adjusted for income growth	$9,779,005	Calculation

According to data reported by the Bureau of Labor Statistics (BLS), the change in the consumer price index from 2014 to 2016 was 0.08 percent, resulting in an inflation-adjusted VSL of $9,307,071. Over the same time period, the change in real disposable income was 3.42 and 1.60 percent from 2014 to 2015 and 2015 to 2016, respectively. Assuming an income elasticity of 1.0, VSL adjusted for inflation and income growth becomes $9,779,005.

A.2.3. Value of a Statistical Life Year (VSLY) in 2016

Value of a statistical life year (VSLY) represents the rate at which an individual substitutes money for gains in life expectancy; with a reduction in mortality risk implying a corresponding increase in life expectancy and a gain in life years (U.S. Department of Health and Human Services ASPE, 2016). VSLY is computed by dividing the VSL by the discounted expected number of life years remaining.

In computing the VSLY, we assumed that the average individual is 40 years old and used the EQ-5D results reported in Hanmer, et al. (2006) to estimate the health-related quality of life in each subsequent year along with the conditional likelihood of survival for each year of age based on the population-averages reported by CDC, as per HHS guidance. This resulted in a VSLY estimate of $497,848 for 2016.

A.2.4. Total Number of Cases per Year

Lessa, et al. (2015) estimate that there were 453,000 incident cases of CDI in the U.S. in 2011, based on the CDC's Emerging Infections Program *C. difficile* surveillance. Adjusting this figure for 3.4 percent population growth from 2011 to 2016, we estimate the number of CDI cases in 2016 at 468,567.

CDC (2013) reported 9,300 cases of CRE infection in 2011, which amounts to 9,620 cases in 2016 after adjusting for population growth.

There were 820,000 cases of gonorrhea in the U.S. in 2015 per the underreporting-adjusted count provided in CDC (2016a). Adjusting this figure for 0.8 percent population growth from 2015 to 2016, we estimate the number of gonorrhea cases in 2016 at 826,703.

We acknowledge that use of overall population growth to estimate number of cases in 2016 is a limitation of our study. We did not have any data to account for other factors that might be affecting market size. However, the supporting model is flexible and can be easily updated to reflect different assumptions regarding number of incident cases.

A.2.5. Health Outcomes

A.2.5.1 CDI Health Outcomes

Figure A - 2 represents the spectrum of clinical manifestations of *C. difficile* infections (CDI) identified in our literature review. Although most patients respond well to standard antibiotic treatments, approximately 20 percent have recurrent episodes of CDI, and some patients go on to develop severe (fulminant) CDI colitis. The majority (80 percent) of patients with severe CDI do not require surgery, but approximately 20 percent require colectomies.

Mortality rates vary with severity of infection and chosen intervention. The CDI-attributable mortality rate is approximately 5.2 percent for patients who do not require surgery. The CDI-attributable mortality rate is approximately 30.7 percent for those requiring colectomy.

We used Varier, et al.'s estimate that those with CDI have a 16 percent probability of developing fulminant colitis to calculate the share of the total CDI population experiencing the most severe symptoms and complications. Varier, et al. (2014) note that there is no consensus definition of severe or fulminant colitis and that rates of progression to fulminant disease range from 5 to 26 percent. Regardless, we use their mean probability of 16 percent to estimate there were 74,971 (468,567 × 0.16) cases of severe CDI in 2016.

We then used Dallas, et al.'s finding that one in five patients with fulminant CDI undergo colectomy to calculate the share of fulminant CDI patients requiring surgery. Of the 14,994 (74,971 × 0.2) patients receiving colectomies, we estimate 4,603 die while in the hospital, 30.7 percent mortality rate, per Halabi, et al. (2014).

As mentioned above, not all severe cases of CDI require surgery, and we use Dallas, et al.'s (2014) 20 percent fulminant-to-colectomy rate to back calculate an 80 percent fulminant-to-medical management rate for an estimated 59,977 (74,971 × 0.8) cases of medically-managed severe CDI in 2016. Since Dallas, et al. (2014) did not provide an associated mortality rate for these patients, we took the weighted average of the two most recent nonsurgical CDI-attributable mortality rates reported in Kwon, et al. (2015) (see Tabak, et al., (2013) and Dubberke, et al., (2008)). This generated a non-colectomy mortality rate of 5.2 percent. Applied to the population of medically-managed severe CDI patients, we estimate there were 3,117 fulminant non-colectomy deaths in 2011.

Having a colectomy affects the likelihood of survival post-surgery even if the surgery is successful. Table A - 15 below reports the probability of death post-surgery. We estimate the present value of the total number of deaths attributable to surgically managed severe CDI that occur one or more year after having a colectomy at 8,812.

Summing our estimated colectomy (4,603), non-colectomy (3,117), and post-colectomy (8,812) deaths, we estimate 16,532 CDI-attributable deaths in 2016. This estimate is more than twice that of the 8,085 CDI-attributable deaths in 2011 reported in the National Vital Statistics System (Murphy, et al., 2015).

Table A - 15. Probability of Death Post Colectomy

Duration	Probability of Death	Source
1-year post surgery	65%	Dallas et al. (2014)
2-year post surgery	71%	Dallas et al. (2014)
5-year post surgery	67%	Dallas et al. (2014)
7-year post surgery	60%	Dallas et al. (2014)
11-year post surgery	51%	Dallas et al. (2014)

As a first step in estimating the characteristics of patients with mild-to-moderate CDI, we subtracted our estimated 74,971 cases of severe CDI from the total of 468,567 cases, generating an estimate of 393,596 mild-to-moderate successful treatment cases.

Another important element in the CDI management landscape is recurrence. Fekety, et al. (1997) report that approximately one in five people have at least one recurrence of CDI, and, applying this rate to the recurrence-susceptible cohort in our data, we calculate there were 90,091 first recurrences in the U.S. in 2016. According to McFarland, et al. (1999), recurrent CDI is not associated with a worsening clinical picture,[26] thus—as shown in Table A - 16 below—we consider the recurrence-susceptible population to include all patients with CDI except those who die or are otherwise incapable of developing future bouts of colitis (due to having undergone colectomy). Given our uncertainty regarding the clinical picture for those with recurrent CDI, we only consider mild-to-moderate QALY losses for recurrence.[27]

Table A - 16. Recurrent CDI

Category	Value	Source/Note
Recurrence rate	20%	Fekety et al. (1997)
Mild-to-moderate CDI diarrhea with colitis - treatment success	393,596	
Severe CDI colitis - medical management/no surgery – survive	56,860	
Total susceptible cases	450,456	Assumes recurrence-susceptible cases are those who survive without requiring colectomy.
First recurrences	90,091	Total susceptible cases × recurrence rate

Table A – 17 provides the QALY losses and durations for each of the clinical manifestations of CDI discussed above. Multiplying the loss in QALYs with the estimated number of patients for the health outcome category, we estimate the total loss in QALYs due to morbidity at 8,697 fo CDI.

[26] A recent study by Olsen et al (2015) finds that recurrent CDI is associated with significantly increased risk of death within 6 months after completion of initial CDI treatment compared with CDI patients who do not develop a recurrence if the recurrence was a moderate-to-severe case. Since we assumed all CDI recurrences to be of mild-to-moderate, we did not estimate any deaths due to recurrent CDI in our model.

[27] QALYs measure the equivalent number of years of life in perfect health lost as a result of the illness and are widely considered to provide some measure of a patient's lost "utility" or preference due to illness (although economists might argue that it is not derived from a well-defined utility function). Intuitively, the QALY weight is a preference ranking bounded by 0 and 1 that reflects a person's state of health (1 signifies perfect health, and 0 indicates health equivalent to being dead).

Table A - 17. *C. difficile*-associated HRQoL, Duration, and Lost QALYs

Health Outcome	Baseline HRQoL	HRQoL	Duration (in Days)	Loss in QALYs
Surgically managed severe CDI – acute disease	0.827 [a]	0.320 [c]	27.00 [f]	0.1273
Surgically managed severe CDI – post-discharge		0.730 [c]	[g]	0.0970
Non-surgically managed severe CDI		0.570 [d]	10.00 [h]	0.0070
Mild CDI	1.000 [b]	0.880 [e]	8.50 [i]	0.0028
Recurrent CDI			26.00 [j]	0.0085

[a] Median EQ-5D scores for 60-69 age group; reported in Sullivan and Ghushchyan (2006).
[b] ERG assumption
[c] Stranges, et al., (2013)
[d] Varier, et al., (2014)
[e] Bartsch, et al., (2013)
[f] Halabi, et al., (2014)
[g] ERG assumes post-colectomy reductions in HRQoL will persist for the rest of the patient's life. See Table A-15 for the post-colectomy survival curve.
[h] Dubberke, et al., (2008)
[i] Kwon, et al., (2015)
[j] McFarland, et al., (1999)

A.2.5.2 CRE Infection Health Outcomes

Figure A - 3 represents the spectrum of clinical manifestations of CRE infections identified in our literature review. Vardakas, et al. (2015) was selected as the starting point for defining our parameters because the study excludes asymptomatic CRE carriers and provides secondary bacteremia rates by primary infection site. We applied Vardakas, et al.'s (2015) infection site breakdown adjusted by expert opinion (Kallen, 2016) to the estimated 9,620 cases of CRE infection in 2016 to generate an estimated number of cases by infection site (see Table A - 18).

Since Vardakas, et al. (2015) do not provide mortality data disaggregated by infection site, we used other studies to estimate the annual number of deaths attributable to CRE infection. Due to high comorbidity and severity of underlying disease, distinguishing between CRE-*attributable* mortality and CRE-*associated* (i.e., crude or all-cause) mortality is difficult. To address this problem, many researchers use carbapenem-susceptible (CSE) infection mortality rates to back calculate the share of CRE-associated deaths that are "attributable" to the resistant bacteria (Falagas, et al., 2014). For example, if patients with intra-abdominal CRE infection have a crude mortality rate of 40 percent, and patients with intra-abdominal CSE infection have a crude mortality rate of 25 percent, then the CRE-attributable mortality rate is the difference between the two, or 15 percent. Similarly, the mortality rates reported in Table A - 18 represent the difference between the crude CRE mortality rates reported in Neuner, et al., (2011), Hauck, et al., (2016), Capone, et al., (2013), and Falagas et al., (2014) and the crude mortality rate of a control cohort of patients with carbapenem-resistant *Klebsiella pneumoniae* urinary colonization (Hauck, et al., 2016).

Table A - 18. CRE Infection Cases by Severity

Infection Site	Number of Cases (National)	Mortality Rate	Deaths	Survivors	Sources
Primary + catheter-related bacteremia	866	23%	197	669	[a, b]
UTI	5,291	0%	0	5,291	[b]
UTI + secondary bacteremia	481	17%	80	401	[a, b, c]
Intra-abdominal	481	29%	137	344	[b, d]
Intra-abdominal + secondary bacteremia	192	24%	46	146	[a, b]
Other	289	29%	82	206	[b, d]
Other + secondary bacteremia	96	41%	39	57	[a, b]
Pulmonary	1,732	18%	438	1,294	[b]
Pulmonary + secondary bacteremia	192	41%	78	114	[a, b]
Total in 2016	**9,620**	**N/A**	**1,097**	**8,522**	

[a] Neuner, et al., (2011)
[b] Hauck, et al., (2016)
[c] Capone, et al., (2013)
[d] Falagas et al. (2014)

Table A - 19 provides the QALY losses and durations for each of the clinical manifestations of CRE infection discussed above. Multiplying the loss in QALYs with the estimated number of patients for the health outcome category, we estimate the total loss in QALYs due to morbidity at 20 for CRE infections.

Table A - 19. CRE Infection-associated HRQoL, Durations, and Lost QALYs

Health Outcome	Baseline HRQoL [a]	HRQoL [b]	Duration (in Days) [c]	Loss in QALYs [d]
Primary catheter-related bacteremia	0.748	0.642	5.00	0.0015
UTI		0.730	1.00	0.0000
Pulmonary		0.580	10.00	0.0046
Intra-abdominal		0.642	4.00	0.0012
Other		0.642	4.00	0.0012
Secondary bacteremia (progresses from primary infection site)				
Primary site: UTI	0.748	0.530	28.00	0.0167
Primary site: Pulmonary				
Primary site: Intra-abdominal				
Primary site: Other				

[a] Average of the median EQ-5D scores associated with the CRE comorbidities identified in Hauck, et al., (2016): diabetes mellitus, renal failure, heart failure, emphysema, and other malignant neoplasm—skin. EQ-5D scores reported in Sullivan and Ghushchyan (2006).
[b] Lee, et al., (2010)
[c] Hauck, et al., (2016)
[d] ERG calculation

A.2.5.3 NGI Health Outcomes

Figure A - 4 and Figure A - 5 illustrate the disease pathways of gonorrhea infections in women and men, respectively. The case counts in these flowcharts are derived from CDC (2016a) and the percentages were compiled by Regnier & Huels (2014). As noted above, we estimated the annual gonorrhea burden at 826,703 cases in 2016. As Figure A - 4 shows, women who progress to pelvic

inflammatory disease (PID) may also experience chronic pelvic pain, ectopic pregnancy, and tubal factor infertility. These health outcomes are excluded from our morbidity and mortality calculations for various reasons. We exclude ectopic pregnancy and tubal factor infertility because there is substantial ambiguity when modeling pregnancy-related health outcomes—not all women become pregnant, not all women *want* to become pregnant, etc. As such, it is impossible to know what percentage of the population with gonorrhea would experience quality of life reductions from pregnancy-related outcomes. We exclude chronic pelvic pain from our analysis because there are insufficient data on the typical duration and characteristics of associated symptoms. Clinicians agree that chronic pelvic pain has a complex natural history and can vary substantially from patient to patient. For some patients, chronic pelvic pain results in a week or two of discomfort every couple years whereas for other patients, chronic pelvic pain results in permanent reductions in quality of life.

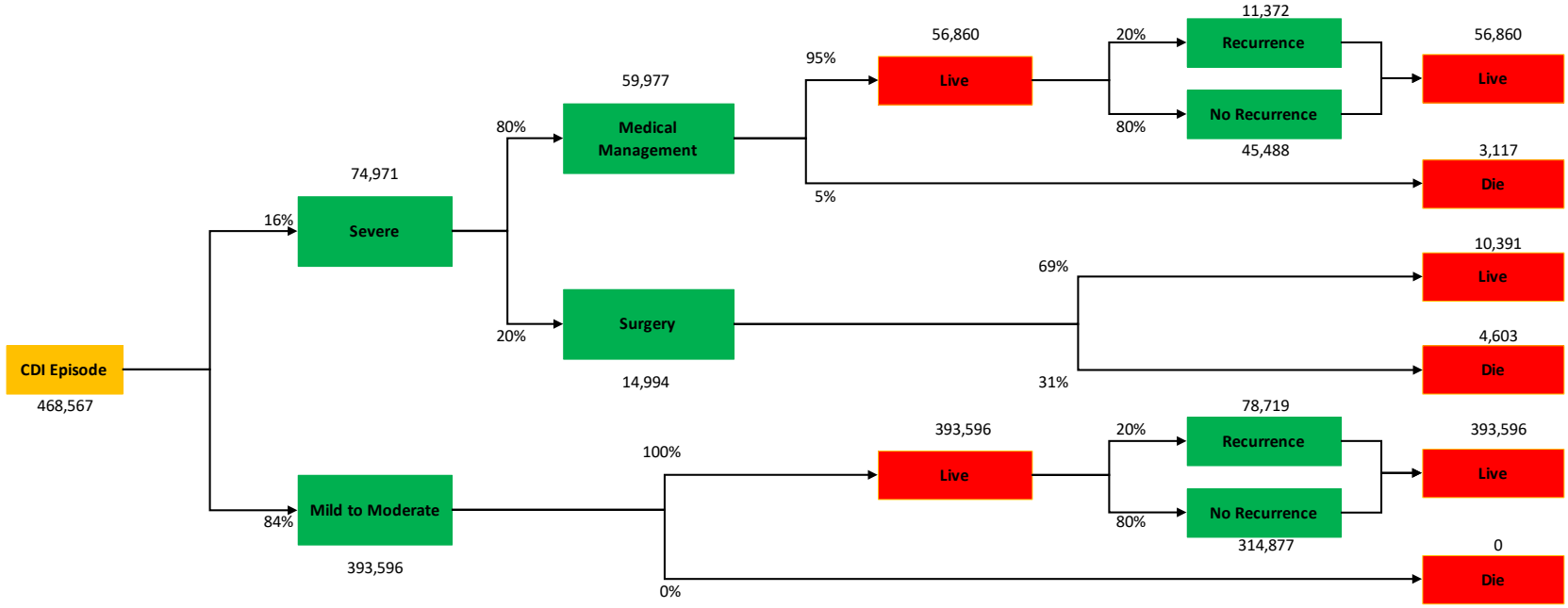
Table A - 20 provides the QALY losses and durations for each of the clinical manifestations of NGI noted in the figures. Multiplying the loss in QALYs with the estimated number of patients for the health outcome category, we estimate the total loss in QALYs due to morbidity at 2,560 for NGI.

Table A - 20. NGI-associated HRQoL, Durations, and Lost QALYs

Cohort	Health Outcome	Baseline HRQoL [a]	HRQoL [a]	Duration (in Days) [a]	Loss in QALYs [b]
Females	PID	0.910	0.570	10.00	0.0093
	No Sequelae - Symptomatic		0.780	28.00	0.0100
Males	Epididymitis	0.920	0.420	7.00	0.0096
	No Sequelae - Symptomatic		0.770	14.00	0.0058

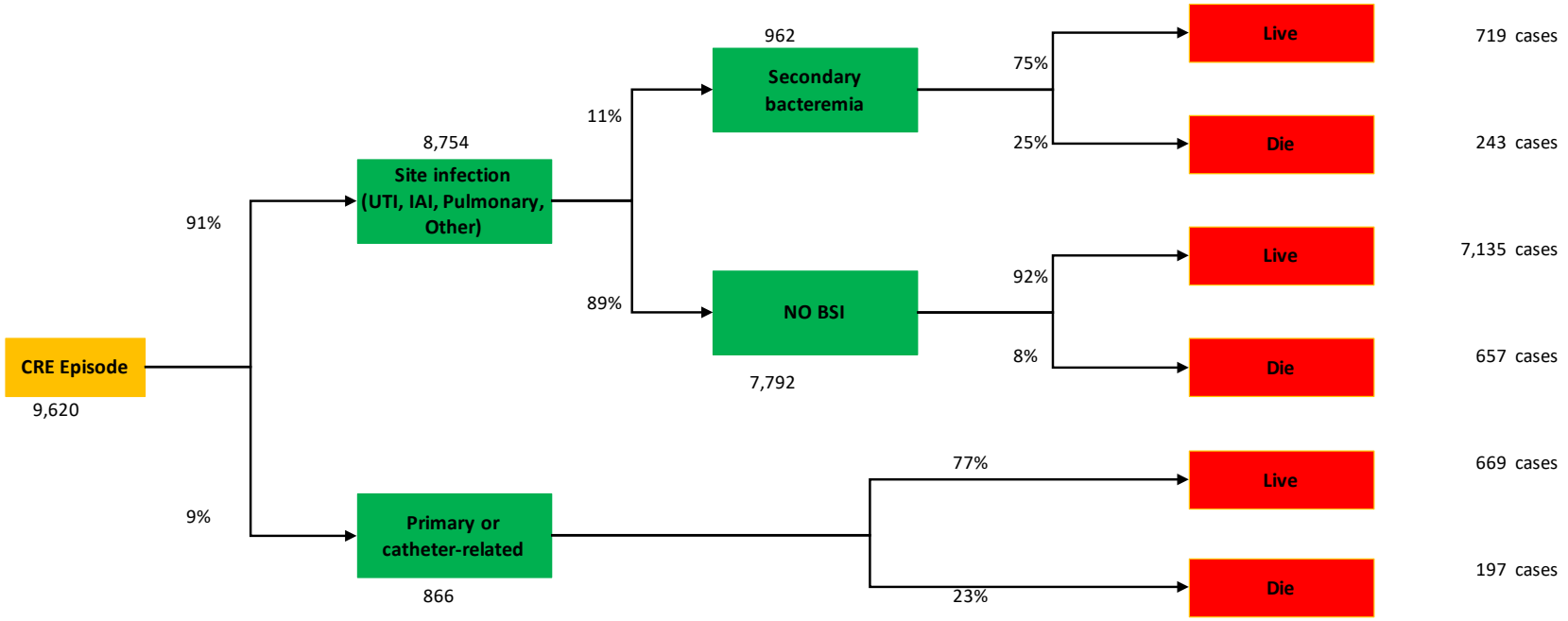
[a] Gift, et al., (2008)
[b] ERG calculation

Figure A - 2. Health Outcomes Associated with CDI [a]



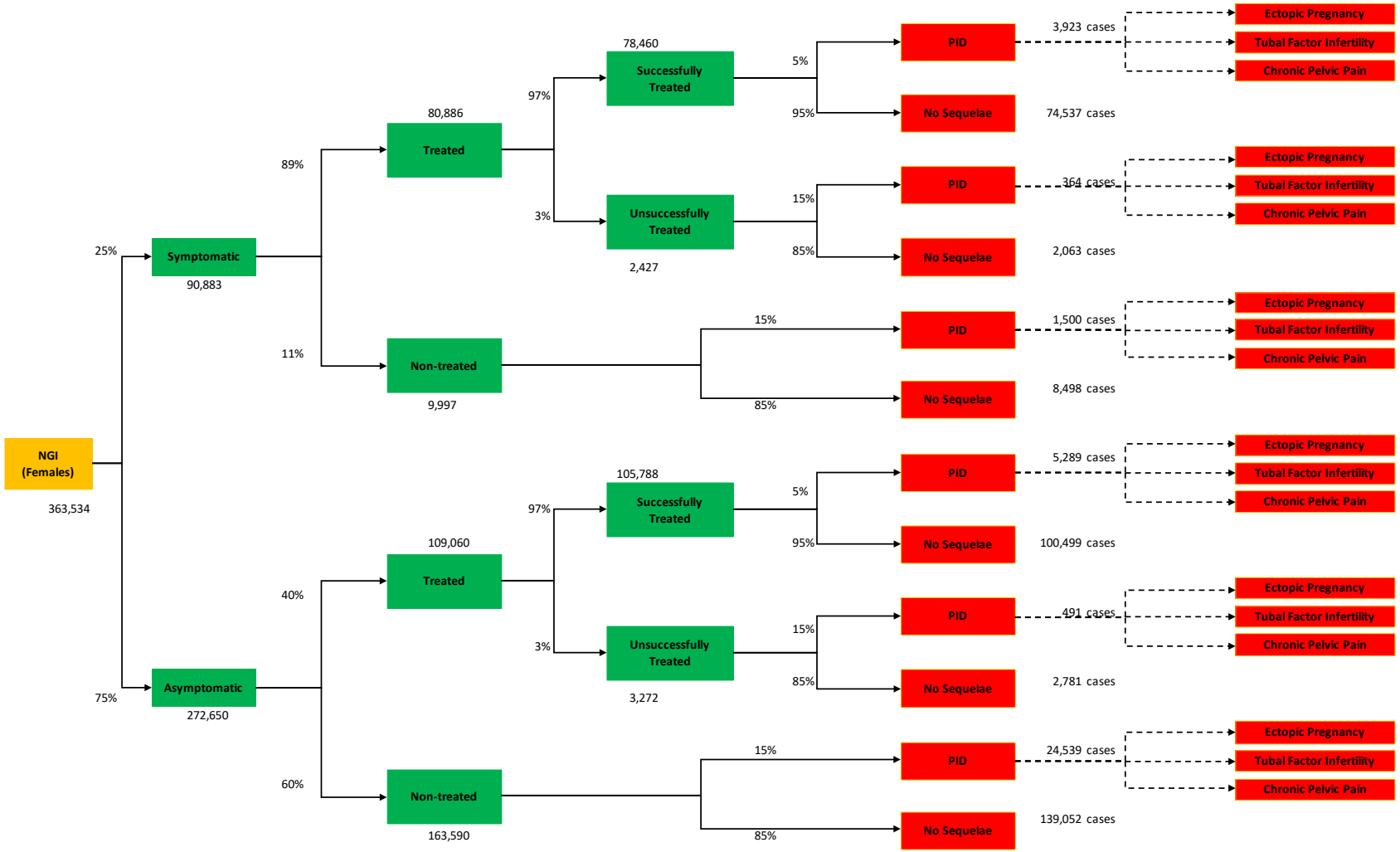
[a] Figures may not add up due to rounding.

Figure A - 3. Health Outcomes Associated with CRE Infection [a]



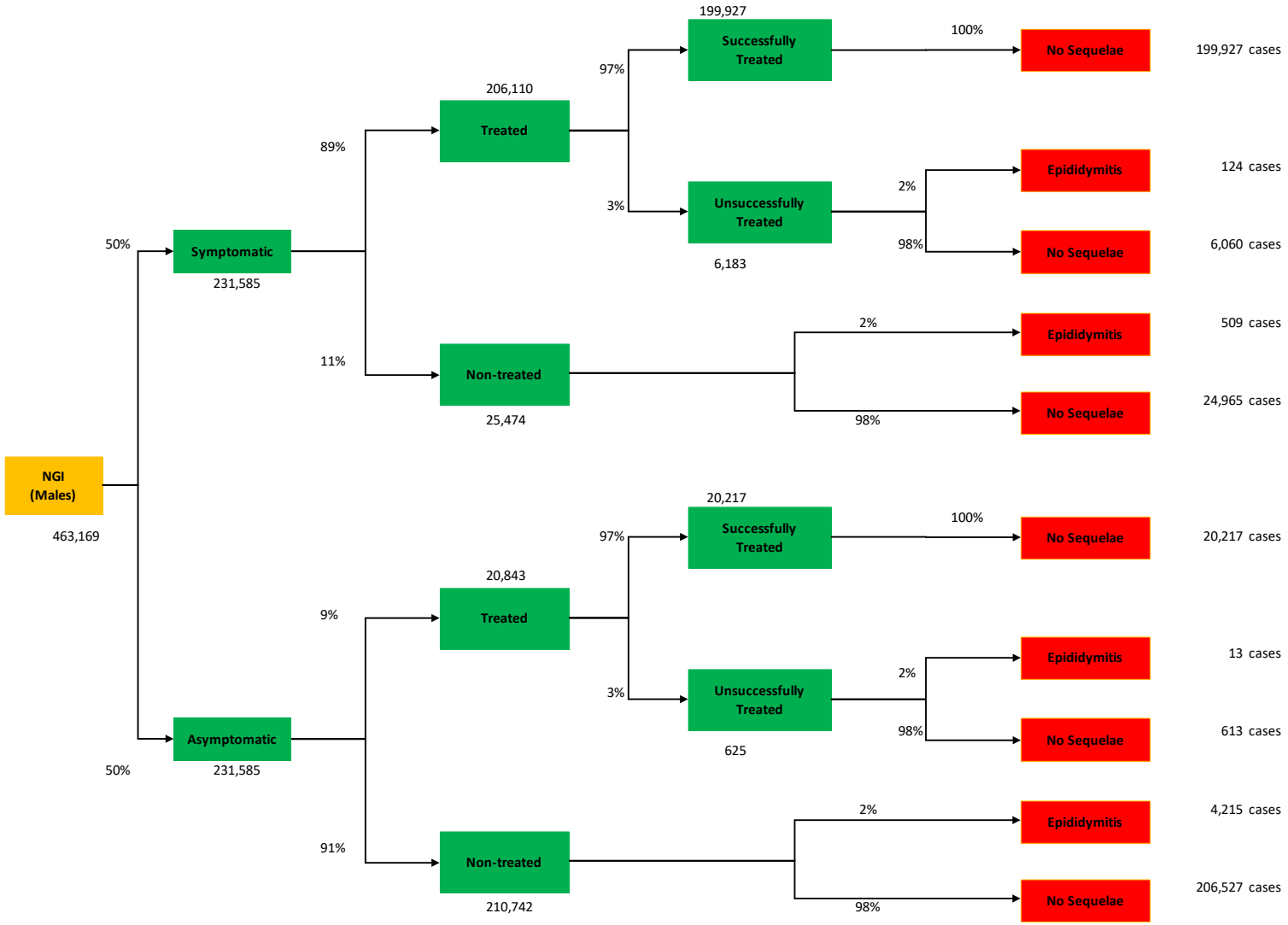
[a] Figures may not add up due to rounding.
UTI = Urinary tract infection
IAI = Intra-abdominal infection
BSI = Bloodstream infection

Figure A - 4. Health Outcomes Associated with NGI for Females [a]



[a] Figures may not add up due to rounding.

Figure A - 5. Health Outcomes Associated with NGI for Males [a]



[a] Figures may not add up due to rounding.