
# Technological Transformation of Microbiology Services: Clinical and Financial Impact

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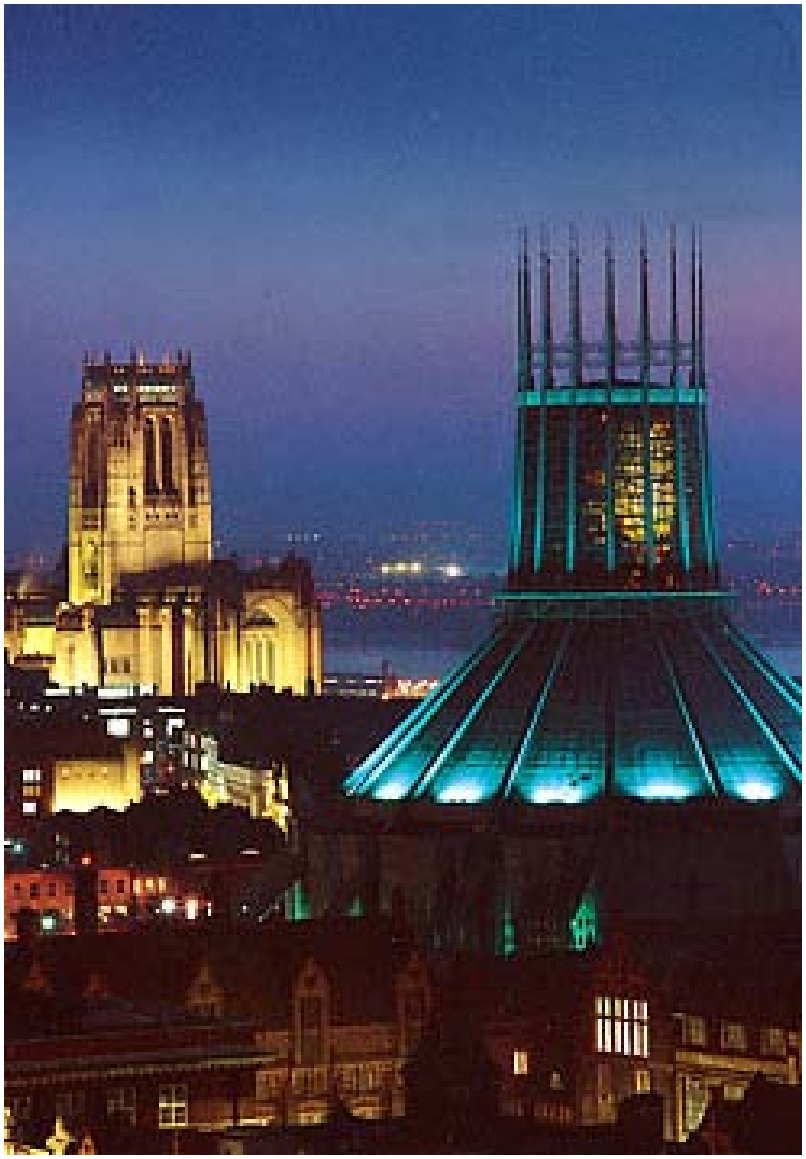



MAGICAL MYSTERY TOUR
PRIVATE

# The Perfect Storm

- Care of the Elderly – physically well, socially engaged and psychologically content.
- Chronic Disease Management including Mental Health and Carer Support.
- Specialist Surgical and Therapeutic Interventions.
- New Science: Pharmaco-Therapeutics and Genetics, Molecular Imaging and Diagnostics.
- Building technologies and flexible designs underpinned with real-time information e.g. Electronic Transfer of Prescriptions, Digital X-ray, Just-in-Time Training Programmes.

# UK Science PLC

- Genetic Profiling and Therapeutic Targeting.
- Proton Beam Therapy and Novel Treatments.
- High-speed informatics and cooling technology.
- Stem-cell based research and new science.
- Prosthetics, regeneration and bio-engineering developments.

# Fiscal constraints

| | | | |
|---|---|---|---|
| 1. | The Depression – 30/34 | : | c. 50 months |
| 2. | 1st Oil Shock – 73/76 | : | c. 40 months |
| 3. | 2nd Oil Shock – 79/83 | : | c. 48 months |
| 4. | DotCom Bust – 90/93 | : | c. 36 months |
| 4. | Banking Bust – 08/? | : | Projected c. 120+ months |

Tight fiscal regime

Real income ⬇

Size of state ⬇

£2 billion black hole in NHS 2015-16

# Pathology in UK

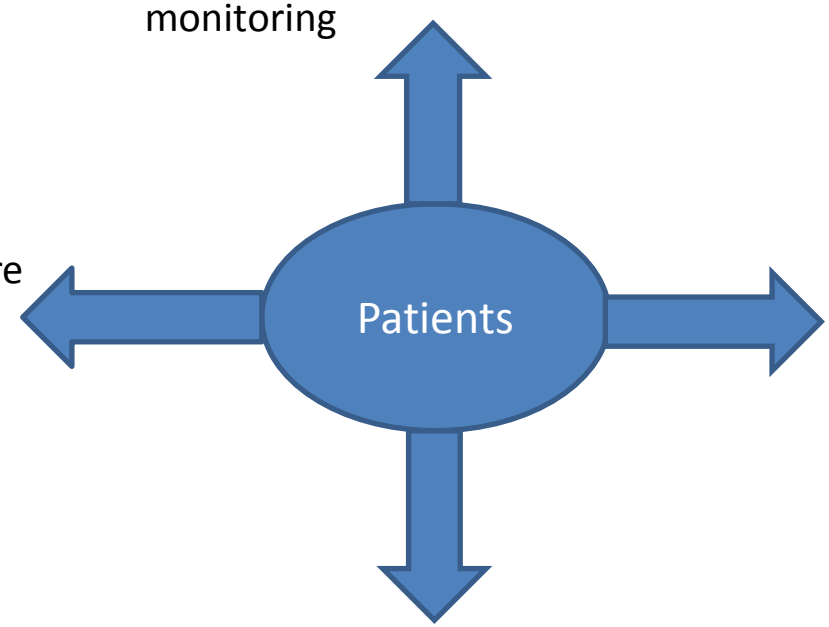
- 500 million biochemistry tests pa
- 130 million haematology tests pa
- 50 million microbiology requests pa
- 13 million histopathology slides pa

- Costs £2.5 billion (NHS England budget 2013/14 £95M)

- Demand growing

# Clinical pathology at a crossroads

- 70-80% of all healthcare decisions
- Diagnosis, treatment, prognosis, monitoring




- New NHS architecture
- Commissioning
- Private sector

- New technologies e.g. whole genome sequencing
- POC

- Carter reforms
- Austerity
- On-going CIP

# Technological Transformation

- Automation
- MALDI-ToF
- Molecular diagnostics

# AUTOMATION

# Automation in Microbiology

- The drive to productivity and efficiency in largely unchanged parts of laboratory
  - Specimen processing
  - Culture
  - Incubation
  - Reading

# Exclusions

- Continuous blood culture monitoring systems


# Exclusions

- Microbial ID/Sensitivity



# Exclusions

- Urine analysers

# Barriers to Automation

- Microbiology is too complex to automate
- No machine can replace a human in the microbiology laboratory
- Cost of automation
- Microbiology laboratories are too small for automation

# Microbiology is too complex to automate

- Many different specimen types
- Urine, blood, tissues, sputum, catheter tips, prosthetic material
- Many different containers and collection systems
- Processing differs
- Media standardisation re lids, height etc.

# No machine can replace a human in the microbiology laboratory

- Flexibility of human
- Interpretative science
- Speed

# Cost of automation

- Not cost effective
- Specimen and test volumes too small

# Microbiology laboratories are too small for automation

- Historically small laboratories attached to hospitals
- Any automation would be underutilised

# Drivers for automation

- Testing volumes increasing year on year
  - Ageing population
  - Infection Control
  - Mutiresistant organsims
  - Public Health
- Consolidation of laboratories
  - 24 hour 7 day per week
- Shortage of trained BMS
- Quality
  - Shorter TrT
  - Traceability and accreditation
- Liquid-based microbiology

# Liquid-based microbiology

# Requirements for automation

- Flexibility
- Space and architecture
- Human working
- Specimen diversity
- Growth

- Intergate with 3rd part supplier platforms

# Specimen processors

- Innova processor (BD Diagnostics, Sparks, MD)
- Previ Isola automated plate streaker (bioMérieux, Inc., Hazelwood, MO)
- Walk-away specimen processor (WASP; Copan Diagnostics, Murrieta, CA)
- InoqulA full automation/manual interaction (FA/MI) specimen-processing device (BD Kiestra B.V., Drachten, Netherlands)


BD
Innova


WASP
WASP


BD Kiestra
BD InoqulA

# BD Kiestra InoqulA full automation/manual interaction (FA/MI)

- Review of streaking utility
- Magnetic bead
- Programmable
- More isolated colonies than manual plating
- Reproducible
- 400 plates/hr (in FA mode)

# Microbiology Total Laboratory Automation

- Common themes
  - Track/conveyor systems
  - High definition imaging
  - Automated incubators
  - Software to integrate processes

- Kiestra TLA (BD Kiestra B.V., Drachten, Netherlands)

# BD Kiestra TLA

- First installation in clinical microbiology laboratory in 2006
- 45 full systems in place
- Modular linked with track system
- SorterA, BarcodA, and InoqulA TLA, ReadA incubators with digital imaging equipment, and the ErgonomicA workbenches
- Automated MALDI picker
- Automated sensitivity testing


SLOYAN
BUILDERS
0151 207 2064
SITE SAFETY
No unauthorised entry
Safety helmets must be worn at all times
Footwear must be worn at all times
Hi-visibility vests are to be worn on site
Danger


FIRE EXIT
PUSH


Henry


FIRE EXIT


1.1
1.2
1.3
1.4
InoculA

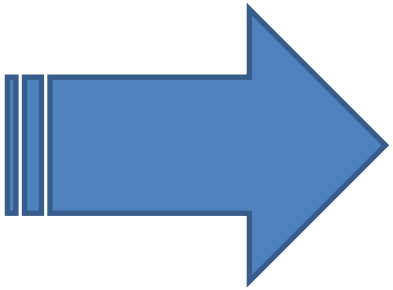

1.3
1.4
1.5
1.6
2.6


1.3
1.4
1.5
1.6

# Increased efficiency??

- Limited peer-review data on both clinical and financial efficiency
- Laboratory Productivity Index (LPI) (number of samples/staff member/day)

- Cambridge UK
- Frimley Park UK
- Dublin Eire



All increased LPI at least 2 fold

# Liverpool

- LPI 28 to 33
- Why?
  - Merger of laboratories
  - Implementation not focused
  - Staff released before fully functional
  - Not 24 hour working
  - Technical difficulties and equipment failure

# MALDI

# Matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry

- Probably biggest single transformation in European microbiology laboratories
- Rapidly established since 2008
- Potentail for automatiion


VITEK MS™

# Methodology – Before MALDI

**Cultured**

URINE BENCH

B/C & MRSA BENCH

PUS BENCH

FAECES BENCH

RESPS BENCH

GENITAL BENCH

**Bench ID after 24hrs (genus ID only)**

- Colony Morphology
- GRAM Film
- Staphaurex
- Strep Grouping Kit
- Oxidase Reagent
- Phadebact Kit
- Anti-Sera
- Etc, etc, etc

**Species ID & Sensitivity – 48-+72hrs**

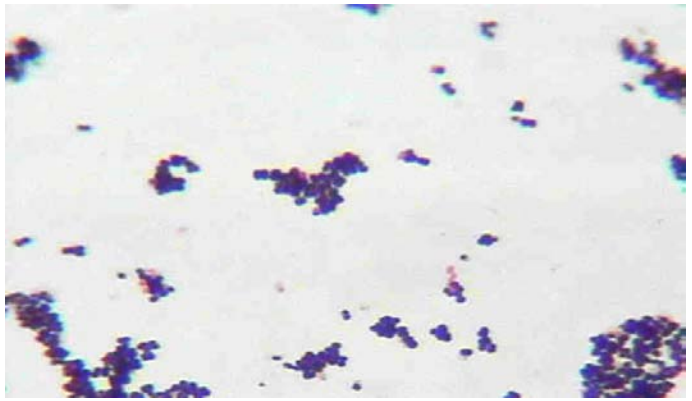

Combination Panels Only

Referral to Reference Lab if required

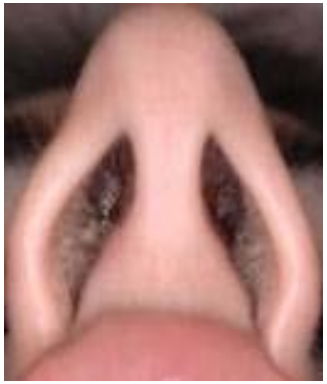
# Coagulase negative Staphylococci (CNS)

Examples – *S.epidermidis, S.capitis, S.saprohyticus, S.haemolyticus*

Vary from white – cream colonies

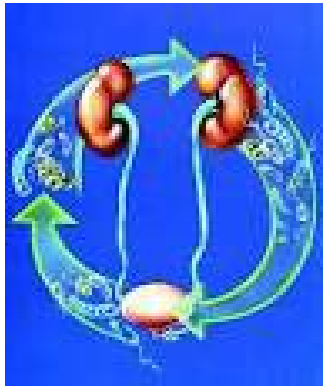


Gram Positive Cocci characteristically in clumps/tetrads



Skin colonisation all CNS– No Infection

To

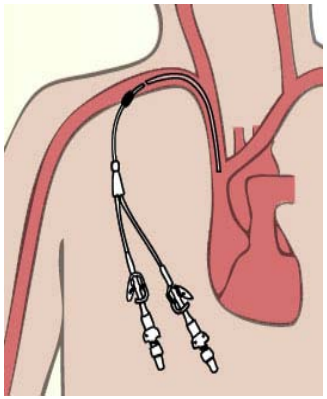


Urinary Tract Infection – *S.saprophyticus*

To

Positive Blood Culture – all CNS

To



CVP Infection – all CNS

# Methodology – after MALDI

Cultured

MALDI ID after 24hrs (Species ID )

Sensitivity– 48-+72hrs

URINE BENCH

B/C & MRSA BENCH

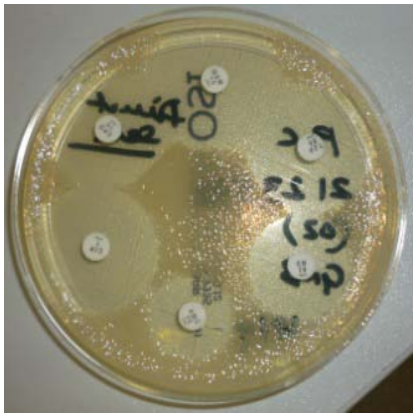
PUS BENCH

FAECES BENCH

RESPS BENCH

GENITAL BENCH



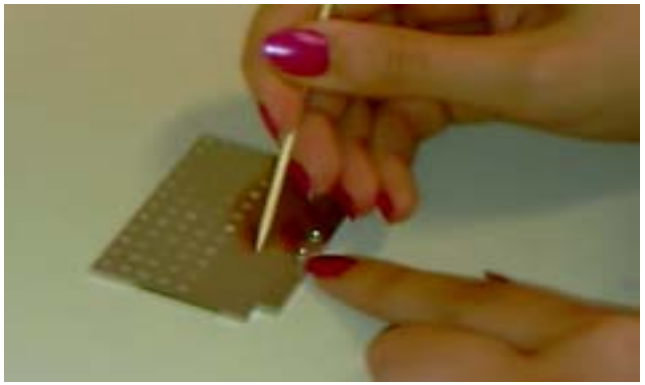


# What is MALDI-TOF?

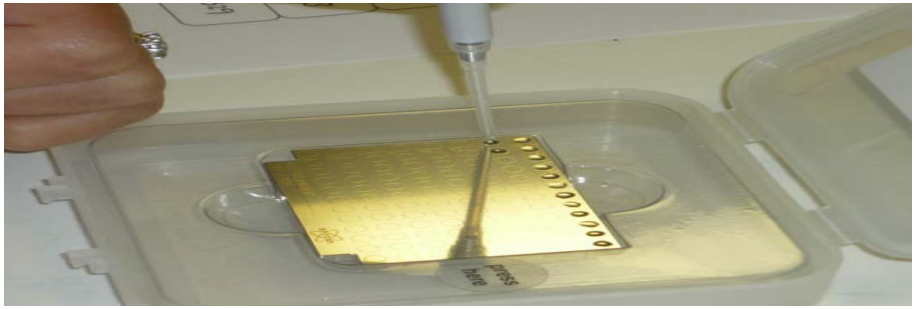
## Matrix Assisted Laser Desorption/ Ionisation - Time Of Flight

**Direct Smear Technique**

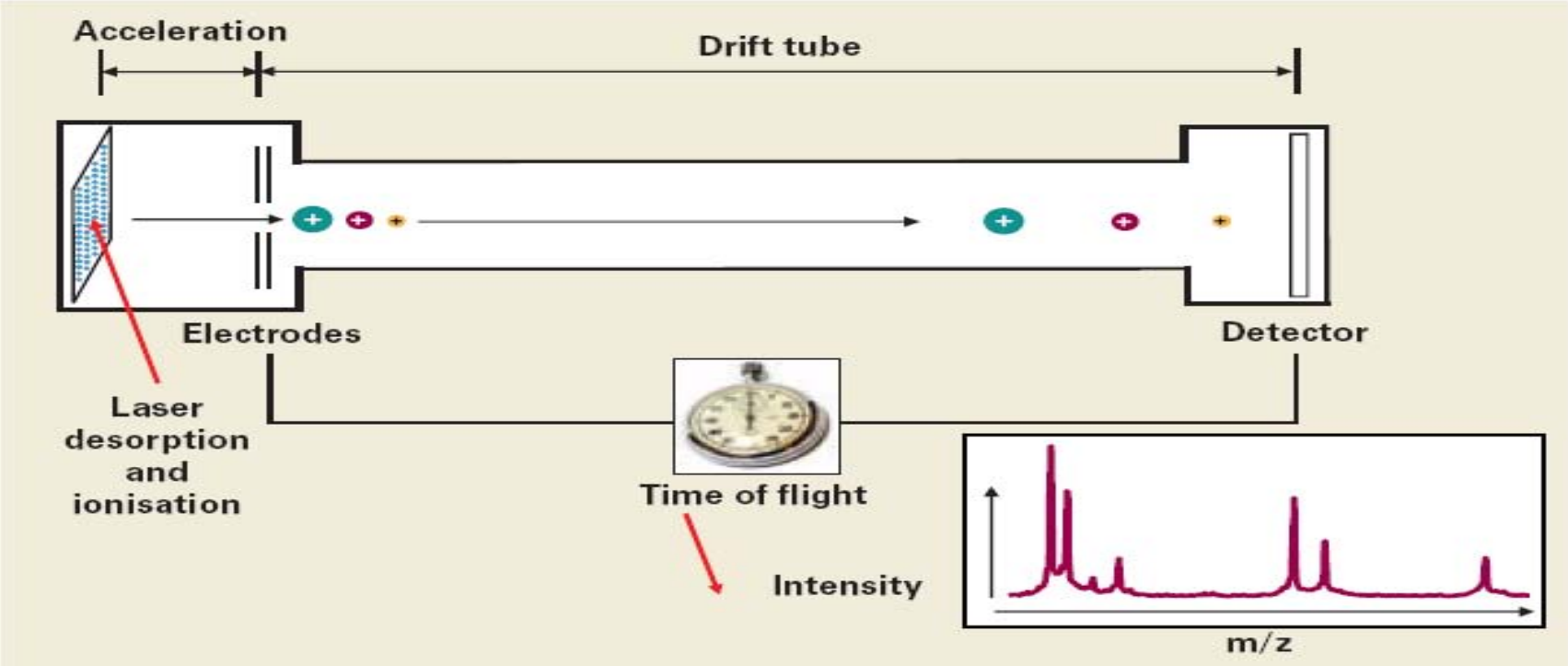
- The organism to be being identified is selected & smeared onto the steel target plate



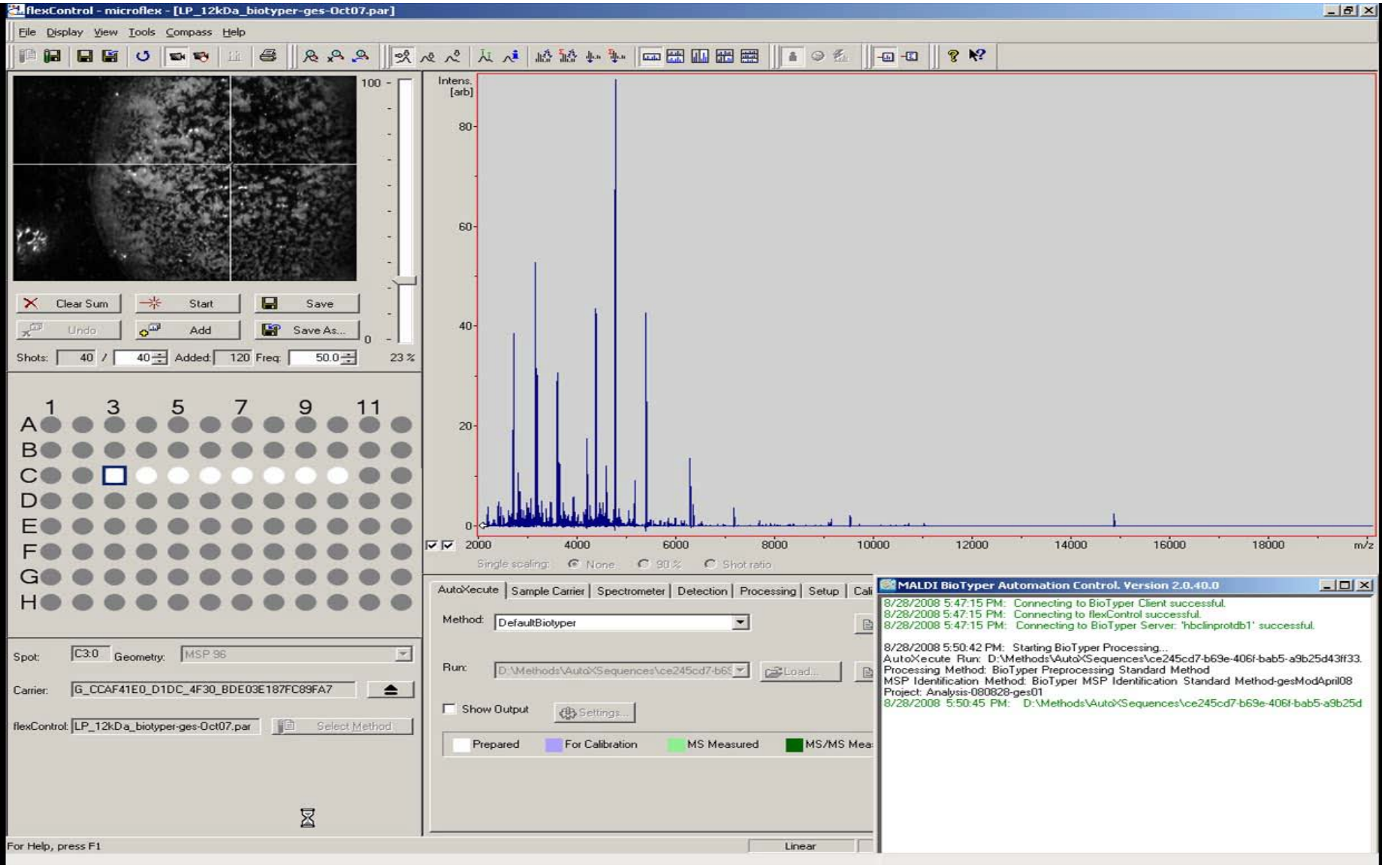
- Target spot fixed with 1µl of Matrix



# What is the Principle of MALDI-TOF ?




- The laser fires on the target spot which generates a cloud of ions
- The ions present are then accelerated up the tube
- The greater the molecular weight of the ions the longer the time of flight
- The time it takes for the ions to reach the detector is measured and converted to Daltons(Da)/molecular weight.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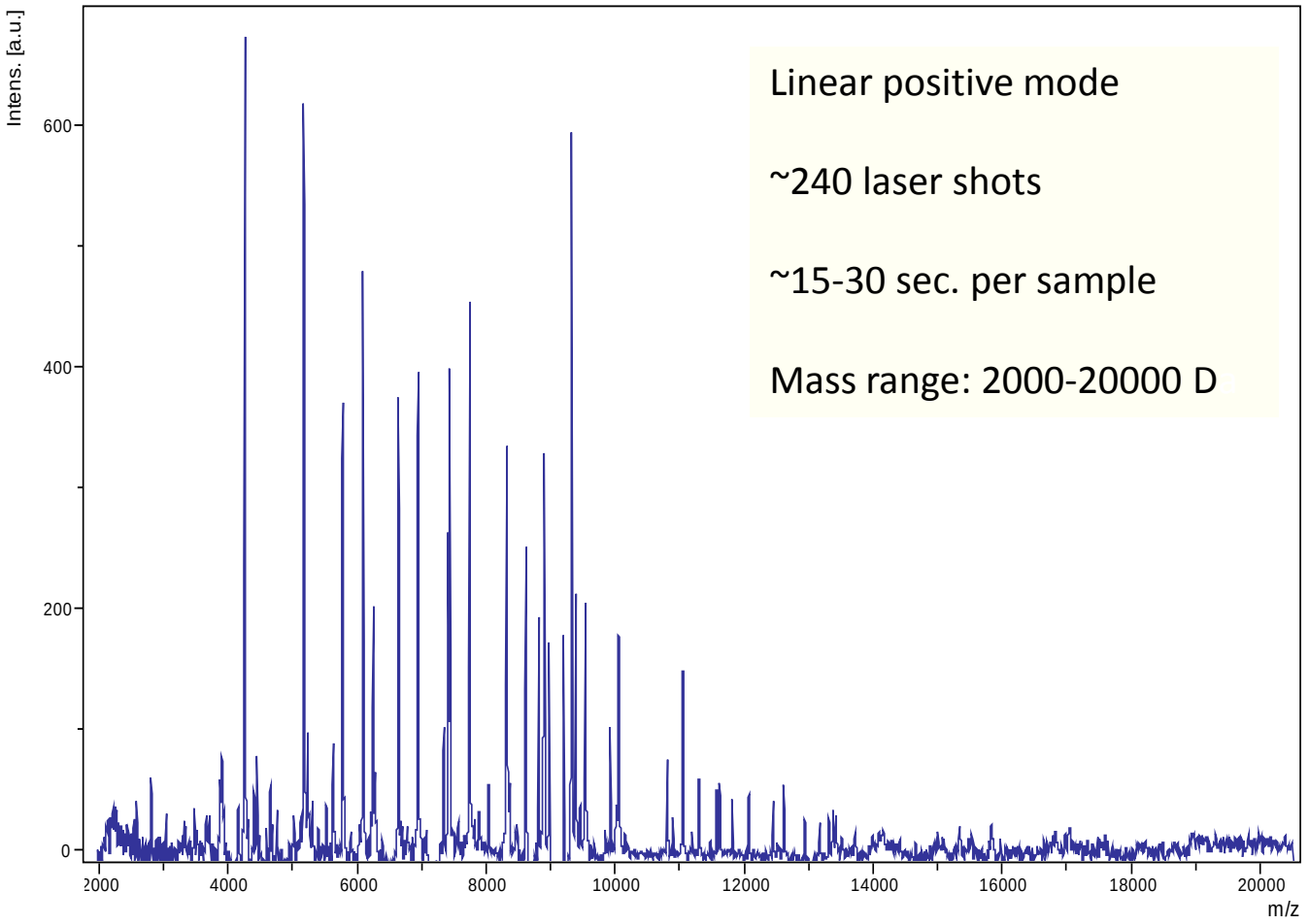
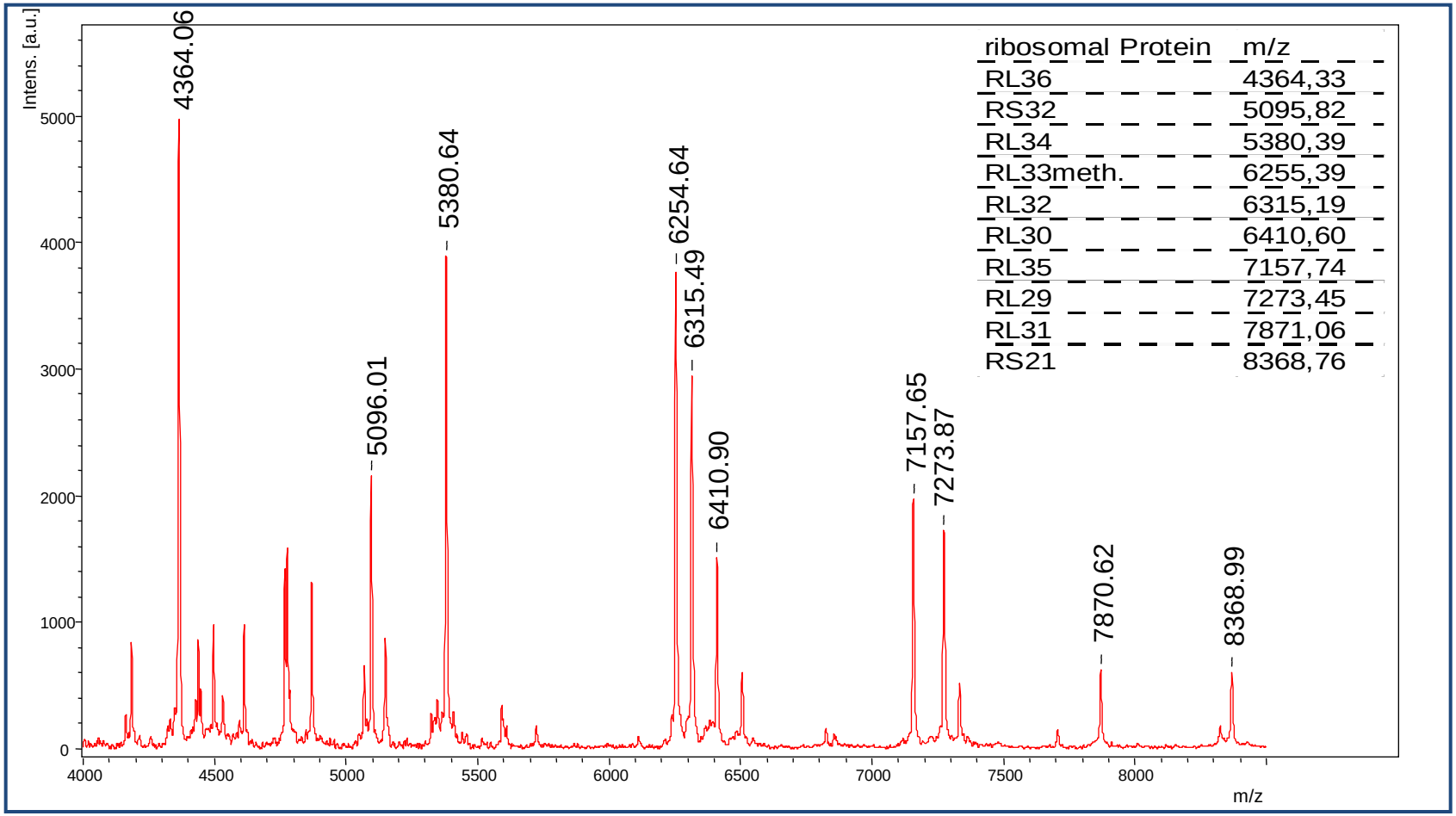
File Display View Tools Compass Help
Clear Sum
Start
Save
Undo
Add
Save As...
Shots: 40 / 40 Added: 120 Freq: 50.0
23 %
Intens. [arb]
m/z
Single scaling: None 90 % Shot ratio
AutoXecute Sample Carrier Spectrometer Detection Processing Setup Cali
Method: DefaultBiotyper
Run:
Load...
Show Output
Settings...
Prepared
For Calibration
MS Measured
MS/MS Mea
Spot: C3:0 Geometry: MSP 96
Carrier: G_CCAF41E0_D1DC_4F30_BDE03E187FC89FA7
flexControl: LP_12kDa_biotyper-ges-Oct07.par
Select Method
MALDI BioTyper Automation Control. Version 2.0.40.0
8/28/2008 5:47:15 PM: Connecting to BioTyper Client successful.
8/28/2008 5:47:15 PM: Connecting to flexControl successful.
8/28/2008 5:47:15 PM: Connecting to BioTyper Server: 'hbclinprotdb1' successful.
8/28/2008 5:50:42 PM: Starting BioTyper Processing...
AutoXecute Run: D:\Methods\AutoXSequences\ce245cd7-b69e-406f-bab5-a9b25d43ff33.
Processing Method: BioTyper Preprocessing Standard Method
MSP Identification Method: BioTyper MSP Identification Standard Method-gesModApril08
Project: Analysis-080828-ges01
8/28/2008 5:50:45 PM: D:\Methods\AutoXSequences\ce245cd7-b69e-406f-bab5-a9b25d
For Help, press F1
Linear

# Typical MALDI-TOF Mass Spectrum



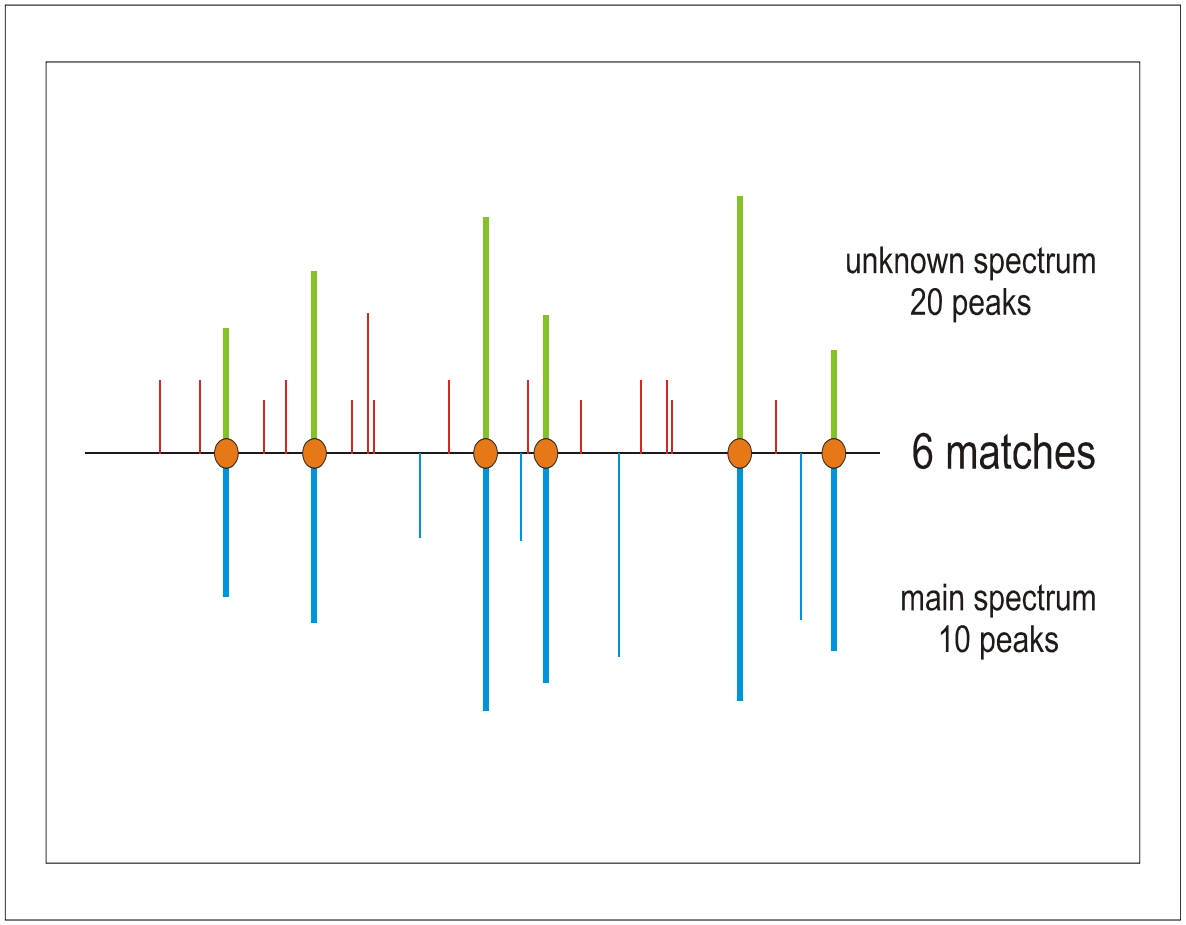

*Haemophilus influenzae*

# The MALDI Biotyper is Robust relying on High Abundance Proteins




E.coli

# Scoring System




Three Calculations

1-Unknowns in reference (6/10)

2- Reference peaks in unknown (6/20)

3 -Score of relative intensities of matching peaks (out of 10)

6 x 3 x Intensity Score

Total score out of 1000

$Log_{10}$ score out of 3

# Scoring

### Meaning of Score Values

| Range | Description | Symbols | Color |
|---|---|---|---|
| 2.300 ... 3.000 | highly probable species identification | (+++) | green |
| 2.000 ... 2.299 | secure genus identification, probable species identification | (++) | green |
| 1.700 ... 1.999 | probable genus identification | (+) | yellow |
| 0.000 ... 1.699 | not reliable identification | (-) | red |

### Result Overview

| Analyte Name | Organism (best match) | Score Value | Organism (second best match) | Score Value |
|---|---|---|---|---|
| Enterococcus faecalis XY_123 BRB (+++) (A) | Enterococcus faecalis | 2.348 | Enterococcus faecalis | 2.198 |
| Enterococcus faecalis XY_123 BRB (+++) (A) | Enterococcus faecalis | 2.331 | Enterococcus faecalis | 2.229 |
| Proteus mirabilis XY_789 BRB (+++) (A) | Proteus mirabilis | 2.579 | Proteus mirabilis | 2.378 |
| Proteus mirabilis XY_789 BRB (+++) (A) | Proteus mirabilis | 2.634 | Proteus mirabilis | 2.394 |
| Pseudomonas aeruginosa MZyme BRB (+++) (A) | Pseudomonas aeruginosa | 2.407 | Pseudomonas aeruginosa | 2.31 |
| Pseudomonas aeruginosa MZyme BRB (+++) (A) | Pseudomonas aeruginosa | 2.456 | Pseudomonas aeruginosa | 2.227 |
| Staphylococcus aureus DSM_19050 BRB (++) (A) | Staphylococcus aureus | 2.136 | Staphylococcus aureus | 2.09 |
| Staphylococcus aureus DSM_19050 BRB (++) (A) | Staphylococcus aureus | 2.288 | Staphylococcus aureus | 2.173 |

# Clinical Examples

Case 1 –
B/C Positive 15/10/11 (Sat) after 24hrs, Gram film – Yeasts

Patient – AP resection in July & developed fistula. Patient ventilated with lines. Patient on Caspofungin.

Day 2 – Yeast grown & Germ Tube Positive

MALDI ID direct from plate on 17/11/11 – *Candida albicans*
Patient antibiotics changed to Fluconazole.

Case 2 -
B/C Collected on 14/11/11 @ 14:10 & came up positive on 15/11/11 before 9am - <24hrs.
Initial Gram film – GPC, clumps ? *Staphylococci*

Sepsityper – *Staphylococcus aureus* before 10am on 15/11/11

Patient Info – Pt on IV Augmentin when result was telephoned. MRSA Neg on 04/11/11.

Consultant Action – De-escalated antibiotic therapy to Flucloxacillin on 15/11/11. Day 2 – *S.aureus* (Cefoxitin =S) growing on plate and identified by Phoenix. Flucloxacillin continued.

# Clinical Examples

Case 3 –
CSF Received on 10/10/11.

Patient admitted with 2/52 history headache, vomiting, increased pressure, ? Meningitis. Patient ventilated and admitted to HDU.

CSF Count – 398 WBC, 80% Polymorphs. NOS in Gram film.

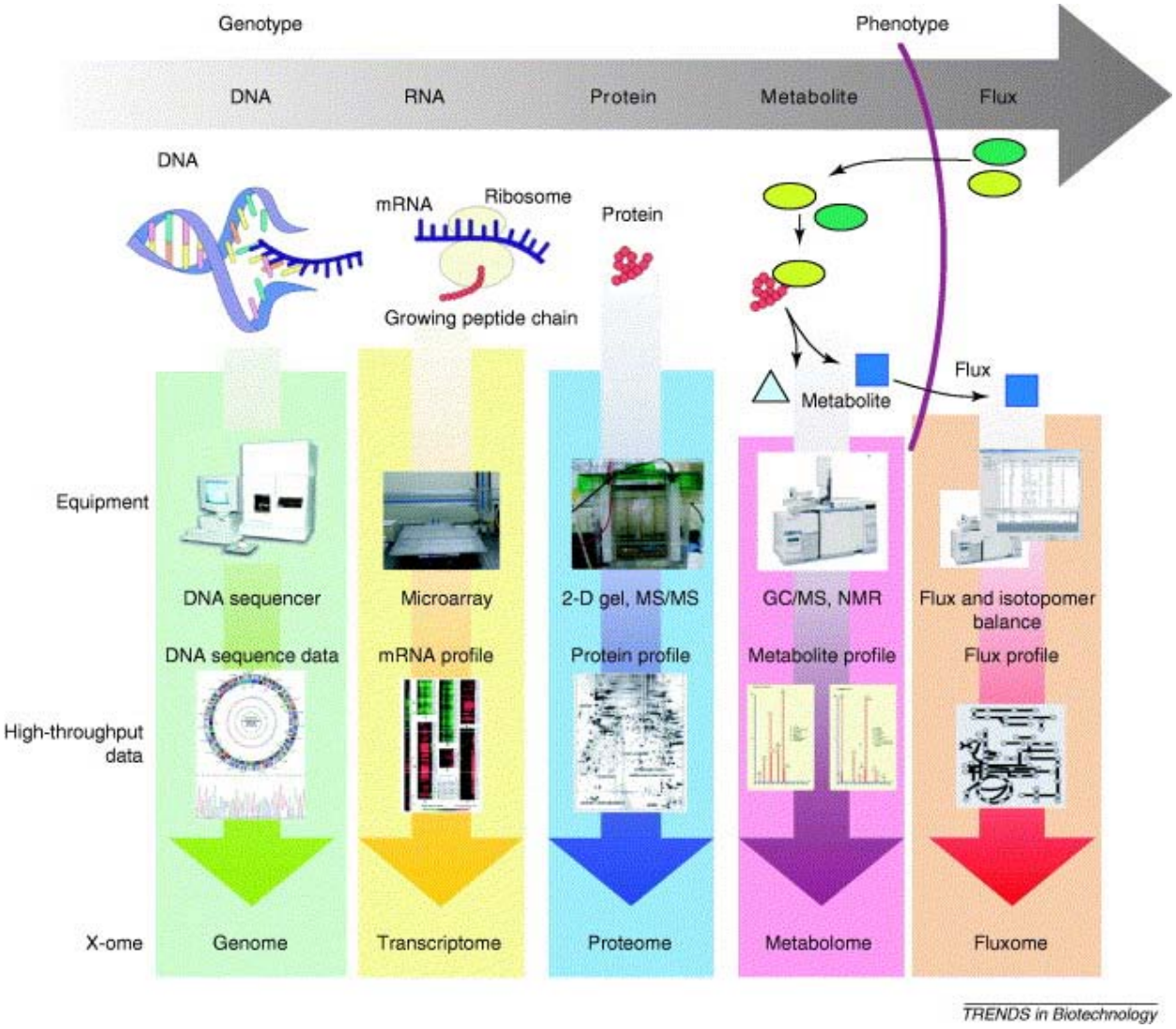
11/10/11-
Cultures - Yeast. Original Gram film reviewed, Still NOS.

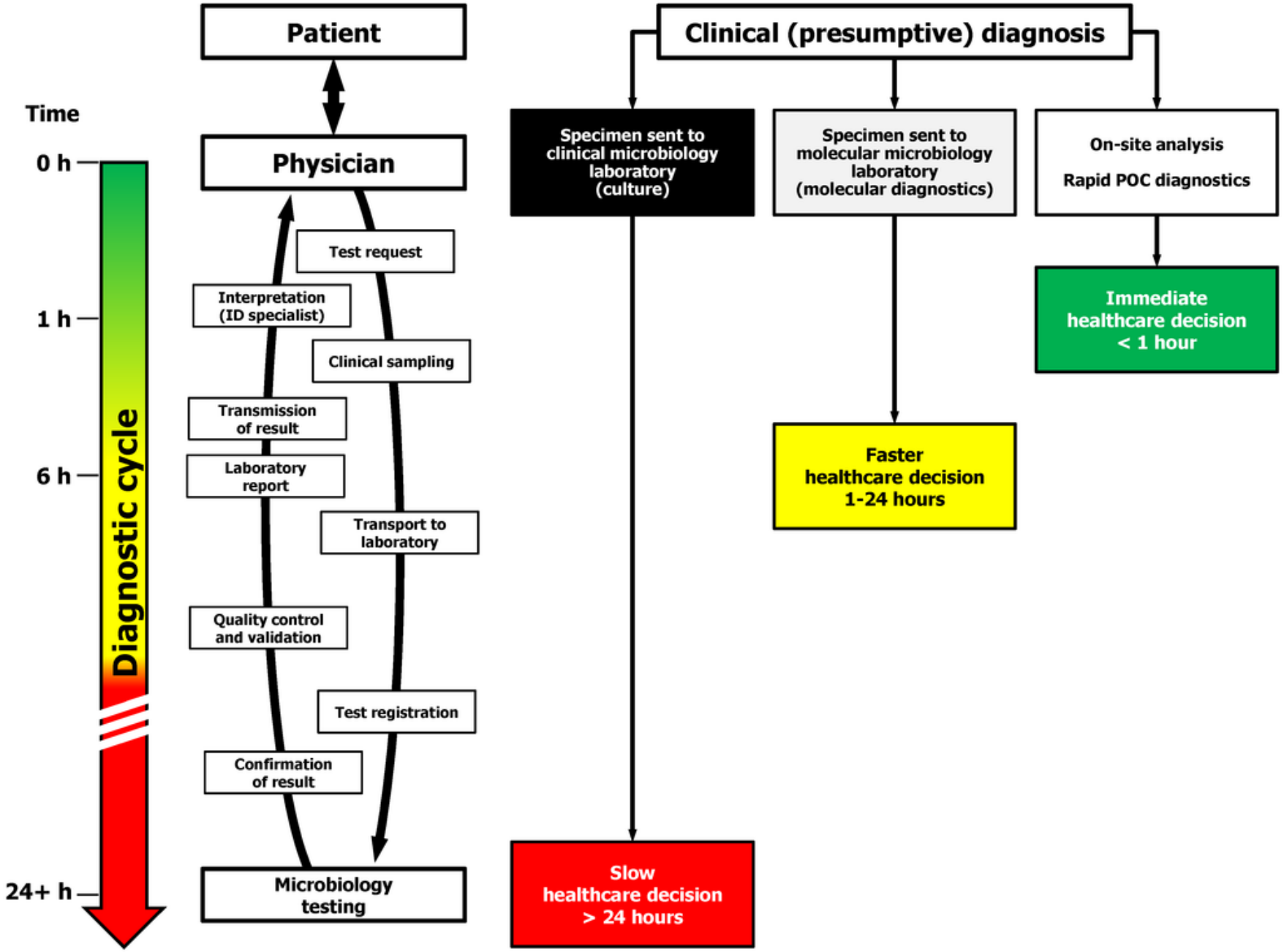
Put straight on MALDI – *Cryptococcus neoformans* – Surprised but ID within 24hrs

MALDI ID – Led the Consultants down a different patient management route.

# MOLECULAR DIAGNOSTICS

# Molecular diagnostics and omics



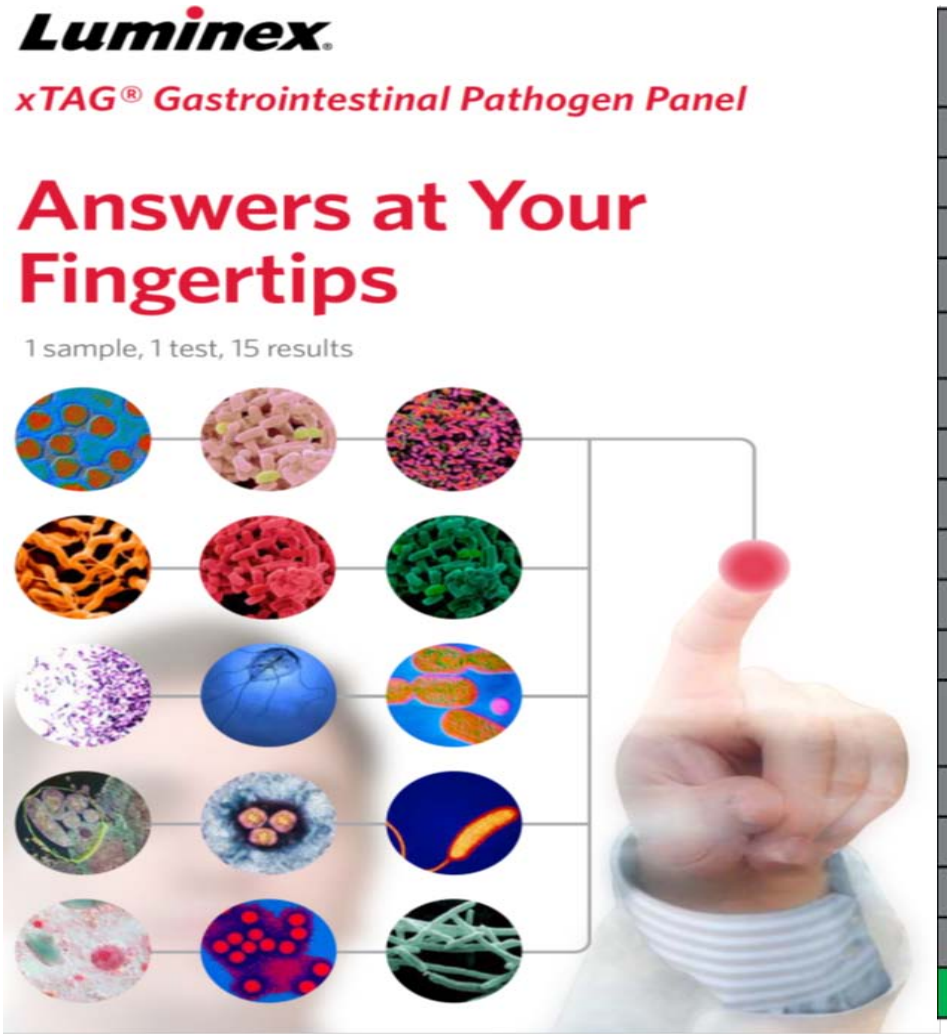

Time
0 h
1 h
6 h
24+ h
Diagnostic cycle
Patient
Physician
Test request
Interpretation (ID specialist)
Clinical sampling
Transmission of result
Laboratory report
Transport to laboratory
Quality control and validation
Test registration
Confirmation of result
Microbiology testing
Clinical (presumptive) diagnosis
Specimen sent to clinical microbiology laboratory (culture)
Specimen sent to molecular microbiology laboratory (molecular diagnostics)
On-site analysis
Rapid POC diagnostics
Immediate healthcare decision < 1 hour
Faster healthcare decision 1-24 hours
Slow healthcare decision > 24 hours

Where do innovative molecular diagnostics fit in???

How do they help?

Are they cost effective across health economy?

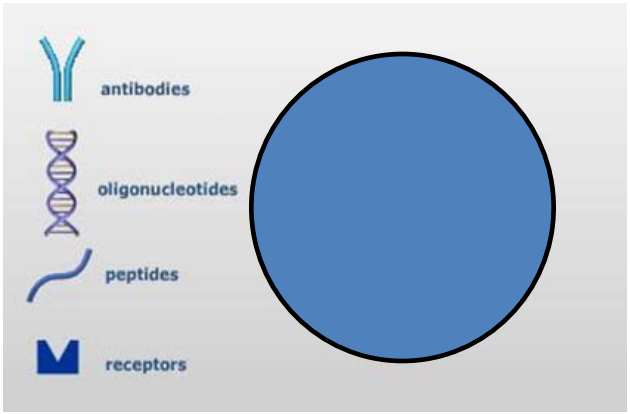
# xTAG GPP




| Reportable Targets | Number of Analytes |
|---|---|
| Adenovirus 40/41 | 1 |
| Rotavirus A | 1 |
| Norovirus GI/GII | 2 |
| *Clostridium difficile* toxin A/B | 2 |
| *Salmonella* | 2 |
| *Shigella* | 1 |
| *Campylobacter (C. jejuni, C. coli, C. lari)* | 1 |
| *Escherichia coli* O157 | 1 |
| Enterotoxigenic *E. coli* (ETEC) LT/ST | 2 |
| *Yersinia enterocolitica* | 1 |
| *Vibrio cholerae* | 1 |
| Shiga-like Toxin producing *E. coli* (STEC) stx 1/stx 2 | 2 |
| *Giardia lamblia* | 1 |
| *Cryptosporidium* | 1 |
| *Entamoeba histolytica* | 1 |
| **Internal control (MS2)** | 1 |
| ***Total*** | ***21*** |

# MICROSPHERES

xMAP Technology uses small microspheres or beads




xMAP® TECHNOLOGY

**Detect up to 500 biological agents simultaneously**

# ARIES – when you need to know


**Sample to answer in under 2 hours**

Flu A/B/RSV

C difficile

Norovirus

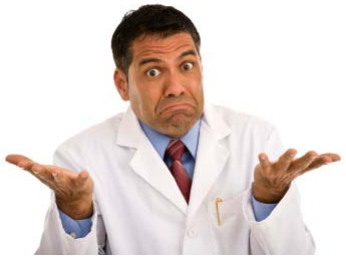
# Infectious Diarrhoea

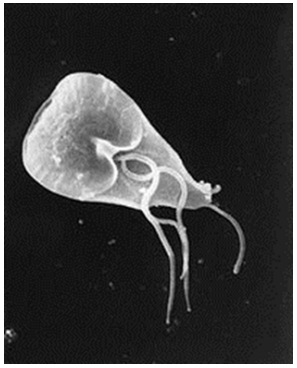
## Context

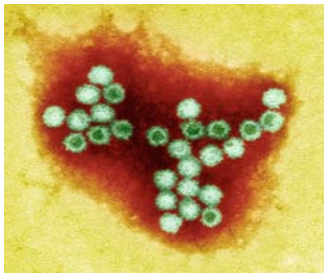
- Aetiology is variable (bacteria, viruses, parasites)
- IID2 study (O'Brien 2011) in community in UK
  - 25% of population have episode of IID annually
  - 2/3 viral, 1/3 bacterial
- Difficult to differentiate clinically

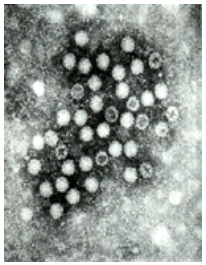

- Poor ascertainment of causes (cause unidentified in >80% of cases)

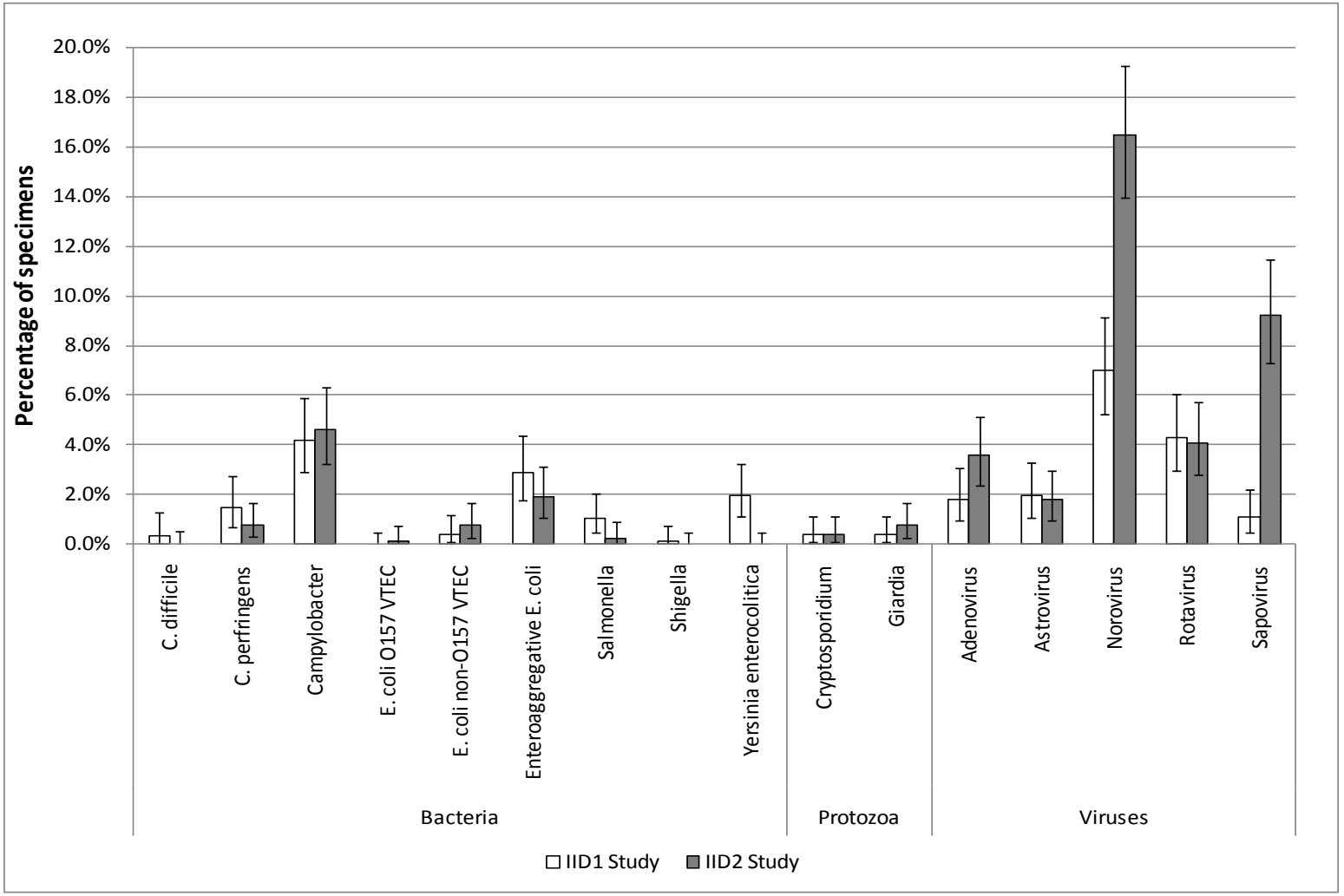
# Clinical confusion










Percentage of specimens
20.0%
18.0%
16.0%
14.0%
12.0%
10.0%
8.0%
6.0%
4.0%
2.0%
0.0%
C. difficile
C. perfringens
Campylobacter
E. coli O157 VTEC
E. coli non-O157 VTEC
Enteroaggregative E. coli
Salmonella
Shigella
Yersinia enterocolitica
Cryptosporidium
Giardia
Adenovirus
Astrovirus
Norovirus
Rotavirus
Sapovirus
Bacteria
Protozoa
Viruses
IID1 Study
IID2 Study

# More than a nuisance

- 2 billion cases of infectious diarrhoea each year globally
- 1.8 million deaths

- In Europe 200,000 cases and 1000 deaths

- In UK
  - 17M cases, 1M GP consultations
  - Major disruption to hospitals with ward closures
  - Leads to bed blocking and loss of tariff
  - Socio-economic impact with loss of days working (11m) and school
  - Estimated financial impact £1.5 billions

# Clinical classification

**Table 1: Important causative agents of gastroenteritis by age group and nature of stool worldwide [4]**

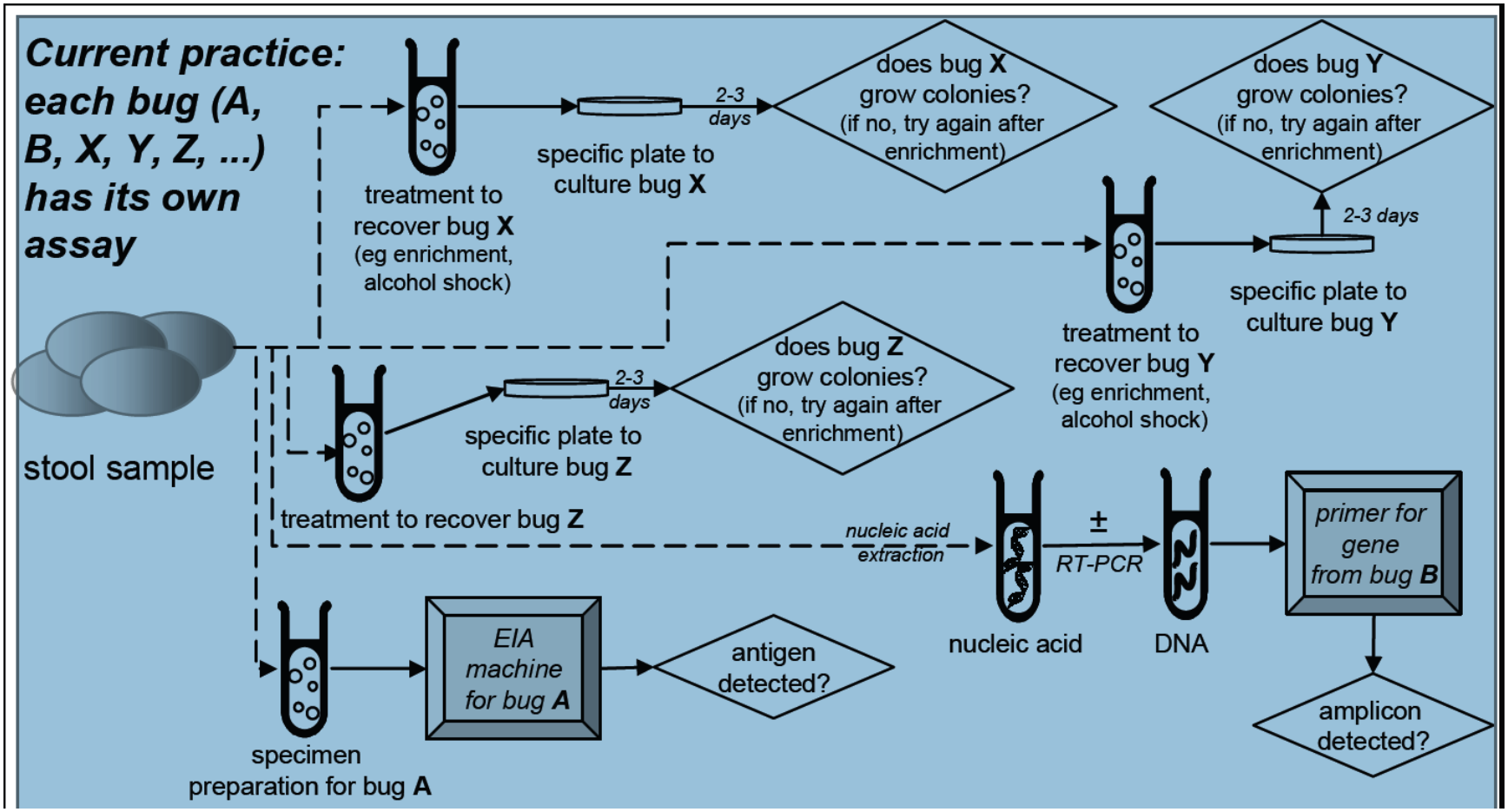
| | |
|---|---|
| **Watery** | |
| ≤ 2 years | Rotavirus, astrovirus, calicivirus, enteric adenovirus, enteropathogenic *Escherichia coli* (EPEC), enterotoxigenic *Escherichia coli* (ETEC), *Vibrio cholerae* |
| 2-5 years | Enterotoxigenic *Escherichia coli* (ETEC), rotavirus, *Shigella, Vibrio cholerae* |
| **Mucousy / bloody** | |
| ≤ 2 years | *Shigella,* shiga-toxin producing *Escherichia coli (STEC), Campylobacter jejuni* |
| 2-5 years | *Shigella*, shiga-toxin producing *Escherichia coli* (STEC), non-typhoidal *Salmonella*, *E. histolytica* |

Guarino A, Albano F, Ashkenazi S, Gendrel D, Hoekstra JH, Shamir R, Szajewska H. ESPGHAN/ ESPID Evidence-Based Guidelines for the Management of Acute Gastroenteritis in Children in Europe Expert Working Group. European Society for Paediatric Gastroenterology, Hepatology, and Nutrition/European Society for Paediatric Infectious Diseases evidence-based guidelines for the management of acute gastroenteritis in children in Europe: executive summary. *J Pediatr Gastroenterol Nutr* 2008;46(5):619-21.

# Current diagnostic strategy

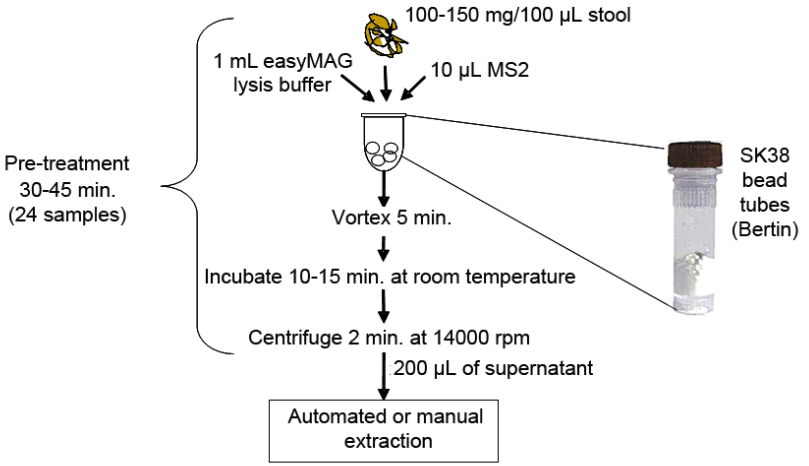
- Fractured
- Inconsistent
- Non-standardised
- Relies on clinical details/demographics/stool type
- Labour intensive
- 5 different methods (bacterial culture, virus PCR, 2 microscopy methods for Cryptosporidium & parasites and EIA CDT)

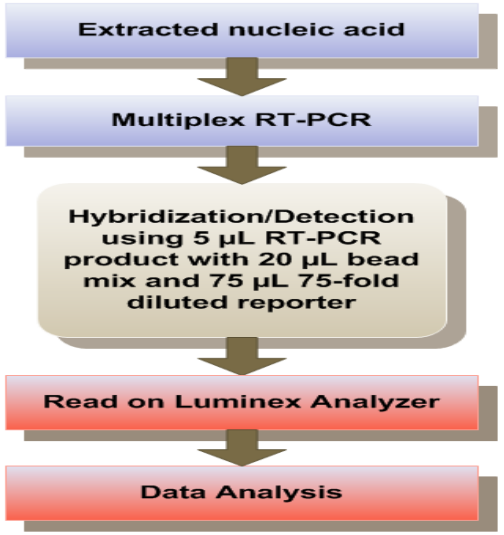
# Current diagnostic strategy



# Method

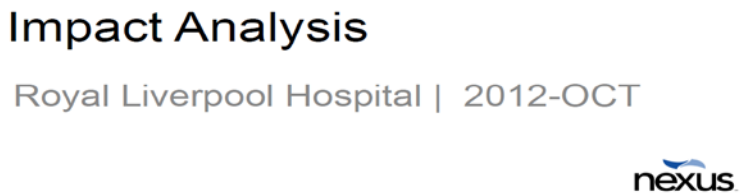
- Pre-treatment
  - maximum extraction efficiency
  - bead beat tubes (parasites)
  - 600µl supernatant used
- Automated extraction
  - QIAsymphony SP Virus/Bacteria Midi Kit
  - Final eluate volume = 60µL
- xTAG GPP Multiplex RT-PCR (10uL extract) followed by hybridisation



# Activity

- Positive Evaluation
- Positive Stake Holder Meeting
- Independent Company engaged by Luminex to look at process

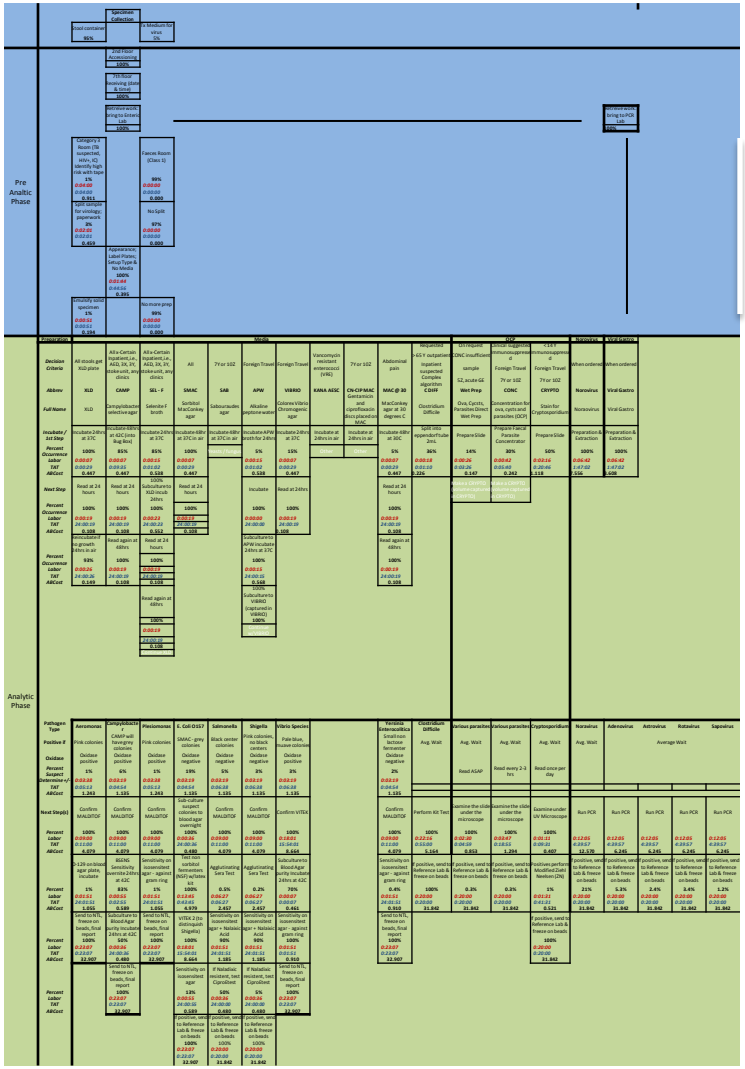



Nexus has applied industrial engineering, quality initiatives, and management science techniques to the healthcare industry for 6 years with consultants who have been in the industry for 20+ years.

# Impact Analysis

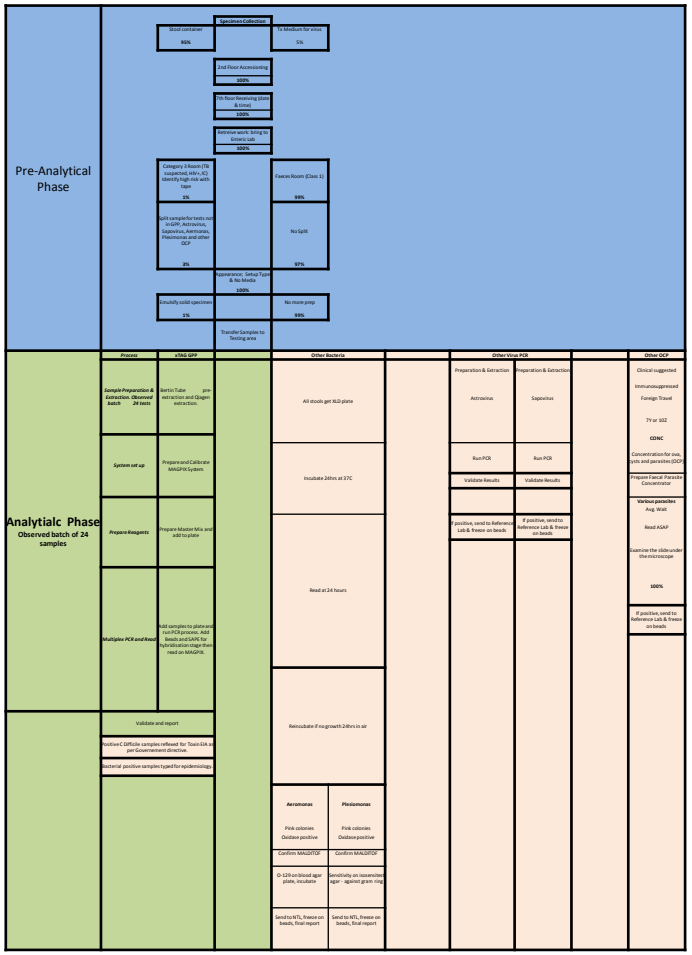
Royal Liverpool Hospital | 2012-OCT

nexus



**17 Pathways with existing testing algorithm**

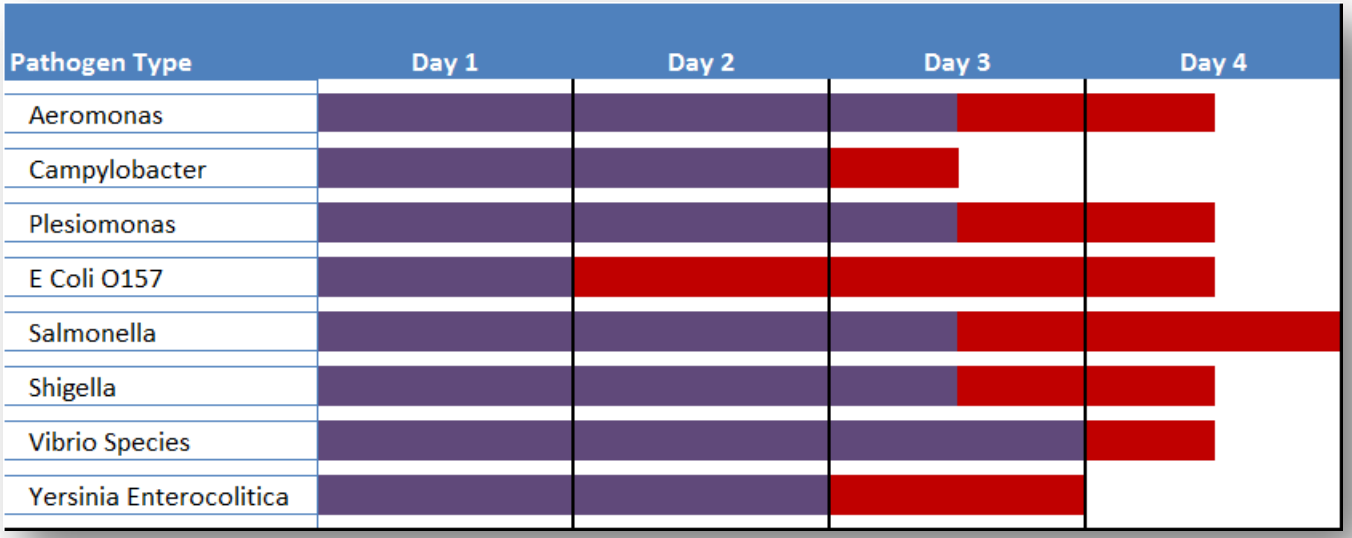
**5 Pathways with GPP**

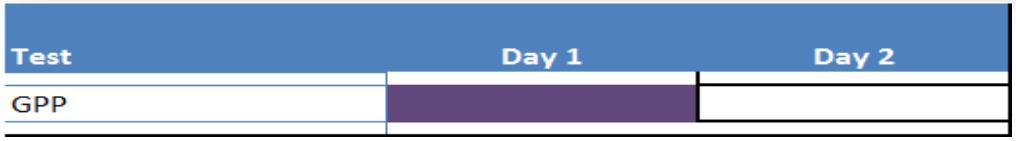


# Impact Analysis

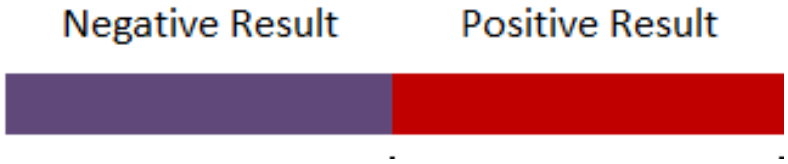
Royal Liverpool Hospital | 2012-OCT

Reduction in TAT



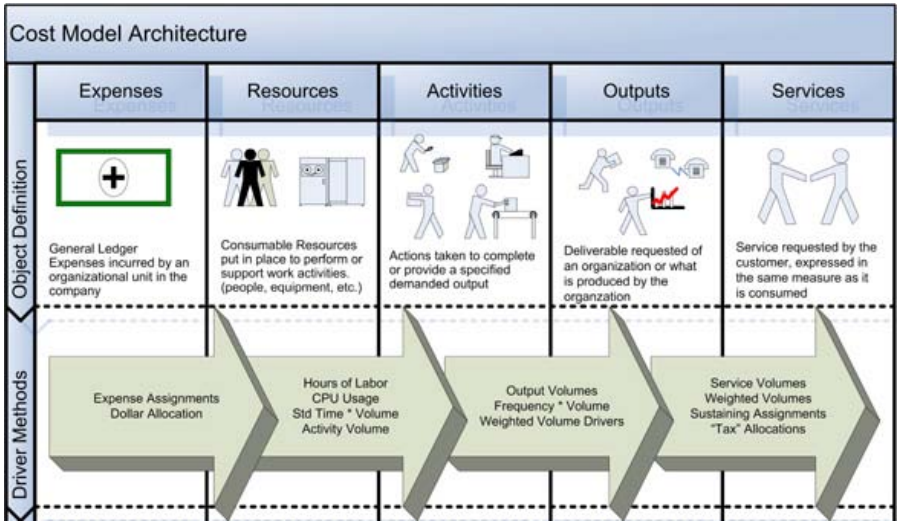




Positive, negative and co-infection results reported at the same time with GPP.



# Activity based costings

- Costing methodology popular in 1980's and increasingly popular again
- Costs based on actual consumption of ALL resources
- More likely to assign indirect (overhead) costs into direct costs

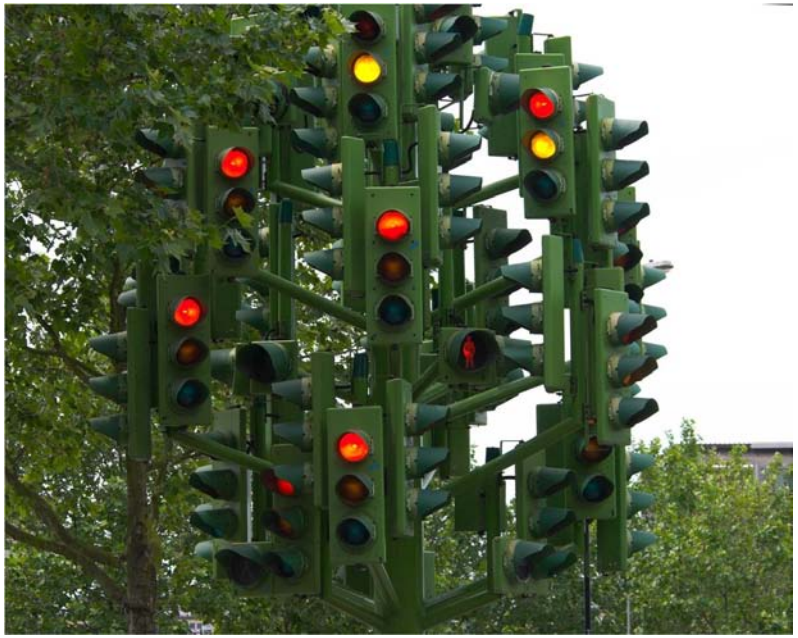


| Pathogen | Annual Volume | Δ Labor | Δ TAT | Δ Cost | GPP Savings |
|---|---|---|---|---|---|
| Aeromonas | 100 | 0.00% | 0.00% | 0.00% | |
| Campylobacter | 5,890 | -8.23% | -86.66% | -4.67% | |
| Plesiomonas | 100 | 0.00% | 0.00% | 0.00% | |
| E Coli O157 | 6,929 | -12.82% | -77.27% | 29.10% | |
| Salmonella | 6,929 | -5.20% | -89.23% | 13.54% | |
| Shigella | 6,929 | -2.82% | -89.20% | 17.31% | |
| Vibrio Species | 346 | -7.87% | -90.86% | -12.56% | |
| Yersinia Enterocolitica | 500 | 16.87% | -86.30% | 60.05% | |
| Clostridium difficile (Faeces Toxin) | 2,522 | -71.47% | 293.97% | -51.11% | |
| Cryptosporidium | 3,465 | 12.19% | 431.35% | 51.60% | |
| Other OCPs | 2,079 | 29.01% | 553.41% | 84.70% | |
| Norovirus | 1,599 | -68.55% | 2.89% | -87.75% | |
| Viral Gastro Test: Adenovirus | 414 | -63.55% | 3.73% | -71.52% | |
| Viral Gastro Test: Astrovirus | 414 | 0.00% | 0.00% | 100.00% | |
| Viral Gastro Test: Rotavirus | 414 | -62.83% | 3.83% | -69.92% | |
| Viral Gastro Test: Sapovirus | 414 | 0.00% | 0.00% | 100.00% | |
| | | | | | £24,690.81 |

| | |
|---|---|
| Not in GPP - retain existing methods | |

# NHS Pathology Reforms

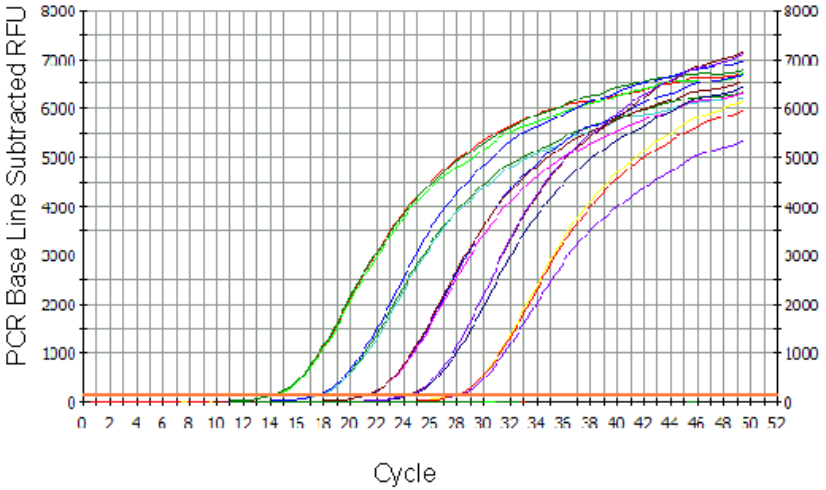
- Carter Report 2006
- NHS cost savings
- “Waste”
- Centralistion/modernisation of pathology services
- Commissioning of pathology services
- Cost improvement programme 4-5% year on year recurrent saving



"We trained hard, but it seemed that every time we were beginning to form up into teams, we would be reorganized. I was to learn later in life that we tend to meet any new situation by reorganizing; and a wonderful method it can be for creating the illusion of progress
while producing confusion, inefficiency, and demoralization."

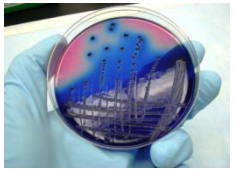
Attributed to Gaius Petronius Arbiter
Greek Naval Officer 66 AD

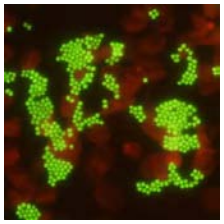
# Molecularisation of Infection Diagnostics



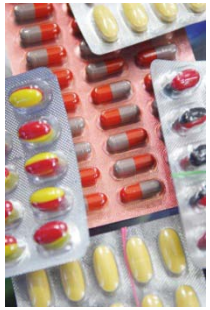


# Slash and burn v silo budgeting



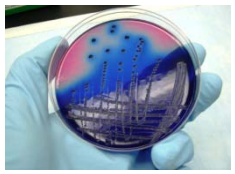
Pathology Silo

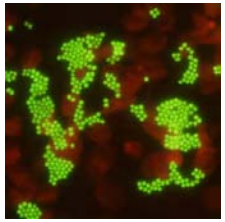



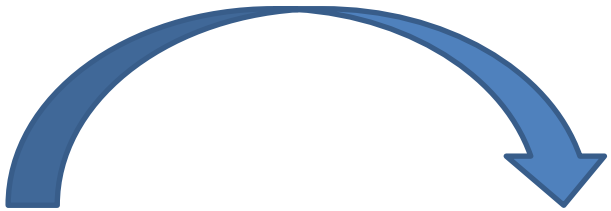
Pharmacy Silo


Bed holding Silo

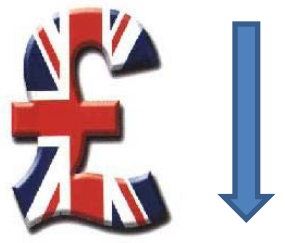
# The Challenge






- Better bed utilisation
- Better use of isolation facilities
- More tariff
- Targeted therapy

Liverpool Clinical Laboratories

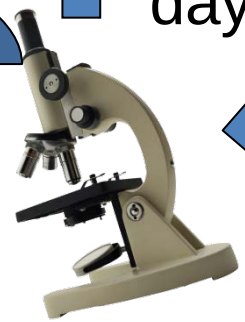
- To create a new, one-health paradigm for detecting and investigating clusters and outbreaks of diarrhoea and vomiting in the community
  - New approach to population sampling
  - New approach to cluster detection
  - Modern microbiological methods
    - Clinical diagnostics
    - Pathogen discovery
  - Integration with veterinary surveillance systems


Outbreak

# How do we Identify Outbreaks Now?

2 to 3 days

Public Health England



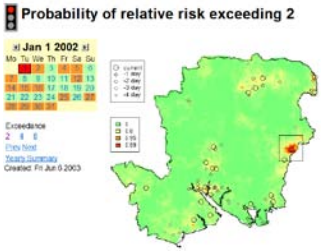
5 days to 9 weeks

# What do we Propose?

Real-time updating

Within the day

Public Health England




Within the day

Whole genome sequencing

- Cluster detection system
  - Ascertainment and Enhancement of Gastrointestinal Surveillance and Statistics (AEGISS)
- Molecular diagnostics
  - Luminex xTAG Gastrointestinal Pathogen Panel (xTAG GPP)
- Microbial genomics
- Small Animal Veterinary Surveillance Network (SAVSNET)
- Livestock surveillance data (AHVLA)

NHS Direct

Public Health England

Cumbria & Lancashire

LANCASTER UNIVERSITY

Lancashire Teaching Hospitals NHS
NHS Foundation Trust

The Royal Liverpool and Broadgreen University Hospitals NHS
NHS Trust

Greater Manchest

Public Health England

Central Manchester University Hospitals NHS
NHS Foundation Trust

Public Health England

Cheshire & Merseyside

Public Health England

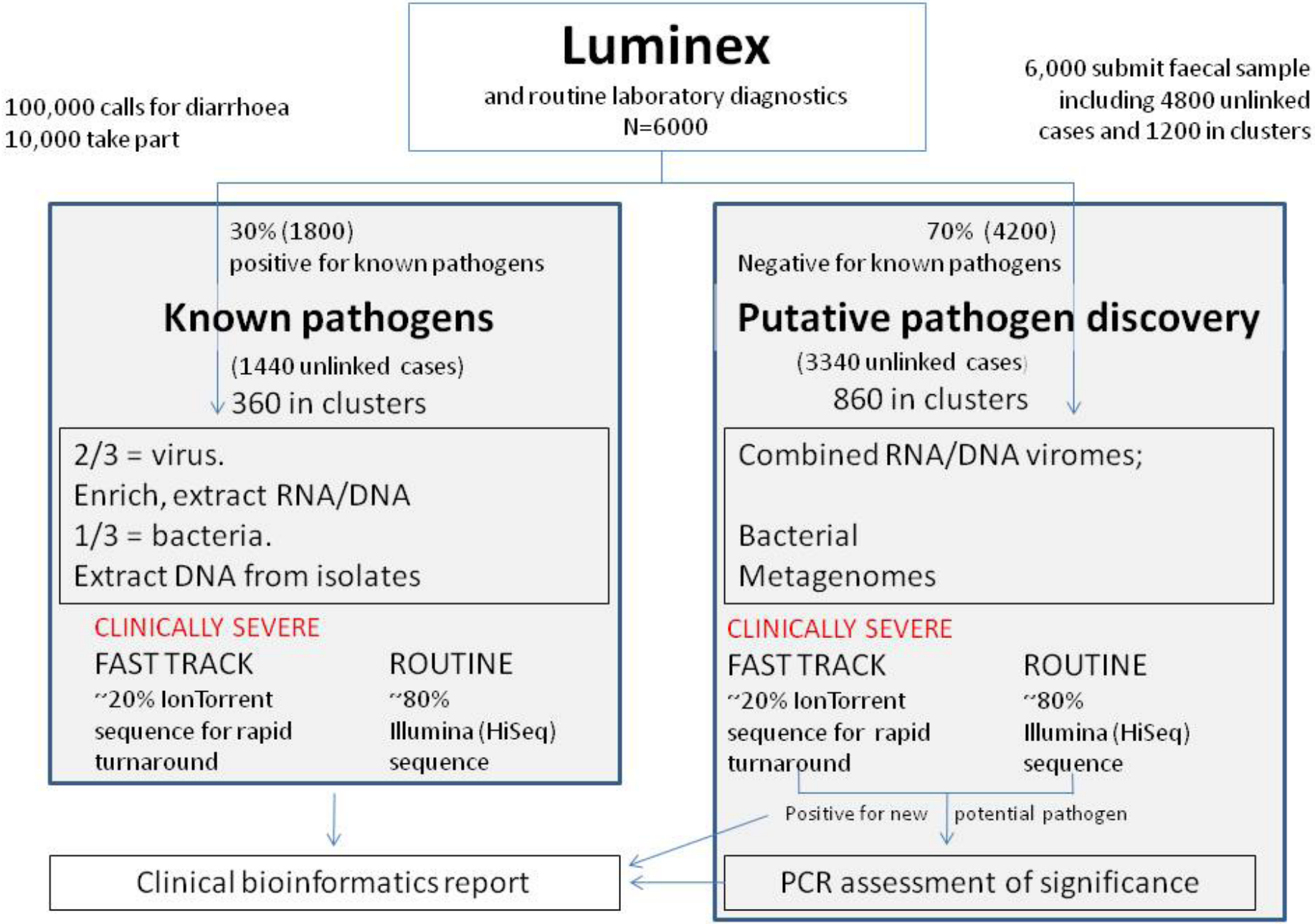
UNIVERSITY OF LIVERPOOL

AHVLA
Animal Health and Veterinary Laboratories Agency

PRIFYSGOL BANGOR UNIVERSITY

SAVSNET

Luminex®


Luminex
and routine laboratory diagnostics
N=6000
100,000 calls for diarrhoea
10,000 take part
6,000 submit faecal sample including 4800 unlinked cases and 1200 in clusters
30% (1800)
positive for known pathogens
Known pathogens
(1440 unlinked cases)
360 in clusters
2/3 = virus.
Enrich, extract RNA/DNA
1/3 = bacteria.
Extract DNA from isolates
CLINICALLY SEVERE
FAST TRACK
~20% IonTorrent sequence for rapid turnaround
ROUTINE
~80%
Illumina (HiSeq) sequence
70% (4200)
Negative for known pathogens
Putative pathogen discovery
(3340 unlinked cases)
860 in clusters
Combined RNA/DNA viromes;
Bacterial
Metagenomes
CLINICALLY SEVERE
FAST TRACK
~20% IonTorrent sequence for rapid turnaround
ROUTINE
~80%
Illumina (HiSeq) sequence
Positive for new potential pathogen
Clinical bioinformatics report
PCR assessment of significance

# A PATHFINDER PROJECT WITH WIDER APPLICATIONS

- Clinical syndromes
  - Respiratory symptoms
- New technologies
  - Incorporate in a modular fashion as they come on stream
- Geographical scalability
  - Local – Regional – National
- Settings
  - Community
  - Hospital

# Advantages of utilising GPP?

- Increased positivity rate with comprehensive panel
- Co-infections
- Faster actionable results
  - Better use of isolation facilities
  - More precision and assurance
- Syndromic assay
  - No sequential or inconsistent testing
- Improved laboratory efficiency
- Improved public health surveillance
- Shapes public health policy

# Disadvantages of utilising GPP assay?

- Acquisition cost
- Confirmatory testing with low level positives?
- Upscaling and automation (though many labs now have work horse NA extraction platforms and robotics)
- Need to agree public health actions on GPP result

# Summary

- Microbiology has responded to clinical, financial, organisational and technological drivers over last decade
- Automation has realised documented efficiencies in some laboratories
- MALDI has been a paradigm shift
- Molecular diagnostics have an increasingly important role to play
- Better action research required to elucidate benefits of all these transformations