Pre-Screening Patients at High Risk for Multi-Drug Resistant Infections

Emery Stephans, CEO

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Prepared by
Enterprise Analysis Corporation (EAC)
2777 Summer Street
Stamford, Connecticut 06905
+1 (203) 348-7001

Introduction, Louis Pasteur

"If it is a terrifying thought that life is at the mercy of the multiplication of these minute bodies [microbes], it is a consoling hope that Science will not always remain powerless before such enemies"

— Louis Pasteur

Paper read to the French Academy of Sciences (29 Apr 1878), published in *Comptes Rendus de l'Academie des Sciences*, **86**, 1037-43, as translated by H.C.Ernst. Collected in Charles W. Eliot (ed.) *The Harvard Classics, Vol. 38; Scientific Papers: Physiology, Medicine, Surgery, Geology* (1910), 366."

Tom Frieden, MD, MPH, Director (Ret.) U.S. Centers for Disease Control and Prevention

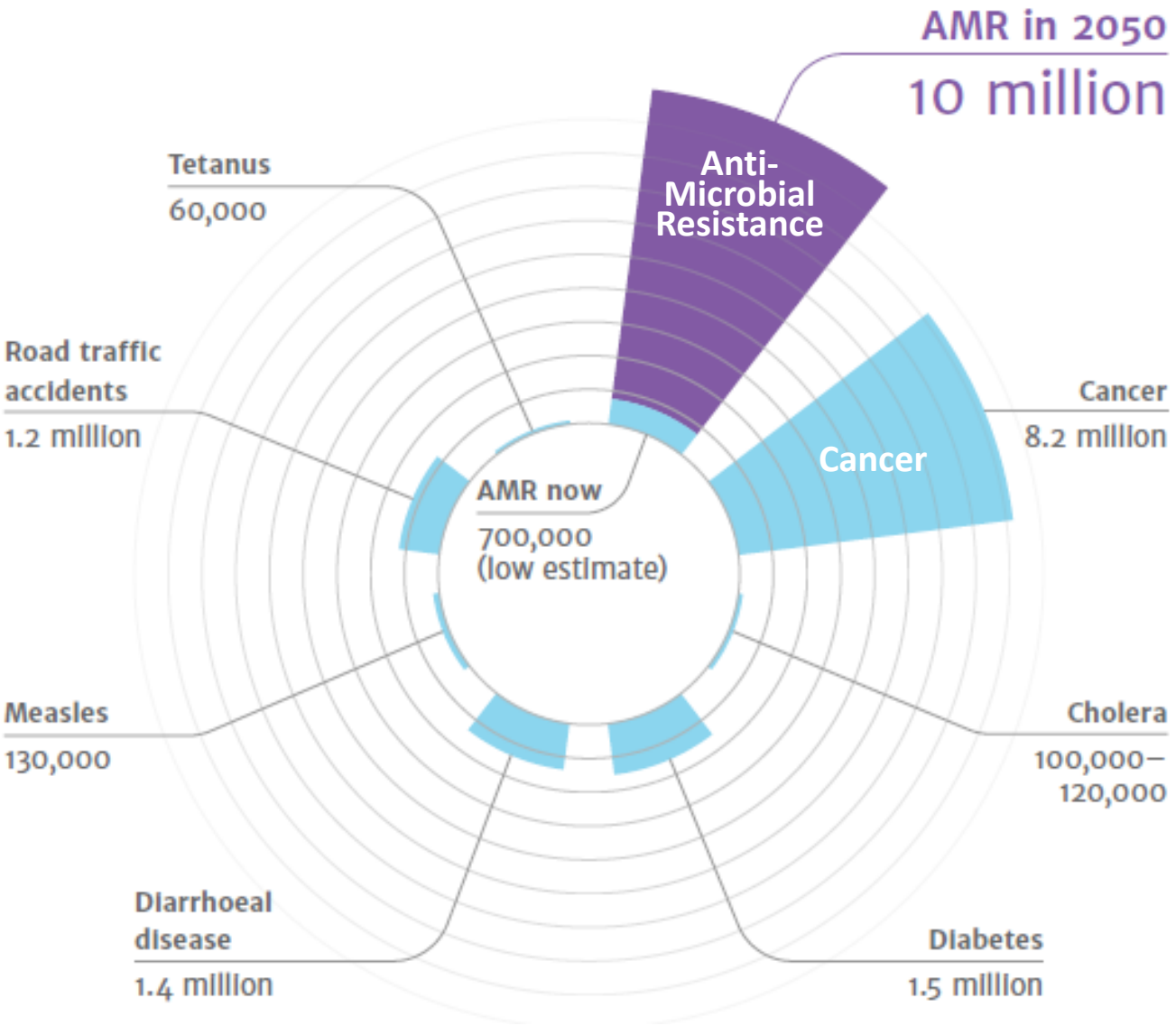
"When first-line and then second-line antibiotic treatment options are limited by resistance or are unavailable, healthcare providers are forced to use antibiotics that may be more toxic to the patient and frequently more expensive and less effective."

"Even when alternative treatments exist, research has shown that patients with resistant infections are often much more likely to die, and survivors have significantly longer hospital stays, delayed recuperation, and long-term disability."

"Efforts to prevent such threats build on the foundation of proven public health strategies: immunization, infection control, protecting the food supply, antibiotic stewardship, and reducing person-to-person spread through screening, treatment and education."

Tom Frieden, MD, MPH, Director, U.S. Centers for Disease Control and Prevention, "Meeting the Challenges of Drug-Resistant Diseases in Developing Countries", Committee on Foreign Affairs Subcommittee on Africa, Global Health, Human Rights, and International Organizations, United States House of Representatives, April 23, 2013

Projected 2050 Global Mortality from Drug-Resistant Infections



[3]*Source: "Tackling Drug-Resistant Infections Globally: Final Report and Recommendations," The Review on Antimicrobial Resistance, Chaired by Jim O'Neill*
https://amr-review.org/sites/default/files/160518_Final%20paper_with%20cover.pdf

MDRO growth stimulated a retrospective outcome study with a statistically significant population at Intermountain Healthcare

Calendar Time Covered	8 years (2008 to 2015)
Total Encounters (inpatient admissions)	900,000
MDRO Cohort	12,750
Average Inpatient Length of Stay	4.1 days
MDRO Cohort Length of Stay	10.2 days

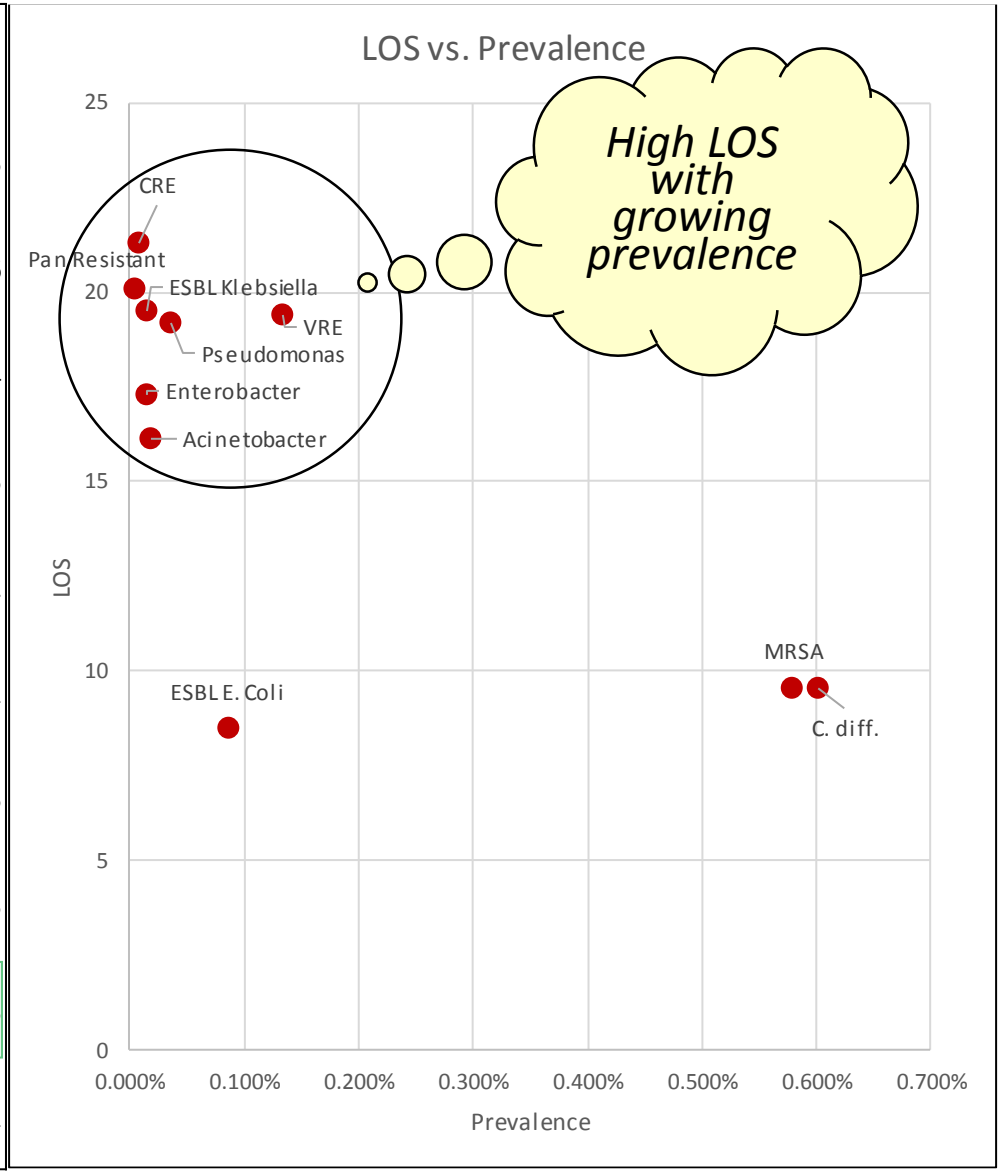
1.42%

2.5x higher

Source: MDRO Retrospective Outcome Study at Intermountain Healthcare; Bert Lopansri, MD, Principal Investigator

Retrospective Outcome Study; Prevalence and Length of Stay (LOS)

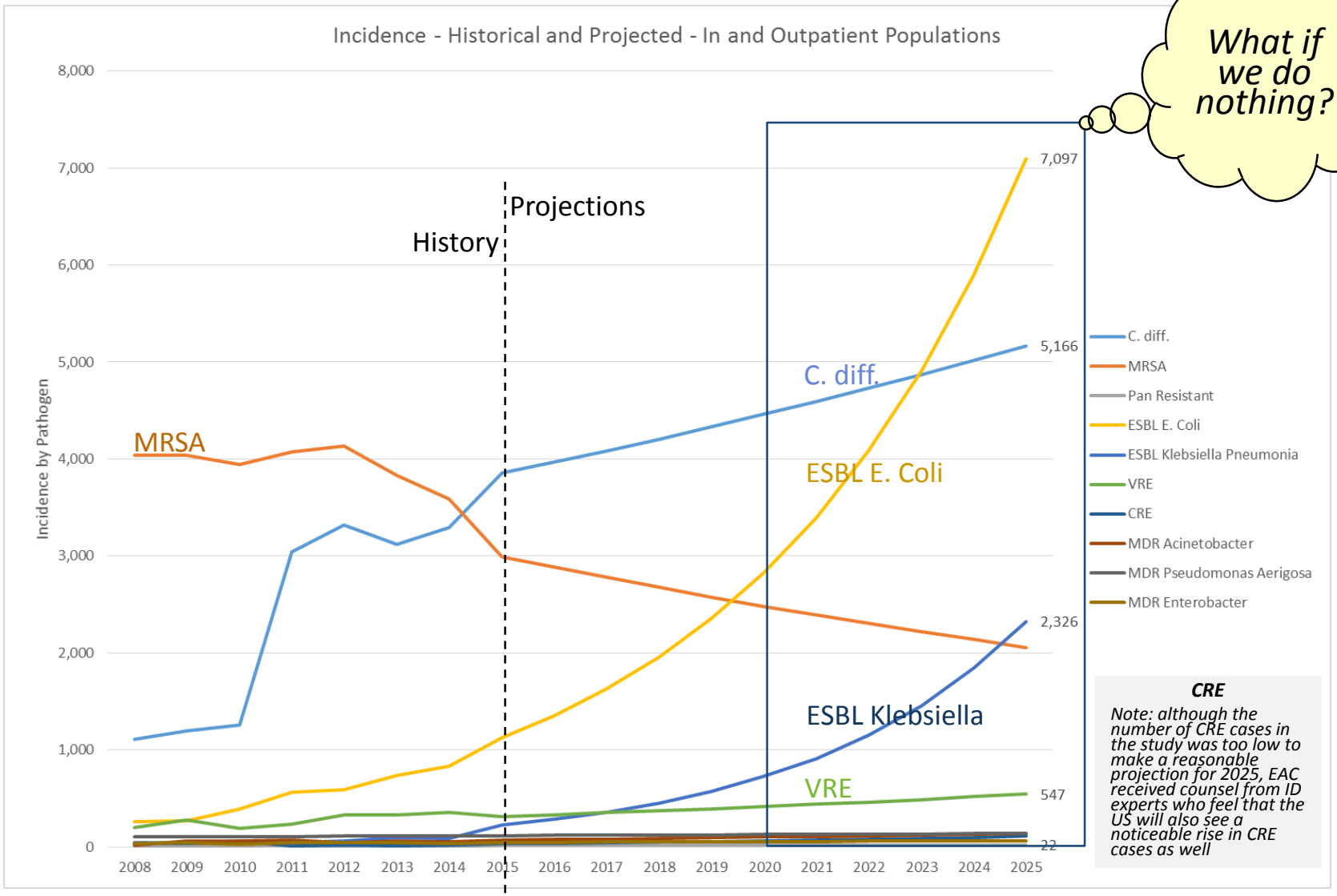
		Prevalence	LOS
1	C. diff.	0.601%	9.5
2	MRSA	0.580%	9.6
3	VRE	0.133%	19.4
4	ESBL E. Coli	0.086%	8.5
5	Pseudomonas	0.035%	19.2
6	Acinetobacter	0.018%	16.1
7	ESBL Klebsiella	0.015%	19.5
8	Enterobacter	0.014%	17.3
9	CRE	0.008%	21.3
10	Pan Resistant	0.005%	20.1



Source: MDRO Retrospective Outcome Study at Intermountain Healthcare; Bert Lopansri, MD, Principal Investigator

Houston We Have a Problem…

Projected incidence for MDRO infections to 2025. Calculations based on 2008-2015 historical growth rates observed in the retrospective outcome study. Projections assume that no infection prevention protocols, beyond those in place in 2015, are instituted



Source for historical data: MDRO Retrospective Outcome Study at Intermountain Healthcare; Bert Lopansri, MD, Principal Investigator

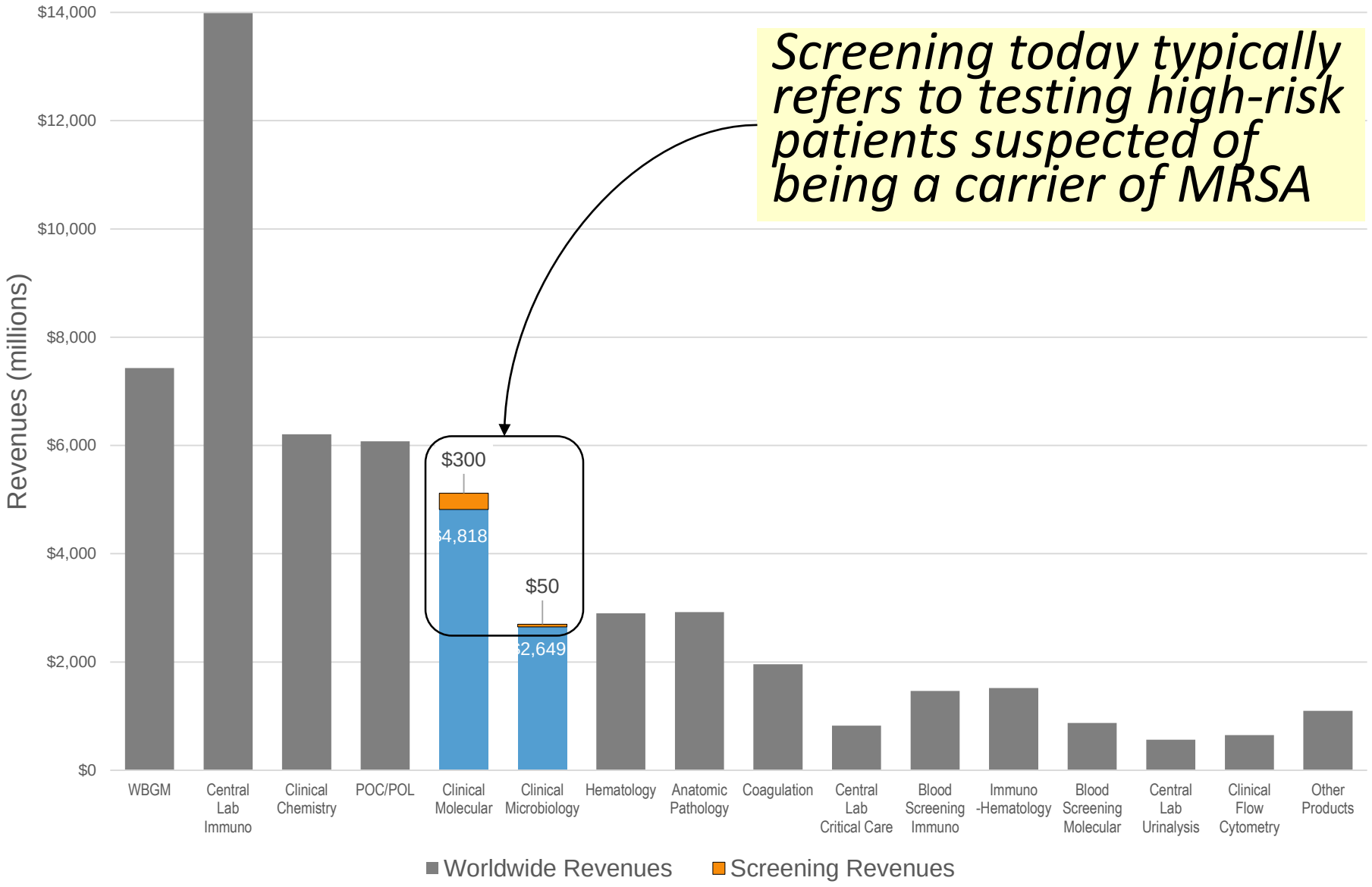
High-Risk Groups Recommended to EAC to Date

EAC maintains an on-going research project to analyze options for targeted screening for cost avoidance. This list was compiled as part of research discussions with ID physicians in selected institutions and networks

Bone marrow transplant patients	Skilled Nursing Facilities (SNF)
Pre-op for prostate surgery (the urologists are screening with stool culture now)	Long-Term Acute Care Hospitals (LTACHs) and Long-Term Care (LTC) facilities
Pre-op for bowel resection surgery; those at high risk for secondary peritonitis	Rehabilitation Facilities
Oncology patients pre chemotherapy that is expected to make them neutropenic	Burn units
Patients admitted with neutropenic sepsis, or sepsis in patients on immune-suppressive drugs such as the new 'biologicals' that target immune system mediators (about a third will have a bowel source for the sepsis; not always detected by culture)	Transfers from acute care setting in (a) other major US urban centers (e.g. Chicago, NY, Miami, LA); (b) international cities with high prevalence of MDRO (e.g. anywhere in Asia, Ukraine, Russia, Israel)
Neonatology for screening of premature infants at risk for onset of sepsis from bowel source after 72 hours of life in NICU	ICUs
Potentially all patients admitted with intra-abdominal sepsis (IAS) - spontaneous peritonitis in setting of ascites, diverticulitis, ruptured bowel, appendicitis, post surgical infections, but especially those with hospital acquired IAS	Colonoscopy unit

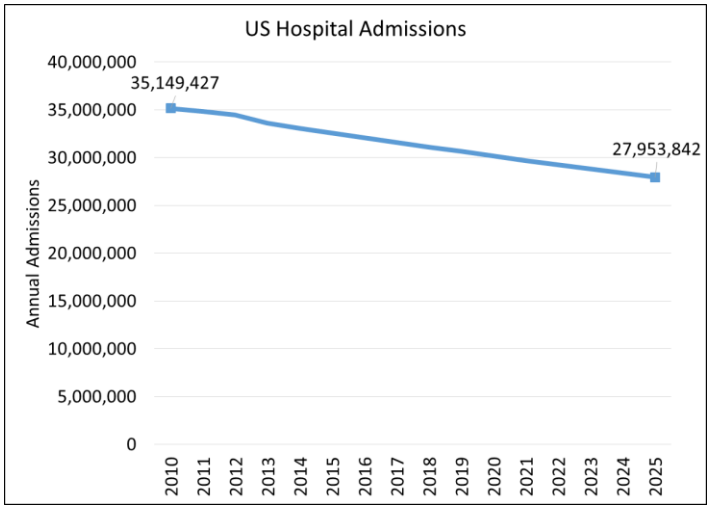
Source: EAC presentation at R.I.D. conference, May 31, 2017, Harvard Club, New York, NY

EAC Modeling for Current Screening Market
(Source: EAC *IVDMARKETREACH* industry modeling tool)



Source: EAC IVDMARKETREACH industry modeling tool

MDRO Study Extended to US Level



Source: AHA Annual Survey data, 2014

MDRO Study Extended to US Level

US Admissions 32,565,619 US Admissions 27,953,842 -1.52%

	MDRO Study			2015			2025		
	Infections	LOS	Total LOS	Prev.	Cases	CAGR	Prev.	Cases	
C. diff.	5,411	9.5	51,632	*0.601%*	195,792	2.210%	0.748%	209,128	
MRSA	5,218	9.6	49,867	*0.580%*	188,808	-3.841%	0.392%	109,552	
VRE	1,197	19.4	23,201	*0.133%*	43,312	1.921%	0.161%	44,969	
ESBL E. Coli	772	8.5	6,548	*0.086%*	27,934	12.476%	0.278%	77,699	
Pseudomonas	317	19.2	6,077	*0.035%*	11,470	1.735%	0.042%	11,694	
Acinetobacter	163	16.1	2,629	*0.018%*	5,898	3.000%	0.024%	6,804	
ESBL Klebsiella	132	19.5	2,573	*0.015%*	4,776	8.114%	0.032%	8,946	
Enterobacter	127	17.3	2,197	*0.014%*	4,595	3.085%	0.019%	5,345	
CRE	75	21.3	1,596	*0.008%*	2,714	3.000%	0.011%	3,131	
Pan Resistant	41	20.1	823	*0.005%*	1,484	1.000%	0.005%	1,407	
	13,453	10.9	147,142	US total	486,784			478,673	CAGR
				Estimated US prevalence (1)	1.49%			1.71%	1.37%
				Estimated US prevalence (2)	2.99%			5.14%	5.56%
				Projected US total	973,567			1,436,020	

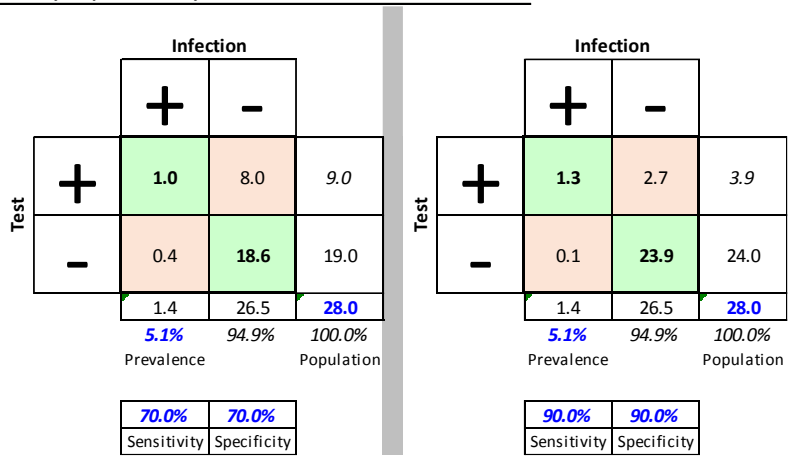
Sources: Prevalence-1, Intermountain Healthcare MDRO study data; Prevalence-2, Magill, NEJM, MARCH 27, 2013; CDC Antibiotic Resistance Threats, US 2013

Sample illustrations from model: not so easy to find target patients…

	2025
Annual US admissions	27,953,842
Estimated US prevalence	5.14%
Estimated MDRO cases	1,436,020

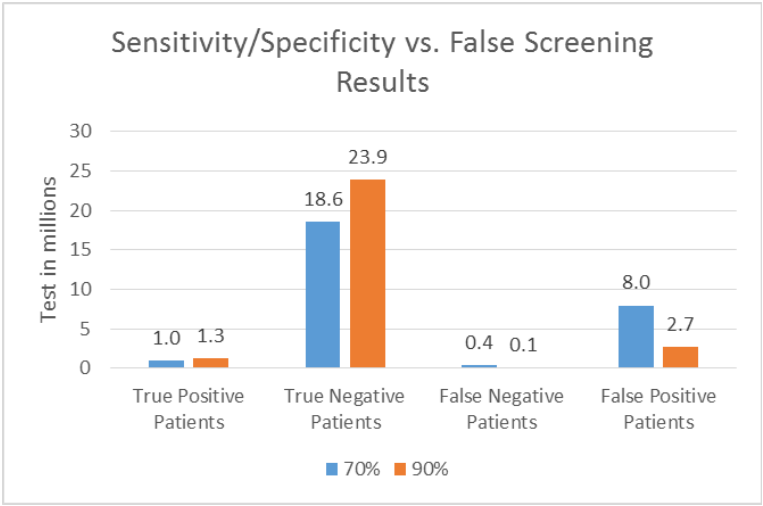
	2025	
Population to screen	27,954,000	
Total Screening Cost A	$1.4	$50.00 $/test A
Total Screening Cost B	$2.8	$100.00 $/test B

	Test-X	Test-Y
Population to find	1,436,000	1,436,000
Sensitivity, specificity	70%	90%

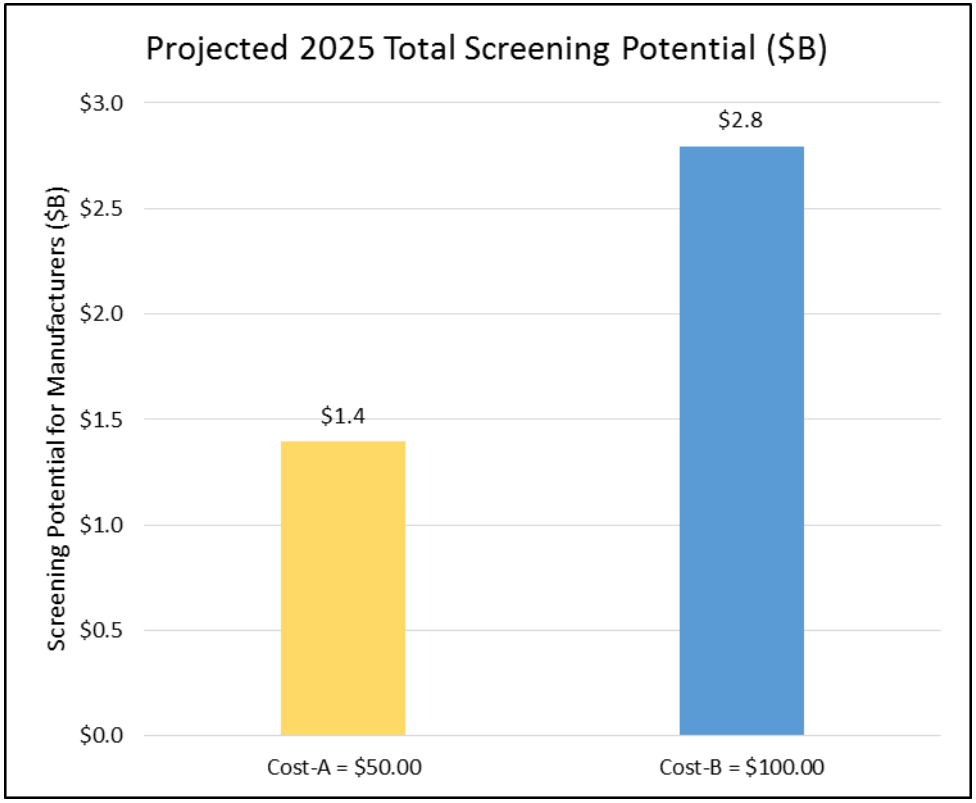


Screening targets: C. diff. and 9 pathogens	
C. diff.	2.244%
MRSA	1.176%
VRE	0.483%
ESBL E. Coli	0.834%
Pseudomonas	0.126%
Acinetobacter	0.073%
ESBL Klebsiella	0.096%
Enterobacter	0.057%
CRE	0.034%
Pan Resistant	0.015%

Source: MDRO Retrospective Outcome Study at Intermountain Healthcare; Bert Lopansri, MD, Principal Investigator



EAC Modeling for Potential 2025 Screening Market Revenues



Selected Pathogen Diagnostic Products and Producers

	MRSA, CRE, and C. diff. Resistance	*Pathogen Identification (ID)*	*Antimicrobial Susceptibility (AST)*
Direct from Specimen*	• Cepheid (Danaher) • BD • Roche • Qiagen • Quidel • Meridian Bioscience • Great Basin • Focus Diagnostics	<u>Single molecular target/Low-plex</u> • Roche Molecular Systems • Abbott • Hologic • Qiagen • Cepheid (Danaher) <u>High Multiplex Molecular Tests</u> • GenMark • bioMerieux/BioFire • Luminex/Verigene • Seegene	There are commercial tests that detect resistance genes (e.g., mecA/C, VRE, carbapenemases) from clinical specimens, but no company can do direct susceptibility tests from specimens
Positive Culture	• BD/Check-Points • OpGen (AdvanDx)	• Luminex/Verigene (blood culture) • bioMerieux BioFire (blood culture) • Accelerate Diagnostics (blood culture) • Bruker biotyper • BD Phoenix • bioMerieux Vitek • Thermo Fisher Sensititre • Beckman MicroScan	• Accelerate Diagnostics • BD Phoenix • bioMerieux Vitek • Beckman MicroScan

**Selected specimens: blood; saliva; nasal, rectal, genital swabs; urine; stool; respiratory; skin; (note: not all manufacturers or methods use every specimen type)*

EAC Summary Observations

The unmet medical need is quickly to be able to identify infected patients (for targeted treatment) and colonized patients (for isolation). Of course the critical factor is the comparatively long time required to give such guidance today.

For infected patients the clinician wants to prescribe first (preferably in one hour) and identify the pathogen (at leisure) later. The company first to achieve this performance can expect to have a significant impact in infectious diseases, especially in MDRO cases.

When the prevalence is low (as fortunately the case still is today) the Dx challenge is quite high. On the other hand healthcare already knows that certain patient populations are at high-risk for MDRO. Screening these might be a reasonable interim step.

A practical 2025 screening program should test for nine pathogens and C. diff. at the prevelances shown in chart 11. Sensitivity and Specificity should be at 90%; test time at 4 hours.