Partnerships to Facilitate Regulatory Submission and Clearance of Tests for Antimicrobial Resistance

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Getting Antimicrobial Resistance Products to Clearance

Novel antimicrobial resistance test

Increasingly difficult pathway to clearance

FDA Clearance

- Complexity of resistance mechanisms for each antimicrobial class
- Numbers of sample types, different transport media, CLIA waived (Y/N)
- Accessing the numbers of specimens now required in clinical trials given the decreasing number of labs willing to participate in trials

Should companies under take this process by themselves?

What partnerships are available?

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The OG- Xpert MTB/RIF

- First demonstration of scalable implementation of direct-from-specimen detection of drug resistance
- Species-specific, nested PCR amplification of MTB drug resistance target (rpoB) (1)
- Detection of rifampin resistance-conferring mutations via molecular beacons (2)
- Launched globally in 2010 with WHO endorsement
- US 510K clearance in 2015 (NIH-supported clinical trial)
- 130 million test cartridges produced to date…112 million since 2015

(1) Detection of a genetic locus encoding resistance to rifampin in mycobacterial cultures and in clinical specimens. Hunt JM. Roberts GD, Stockman L, Felmlee TA, Persing DH. Diagn Microbiol Infect Dis. 1994 18(4):219-27.

(2) Rapid molecular detection of tuberculosis and rifampin resistance. Boehme CC, Nabeta P, Hillemann D, Nicol MP, Shenai S, Krapp F, Allen J, Tahirli R, Blakemore R, Rustomjee R, Milovic A, Jones M, O'Brien SM, Persing DH, Ruesch-Gerdes S, Gotuzzo E, Rodrigues C, Alland D, Perkins MD. N Engl J Med. 2010 Sep 9;363(11):1005-15.

Questions I’ve gotten since MTB/RIF launch

- Can we get the equivalent of MTB/RIF for NG ceftriaxone resistance?
- Can we get a cartridge for NG fluoroquinolone susceptibility?
- Can I get a direct-from urine test for ESBL-producing organisms?
- Can we get a cartridge for direct detection of ESBLs and carbapenemases for severe lower respiratory infections and complicated UTI/urosepsis cases? “As an ED doc, this would be a game changer for me.”

But are we OK, in the latter two cases (and unlike MTB/RIF) with not identifying the organism at the species level when reporting the presence of a drug resistance allele?

The geno-pheno connection is strong for predicting drug resistance, but as not strong for predicting susceptibility…..so conventional susceptibility testing still required.

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Xpert® Carba-R Test Detects Carbapenem-Resistance Genes

Cartridge detects five families of carbapenem-resistance genes:

bla$_{KPC}$, *bla*$_{NDM}$, *bla*$_{VIM}$, *bla*$_{OXA-48}$, *bla*$_{IMP}$

Time to result:

~50 minutes

Samples types:

- *Rectal swabs*
- *Peri-rectal swabs*
- *Carbapenem non-susceptible colonies*
  - Tests on pure cultures can be used to formulate therapeutic strategies

Infection control

Antimicrobial stewardship

Approximately 1 year to complete the complete the regulatory process

US-IVD. For *In Vitro* Diagnostic Use
CE-IVD. *In Vitro* Diagnostic Medical Device. May not be available in all countries

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Xpert® Carba-R

3 Device Intended Use

The Xpert Carba-R Assay, performed on the GeneXpert® Instrument Systems, is a qualitative *in vitro* diagnostic test designed for the detection and differentiation of the bla_{KPC}, bla_{NDM}, bla_{VIM}, bla_{OXA-48}, and bla_{IMP} gene sequences associated with carbapenem-non-susceptibility. The test utilizes automated real-time polymerase chain reaction (PCR).

The Xpert Carba-R Assay is intended as an aid to infection control in the detection of carbapenem-non-susceptible bacteria that colonize patients in healthcare settings. A negative Xpert Carba-R Assay result does not preclude the presence of other resistance mechanisms.

The Xpert Carba-R Assay is for use with the following sample types:

Pure Colonies

The assay is performed on carbapenem-non-susceptible pure colonies of *Enterobacteriaceae*, *Acinetobacter baumannii*, or *Pseudomonas aeruginosa*, when grown on blood agar or MacConkey agar. For testing pure colonies, the Xpert Carba-R Assay should be used in conjunction with other laboratory tests including phenotypic antimicrobial susceptibility testing.

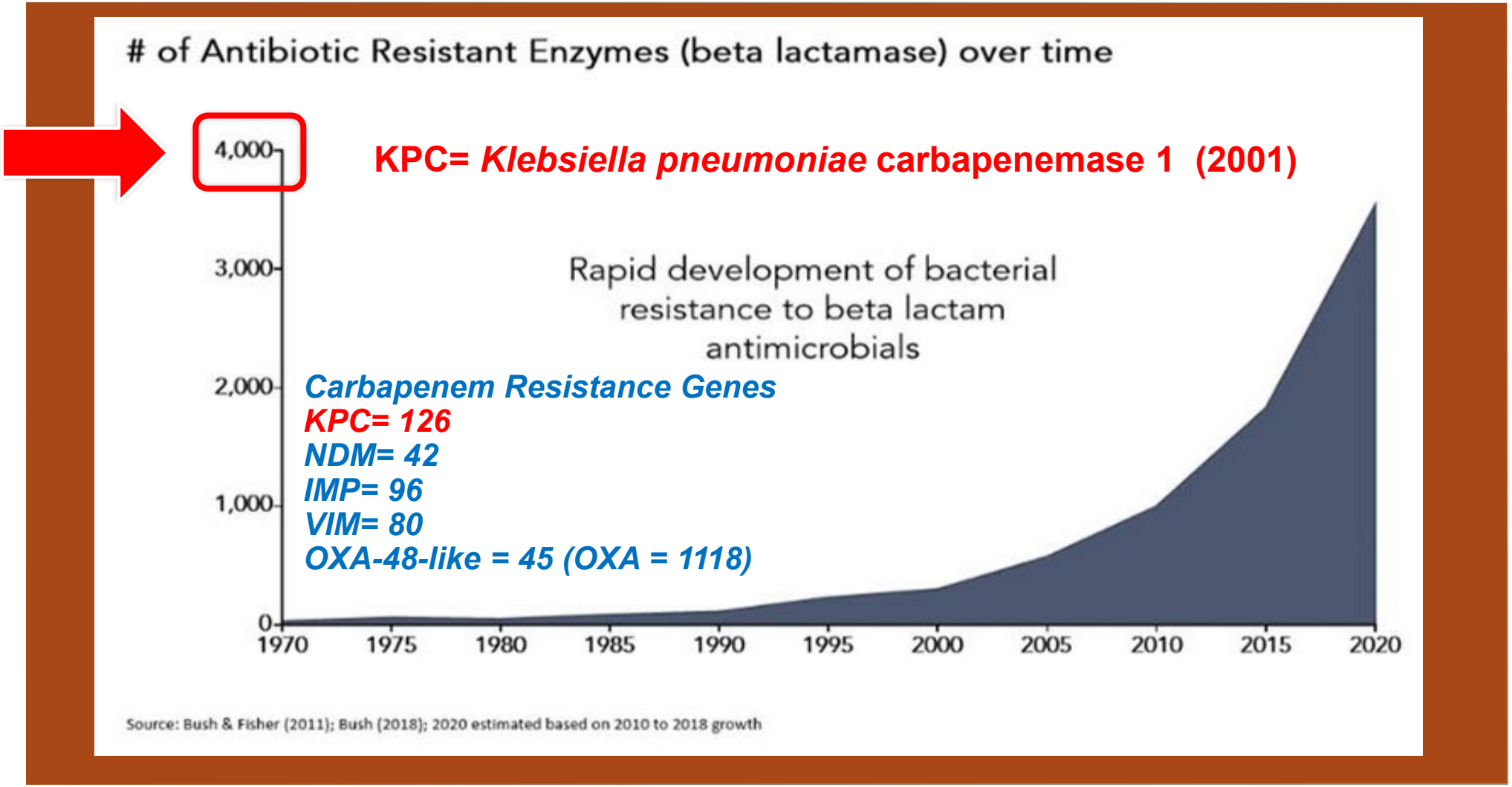
The identification of a bla_{IMP}, bla_{NDM}, or bla_{VIM} metallo-beta-lactamase gene (i.e., the genes that encode the IMP, NDM, and VIM metallo-beta-lactamases, respectively) may be used as an aid to clinicians in determining appropriate therapeutic strategies for patients with known or suspected carbapenem-non- susceptible bacterial infections.

Rectal and Perirectal Swab Specimens

The assay is performed on rectal and perirectal swab specimens from patients at risk for intestinal colonization with carbapenem-non-susceptible bacteria. Concomitant cultures are necessary to recover organisms for epidemiological typing, antimicrobial susceptibility testing, and for further confirmatory bacterial identification.

The Xpert Carba-R Assay, when performed on rectal and perirectal swab specimens, is not intended to guide or monitor treatment for carbapenem-non-susceptible bacterial infections or to determine infection from carbapenem-non-susceptible bacteria.

Challenges of Antimicrobial Resistance: Beta-Lactamases



Bush K. Antimicrob Agents Chemother. 2018 Sep 24;62(10):e01076-18. doi: 10.1128/AAC.01076-18
http://www.bldb.eu/Enzymes.php accessed 14-SEP- 2022

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Xpert® Carba-R

Table 2. Overall Xpert Carba-R Performance vs. Reference Culture + Sequencing

		Culture + Sequencing		
		Pos	Neg	Total
Xpert Carba-R	Pos	142	7	149
	Neg	5	479	484
	Total	147	486	633
	Sensitivity: 96.6% (95% CI: 92.2–98.9) Specificity: 98.6% (95% CI: 97.1–99.4)			

Table 4. Xpert Carba-R Assay Table of All Results by Individual Target

		Culture + Sequencing						
		IMP-1+	VIM+	NDM+	KPC+	OXA-48+	NEG	Total
Xpert Carba-R	IMP-1+	26	0	0	0	0	0	26
	VIM+	0	29	0	0	0	1	30
	NDM+	0	0	26	0	0	1	27
	KPC+	0	0	0	29	0	4	33
	OXA-48+	0	0	0	0	38	1	39
	NEG	1	2	0	1	2	3004[a]	3010
	Total	27	31	26	30	40	3011	3165

Table 11. List of Carbapenemase-Producing Organisms and Concentrations (CFU/mL) Tested Using the Xpert Carba-R Assay (Continued)

Organism	Strain ID	Confirmed Characteristic	Test Concentration (CFU/mL)
Pseudomonas aeruginosa	PA3	KPC-2	100
Serratia marcescens	CGNC	KPC-2	100
Enterobacter cloacae	CFVL	KPC-2	100
Escherichia coli	COL	KPC-2	100
Escherichia coli	NCTC 13476	IMP	100
Acinetobacter baumannii	695	IMP-1	450
Enterobacter cloacae	2340	IMP-1	100
Klebsiella pneumoniae	IMPBMI	IMP	100
Acinetobacter baumannii	Yonsei_1	IMP	500
Acinetobacter baumannii	Yonsei_2	IMP	500
Klebsiella pneumoniae	6852	IMP-1	100
Pseudomonas aeruginosa	MKAM	IMP-1	200
Pseudomonas aeruginosa	70450-1	IMP	100
Pseudomonas aeruginosa	3994	IMP-10	200
Pseudomonas aeruginosa	NCTC 13437	VIM-10	400
Klebsiella pneumoniae	NCTC 13439	VIM-1	100
Klebsiella pneumoniae	NCTC 13440	VIM-1	100
Pseudomonas aeruginosa	758	VIM	400
Klebsiella pneumoniae	PA_87	VIM	100
Pseudomonas aeruginosa	B92A	VIM	100
Pseudomonas aeruginosa	Col1	VIM-2	400
Serratia marcescens	BM19	VIM-2	100
Escherichia coli	KOW7	VIM-4	100
Klebsiella pneumoniae	DIH	VIM-19	200
Klebsiella pneumoniae	NCTC 13443	NDM-1	100
Klebsiella pneumoniae	ATCC BAA-2146	NDM-1	100
Klebsiella pneumoniae	34262	NDM	100
Acinetobacter baumannii	AB-GEN	NDM-1	100
Enterobacter cloacae	3047	NDM-1	100
Proteus mirabilis	7892	NDM-1	100
Salmonella spp.	CAN	NDM-1	100
Acinetobacter baumannii	EGY	NDM-2	100
Escherichia coli	I5	NDM-4	100
Escherichia coli	405	NDM-5	100
Klebsiella pneumoniae	NCTC 13442	OXA-48	100
Klebsiella pneumoniae	OM11	OXA-48	100
Enterobacter cloacae	501	OXA-48	100
Klebsiella pneumoniae	DUW	OXA-48	100

Strain ID	Organism	Resistance Marker with Variant Information
NCTC 13442	*Klebsiella pneumoniae*	OXA-48
OM11	*Klebsiella pneumoniae*	OXA-48
501	*Enterobacter cloacae*	OXA-48
DUW	*Klebsiella pneumoniae*	OXA-48
OM22	*Escherichia coli*	OXA-48
BOU	*Enterobacter cloacae*	OXA-48
TUR	*Enterobacter cloacae*	OXA-48
11670	*Escherichia coli*	OXA-48
MSH2014-64	*Klebsiella pneumoniae*	OXA-181
MSH2014-72	*Escherichia coli*	OXA-181
B108A	*Klebsiella pneumoniae*	NDM, OXA-181
C10192-DISCS	*Enterobacter aerogenes*	NDM, OXA-181
KP-OMA3	*Klebsiella pneumoniae*	NDM-1, OXA-181
166643	*Klebsiella pneumoniae*	OXA-181
42194	*Klebsiella pneumoniae*	OXA-181
1300920	*Klebsiella pneumoniae*	NDM, OXA-181
MSH2014-69	*Klebsiella pneumoniae*	NDM, OXA-181
74	*Escherichia coli*	OXA-181
NCTC 13476	*Escherichia coli*	IMP-1
695	*Acinetobacter baumannii*	IMP-1
2340	*Enterobacter cloacae*	IMP-1
IMPBMI	*Klebsiella pneumoniae*	IMP-1
6852	*Klebsiella pneumoniae*	IMP-1
Yonsei_1	*Acinetobacter baumannii*	IMP-1
Yonsei_2	*Acinetobacter baumannii*	IMP-1
70450-1	*Pseudomonas aeruginosa*	IMP-1
3994	*Pseudomonas spp.*	IMP-10
MKAM	*Pseudomonas aeruginosa*	IMP-1
5344	*Pseudomonas aeruginosa*	IMP-2
G029	*Salmonella spp*	IMP-4
3985	*Pseudomonas aeruginosa*	IMP-11
4032	*Pseudomonas aeruginosa*	IMP-6
3424	*Pseudomonas aeruginosa*	IMP-7[a,b]
32443	*Klebsiella pneumoniae*	IMP-13[a]
92	*Pseudomonas aeruginosa*	IMP-14[a,b]

DNA sequence analysis as gold standard, dozens of strains needed for contrived specimens

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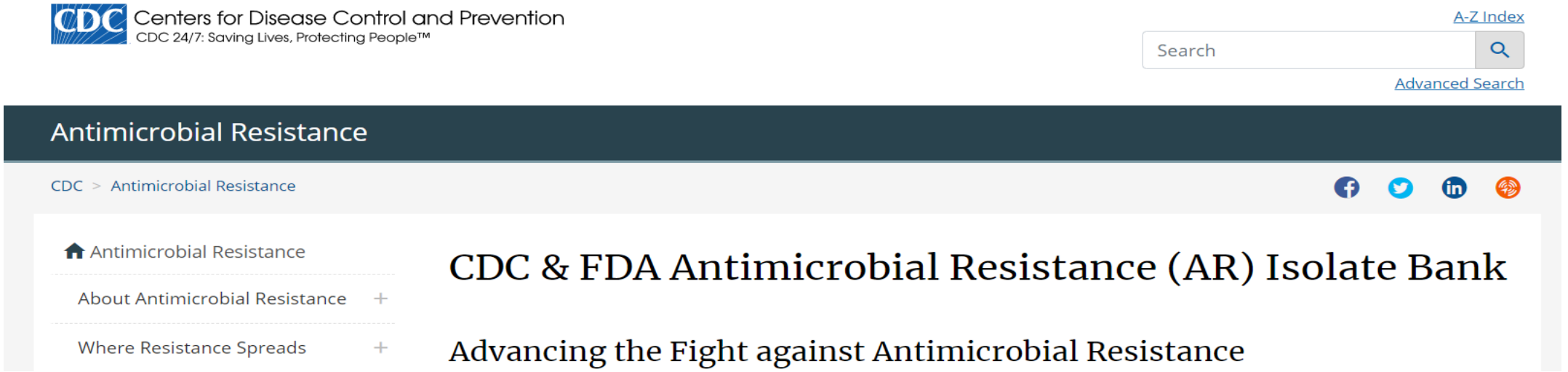
Government partners are critical



Bank has bacterial isolates with emerging antimicrobial resistance genes that have been confirmed by DNA sequence analysis; This is a very valuable resource that is continually adding new isolates with new resistance mechanisms

Facilitating submissions: Public-Private Partnerships

An example of a partner that could (theoretically) help shepherd submissions through FDA

https://www.nibib.nih.gov/covid-19/radx-tech-program/ITAP. Accessed 14-Sept 2022

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ITAP Mission

The National Institutes of Health (NIH) Rapid Acceleration of Diagnostics (RADx) initiative has established the Independent Test Assessment Program (ITAP) in order to accelerate regulatory review and availability of high-quality, accurate, and reliable over-the-counter COVID-19 tests to the public.

- "NIH's Rapid Acceleration of Diagnostics (RADx) Tech network of experts from government, academia, and industry work together with FDA, CDC, and other HHS specialists **to assess and conduct studies** on over-the-counter tests.
- This coordinated effort allows companies to **compile proper data, work towards the right benchmarks for performance, and support other needs** that will help ensure they are providing the **best submissions** possible for FDA's regulatory review.
- The goal is to **accelerate the availability of more high-quality, accurate, and reliable over-the-counter tests** to the public as quickly as possible."
- Can ITAP/RADx be utilized for novel antimicrobial resistance tests in the future?

https://www.nibib.nih.gov/news-events/newsroom/two-new-over-counter-home-covid-19-tests-brought-us-market-quickly-biden-harris-administration. Accessed 14 Sept 2022

Summary

- Technology for direct detection of drug resistance exists and has proven to be effective when results are delivered in an actionable timeframe
- Significant potential exists for high-impact rapid AMR testing in patients with sepsis and “sepsis-adjacent” conditions
- Public-private partnerships are going to be critical to facilitate timely FDA clearance of novel products to identify antimicrobial-resistant infections
- Partners who can work with FDA throughout the registration process will be key in the future, but they need to anticipate a step-up in trial complexity

Thank You

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