The new era of diagnostics: will it ever happen? ERS Conference 29 September 2019 Madrid, Spain

Herman Goossens University Hospital of Antwerp, Belgium



Conflict of interest disclosure



X I have no real or perceived conflicts of interest that relate to this presentation.

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"We are entering an era when **priority** of microbiological examinations for diagnosis of respiratory tract infections substantially **increases**"

Bartlett JG; Clin Infect Dis 2004, 39: 170-172

Agenda: Era of what?

- Era of investment
- Era of diagnostic tests
- Era of technologies
- Era of patient enrichment in clinical trials
- Era of diagnostic testing
- Era of value based diagnostics

Projects funding by the EU, 2007-2013, by priority topic with total funding



Kelly et al, Lancet Infect. Dis. 2015

Forecasting IVD Market in 2011

- IVDs will be the world's largest medtech sector in 2018
- Projected 2018 sales \$9.9 billion
- Five year compounded annual growth rate 4.8%



http://www.prnewswire.com/news-releases/medtech-market-to-achieve-global-sales-of-440-billion-by-2018-172274151.html

http://www.aacc.org/publications/cln/2012/ExpoIssue/Pages/RecordBreaking2012ClinicalLab.aspx# http://www.marketsandmarkets.com/Images/ivd-in-vitro-diagnostics-market.jpg Diagnostics affect around 60-70% of all clinical decisions (Garber et al, The Innovation Journal, 15, 2010)

Diagnostics only account for 0.8% of total healthcare expenditure in Europe

(MedTech Europe, Report 2016)

Funding Opportunities: The 3 Diagnostics Prizes

	Longitude Prize 2014	Horizon 2020 Antibiotics Inducement Prize	2014 US AMR Diagnostics Prize
Prize Fund	£10M (\$16M)	€1M (\$1.3)	\$20M
Opens for Submissions	Fall 2014	2015	2015
Award Date	2020	Late 2016	TBD
Prize Statement	"will reward a solution that enables doctors, nurses and patients to better target their treatment, and helps ensure that right antibiotic is used at the right time."	"will be awarded to the most significant development towards an accurate point-of-care solution which can prove a sustained reduction in the number of unnecessary courses of antibiotics prescribed for an upper respiratory tract infection, in the primary care setting of different European countries."	The launch of a \$20 million to facilitate the development of a rapid diagnostic test to be used by health care providers to identify bacterial infections at the point of patient care.

http://www.nesta.org.uk/sites/default/files/kcfinder/files/H2020%20Longitude%20AMR%20Comparison.pdf http://www.whitehouse.gov/blog/2014/09/18/new-executive-actions-combat-antibiotic-resistance-and-protect-public-health

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Diagnostic tests

Diagnostic lab/microbiology service in hospital

- Big instruments
- Expensive
- High throughput
- Automation
- Inpatient settings

Point of Care Testing (POCT)

- Small instruments
- Cheaper
- Fast turnaround time (TAT)
- Usually 1 sample per run
- Easy-to-use
- Outpatient settings



Landscaping of diagnostic tests for RTI

Gather information on the diagnostic tests for Respiratory Tract Infections (RTIs) available in the market or under development

Structure:

- General information
- Specifications
- Validation
- Company capacity
- Regulation
- Clinical studies
- Website

Database



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General information

- Number of tests identified for respiratory tract specimens: 284
- Number of manufacturers: 69
- Suitability for POC testing: 37.7%
- Method
 - 37.7% immunoassays
 - 35.9% NAAT



Tsunami of instruments

Fast systems

Alere: i Isothermal amplification: NEAR 15 min Influenza test



Xagenic: X1 Nanostructured microelectronic sensors: 20 mins; 50 targets test



Handheld devices Micronics: PanNAT

1 hour; 3 targets test H: 20 cm / Depth= 34.5 cm / Width: 12 cm



Epistem: Genedrive 1 hour real-time PCR test





Agenda: Era of what?

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Smartphone app for non-invasive detection of anemia using only patient-sourced photos





Mannino et al, Nature Comm 2018 9(1): 4924

Antilope Dx for home testing



Image engineering prototype

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A P. aeruginosa - Focused VAP Programme

- Standard non-inferiority Phase 3 study¹
 - Need 336/arm or 672 evaluable patients total
- If only 10% yield P. aeruginosa,
 - We need 6,720 patients ... for ONE trial!

Conclusion: We need rapid diagnostic tests to enrich patient population in clinical trials

¹Assumes 80% success rates, 10% margin, and 90% power.



Kostyanev, T, et al. J. Antimicrob. Chemother. 2016

Examples of clinical trials in IMI where rapid diagnostics are needed

- Phase II RCT with anti-α-toxin staphylococcal antibody MEDI4893 for prevention of HABP/VABP (MedImmune):
 - Diagnostic test needed: rapid detection of *S. aureus* in ETA
- Phase II RCT trial with anti-pseudomonas antibodies MEDI3902 for prevention of HABP/VABP (MedImmune)
 - Diagnostic test needed: rapid detection of *P. aeruginosa* in ETA
- Phase III RCT of minocycline in subjects with HABP/VABP caused by Acinetobacter baumannii complex (Medicines Company)
 - Diagnostic test needed: rapid detection of *A. baumanii* in ETA
- Phase III Randomized trial with S-649266 for the treatment of severe Infections caused by Carbapenem-resistant Gram-negative bacteria (Shionogi)
 - Diagnostic test needed: rapid detection of CR-organisms and/or Carbapenemase genes



For Cepheid Media & Investor Inquiries: Jacquie Ross, CFA +1 408-400-8329 corporate.communications@cepheid.com

CEPHEID ANNOUNCES DIAGNOSTIC COLLABORATION WITH MEDIMMUNE AND COMBACTE TO FACILITATE CLINICAL TRIALS OF NEW MONOCLONAL ANTIBODIES TO PREVENT SERIOUS INFECTIOUS DISEASES

GeneXpert Systems and Xpert Tests Expected to Enhance Efficiency of Clinical Trials

SUNNYVALE, CALIF. — January 13, 2016 — Cepheid (Nasdaq: CPHD) today announced a collaboration with MedImmune, the global biologics research and development arm of AstraZeneca, and COMBACTE, a European public/private partnership set up to promote the development of new drugs in the anti-infectives field, to develop a series of rapid diagnostic tests to identify *Staphylococcus aureus* (*S. aureus*) and *Pseudomonas aeruginosa* (*P. aeruginosa*) in respiratory secretions of mechanically ventilated patients. These tests will be used to help identify patients for MedImmune's MEDI4893 and MEDI3902 clinical programs, which are being conducted within the COMBACTE consortium to explore the use of biologics in preventing ventilator associated pneumonia (VAP) infections in intensive-care-unit (ICU) patients.

Lessons learned in COMBACTE on role of diagnostics

to aid patient enrolment in COMBACTE clinical trials with narrow spectrum drugs (4/9 intervention trials)



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- 80% of antibiotics are prescribed in primary care
- Acute RTIs most common reason for GP consultation
- Most infections are due to viruses
- Evidence of over prescribing by GPs
- Overprescribing is linked to increased antibiotic resistance



Antibiotics for non-pneumonic respiratory-tract infections

Amoxicillin for acute lower-respiratory-tract infection in primary care when pneumonia is not suspected: a 12-country, randomised, placebo-controlled trial

Paul Little, Beth Stuart, Michael Moore, Samuel Coenen, Christopher C Butler, Maciek Godycki-Cwirko, Artur Mierzecki, Slawomir Chlabicz, Antoni Torres, Jordi Almirall, Mel Davies, Tom Schaberg, Sigvard Mölstad, Francesco Blasi, An De Sutter, Janko Kersnik, Helena Hupkova, Pia Touboul, Kerenza Hood, Mark Mullee, Gilly O'Reilly, Curt Brugman, Herman Goossens, Theo Verheij, on behalf of the GRACE consortium



"Little and colleagues have generated convincing data that should encourage physicians in primary care to **refrain from antibiotic treatment** in low-risk patients in whom pneumonia is not suspected. ...

Guidance from measurements of specific **blood biomarkers** of bacterial infection might help to identify the few individuals who will benefit from antibiotics despite the apparent absence of pneumonia and avoid the toxic effects and costs of those drugs and the development of resistance in other patients."

Editorial Published Online December 19, 2012 Little P et al Lancet Infect Dis 2013;13: 123–29

Effects of internet-based training on antibiotic prescribing rates for acute respiratory-tract infections: a multinational, cluster, randomised, factorial, controlled trial



Paul Little, Beth Stuart, Nick Francis, Elaine Douglas, Sarah Tonkin-Crine, Sibyl Anthierens, Jochen W L Cals, Hasse Melbye, Miriam Santer, Michael Moore, Samuel Coenen, Chris Butler, Kerenza Hood, Mark Kelly, Maciek Godycki-Cwirko, Artur Mierzecki, Antoni Torres, Carl Llor, Melanie Davies, Mark Mullee, Gilly O'Reilly, Alike van der Velden, Adam W A Geraghty, Herman Goossens, Theo Verheij, Lucy Yardley, on behalf of the GRACE consortium

- Countries: UK, Poland, Spain, the Netherlands, Belgium
- Baseline in 6,774 patients and 4,358 patients post-test
- 2x2 factorial design (Communication, CRP, Usual care)



	Usual care		Communication					
 Usual care	Usual care	58%	Communication training 41%					
CRP	CRP training	35%	CRP + Communication training 31%					

Little et al Lancet 2013

Link between CRP test and Antibiotic Use



Adapted from: European Centre for Disease Prevention and Control http://ecdc.europa.eu/en/

Impact of e-POCT implementation on antibiotic prescription

Outcome	e-POCT arm, percent (<i>n/N</i>)	ALMANACH arm, percent (<i>n/</i> N)	Risk difference (95% CI)	Risk ratio (95% CI)	<i>p</i> -Value ¹
Primary outcome					
Clinical failure by day 7	2.3 (37/1,586)	4.1 (65/1,583)	-1.7 (-3.0, -0.5)	0.57 (0.38, 0.85)	0.005
Secondary outcomes					
Primary referrals	6.6 (104/1,586)	2.9 (46/1,583)	3.6 (2.2, 5.1)	2.26 (1.61, 3.17)	< 0.001
Antibiotic prescription at day 0 <	11.5 (182/1,586)	29.7 (470/1,583)	-18.2 (-21.0, -15.5)	0.39 (0.33, 0.45)	< 0.001
Severe adverse events by day 30	0.6 (10/1,586)	1.5 (24/1,583)	-0.9 (-1.6, -0.2)	0.42 (0.20, 0.87)	0.02
Secondary admissions	0.4 (7/1,586)	1.2 (19/1,583)	-0.8 (-1.4, -0.1)	0.37 (0.15, 0.87)	0.02
Deaths	0.2 (3/1,586)	0.4 (6/1,583)	-0.2 (-0.6, 0.2)	0.50 (0.12, 2.00)	0.32

Table 4. Primary and secondary study outcomes of the randomized study (per-protocol population).

¹Chi-squared test.

Potential impact of e-POCT in children in Tanzania: 28 million unnessary antibiotics saved per year

Keitel et al, PLOS Medicine 2017

Jim O'Neill AMR Review

Review on Antimicrobial Resistance

In 2014, the UK Prime Minister David Cameron commissioned the independent Review on Antimicrobial Resistance, Chaired by macroeconomist Jim O'Neill, to examine the growing threat of AMR from an economic perspective and to recommend solutions. The Review has been co-sponsored by the Wellcome Trust and the Department of Health. Over the last 19 months the Review has published eight thematic papers that address different aspects of the problem of AMR. These are as follows:

- Antimicrobial Resistance: Tackling a crisis for the health and wealth of nations, December 2014
- Tackling a global health crisis: Initial steps, February 2015
- Securing new drugs: The pipeline of antibiotics, May 2015
- Rapid Diagnostics: Stopping unnecessary use of antibiotics, October 2015

- Safe, secure and controlled: Managing the supply chain of antimicrobials, November 2015
- Antimicrobials in agriculture and the environment: Reducing unnecessary use and waste, December 2015
- Vaccines and alternative approaches: Reducing our dependence on antimicrobials, February 2016
- Infection prevention, control and surveillance: Limiting the development and spread of drug resistance, March 2016

This is the final report that pulls together all our previous recommendations as a package of actions that we believe will be seded to tackle this rising threat.

Fifth recommendation: "Rich countries must lead the way to change this: they should make it mandatory that by 2020 the prescription of antibiotics will need to be informed by data and testing technology wherever available and effective in informing the doctor's judgement to prescribe"

THE WALL STREET JOURNAL.

Doctors Test Tools to Predict Your Odds of a Disease

Program aims to calculate the likelihood that a patient has an illness, enabling doctors to order fewer tests and prescribe fewer antibiotics

By LUCETTE LAGNADO

May 30, 2016 2:46 p.m. ET

"I can either prescribe \$4 penicillin" on the chance that a patient has a strep infection, Dr. Beasley says. Or he can order a \$51 strep test to make certain the person does. For a patient struggling to make ends meet financially, he says he prefers the \$4 penicillin.

Business Case

- Value of Dx is under-appreciated: Low cost of Abx versus Dx
- Reimbursement is not value driven

- Especially in primary care, lack of
 - Evidence of utility/outcome benefit and costbenefit studies
 - Economic incentives
 - Alignment of stakeholder interests

Challenges for rapid diagnostic testing

There is a <u>dearth</u> <u>of studies</u> which can provide the evidence of the value of diagnostics in well-characterised situations, and the lack of such evidence has been a hindrance for diagnostic innovation.

nclear technological and medical <u>needs.</u>

> <u>Guidelines</u> deemphasizing diagnostic microbiology.

Controversial role in antibiotic The current diagnostic <u>business</u> <u>model</u> - focused on technology used, lab activity measures, and complexity indicators – is <u>antiquated.</u> The <u>current financial</u> <u>framework</u> (i.e. inadequate reimbursement, reimbursement based on technology rather than medical value) <u>does not</u> <u>encourage innovation</u> related to diagnostic tests.

Regulatory approval has historically been based on <u>analytical</u> <u>performance</u>, rather than on clinical effectiveness.

Lack of <u>cost-benefit</u> studies . Psychological, social, economical, ethical, organisational <u>barriers</u> <u>prevent the uptake and</u> <u>development</u> of diagnostics for antimicrobial stewardship.

H. Goossens, Lancet Infectious Diseases Commission on Antibiotic Resistance, part 3, 18 December, 2013

Agenda: Era of what?

- Era of investment
- Era of diagnostic tests
- Era of technologies
- Era of patient enrichment in clinical trials
- Era of diagnostic testing
- Era of value based diagnostics

The VALUE-Dx Consortium

Objectives of VALUE-Dx

Helping to build the economic case for rapid diagnostics as a public good in the fight against AMR

1. To design a health-economic framework (HEF) to assess and demonstrate the value of diagnostics both for individual patients and for public health impact by reducing antibiotic use and subsequent antibiotic resistance among patients.

2. To establish a sustainable European Standardised Care Network adequately trained and resourced to conduct clinical trials evaluating the value of diagnostics.

3. To design and implement clinical studies to demonstrate the value of diagnostics in the optimal management of Community-Acquired Acute Respiratory Tract Infections (CA-ARTIs) 4. To explore, define and attempt to resolve the psychological, ethical and social barriers which prevent the more widespread adoption of diagnostics delivering healthcare to the population.

Gantt Chart

Access to Clinical Trial Networks

Primary	Hospital						
care	care + Labs						
>200 primary care	>900 hospitals and >80						
practises in >20	labs in >40 European						
European countries	countries						
And the second s	COMBACTE						

- ✓ Recruited over 20,000 patients into clinical studies on ARTI in GRACE and other studies.
- Randomised 3,268 participants in a response-adaptive platform trial of a drug for a CA-ARTI in PREPARE.

Chris Butler

 ✓ Active a.o in ZIKACTION, PREPARE, C4C (IMI-2)

Carlo Giaquinto

Long Term Care

Nursing homes and rehabilitation centres in 11 countries in Europe and Israel with more than 14,000 LTCF beds

 Experience in clinical trials on antibiotic use, influenza epidemiology and vaccines, microbiome and more.

> Evelina Tacconelli Mical Paul

Adapted from Okeke et al, Drug Res Updates, 2011