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MALDI-TOF MS and its impact on patient care

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BSAC Spring Conference 2018

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MALDI-TOF Mass Spectrometry and its impact on patient care

Outline

- Briefly describe the technology
- Current use in pathogen identification in clinical microbiology (bacteria & yeasts)
- Direct use in blood cultures
- MALDI-TOF MS and total laboratory automation
- Future directions

No declarations or conflicts of interest

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MALDI-TOF Mass spectrometry

Matrix

Assisted

Laser

Desorption

Ionisation

Time

Of

Flight

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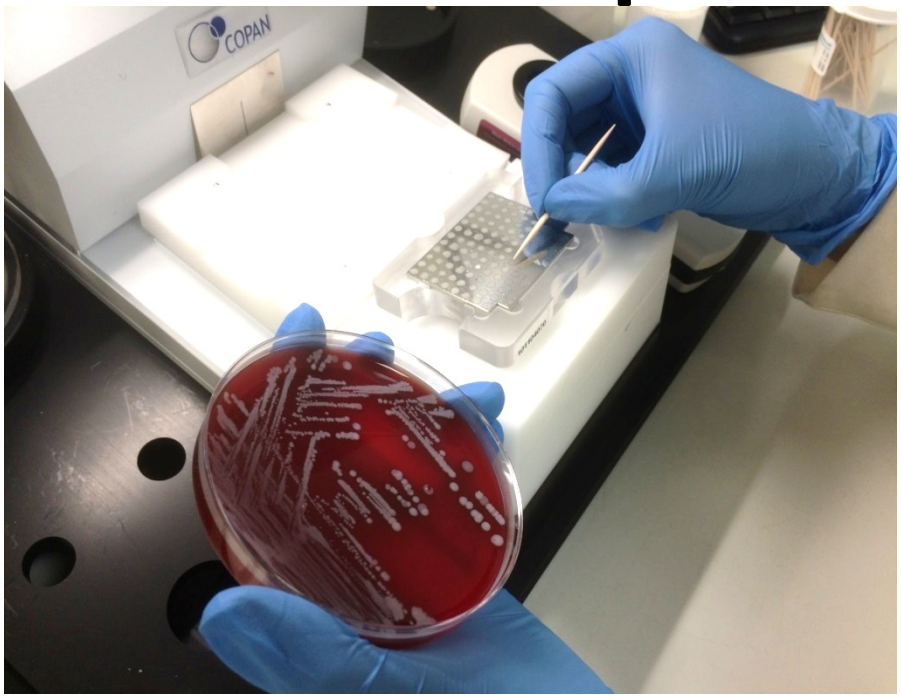
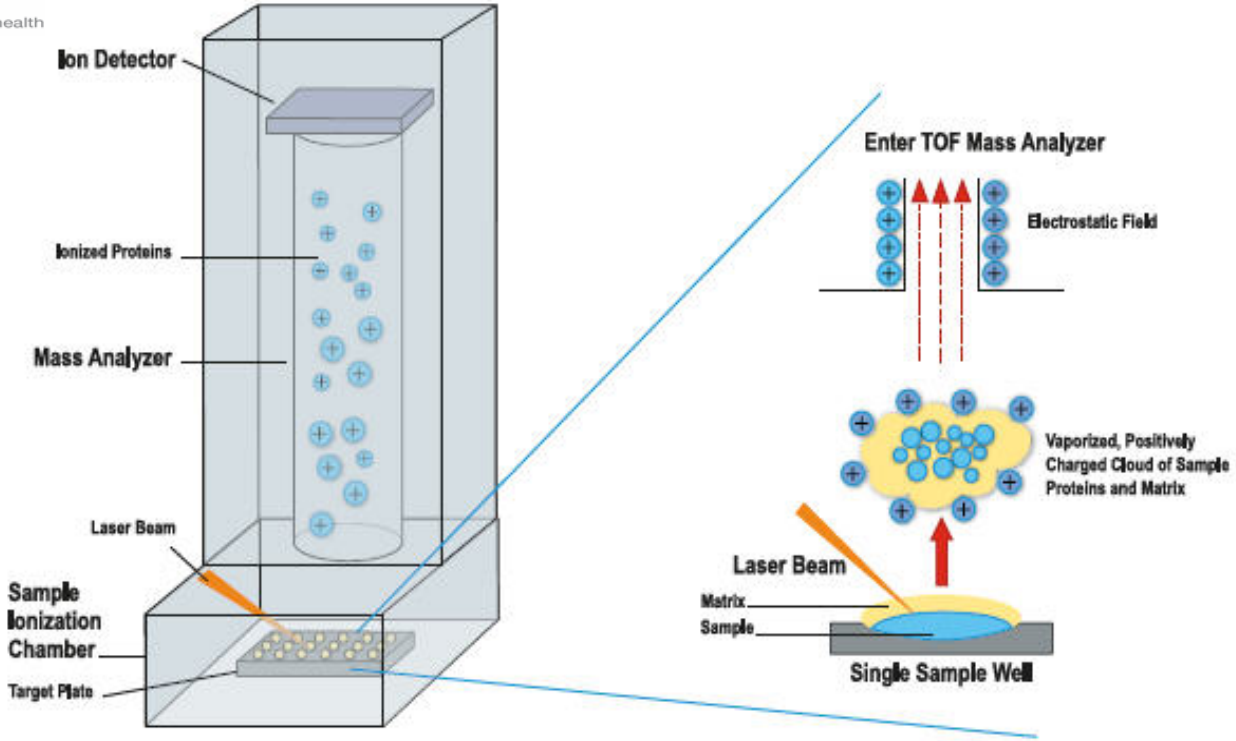
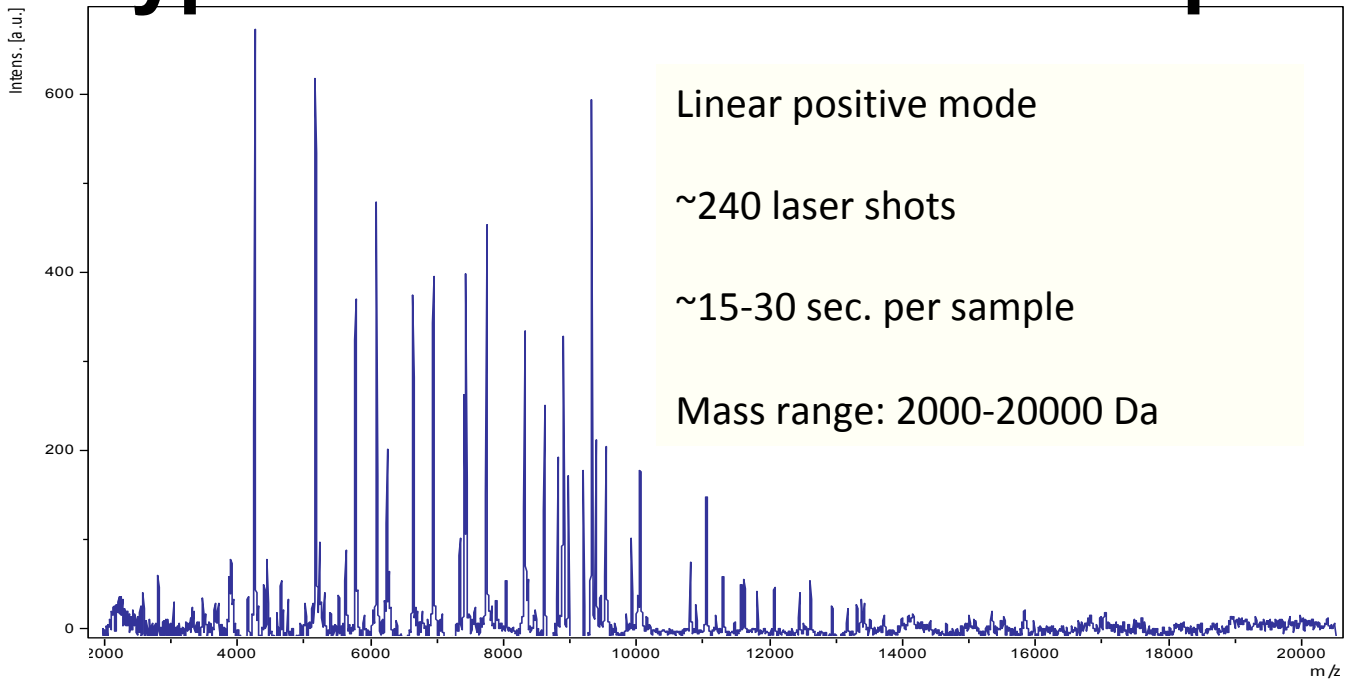
MALDI-TOF Mass spectrometry





Matrix-assisted laser desorption ionisation- time of flight mass spectrometer.
Schreiber,K. https://news.mayomedicallaboratories.com/2015/04/13/maldi-tof-ms-for-the-diagnosis-of-infectious-diseases-2

Typical MALDI-TOF Mass Spectrum



Linear positive mode

~240 laser shots

~15-30 sec. per sample

Mass range: 2000-20000 Da

Haemophilus influenzae

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Evaluation of Platforms

Table 1. Examples of Recent Evaluations of Matrix-Assisted Laser Desorption Ionization–Time of Flight Mass Spectrometry for Routine Bacterial Identification

	Isolates			% Identification				
System	No.	Type	Period of Isolate Collection	Genus Level	Species Level	Country	Comparator	Reference
Bruker Biotyper	1013	Bacteria	2 mo	99%	97%	France	Phoenix, API, Biochemical	[72]
Bruker Biotyper	468	Bacteria	3 mo	97%	92%	Japan	MicroScan, API, Phoenix	[73]
Bruker Biotyper	2781	Bacteria	1 mo	96%	85%	Australia	VITEK2, API, Biochemical	[74]
Vitek MS[a]	767	Bacteria	6 wk	95%	87%	France	VITEK2	[8]
Bruker Biotyper/ Vitek MSb	986	Bacteria	3 mo	96%/94%	93%/93%	Belgium	Bruker Biotyper compared to Vitek MS	[6]

[a] v1 system/v1.1 database.

[b] Prerelease version of v1.1 database.

Patel R. Clinical Infectious Diseases (2013); 57:564-72

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Replacement of conventional identification tests

- Gram stain
- Oxidase; Catalase tests
- Latex agglutination tests
- Tube coagulase
- Dnase plates
- Bile Aesculin plate
- Gonochek test
- Phadebact
- X and V factors
- Tributyrin test
- API Strips (except enterics)
- VITEK GNID and GPID cards
- Bordetella antisera

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Implementation

- Fitted well with routine flow
- Straightforward calibration, target cleaning & maintenance
- Training – minimal
- Health and safety - minimal impact
- Time to identification reduced
- Less use of Reference laboratory / 16 S PCR
- New names…..

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MALDI-TOF Mass spectrometry

Advantages

- Ability to identify the increasing numbers of micro-organisms
- Single colony only required
- Rapid turnaround time - minutes
- Minimal training & ease of use
- Cost-effective consumables
- Reproducibility
- Potential of direct use on clinical samples
- Databases can be expanded locally
- “Green” technology

Limitations

- Cost of instrument – initial outlay
- Does not provide antimicrobial susceptibility results
- Some closely related organisms not differentiated e.g. *Escherichia coli/ Shigella* sp. & *Streptococcus mitis/ oralis* and *Streptococcus pneumoniae*
- Machine failure
- Loss of “traditional” microbiology skills
- Requires database to be regularly updated

Tan KE et al., J Clin Micro 2012; 50: 3301-8

- Prospective evaluation, Johns Hopkins hospital laboratory
- “Maldi protocol” vs. “standard protocol”
- 2,214 specimens , various benches
- 952 isolates (824 bacterial & 128 yeast)
- Identifications 1.45 days earlier ($P<0.001$) than standard identification methods
- Projected savings consumables/labour costs 56.9% in 12 months

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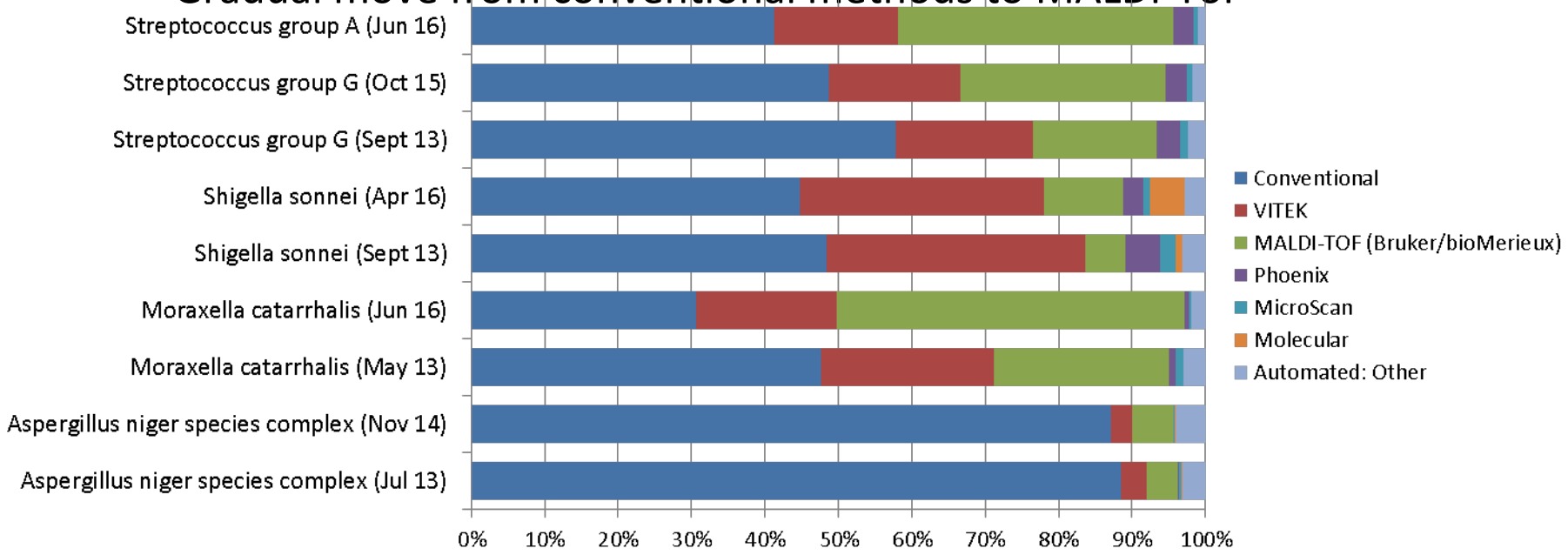
Methods used by participants to identify pathogens sent out in UK NEQAS General bacteriology scheme

– Gradual move from conventional methods to MALDI-ToF



Slide courtesy of Shila Seaton,UKNEQAS

Antimicrobial susceptibility testing and MALDI-TOF MS

- No direct identification of antimicrobial susceptibility

- Confirmation of identification of an isolate can infer inherent resistance patterns or intrinsic susceptibility

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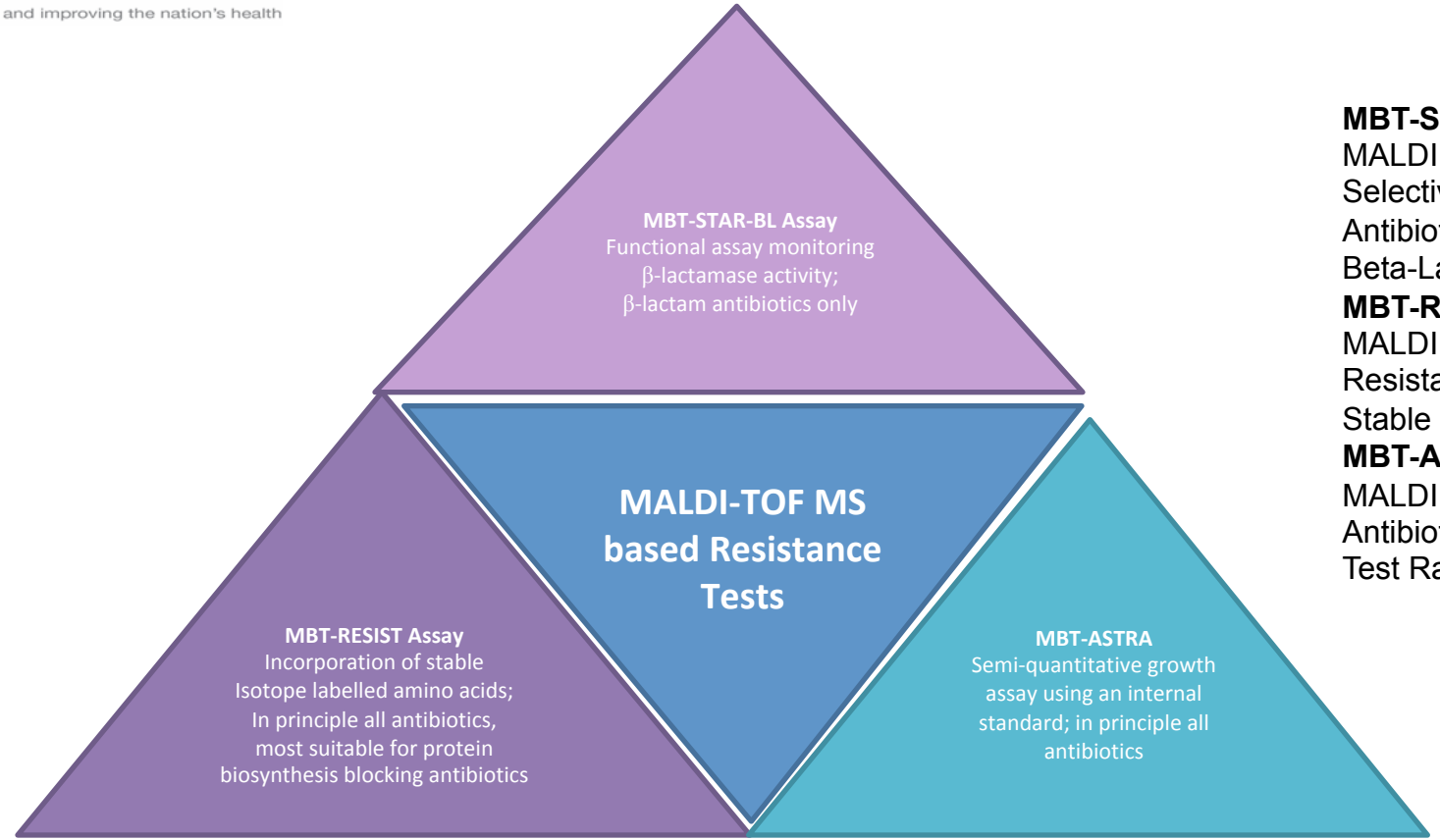
Overview of MALDI-TOF MS based resistance tests currently under investigation:



From: Sparbier K et al. Methods 104 (2016) 48-54

MBT-STAR-BL Assay, MALDI Biotyper-Selective Testing of Antibiotic Resistance-Beta-Lactamase Assay;
MBT-RESIST Assay, MALDI Biotyper-Resistance Test with Stable Isotopes Assay;
MBT-ASTRA, MALDI Biotyper-Antibiotic Susceptibility Test Rapid Assay

Antimicrobial susceptibility testing and MALDI-TOF MS

	Organism	resistance
Sakarikou C, et al. BMC Microbiol. 2017; 17(1): 54	*Klebsiella pneumoniae*	Incubation with Ertapenem for detection of CPE
Sparbier K et al. J Clin Microbiol. 2013; 51(11): 3741	*Staphylococcus aureus*	Meticillin resistance detection by stable-isotope labelling amino acids
Maxson T. PLoS ONE 2017; 12(8): e0183899	*Staphylococcus aureus*	Oxacillin, Ciprofloxacin, Cefepime, Vancomycin Semiquantitative method (MBT-ASTRA software)

Direct use of MALDI-TOF MS on positive blood cultures

- Blood culture usually triggers ~ 10^7/ml

- MaldiTOF limitation of detection ~10^5/ml

OR

Direct use of MALDI-TOF MS on positive blood cultures : clinical impact

- 115 patient episodes positive blood cultures
- 73 (63.5%) Direct id by MALDITOF-MS
- 70/73 (95.9%) concordant result with subsequent culture
- 28/115 (24.3%) having the ID on Day 1 would have had clinical benefit

French et al. (2016). PLoS ONE 11 (12):e0169332.

Direct use of MALDI-TOF MS on positive blood cultures : clinical impact

Clinical Impact	Number of cases (28)
Selection of antimicrobial agents	11
Identifying source of infection/further investigation	11
Determining clinical significance	14
Infection Control Intrevention	0

French et al. (2016). PLoS ONE 11 (12):e0169332.

Direct use of MALDI-TOF MS on positive blood cultures

- 277 episodes bacteraemia (157 adult&40 paed)
- 71% direct microbial ID obtained

	Contamination confirmed	Modification of treatment regimen
Adult (157)	8.9%	13.38%
Paediatric (40)	37.5%	2.5%

Martiny D, et al.. Clin Microbiol Infect 2013; 19:E568 – 81

Direct use of MALDI-TOF MS on positive blood cultures – antimicrobial stewardship

- 143/165 (86.7%) monomicrobial bacteraemia correctly identified at genus level.
- Gram stain: impact in 20.8%
- MALDI ID: modification empirical Rx in 35.1%
- MALDI ID: modification 16/27 (59.3%) of monomicrobial bacteraemia caused by AmpC-producing Enterobacteriaceae.
- Early appropriate broadening of the antibiotic spectrum in 31/71 (43.7%).

Clerc *et al. Clin Infect Dis* 2013;**56**(8):1101–7

MALDI-TOF MS & Total laboratory automation (TLA)

Mutters et al. Ann Lab Med 2014; 34:111

- BD Kiestra™ TLA + MALDI-TOF Ms compared to conventional methods 219 BC isolates
- 30.6 hr faster pathogen identification
- 12% (24/200) antibiotic adjusted due to Early Id (no susceptibility testing)

Theparee et al. J Clin Micro 2018; 56: 1-8

- BD Kiestra™ TLA + MALDI-TOF MS for > 61000 urine samples
- Retrospectively assessed TAT's before & after implementation
- Median TAT to organism ID MALDI-TOF MS from 21.33 h to 18.02h
- Median TAT to organism ID after TLA + MALDITOF-MS from 18.02h to 16.79h
- Impact on time to AST reports

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Future directions

- MALDI-TOF MS has revolutionised the routine identification of bacteria & yeast isolated in clinical microbiology laboratories
- Accurate & timely ID impacts on patient management
- Direct use in clinical samples e.g. blood culture has impact on antibiotic prescribing as well as work of infection specialist
- Combination with total laboratory automation systems can further reduce TAT identification & thereby patient care.
- Further work required on AMS