

The new era of diagnostics: will it ever happen?

ERS Conference

29 September 2019

Madrid, Spain

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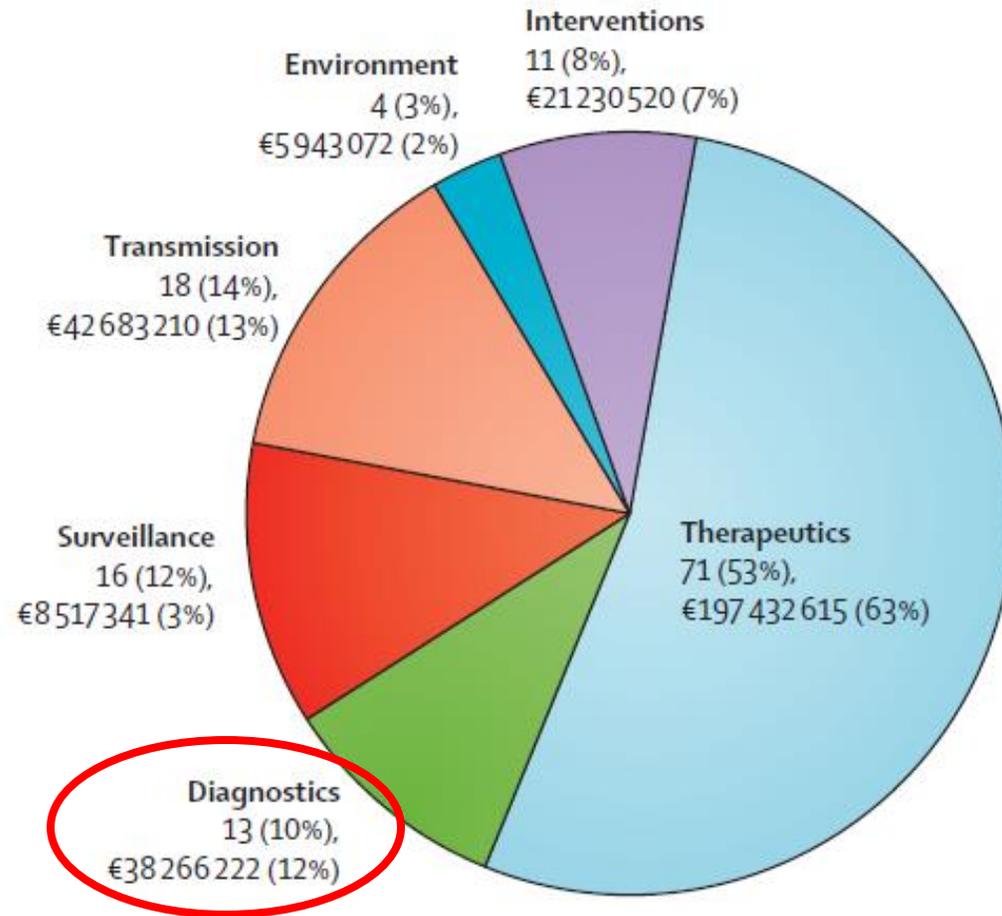
*“We are entering an era when **priority** of microbiological examinations for diagnosis of respiratory tract infections substantially **increases**”*

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

Agenda: Era of what?

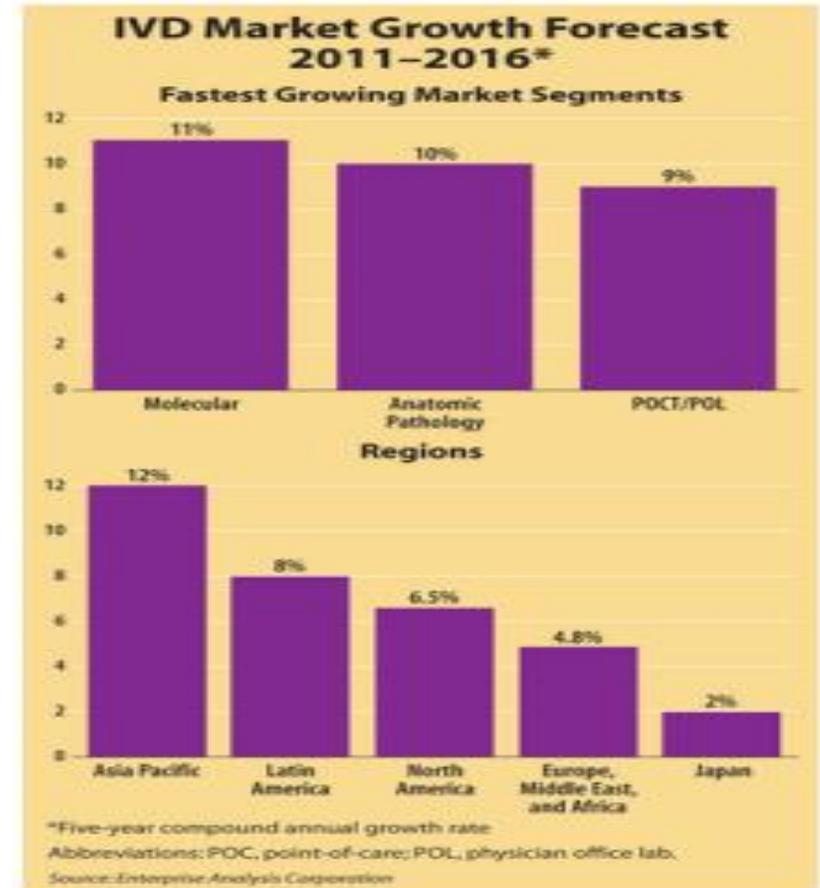
- Era of investment
- Era of diagnostic tests
- Era of technologies
- Era of patient enrichment in clinical trials
- Era of diagnostic testing
- Era of value based diagnostics

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



Forecasting IVD Market in 2011

- IVDs will be the world's largest med-tech 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.

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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

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

ND4ID

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

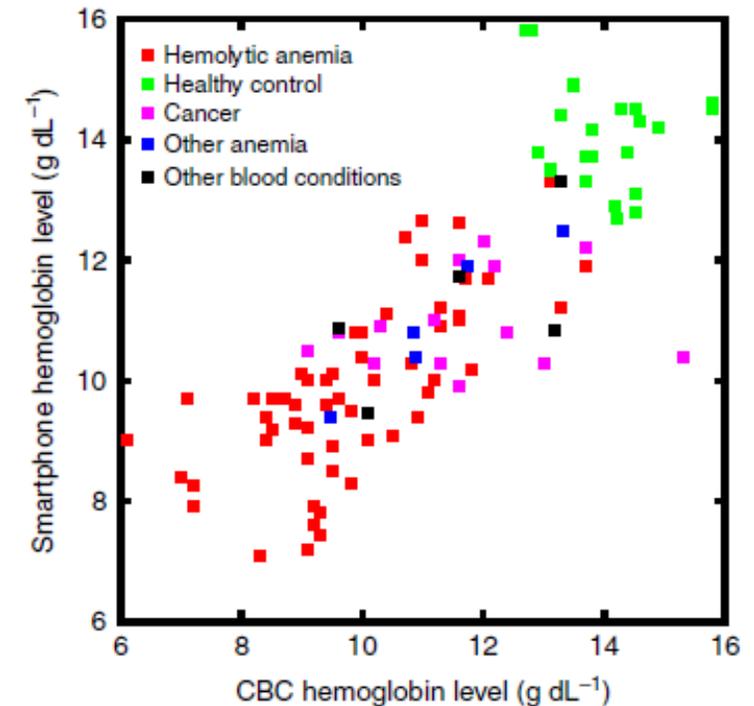
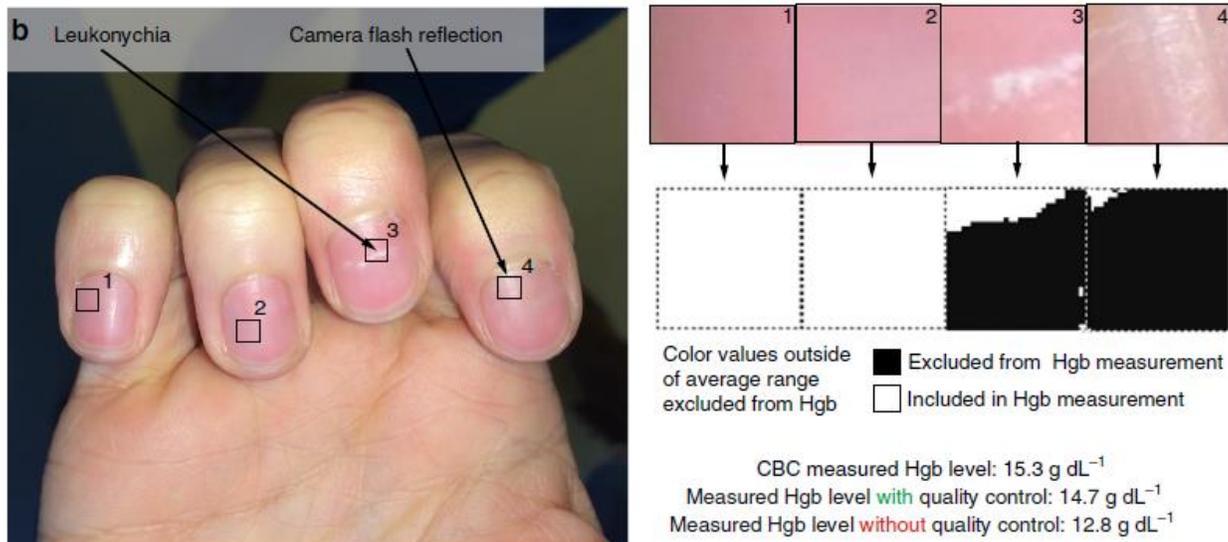
1 hour real-time PCR test



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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

Agenda: Era of what?

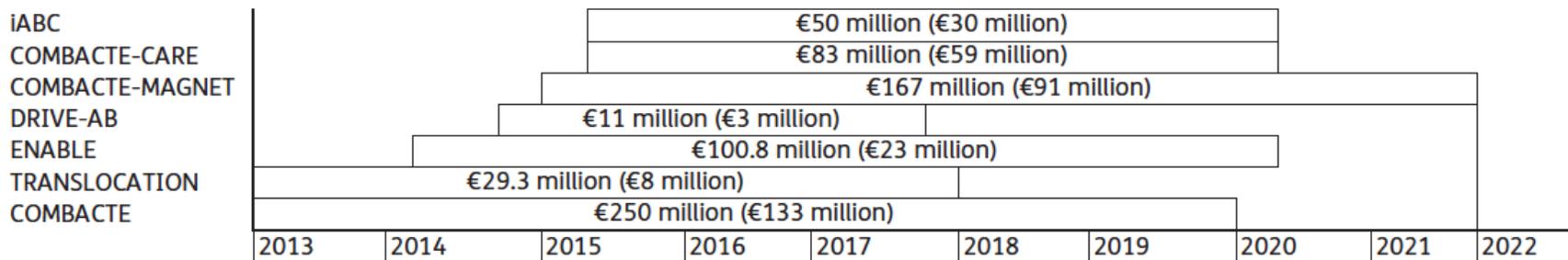
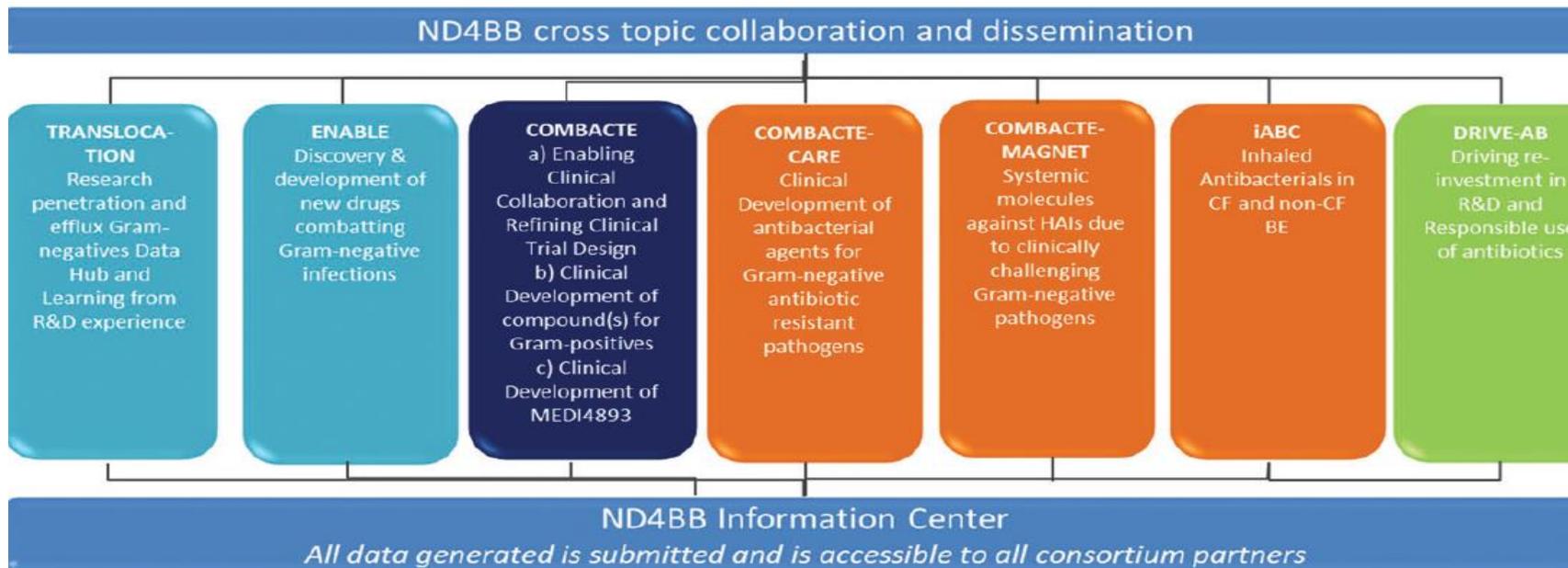
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A *P. aeruginosa* - Focused VAP Programme

- 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.



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. baumannii* 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



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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)

Unclear function
and performance
characteristics

How will test be used?
What are required performance characteristics to aid patient enrolment?

Schism between pharma
and diagnostic companies

Pharma: rapid triage test targeting limited number of organisms in a specific sample
Diagnostic companies: broad range tests

Unclear exploitation

How is the test developed into labeled product?
Who will pay for the test?

Regulatory blind-spots

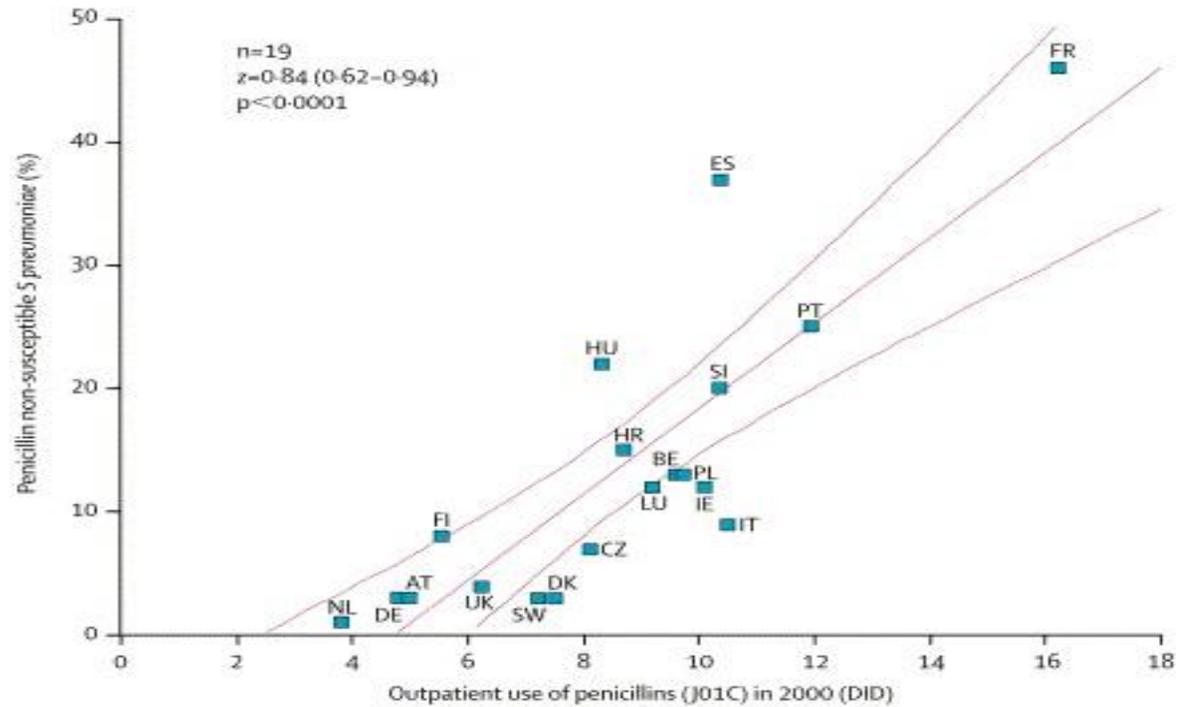
Potential regulatory needs discussed too late and/or conflicting feedback

Demand of pharma to
perform test outside of
microbiology lab

Purchasing and logistical challenges
Challenges to organise, track and train Healthcare Workers
Maintenance, Q-controls and test support
Miscommunication between pharma, diagnostic company, micro lab, and CRO

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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 Mölsted, 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.”*

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



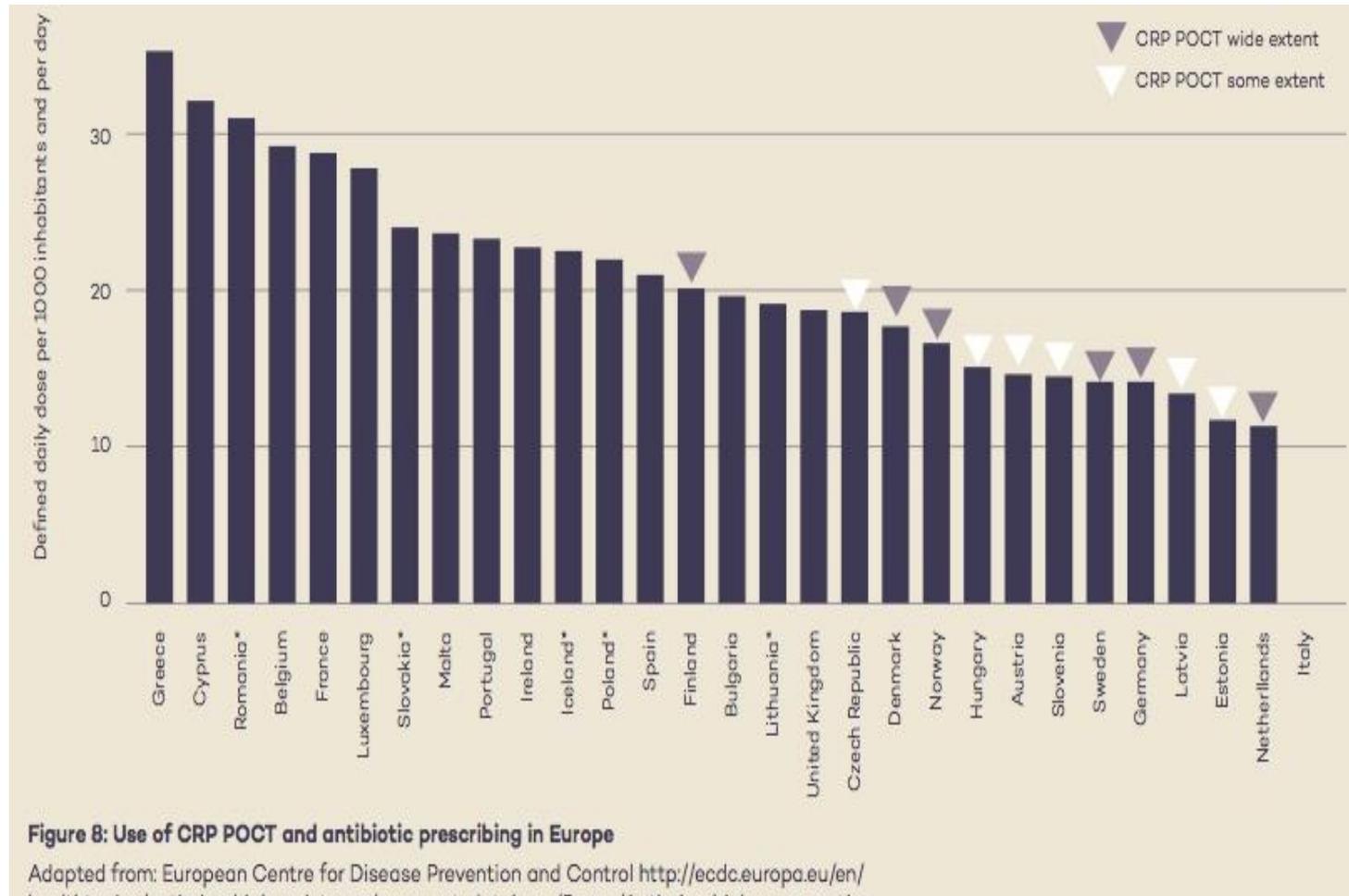
Paul Little, Beth Stuart, Nick Francis, Elaine Douglas, Sarah Tonkin-Crine, Sibyl Anthierens, Jochen W L Cals, Hasse Melbye, Miriam Santer, Michael Moore, Samuel Coenen, Chris Butler, Kerenza Hood, Mark Kelly, Maciek Godycki-Cwirko, Artur Mierzecki, Antoni Torres, Carl Llor, Melanie Davies, Mark Mullee, 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%

Link between CRP test and Antibiotic Use



Impact of e-POCT implementation on antibiotic prescription

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

Outcome	e-POCT arm, percent (n/N)	ALMANACH arm, percent (n/N)	Risk difference (95% CI)	Risk ratio (95% CI)	p-Value ¹
<i>Primary outcome</i>					
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
<i>Secondary outcomes</i>					
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

¹Chi-squared test.

Potential impact of e-POCT in children in Tanzania:

28 million unnecessary antibiotics saved per year

Jim O'Neill AMR Review

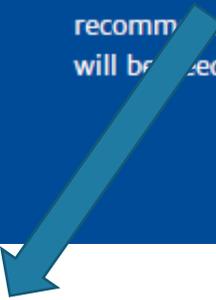
Review on Antimicrobial Resistance

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 needed 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.

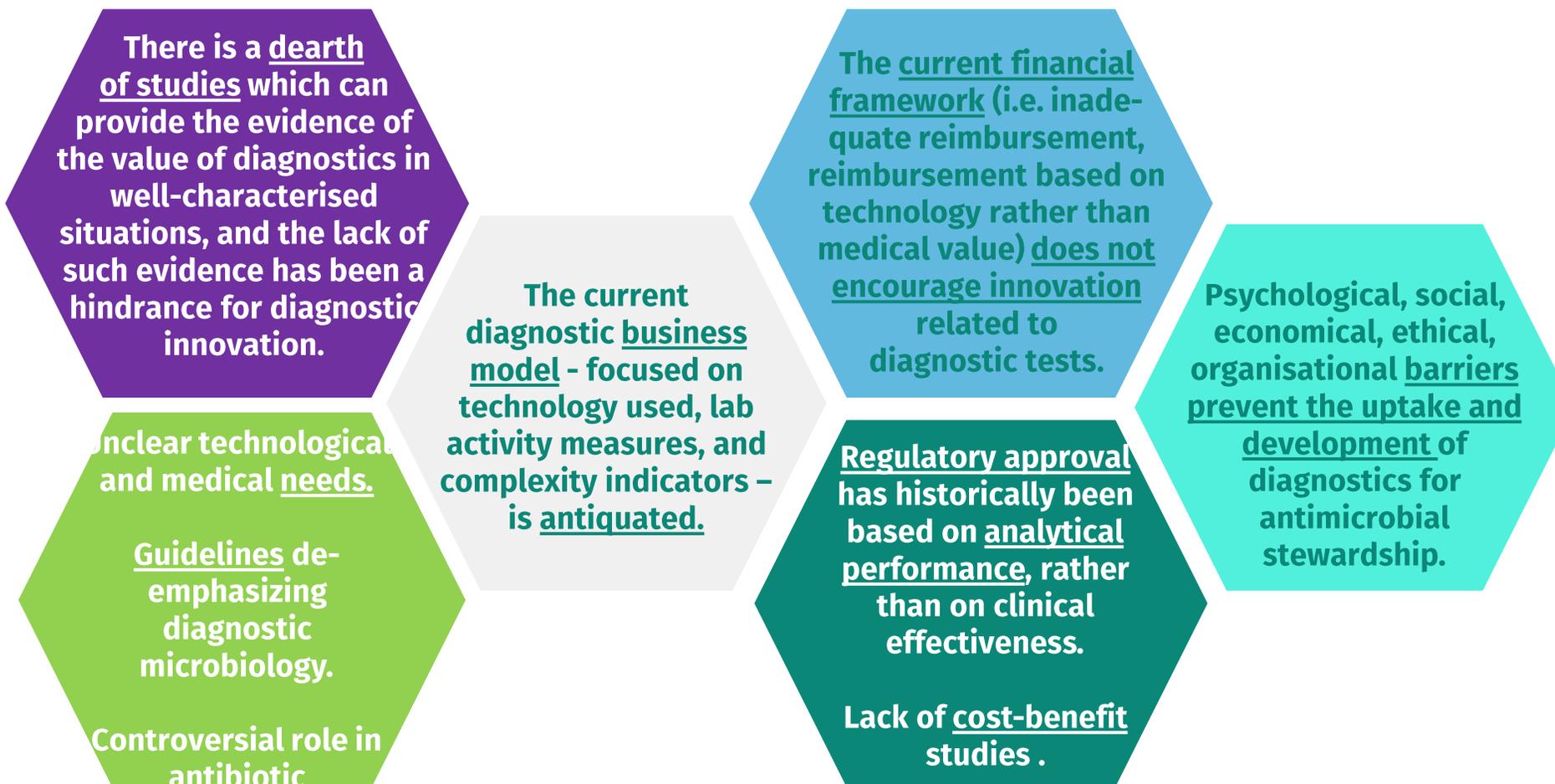
- **Business Case**

- 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 cost-benefit studies
- Economic incentives
- Alignment of stakeholder interests

Challenges for rapid diagnostic testing



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The VALUE-Dx Consortium



UNIVERSITÀ di VERONA



THE UNIVERSITY of EDINBURGH



University Medical Center Groningen



RAMBAM Health Care Campus



NICE National Institute for Health and Care Excellence

Gesundheit Österreich GmbH



Objectives of VALUE-Dx

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

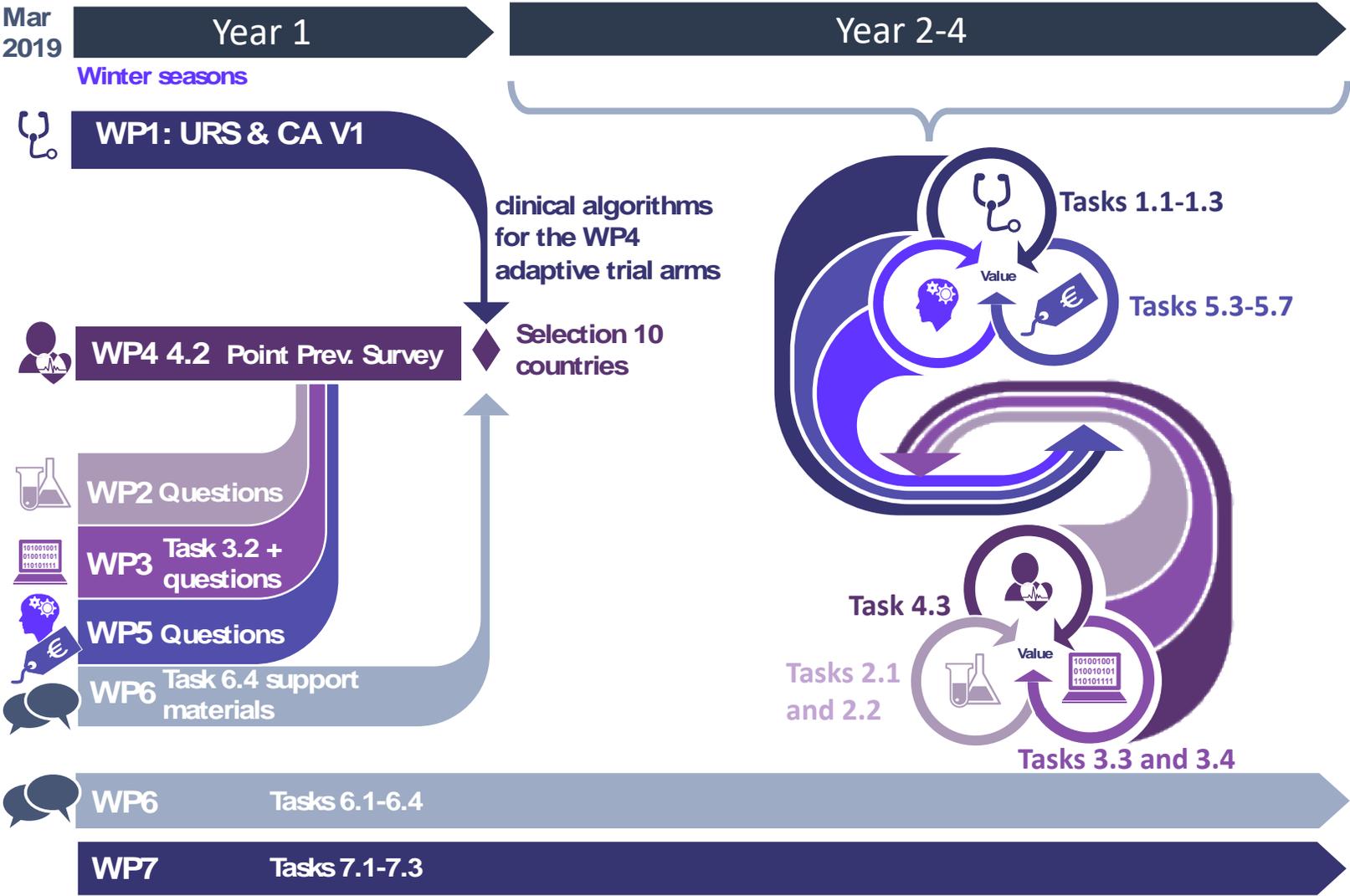
1. To **design a health-economic framework (HEF)** to assess and demonstrate the value of diagnostics both for individual patients and for public health impact by reducing antibiotic use and subsequent antibiotic resistance among patients.

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 care

>200 primary care practises in >20 European countries



- ✓ 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



Hospital care + Labs

>900 hospitals and >800 labs in >40 European countries



- ✓ COMBACTE projects are managing >20 trials, including phase I – III trials for many new compounds against multi-resistant bacteria, and recruited over 20,000 patients.

Marc Bonten (CLIN-Net)
Herman Goossens (LAB-Net)



Paediatric care

90 paediatric clinical sites in 18 countries



- ✓ Network of hospital sites of neonates and children.
- ✓ 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

The era of diagnostic testing will happen, but... be patient!

