Diagnostics as a Resistance Combatting Strategy

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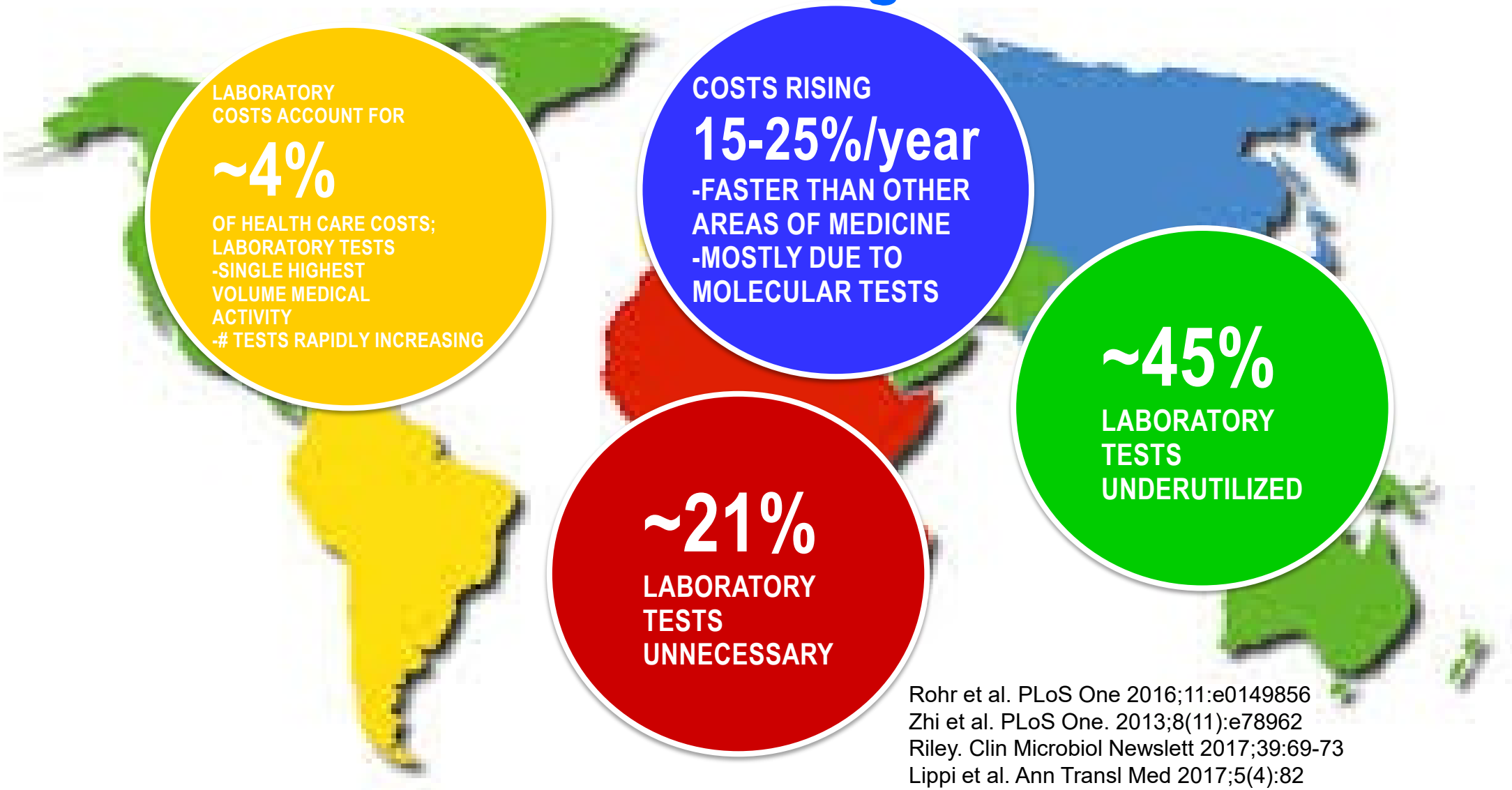
70% Clinical Decisions Substantially Based on Results of Diagnostic Tests



Rohr et al. PLoS One 2016;11:e0149856
Zhi et al. PLoS One. 2013;8(11):e78962
Riley. Clin Microbiol Newslett 2017;39:69-73
Lippi et al. Ann Transl Med 2017;5(4):82

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WHO

Priority Pathogens List (for R&D of New Antibiotics)

Critical

- *Acinetobacter baumannii,* carbapenem-resistant
- *Pseudomonas aeruginosa,* carbapenem-resistant
- *Enterobacteriaceae,* carbapenem-resistant, 3rd generation cephalosporin resistant

High

- *Enterococcus faecium*, vancomycin-resistant
- *Staphylococcus aureus*, methicillin-resistant, vancomycin intermediate and resistant
- *Helicobacter pylori*, clarithromycin resistant
- *Campylobacter*, fluoroquinolone-resistant
- *Salmonella* spp., fluoroquinolone-resistant
- *Neisseria gonorrhoeae*, 3rd generation cephalosporin-resistant, fluoroquinolone-resistant

Medium

- *Streptococcus pneumoniae*, penicillin non-susceptible
- *Haemophilus influenzae*, ampicillin-resistant
- *Shigella* spp., fluoroquinolone-resistant

CDC

Urgent Threats

- Carbapenem-resistant *Acinetobacter*
- *Candida auris*
- *Clostridioides difficile*
- Carbapenem-resistant *Enterobacteriaceae*
- Drug-resistant *Neisseria gonorrhoeae*

Serious Threats

- Drug-resistant *Campylobacter*
- Drug-resistant *Candida*
- Extended-spectrum β-lactamase-producing *Enterobacteriaceae*
- Vancomycin-resistant Enterococci
- Multidrug-resistant *Pseudomonas aeruginosa*
- Drug-resistant nontyphoidal *Salmonella*
- Drug-resistant *Salmonella* serotype Typhi
- Drug-resistant *Shigella*
- Methicillin-resistant *Staphylococcus aureus*
- Drug-resistant *Streptococcus pneumoniae*
- Drug-resistant Tuberculosis

Concerning Threats

- Erythromycin-resistant group A Streptococcus
- Clindamycin-resistant group B Streptococcus

Watch List

- Azole-resistant *Aspergillus fumigatus*
- Drug-resistant *Mycoplasma genitalium*
- Drug-resistant *Bordetella pertussis*

Classic Diagnostic Paradigm

Is the patient's clinical presentation caused by an infection?

What is (are) the causative pathogen(s)?

Which treatment should be administered?

Classic approach contributing to antimicrobial resistance crisis and failing because of it…

Classic Diagnostic Paradigm

Is the patient's clinical presentation caused by an infection?

History/Physical (+)

Imaging (+)

Laboratory tests (+)

What is (are) the causative pathogen(s)?

Culture (+/-)

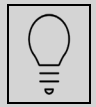
Serology (+/-)

Molecular diagnostics (+/-)

Which treatment should be administered?

Culture → AST (+)

New Diagnostics



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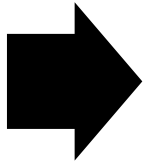
Theranostics

- Think about diagnostics differently – answer the treatment question "up-front" ☺

Is the patient's clinical presentation caused by an infection?



What is (are) the causative pathogen(s) – culturable or fastidious? – and what treatment should be given?

~~Which treatment should be administered?~~

Creative use of technology can help

… and fortunately, we are in a technology revolution!

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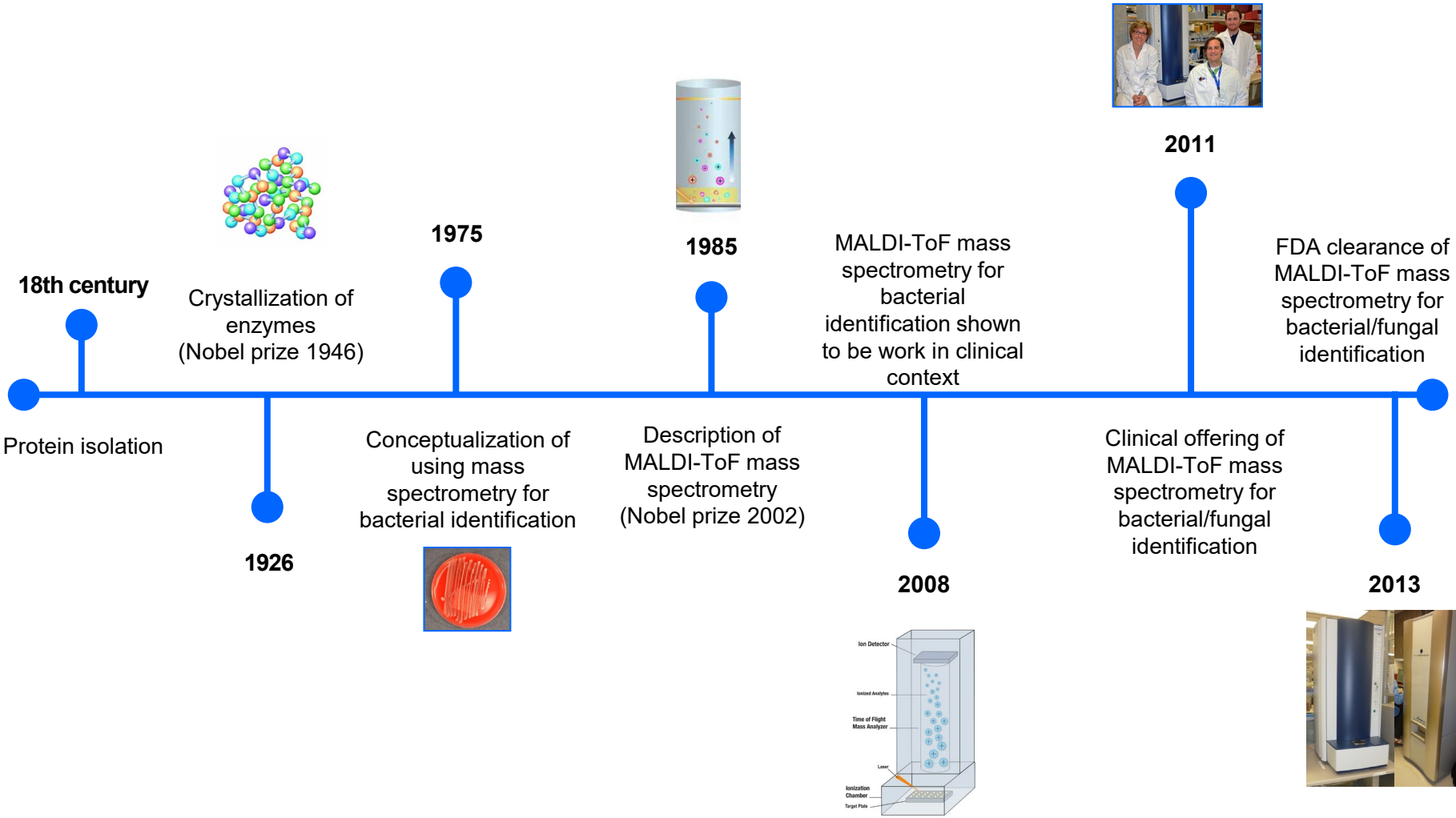
Technology Revolution Proteomics



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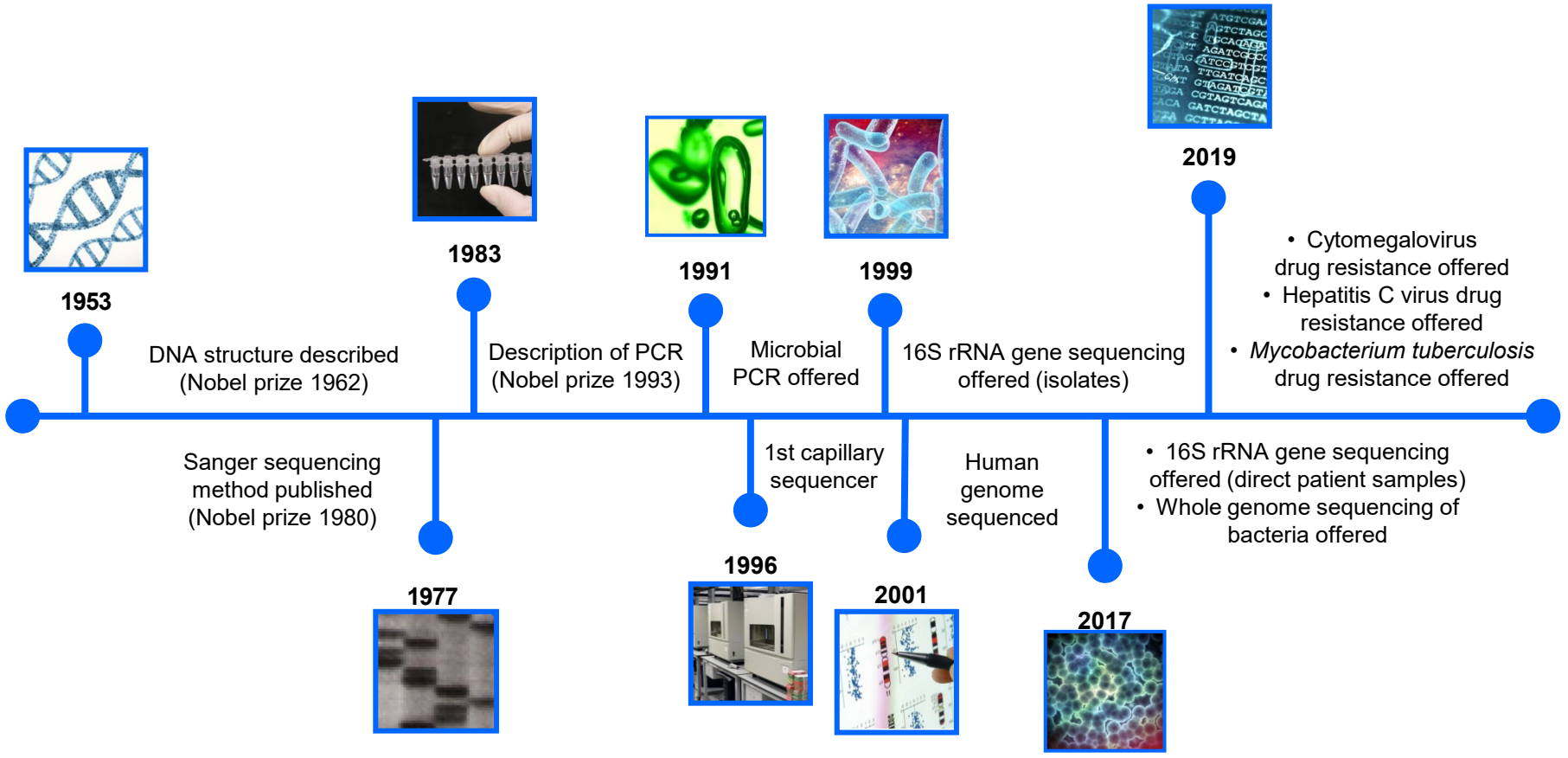
Technology Revolution
NAAT and Sequencing-Based Diagnostics



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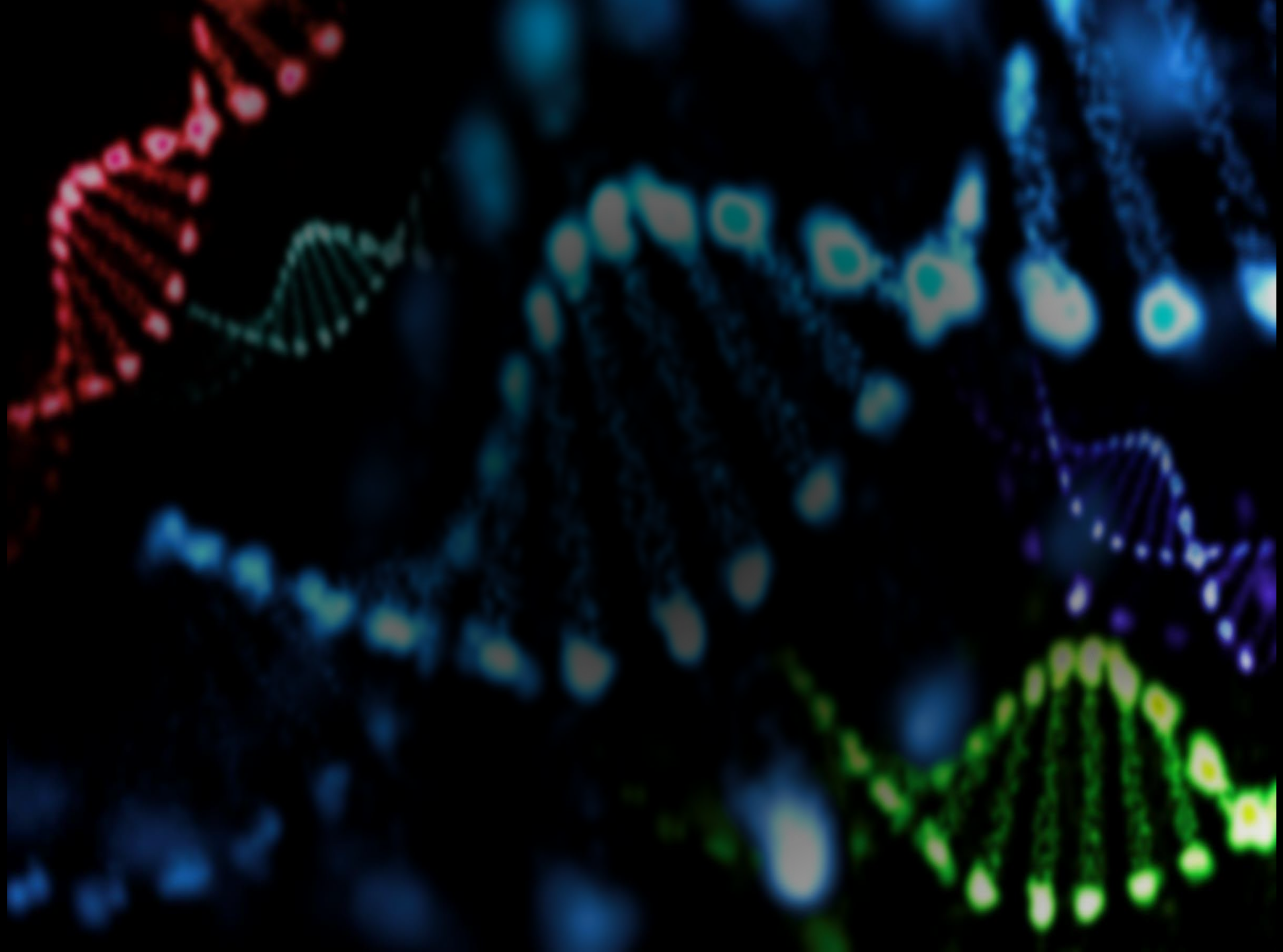
Technology Revolution: Microbial Real-Time PCR Assays Developed @ Mayo Clinic, 2000–2020

2000	Herpes simplex virus*
2001	*Bacillus anthracis*
	Cytomegalovirus*
	*Toxoplasma gondii**
2002	*Bordetella pertussis/parapertussis**
	Streptococcus pyogenes
	Enterovirus
	Varicella zoster virus*
2003	*Tropheryma whipplei**
	*Babesia microti**
	BK virus*
	Ehrlichia/Anaplasma species*
	Epstein–Barr virus (qualitative)*
	JC virus*
	*Borrelia burgdorferi**
2004	*Bartonella* species*
	*vanA/vanB**
	Parvovirus B19*
2005	Influenza A/B
	Pneumocystis jirovecii
	BK virus (quantitative)
	Epstein–Barr virus (quantitative)
	Human herpesvirus-6
	Plasmodium species
	West Nile virus
2007	*Clostridioides difficile*
	Coccidioides immitis/posadasii
	Staphylococcus aureus
	Mycobacterium chelonae/abscessus
2008	Adenovirus

2009	*Legionella* species
	bla_{KPC}
	Mycobacterium tuberculosis complex
2010	*Salmonella* species
	Shigella species
	Campylobacter species
	Yersinia species
	Shiga toxin
2011	*Mycoplasma genitalium*
	Mycoplasma hominis
	Ureaplasma urealyticum/parvum
	Histoplasma/Blastomyces species
2012	*Mycobacterium tuberculosis* complex species
2013	*Coxiella burnetii*
	bla_{NDM}
	Mycoplasma pneumoniae
2014	*Babesia* species
	Borrelia mayonii
2015	Microsporidia
2016	*Borrelia miyamotoi*
2017	$bla_{OXA48\text{-}like}$
	bla_{VIM}
	Kingella kingae
	Acanthamoeba species
	Free-living amoeba
	Norovirus
2020	*mecA*
	Helicobacter pylori
	Candida auris
	SARS coronavirus-2

Microorganisms marked by an asterisk (*) were detected with conventional PCR assays with Southern blot detection developed and deployed in the 1990s prior to conversion to real-time PCR assays

Patel. Clin Chem. 2022;68:10-15



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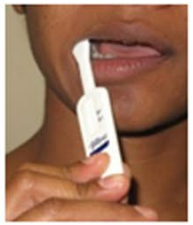
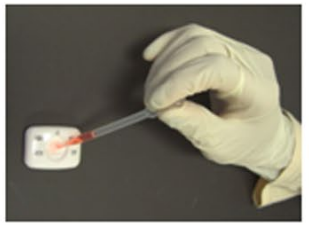
Technology Revolution
Point of Care Diagnostics

TPP1: HOME	TPP2: COMMUNITY	TPP3: CLINIC / HEALTH POST (Out-patient)	TPP4: PERIPHERAL LAB	TPP5: HOSPITAL (In-patient)
Self-testing (home-based) User: Lay person Device: RDT (pregnancy-type) or dipstick Purpose: Self assessment and referral	**Testing in the community by health workers** (e.g. village workers, paramedics) User: Minimally trained health worker Device: RDT Purpose: Triage and referral	**Testing in the clinic by healthcare providers** (e.g. doctors, nurses) User: Clinic staff Device: RDT, handheld instruments Purpose: Diagnosis and treatment	**Testing in the peripheral laboratory** User: Lab tech Device: RDT, molecular tests, ELISA, microscopy, etc Purpose: Diagnosis treatment monitoring	**Testing of in-patients in hospitals** (e.g. ER, OR, ICU) User: Hospital staff Device: RDT, molecular, smears, etc. Purpose: Diagnosis treatment monitoring
Simplest				*Relatively sophisticated*
				
HIV self-testing	Malaria, HIV, dengue	HIV, malaria, syphilis, dengue, Strep A	TB, HIV, malaria, HBV, C.diff, CD4, HCV, MRSA, flu, UTI, viral loads, etc.	TB, HIV, malaria, HBV, HCV, flu, MRSA CD4, Strep A, C.diff, etc.

Dolen et al. Changing Diagnostic Paradigms for Microbiology: Report on an AAM Colloquium ASM 2017

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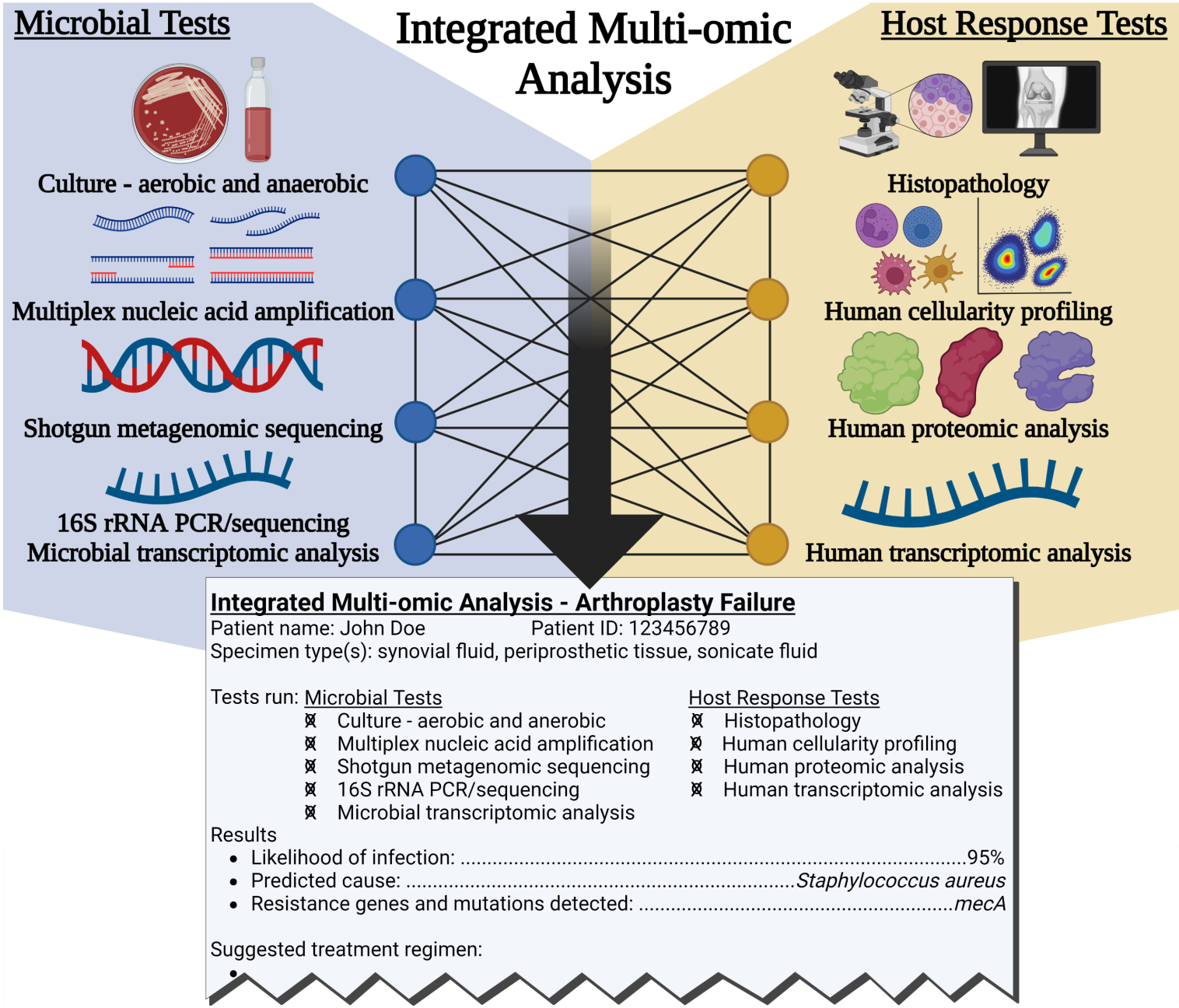
Rapid Detection & Simultaneous Resistance Profiling

- Xpert (Cepheid)
  - MRSA/SA Nasal Complete Assay, SSTI Assay
  - MTB/RIF Assay
- Detection and macrolide susceptibility prediction
  - *Mycoplasma pneumoniae*
  - *Helicobacter pylori* detection (stool)
- *Neisseria gonorrhoeae* ciprofloxacin susceptibility prediction

Futuristic Vision
→ Complex Infection



Fisher and Patel. Antibiotics. 2023;12(2):296

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Conclusions

- Many current microbiology diagnostics antiquated, poorly used
- Technology revolution
  - Bringing major advances
- How to move to the future
  - Demonstration of value
- The deliverables
  - Improved health (patients, society, AMR)
    - Less impact of AMR
  - Changes to healthcare delivery