15 MARCH 2017 PULLMAN LONDON ST PANCRAS HOTEL

DIGGING DEEPER INTO THE CHALLENGE OF EARLY DIAGNOSIS OF SEPSIS

YOU ARE INVITED TO PARTICIPATE IN AN EXPERT PANEL ASSEMBLED TO PROVIDE IN-DEPTH GUIDANCE TO OUR NEW PROJECT, HELPING US TO ACHIEVE STEP-CHANGES IN THE ACCURACY, RELEVANCE, PRACTICALITY AND COST OF SEPSIS DIAGNOSIS

EXPERT SPEAKERS INCLUDE:

Professor Mervyn Singer
Prof of Intensive Care Medicine, University College London

Dr David Brealey
Clinical lead for critical care trials and the anaesthetic lead for the hyper-acute stroke unit, University College Hospital

Professor Peter A. Lambert
Professor of Microbial Chemistry in Life and Health Sciences, Aston University

Dr Louise Johnston
IVD evaluation methodologist, NIHR

Dr Sara Graziadio
IVD evaluation methodologist, NIHR

Professor Paul Davis
Chief Scientific Officer, Mologic

FOR YOUR ATTENDANCE MOLOGIC HAS DONATED TO:

intensive care society
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IN ASSOCIATION WITH:

University College London Hospitals NHS Foundation Trust

Aston University Birmingham

NHS National Institute for Health Research
Diagnostic Evidence Co-operative Newcastle

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Researched & Developed By:

MOLOGIC
BIG IN TINY SCIENCE

WHAT DO WE THINK WE KNOW ABOUT SEPSIS?

Mologic's understanding of sepsis is that it's caused by the body's dysregulated immune response to pathogens in the bloodstream. It is one of the most common deadly diseases and one of the leading causes of death in the developed world exerting a huge human and economic toll. In the UK there are over 100,000 cases and 37,000 deaths annually.

Global estimates indicate an incidence of 300 cases per 100K population per year with more than 1 million cases in the US and 900K in Europe. (Hall 2011, CDC, Surviving Sepsis.). Despite decades of research and efforts to improve treatment, sepsis still has published mortality rates of 29% to 50% with a cost of €25K per patient. (Vincent CCM 2006). This results in incremental direct costs to the NHS of £2.5B and to the US of $17 billion annually. (UK Sepsis Trust 2013). With the aging of global populations, sepsis incidence has been increasing rapidly, by about 10% in the decade to 2013. Incidence is 50% greater than myocardial infarction, and 33% greater than stroke. Sepsis is a condition whose diagnosis is fraught with challenges. It is not a discrete, binary diagnosis but rather a continuum whose gradations are often unclear. "New International Sepsis Definitions", published in February 2016, placed emphasis on the development of organ dysfunction related to a dysregulated host response to suspected or confirmed infection. Rapid diagnosis is critical to the effective treatment of the patient and offers the prospect of reduced mortality but existing diagnostic tools (i.e., lactate, blood culture, WBC counts, CRP, etc.) lack the sensitivity and/or specificity needed for effective stratification by degree (or extent) of sepsis to enable early, effective treatment. It has been reported that the risk of mortality increases by 7.6% for every hour's delay in administration of antimicrobials (Kumar 2006).

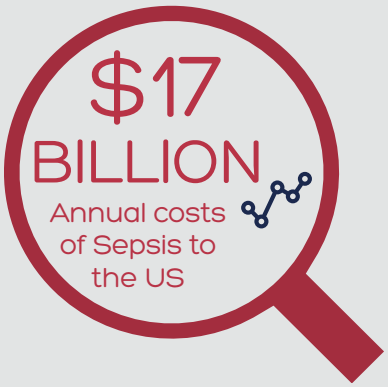
In the light of these observations, Mologic has concluded that an easy-to-use, 10 minute lateral flow based multiplex blood biomarker assay would be useful in hospital A&E units, wards and intensive care units. Such a test should be useable by bedside nurses to provide rapid identification of incipient sepsis. This would enable faster treatment, stratification of patients by degree of risk into appropriate care areas, and financial savings in hospital systems by both reducing complications and overtreatment. The tests would need to be be compatible with a sample of whole blood which could be obtained from a fingerprick or a venous blood sample.

In the UK there are over 100,000 cases and 37,000 deaths annually.

Global estimates indicate an incidence of 300 cases per 100K population per year

more than 1 MILLION cases in the US and 900K in Europe.

Annually, Sepsis costs the NHS £2.5BN



MOLOGIC'S SEPSIS DIAGNOSTIC TECHNOLOGY

The Mologic sepsis alert test is being designed to provide rapid discrimination of infectious versus non-infectious causes of a dysregulated host response. The objective is to provide faster treatment, clear stratification of patients by degree of risk into appropriate care areas, and financial savings in hospital systems by both reducing complications and overtreatment.

Early stratification of patients into sepsis and non-sepsis will enable earlier antibiotic treatment of those with sepsis and reduce antibiotic overuse on those without sepsis. The UK Five Year Antimicrobial Resistance Strategy 2013 to 2018 (DoH, DEFRA) identifies, "optimising prescribing practice through implementation of antimicrobial stewardship programmes that promote rational prescribing and better use of existing and new rapid diagnostics" as one of 7 Key Areas for Action. The rapid sepsis test will support this goal and is expected to be useful in the ICU, A&E and hospital wards. Once treatment has begun, ongoing testing can track response to treatment and indicate when it is safe to stop antibiotic use. Reduction of the inappropriate use of antibiotics will greatly reduce the occurrence of adverse drug reactions, some of which can be severe (e.g. nausea, vomiting, diarrhoea and Clostridium difficile infection). Discussions with clinical experts including Professor Mervyn Singer (Clinical Professor of Intensive Care Medicine at UCL) indicate that a reliable test with a rapid result and simplicity in use would be readily adopted for use at the on first suspicion of sepsis for early stratification. It would also be valuable as an ongoing monitor to provide an indication of when to stop treatment.

"Discussions with clinical experts including Professor Mervyn Singer (Clinical Professor of Intensive Care Medicine at UCL) indicate that a reliable test with a rapid result and simplicity in use would be readily adopted for use at the on first suspicion of sepsis for early stratification"

NEW TECHNOLOGY- "ADUPS"

Some of the biomarkers of incipient sepsis, such as IL-6, are present in low abundance, to the extent that they can only be detected with specialised, expensive assay equipment. Mologic's "ADUPS" technology (Analyte Dependent Unmasking of Particle-binding Sites) is being developed to use special bispecific antibodies and antibody-dependent peptidase activation of capture ligands to extend sensitivity to new levels not previously possible, bringing quantitative detection of Il-6 within reach. With this and other variants of the long established lateral flow immunoassay (LFIA) platform, Mologic is looking to achieve step-change improvements in sensitivity (to pg/ml LLoD) and dynamic range (allowing simultaneous assay of relatively high concentration biomarkers (e.g. ug/ml) and relatively low concentration biomarkers (e.g. pg/ml) on the same test strip). In addition, the new technology is intended to enable competitive, single-site immunoassays to be transformed into the same, positive signal mode as double antibody sandwich immunoassay, which is a much-preferred assay mode for several reasons.

These new test systems are to be brought to bear on the challenge of early sepsis diagnosis at the point of care.

"The new technology is intended to enable competitive, single-site immunoassays to be transformed into the same, positive signal mode as double antibody sandwich immunoassay, which is a much-preferred assay mode for several reasons."

SPEAKERS

Professor Mervyn Singer

Prof of Intensive Care Medicine, University College London

Mervyn Singer is Prof of Intensive Care Medicine at University College London and the first UK NIHR Senior Investigator in Critical Care. He co-chaired the International Sepsis Redefinitions "Sepsis-3" Task Force and is Treasurer of the International Sepsis Forum. He researches sepsis pathophysiology, management and diagnostics. He has been Principal Investigator or Co-Investigator in multiple academic and industry-supported Phase II and Phase III studies in infection, sepsis and septic shock including CORTICUS, ProMISe, LeoPARDS, RADICAL, and OASIS. He is Principal Clinical Investigator of a DSTL-funded study of novel PCR-based sepsis biomarkers and a Lead Co-investigator within the EU-funded European Sepsis Academy Marie Curie Integrated Training Network.

Dr David Brealey

Clinical lead for critical care trials and the anaesthetic lead for the hyper-acute stroke unit, University College Hospital

David Brealey qualified from University College London Medical School in 1994 and initially started a career in medicine before becoming interested in critical care. He joined the Bloomsbury Institute of Intensive Care Medicine as Clinical Lecturer in 1998 and was a key member of the team that altered the understanding of oxygen utilisation in critical illness. David has published widely in the area. During this time he was also involved in a number of other clinical trials, translational and basic science projects. In 2003, David joined the North Central London School of Anaesthesia training programme completing advanced training in both Intensive Care Medicine and Neuroanaesthesia. Following completion of the programme he joined the departments of anaesthesia and critical care at UCH as a consultant in 2010. David is currently clinical lead for critical care trials and the anaesthetic lead for the hyper-acute stroke unit.

Professor Peter A. Lambert

Professor of Microbial Chemistry in Life and Health Sciences, Aston University

Peter Lambert is Professor of Microbial Chemistry in Life and Health Sciences at Aston University, working on rapid tests for diagnosis of infection and new ways to overcome antibiotic resistance and treat bacterial infections. He worked on the discovery of new antibiotics in the UK Pharmaceutical Industry in the 1970s. He moved to Aston University as a Lecturer in Microbiology in 1980 where he has continued his research on antibiotic resistance, epidemiology of infection, healthcare-related infections and mechanisms of bacterial virulence.

SPEAKERS

Dr Louise Johnston

IVD evaluation methodologist, NIHR

Louise joined the NIHR DEC in October 2015. Prior to this she was a Research Associate at the Institute of Genetic Medicine, Newcastle University, where she worked in the field of rare disease research.

She is a fully trained Clinical Scientist specialising in Genetics and has a solid research background in medical microbiology.

Dr Sara Graziadio

IVD evaluation methodologist, NIHR

Sara joined the NIHR Newcastle DEC in August 2015 after being a Research Associate at Institute of Neuroscience, Newcastle University since 2009. She is a scientist with ten years' training in statistics and has a strong academic background in the analysis and interpretation of large and complex datasets. Sara has significant knowledge of study design, and extensive experience of project coordination - facilitating national and international collaborations.

Professor Paul Davis

Chief Scientific Officer, Mologic

Chief Scientific Officer, Mologic. Paul is a scientific innovator and entrepreneur with >100 publications and >60 patents, and decades of experience in applied healthcare diagnostics, antibody engineering and inflammation biomarkers. He is an honorary professor at Warwick, University of Kent, UCL and Cardiff Universities. He has successfully managed numerous grant-funded collaborative R&D projects involving academia and industry. Ten years ago, he co-founded Mologic where he is a director and Chief Scientific Officer. He was a Senior Scientist in Unilever Research, where he led research in Immunology, including diagnostics, vaccines, allergy and antibody-engineering. He is best known for his early work in medical diagnostics, when he was one of the scientists who founded Unipath, maker of the "Clearblue" pregnancy test, and inventor of much of the underlying immunoassay technology for home diagnostic tests. He has founded 8 companies in the UK.

ATTENDEES:

INTENSIVE CARE/CRITICAL CARE

- **Mervyn Singer**, Professor of Intensive Care Medicine, University College London.
- **Tony Gordon**, Professor of Anaesthesia and Critical Care at Imperial College, consultant in Intensive Care Medicine at Charing Cross Hospital.
- **David Brealey**, Consultant in Critical Care & Anaesthesia, clinical lead for critical care trials, UCLH.
- **Manu Shankar-Hari**, Consultant in intensive care medicine, Guys and St Thomas Hospitals.
- **Shane Tibby**, Consultant in Paediatric Intensive Care, Evelina London Children's Hospital, St Thomas' Hospital.

EMERGENCY/ACUTE MEDICINE

- **Tim Coats**, Professor of Emergency Medicine, University of Leicester.
- **Ashley Price**, Consultant in infectious disease and in acute medicine, Royal Victoria Infirmary, Newcastle upon Tyne.
- **Matthew Inada-Kim**, Consultant in Acute Medicine at HHFT and Lead for Deterioration at Wessex Patient Safety Collaborative, Chair of the Wessex sepsis network, co-lead of the National sepsis AHSN cluster, NHS England, Health Education England and the Clinical Human Factors Group.

NEONATAL/PAEDIATRICS

- **Alan Fenton**, neonatology - lead clinician for the Newcastle Neonatal Service at the RVI in Newcastle.
- **Marieke Emonts**, board member of the European Society of Paediatric Infectious Diseases, Consultant Paediatrician at Great North Children's Hospital, RVI.

ASTON UNIVERSITY

- **Peter Lambert**, Professor of Microbial Chemistry, Life and Health Sciences, Aston University, Birmingham. Interests: infectious diseases, their diagnosis and treatment.
- **Ann Vernallis**, Senior Lecturer in Cell Biology, Life and Health Sciences, Aston University, Birmingham. Interests: cytokines and other mediators of inflammation.

INNOVA PARTNERSHIPS

- **Paul Meakin**, Director of Business Development. Innova Partnerships Ltd. A background of agri-tech and life sciences, with a focus on point of care diagnostics from the perspective of end-users and markets.

MOLOGIC LTD

- **Paul Davis**, Chief Scientific Officer, is a scientific innovator and entrepreneur with >100 publications and >60 patents, and decades of experience in applied healthcare diagnostics, antibody engineering and inflammation biomarkers. He is best known leading the development of the "Clearblue" pregnancy tests, and as a named inventor on the principle patents behind lateral flow technology.
- **Gita Parekh**, R&D Manager, has over 12 years' experience managing successful IVD R&D projects in Australia, US, Thailand, India and the UK.
- **Chris Dunston**, Project leader, has over 10 years of research experience in the field of infection and immunology and is particularly interested in understanding the host response to infection.
- **Chris Jones**, Chairman, has spent over 25 years in sales, marketing, commercialization and management of diagnostic and medical device companies.
- **Barbara Fallowfield**, Commercial Manager, Barbara has been involved in the IVD industry for over 20 years, working in both national and international sales and marketing roles. More recently she was Managing Director at BIVDA, the national trade association for the IVD industry.

NIHR DIAGNOSTIC EVIDENCE CO-OPERATIVE NEWCASTLE

- **John Simpson**, Director, NIHR Diagnostic Evidence Co-operative Newcastle. John is Dean of Translational Research and Professor of Respiratory Medicine, Newcastle University.
- **Michael Power**, Deputy Director, NIHR Diagnostic Evidence Co-operative Newcastle. He has 10 years' experience in developing evidence-based guidance for the NICE's Clinical Knowledge Summaries (CKS).
- **Louise Johnston**, IVD evaluation methodologist, NIHR Diagnostic Evidence Co-operative Newcastle. She is a fully trained Clinical Scientist specialising in Genetics and has a solid academic background in immunology.
- **Sara Graziadio**, IVD evaluation methodologist, NIHR Diagnostic Evidence Co-operative Newcastle. She is a scientist with ten years' training in statistics and has a strong academic background in the analysis and interpretation of large and complex datasets.

INSTITUTE OF HEALTH AND SOCIETY, NEWCASTLE UNIVERSITY

- **Stephen Rice**, Senior Research Associate within the Health Economics Group and Evidence Synthesis, Institute of Health and Society, Newcastle University. He has conducted several systematic reviews, network meta-analyses and economic analyses in areas such as NSAIDS after major surgery, breastfeeding, osteoporosis, acupuncture, ankylosing spondylitis and deep vein thrombosis.

AGENDA

Workshop to discuss challenges in managing patients with suspected sepsis and how diagnostic/screening/monitoring IVD testing could help

Chair: Professor Mervyn Singer, Prof of Intensive Care Medicine, University College London

10.30-10.40 Welcome and introductions

Chair: Dr Louise Johnston, IVD evaluation methodologist, NIHR

10.40-10.50 Introduction from the Diagnostic Evidence Cooperative (DEC) Newcastle

Chair: Dr David Brealey, Clinical lead for critical care trials and the anaesthetic lead for the hyper-acute stroke unit, University College Hospital

10.50-11.30 Sepsis: Unmet need for diagnostics in infection and sepsis

- What are the current challenges for diagnosing sepsis?
- How do they vary by clinical scenario (including post-surgical, A&E, GP surgery, paediatrics and neonatology)?
- What are the most important clinical needs?

For each of the clinically and economically important clinical scenarios:

- 1. What would an ideal diagnostic test for sepsis look like?
  - a. How would it fit with methods for assessing severity of illness and risk of sepsis such as NEWS, qSOFA, SIRS….?
  - b. How would it fit with other diagnostics (for inflammation ± sepsis)
- 2. How would rapid diagnostic tests for sepsis change patient management or improve patient outcomes?
  - a. Rule out tests?
  - b. Rule in tests:
    - i. Without pathogen identification?
    - ii. With pathogen identification?
    - iii. With pathogen and antibiotic susceptibility/resistance?

Chair: Professor Mervyn Singer, Prof of Intensive Care Medicine, University College London

11.30-12.00 Challenges in evaluating new diagnostics

- How do recent changes in the definition of sepsis (e.g. Sepsis-3) affect the interpretation of previous and future evaluations of diagnostic tests for sepsis?
- How should the evaluation of new tests take account of the uncertainties introduced by using a reference test that cannot be perfect, e.g. because the diagnosis if infection is not 100% accurate?
- How would a new diagnostic sit with national guidelines e.g. NICE?
- What factors might inhibit or facilitate adoption of a rapid sepsis test?
  - Test accuracy
  - Test usability
  - Test cost
  - Anything else?
- How would you like to see these characteristics evaluated and documented? E.g. Peer reviewed publications of scientific studies, marketing information.
- What benefits or harms should be investigated when evaluating a rapid test for sepsis?

Chair: Dr Sara Graziadio
IVD evaluation methodologist, NIHR

12.00-12.25 **Needs and challenges for sepsis clinical decision aid**

- What additional data should be evaluated for incorporation in the CDA?
  - "Red flag" criteria? (e.g. systolic blood pressure <90 mm Hg, heart rate >130 bpm, respiratory rate >25/min, A or V on the AVUP scale of consciousness, …)
  - Severity scores or their items (e.g. NEWS, qSOFA, SOFA, SIRS, …)
  - Other data?
- Is this data generally available in the electronic medical record or laboratory information system, or are there significant variations in availability?
- Is there any data that would be worth entering manually?
- How should the CDA present the risk of sepsis (or infection):
  - Raw data (concentrations for each biomarker individually)?
  - Percentages (i.e. risk/probability)?
  - Traffic light (i.e. green, amber, and red — for low, medium, and high risk)?
  - Black/white output (i.e. 2 levels: sepsis/no sepsis diagnosis)?
  - Other?
- How should the CDA present its management information and advice:
  - On paper and/or electronically?
  - Narrative (as in a guideline) and/or graphically (as in an algorithm)
- What are challenges in implementing the CDA are anticipated with respect to:
  - Identifying the users
  - Usability?
  - Acceptability?
  - Practicality?

12.25-1.00 **Lunch**

Chair: Professor Paul Davis, Chief Scientific Officer, Mologic

1.00-2.00 **The prototype MOLOGIC sepsis test**

- Introduction to Mologic and Sepsis diagnostic
- What other tests are already available or in existence?
- What experience do people have with other diagnostic tests?
- Brief overview of strategy: NAT, Cytokines/Chemokines, other biomarkers
- What physiological/cellular events do we want to detect?
- Evidence to date (Peter Lambert)

Chair: Professor Mervyn Singer, Prof of Intensive Care Medicine, University College London

2.00-3.15 **Discussion on trial designs**

- What is the best route to evaluating/validating the technology?
  - study aims
  - trial design

Chair: Professor Mervyn Singer, Prof of Intensive Care Medicine, University College London

3.15-3.30 **Discussion and future direction**

- Route to acceptance (future multicentre studies

3.30 **Coffee break and depart**

DELIVERABLES FROM THE WORKSHOP

- The discussions will be recorded and the conclusions summarized.
- A questionnaire for wider distribution to clinicians to evaluate the current pathway and the clinical need to facilitate management of patients will be finalized during the workshop. It will be used to survey clinicians in different fields and settings. The outputs of the survey will be one of the deliverables for Mologic project.

INTRODUCING MOLOGIC

Mologic is a diagnostics SME, located near Bedford, UK with a focus on infectious and inflammatory diseases.

One of the company's main objectives is to develop new, simple technologies for use by patients in their own home, which is especially relevant to people who suffer from chronic inflammatory diseases, such as COPD.

Simple diagnostic technologies are also relevant for use at the point of care, in consulting rooms on the wards. In order to meet these objectives, Mologic's R&D programmes are directed to both biomarker discovery and assay platform development. In the pursuit of simple-to-use, frequent diagnostic tests, the Mologic team is pioneering the use of biomarkers that end up in the urine, effectively harnessing the principles of urinary proteomics in multiplex assays of a few selected indicative biomarkers.

Mologic has a complete 'end to end' capability in immunodiagnostics, antibody technology, peptide synthesis, vaccines, enzymology and bioscience innovation, from innovation through reagent development to low volume manufacture. Contract partnering projects are a major and growing business activity. The company's diagnostics R&D has now expanded beyond human healthcare to non-human applications, such as veterinary, environmental and food chain.

Although Mologic was owned by the multinational diagnostics company Alere Inc. from 2009 to 2014, the company became independent again at the start of 2015. With independence and financial backing, Mologic's R&D capability has become fully liberated to develop novel technologies and create new solutions to difficult problems.

Mologic now has a portfolio of products at various stages of development, including:

1. Bacterial vaginosis diagnostic (professional use)
2. Bacterial vaginosis and thrush diagnostic (in-home use)
3. Urinary tract infection diagnostic (professional use)
4. Ultra-low cost glucose sensor (in-home use)
5. Peritoneal dialysis infection diagnostic (in-home use)
6. Periodontitis/perioimplantitis diagnostic (professional dentist use)
7. SEPSIS Diagnostic (professional use)
8. Low cost dengue fever diagnostic (professional use)
9. Pan fever diagnostic (2nd generation product)
10. Cystic Fibrosis exacerbation monitor (in-home use)
11. COPD exacerbation monitor (in-home use)

Recently Mologic received a substantial grant from the Bill & Melinda Gates Foundation to establish the CENTRE FOR ADVANCED RAPID DIAGNOSTICS within Mologic, to create a step-change in high sensitivity, low cost, POC diagnostic technology.

MOLOGIC PRODUCTS

MOLOGIC

A RAPID, POINT-OF-CARE TEST FOR THE DIAGNOSIS OF BACTERIAL VAGINOSIS

MOLOGIC.CO.UK

PROFESSIONAL USE

MOLOGIC

SIMPLE, RAPID DIAGNOSTIC FOR URINARY TRACT INFECTIONS

PRODUCT OVERVIEW DOCUMENT

MOLOGIC.CO.UK

PRE-CLINICAL EVALUATION

MOLOGIC

PERITONEAL DIALYSIS INFECTION DIAGNOSTIC

HOME USE PRODUCT

MOLOGIC.CO.UK

MOLOGIC

COPD EXACERBATION ALERT AND STRATIFICATION

PRODUCT FAMILY OVERVIEW DOCUMENT

MOLOGIC.CO.UK

PROFESSIONAL USE

MOLOGIC

CF EXACERBATION ALERT FOR PATIENT STRATIFICATION

PRODUCT FAMILY OVERVIEW DOCUMENT

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INNOVATION IN SMBG 'ENZYME FREE'

ULTRA LOW COST ELECTRODE SYSTEM

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PROFESSIONAL USE

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DENTiPLEX
DENTAL DIAGNOSTIC

CHAIR-SIDE DIAGNOSTIC TO MEASURE GUM DISEASE STATUS
MEASUREMENT OF PROTEASE ACTIVITY ON LATERAL FLOW ASSAY

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Bespoke LFD manufacture service, where every product is treated individually

- No job too small
- Access to our global network of commercial partners for scale up and distribution options
- Understanding the value of grant support, we are willing to consider co-applications to any form of assistance, as an SME partner
- ISO:13485 & ISO:9001 Certification
- Capability includes final product assembly

It all starts with dialogue, so please get in contact with us

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