Laboratory Automation in Microbiology: Accelerating the impact through AI and Digital Imaging

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Disclosures

- I have served as a consultant for Clever Culture Systems and Thermo Fisher Scientific

- I developed the presentation and the opinions expressed are my own

Learning Objectives

- Describe the current challenges and drivers within the microbiology laboratory environment
- Understand the bottleneck in various workflows that heavily rely on skilled labor and how laboratory automation can be incorporated into routine clinical microbiology
- Review the downstream implications of reviewing negative cultures from a workflow

What is AI and Machine Learning?

- Artificial Intelligence has become a buzzword through healthcare and now in microbiology
  - What does it mean?

- Artificial Intelligence is an old area of research in the computer science domain
  - Concept has existed for centuries – serious work began in the 1940s
  - Neural networks were first proposed in the 1970s, but were not practical
  - Deep learning as we know it began in the mid-2000s

- Artificial Intelligence aims to make an artificial mind
  - Does not get bored
  - Does not make mistakes

Examples of machine learning and deep learning are everywhere

- It's how Netflix knows which show you'll want to watch next
- How Facebook knows whose face is in a photo
- How a customer service representative will know if you'll be satisfied with their support before you even take a customer survey

And now…how an instrument can tell if your urine culture is negative of contains Gram-negative rods or MRSA???

Automating microbiology with AI

- Microbiology is often overlooked – not a ‘cool’ area
  - Lacks standardisation and existing automation/digitisation

- Microbiology is often considered a very manual field
  - Some tests are critical, often hard to automate with traditional methods
  - Disconnect in daily workflow creates gaps in attention at times
  - Often difficult to standardize
  - Do you provide the same quality read on the first plate as the hundredth plate?

- Microbiology is a pathology service which is aimed at performing tests
  - Cultures plates are used to make the invisible visible
  - Critical in patient care

- AI allows the superfluous aspects of microbiology to be removed
  - Let “us” (microbiologists) focus on important cases

- A key barrier to real-world adoption is a lack of standard methods
  - All labs have a different set of procedures for their microbiology work

Current challenges in microbiology lab

- Increasing pressure for “on demand” testing and rapid turnaround times for results
- Valuable microbiologist time is used to screen negative cultures and report results
- Shortage of microbiologists
  - 5.93% vacancy rate and declining new qualified personnel coming through education[1]
  - COVID-19 has heightened this shortage and highlighted the benefits of automation
- Inefficient use of qualified personnel
  - Nearly 60% of urine culture are negative [2,3]
  - >90% of MRSA/VRE culture plates are negative[4]

1. Garcia et al., 2018. The American Society for Clinical Pathology’s 2016-2017 Vacancy Survey of Medical Laboratories in the United States.
2. Millán-Lou et al., 2018. Comparing Two Automated Techniques for the Primary Screening-Out of Urine Culture.
3. *Mejuto et al., 2017.* Automated Flow Cytometry: An Alternative to Urine Culture in a Routine Clinical Microbiology Laboratory?
4. *Hassoun et al, 2017.* Incidence, prevalence, and management of MRSA bacteremia across patient populations-a review of recent developments in MRSA management and treatment.

What is holding the implementation back in the lab?

- Lack of awareness of the capabilities of AI in the microbiology lab
  - Platforms can do more than just screen
  - Drives workflow efficiencies
- Installation of automation often results is overall improved laboratory workflows
  - Automation requires a consistent approach
- Automation in microbiology has a bad reputation
  - Historically, systems hard to integrate
  - Modular system are easier – each module is integrated individually, rather than needing the entire workflow to be done in one go
- Complexity of LIS integration
  - Microbiology often not considered explicitly in LIS software
  - Then hard to integrate

What is AI and Machine Learning: How can tools help?

- Machine learning is an application of AI that includes algorithms that parse data, learn from that data, and then apply what they've learned to make informed decisions.

- When we say something is capable of "machine learning", it means it's something that performs a function with the data given to it and gets progressively better over time.

- A deep learning model is designed to continually analyze data with a logic structure similar to how a human would draw conclusions. To achieve this, deep learning applications use a layered structure of algorithms called an artificial neural network.

AI for Clinical Microbiology: The difference between robotics and decision-making tools

- How can you tell what is intended to be “called” or reported?
- How can AI “tools” help DECIDE which work requires our attention and which cases don’t?
- How can we provide tools to our staff that scales their efforts “up” to their expected job descriptions?

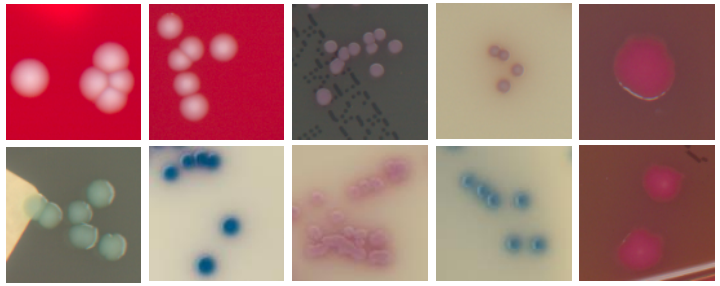
AI for Clinical Microbiology: The difference between robotics and decision making tools

"The analogy to AI/deep learning is that the rocket engine is the deep learning models (algorithms) and the fuel is the huge amounts of clinical cases we can feed to these algorithms."

FDA currently lists 343 approved devices for use as Medical Devices

AI for Microbiologists, by Microbiologists

Artificial intelligence that thinks like you do



Colony recognition

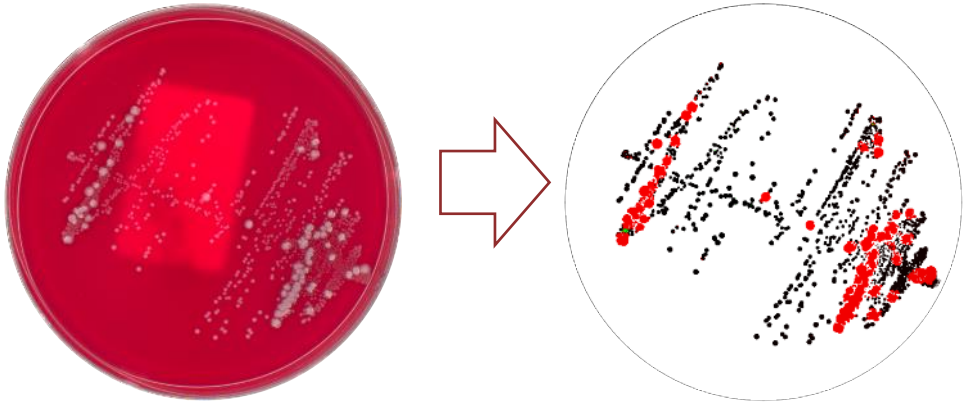


Plate image

AI reconstructed image

Machine learning developed by microbiologists
Colony recognition used as an input

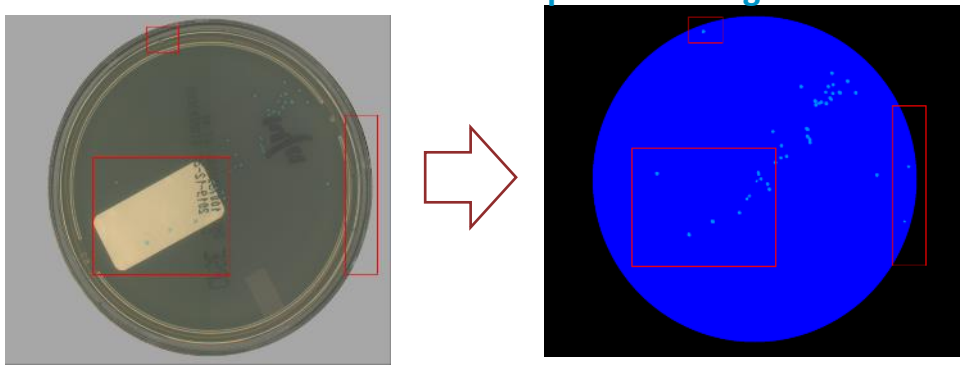
Decision rules apply logic like a microbiologist
Plates screened for significant bacterial growth

Real time decision making powered by automation
Plates interpreted every 18 seconds

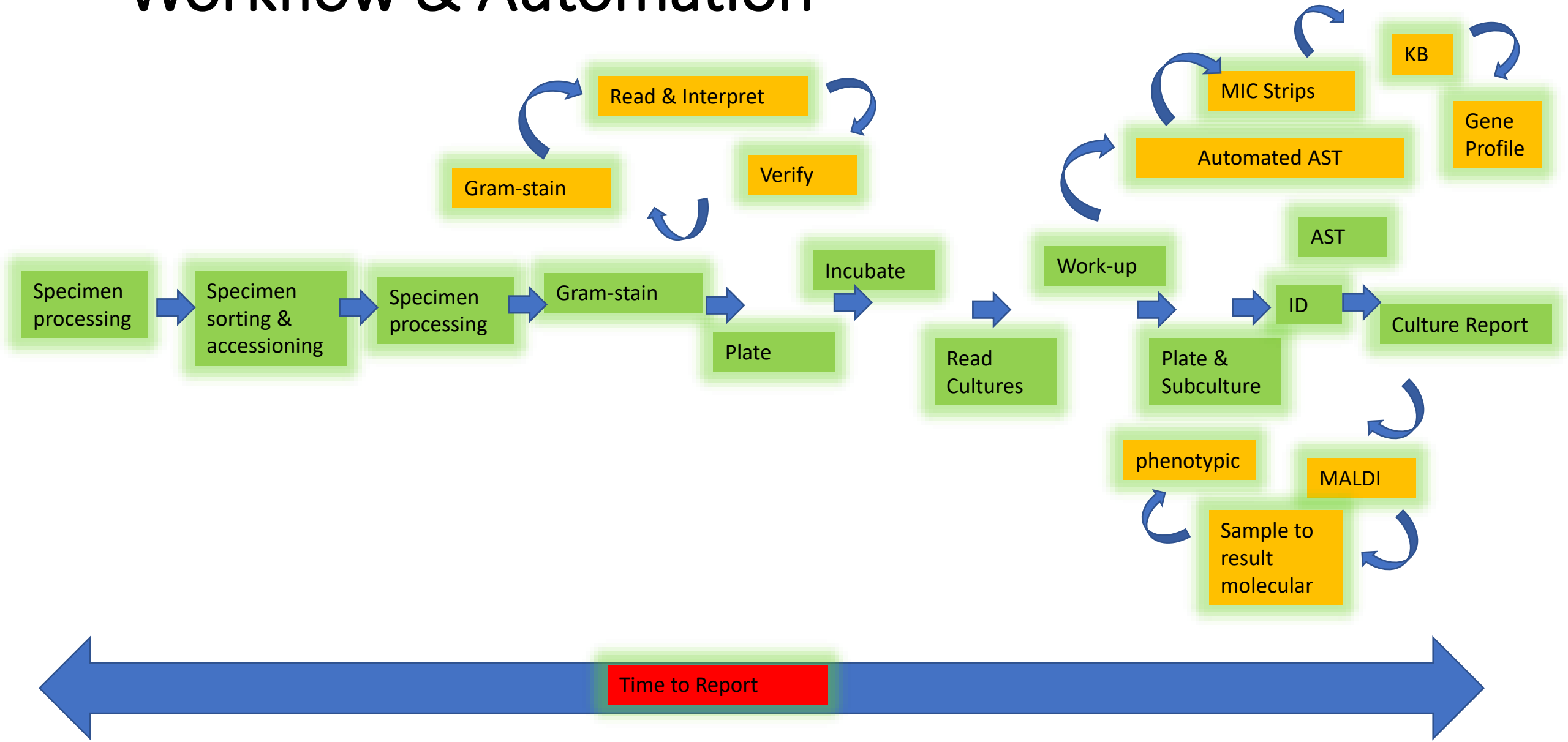
Unique imaging system – pixel by pixel analysis
Intelligent translation of colonies to pixels

Powerful algorithms
Accurate reading and interpretation

Accurately identifies colonies at plate edges and those obscured by labels and other plate markings



Workflow & Automation



We Need Contemporary Tools!

Total lab automation

MALDI- ID

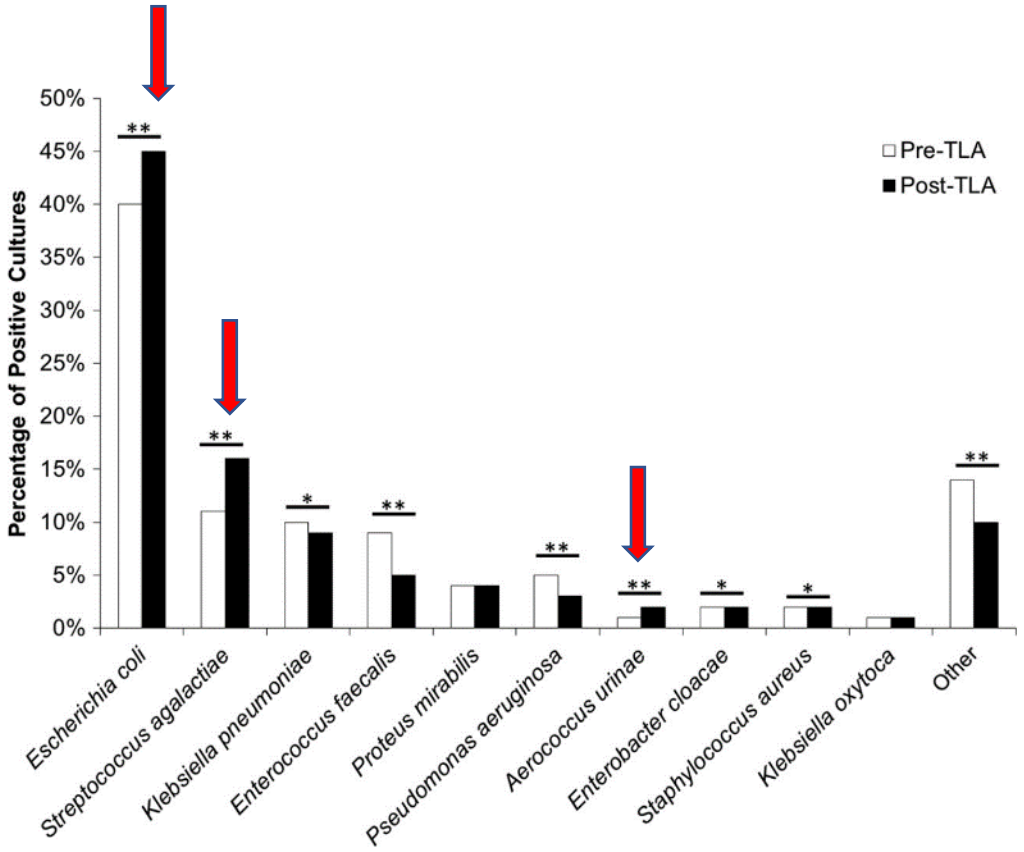
Molecular detection for resistance mechanisms

Automated AST

Gram stain analysis

Slide Credit: Esther Babady MSKCC

Does Lab Automation Work?



Organism	No. of times organism reported per 1,000 urine cultures		% change	*P* value
	Pre-TLA	Post-TLA		
Escherichia coli	79.4	101.2	+27	<0.0001
Klebsiella spp.	22.9	24.0	+5	0.24
Streptococcus agalactiae	22.2	36.7	+66	<0.0001
Aerococcus urinae	2.2	4.4	+103	<0.0001
Staphylococcus saprophyticus	1.0	2.3	+126	<0.0001
Neisseria gonorrhoeae	0.2	1.0	+371	<0.0001
Actinotignum schaalii	0.1	0.13	+33	0.77
Streptococcus pneumoniae	0.02	0.1	+312	0.27
Alloscardovia omnicolens	0.0	0.06	NA	0.30

[a]TLA, total laboratory automation; NA, not applicable.

Urine Cultures : Retrospective, non-controlled, Pre vs Post analysis (40,597 pre vs. 68,905 post) 24/7 set up day shift reading

Conclusion: advantages of lab automation quick set up with optimized & standardized incubation conditions

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Increased Yield in Detection Copan WASP® vs Manual for Urine Cultures

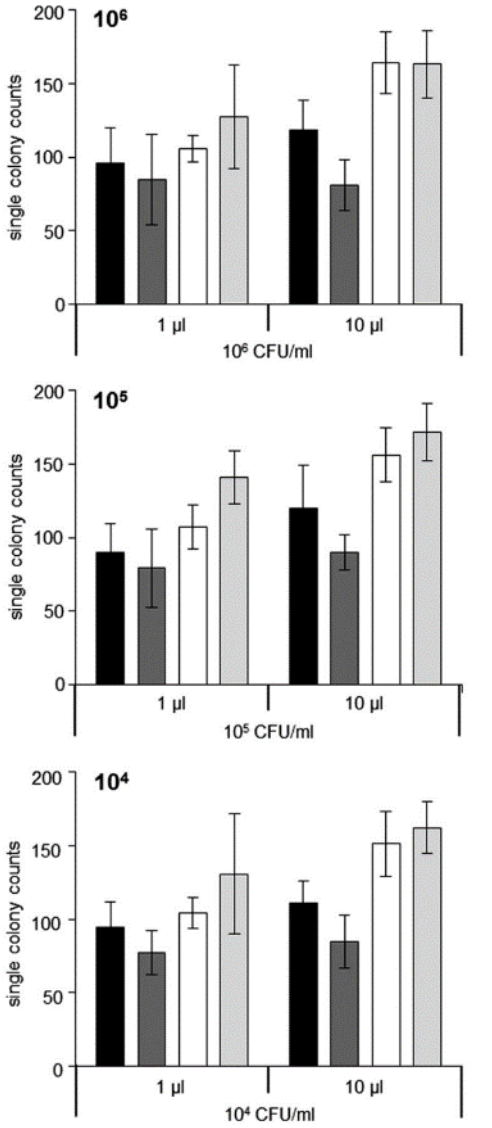

TABLE 1 Results of the head-to-head comparison of clinical samples (10-µl inocula)

Parameter	No. (%) of samples with indicated parameter (n = 379)[a]					
				Nonidentical		
	Manual	WASP	Identical	Manual > WASP	WASP > manual	P value
Morphologies			177 (46.7)	**22 (5.8)**	**180 (47.5)**	0.000
CFU/ml			239 (63.1)	**14 (4.8)**	**122 (32.2)**	0.000
Recovered species			287 (75.7)	**26 (6.9)**	**66 (17.4)**	0.000
Total no. of MALDI-TOF identifications	**253**	**313**				0.000
Total no. of susceptibility tests	149	163				0.337
Clinical report			199 (52.5)	180 (47.5)[c]		
Positive result	141 (37.2)	153 (40.4)				
Negative result	238 (62.8)	226 (59.6)				
Possible pathogens[b]	159 (42)	172 (45.4)				
Contamination	10 (2.6)	10 (2.6)				

[a] Manual inoculation versus WASP inoculation (10-µl loop). Significant differences are indicated in bold (nonparametric Wilcoxon signed-rank test, $P < 0.05$; crosstab chi-square test of independence, $P < 0.05$).

[b] Possible pathogens: Gram-negative rods; *Staphylococcus aureus*; *Staphylococcus lugdunensis*; *Staphylococcus saprophyticus*; *Streptococcus group* B, C, or G; enterococci; yeasts; *Corynebacterium glucuronolyticum*; *Corynebacterium urealyticum*.

[c] Pooled number of nonidentical clinical reports comparing manual and WASP inoculation.

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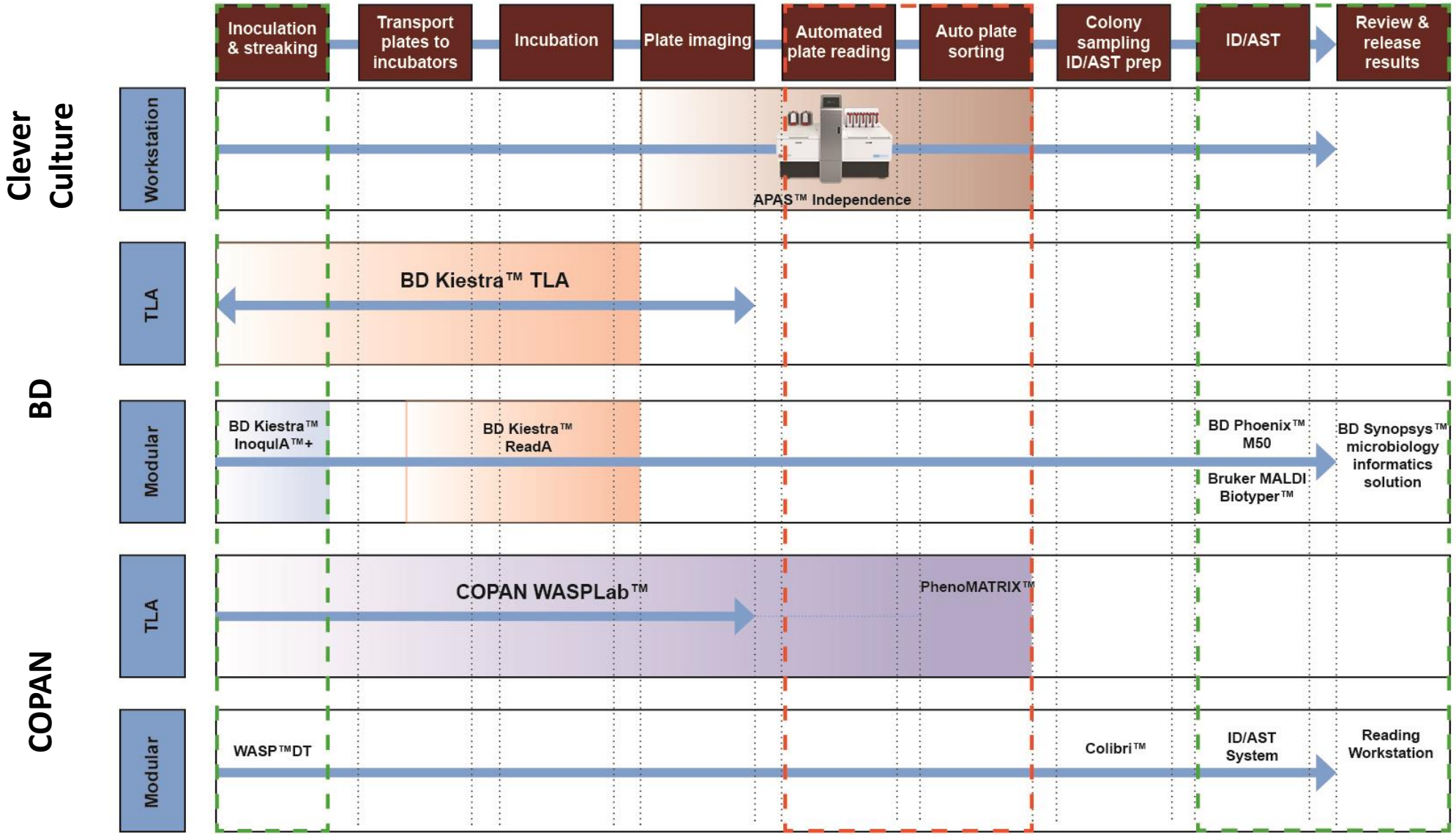
Overview of Culture-based Automation in Microbiology



WASP®DT and WASPLab® are registered trademarks and Colibi and PhenoMATRIX are trademarks of Copan Diagnostics. Kiestra, Phoenix, Synopsys and InoqulA are registered trademarks of Becton Dickinson. APAS is a trademark of Clever Culture Systems.

Automation Options : focus on help with plate reading

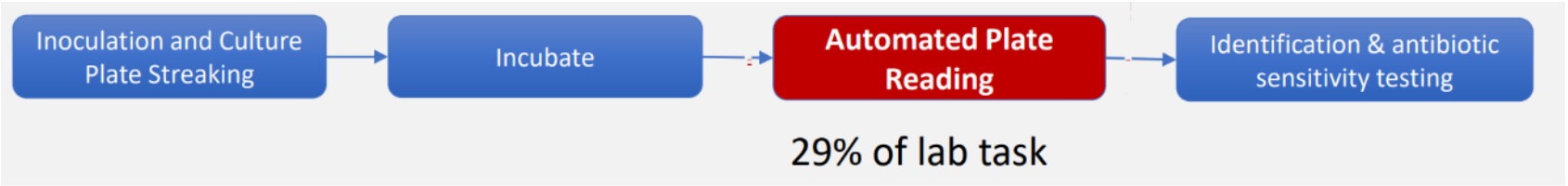
COPAN WASPLab™

BD Kiestra™ Total Lab Automation

Clever Culture Systems APAS™ Independence

APAS Independence difference:

- First FDA-cleared system for automated reading and interpretation
- Modular design- works with other solutions
- Lower acquisition threshold



For more information on the Clever Culture Systems APAS Independence, see Special Use Conditions for K183648 & K200839.

Routine Microbiology Workflow

Specimen received into Laboratory Testing Facility → Specimen received into Microbiology Laboratory → Specimen processed according to SOPs → Culture Plate reading

- No significant growth → LIS result entry → Authorise/Release report
- Significant Growth → ID/AST → LIS result entry + Authorise/Release report

APAS Independence workflow

Specimen received into Laboratory Testing Facility → Specimen received into Microbiology Laboratory → Specimen processing facilitated with APAS

Streamlined processing to utilise APAS

APAS Faster Processing 200/hr

Automated interpretation and reporting

- No significant growth + LIS entry (Auto authorise/release) → Not required → Not required
- Significant Growth/Review → ID/AST → LIS result entry + Authorise/Release report

Microbiologist Review Less plates to report

Decrease in unnecessary work

Less reports to authorise

Areas of efficiency introduced

No Sig Growth / Negative rates
Up to 70%+ for Urines
Typically >90% for MRSA, VRE, GrpA

AI in Microbiology – Plate Reading Comparisons

	APAS	PhenoMATRIX™	BD
Description	Autoverification of negative culture plates Growth description provided for positive plates	PhenoMATRIX customized for each installation Pre-sorts plates for microbiologist review	Urine culture application batches plates for review by microbiologist No automatic release of culture plates
Workflow	Flexible agnostic- can be deployed with or without other automation	Requires full COPAN WASPLab™ TLA	Requires BD Kiestra™ TLA or BD Kiestra™ ReadA Deployed via BD Synapsis™ middleware solution
Images	Plates imaged after incubation	T_0 and T_n images taken	T_0 and T_n images taken
Regulatory	Class II Medical Device (US)	Laboratories required to self-validate	Class I Medical Device (US)
Specimen Types	Available: Urine, MRSA	Chromogenic detection module: • MRSA, VRE, ESBL, Group B and A Strep Growth detection module: • Urine	Available: Urine
Media Supported	Thermo Scientific™ Blood Agar (TSA with Sheep Blood), MacConkey Agar, Spectra™ MRSA Agar BD BBL CHROMagar™ MRSA II Agar	Laboratories required to self-validate	Works with BD media only
Clinical Evidence	>15 publications and posters	Several publications demonstrating performance for VRE, MRSA, Group B Strep	1 paper identified

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Impact of AI in the microbiology lab: Intelligence

Clinical Evaluation: APAS Screening for Urine cultures

American Society for Microbiology
Journal of Clinical Microbiology

APAS® identification performance by colony type	Sensitivity	Specificity
Blood agar (all)	99.1%	99.3%
MacConkey (all)	99.4%	99.3%
Lactose-fermenters on Blood agar	98.9%	NR
Lactose-fermenters on MacConkey agar	99.2%	98.1%

Glasson, et al., 2016. Evaluation of an Image Analysis Device (APAS) for Screening Urine Cultures.

"All cases of clinical infection were detected by APAS and its associated decision algorithm during the study."

"The morphological identification of colonies showed a high level of performance for the colony types typical of E. coli and other enteric bacilli."

TABLE 2 Organisms detected by APAS compared with those by the routine laboratory reports

Organism	No. of cases detected by APAS	No. of cases reported by the laboratory
Escherichia coli	339	341
Enterococcus faecalis	38	38
Klebsiella pneumoniae	21	21
Proteus mirabilis	19	19
Pseudomonas aeruginosa	18	19
Staphylococcus saprophyticus	14	14
Klebsiella oxytoca	8	8
Staphylococcus epidermidis	7	7
Streptococcus agalactiae	6	6
Enterobacter aerogenes	5	5
Citrobacter koseri	5	5
Enterobacter cloacae complex	3	3
Morganella morganii	3	3
Viridans streptococci	3	3
Candida albicans	2	2
Citrobacter freundii	2	2
Staphylococcus, coagulase negative	2	2
Acinetobacter spp.	1	1
Aerococcus urinae	1	1
Candida spp.	1	1
Enterococcus faecium	1	1
Raoultella spp.	1	1
Serratia liquefaciens	1	1
Serratia ureilytica	1	1
Staphylococcus aureus	1	1
Staphylococcus haemolyticus	1	1
Staphylococcus hominis	1	1
Streptococcus dysgalactiae	1	1
Total	506	509

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ANNALS OF LABORATORY MEDICINE

Multicenter Evaluation of an Image Analysis Device (APAS): Comparison Between Digital Image and Traditional Plate Reading Using Urine Cultures

John Glasson, M.S.[1], Rhys Hill, B.S.[1,2], Michael Summerford, B.S.[1], Dianne Olden, Ph.D.[3], Fotula Papadopoulos, B.S.[4], Stephen Young, Ph.D.[5], and Steven Giglio, Ph.D.[1]

LBT Innovations Ltd.[1], Adelaide, Australia; Australian Centre for Visual Technologies[2], University of Adelaide, Adelaide, Australia; Australian Clinical Laboratories (formerly Healthscope Pathology)[3], Clayton, Australia; SydPath[4], St Vincent's Pathology, Darlinghurst, Australia; Tricore Reference Laboratories[5], Albuquerque, NM, USA

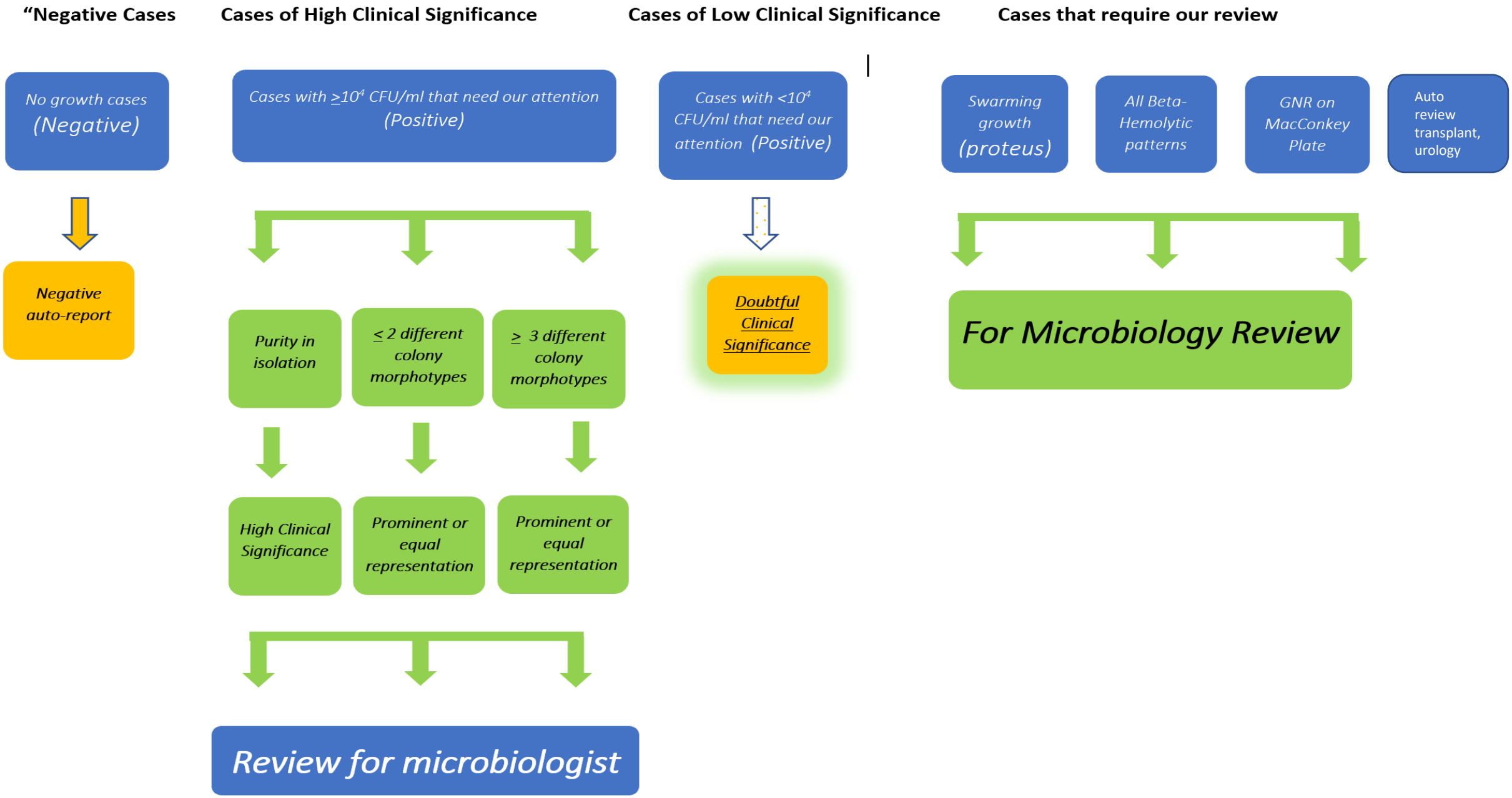
- 2017
- Publishing FDA Clinical Trial , c. 10,000 patients (US, AU)
- Overall diagnostic sensitivity of 99.0%, specificity of 84.5%

Table 2. Summary of APAS performance with urine cultures across three centers

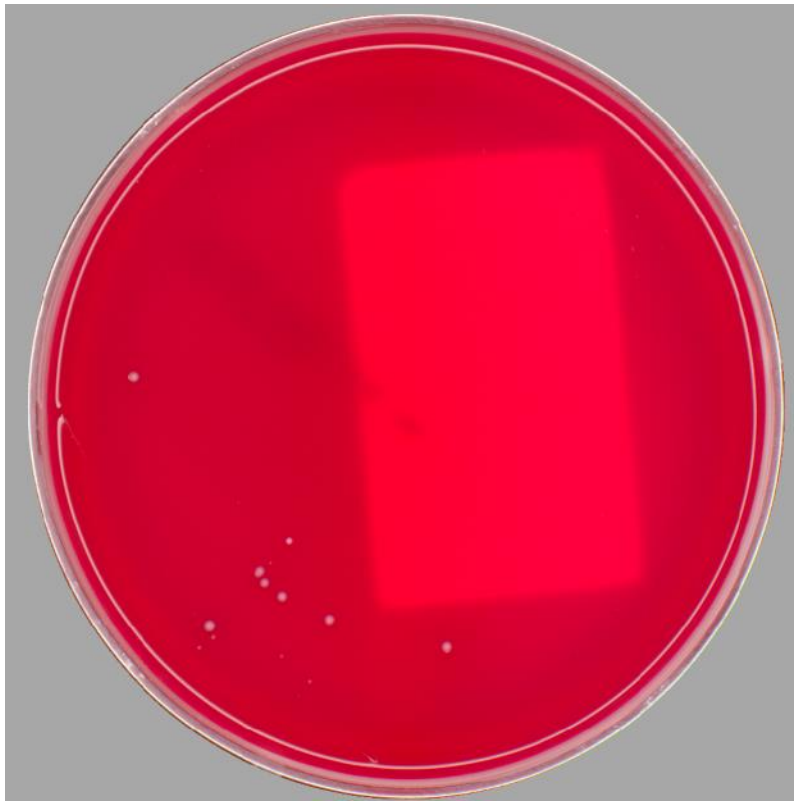
	Total cases	True positive	True negative	False positive	False negative	% Sensitivity (95% CI)	% Specificity (95% CI)
Site 1	5,634	4,144	1,490	270	41	99.0 (98.7–99.3)	81.9 (79.8–83.8)
Site 2	1,769	1,256	513	75	15	98.8 (98.0–99.3)	85.4 (82.1–88.2)
Site 3	1,821	1,184	637	63	13	98.9 (98.1–99.4)	90.1 (87.5–99.2)
Pooled	9,224	6,584	2,640	408	69	99.0 (98.7–99.2)	84.5 (83.1–85.9)

The Role of Laboratory Automation in Screening and Reviewing Urine Cultures

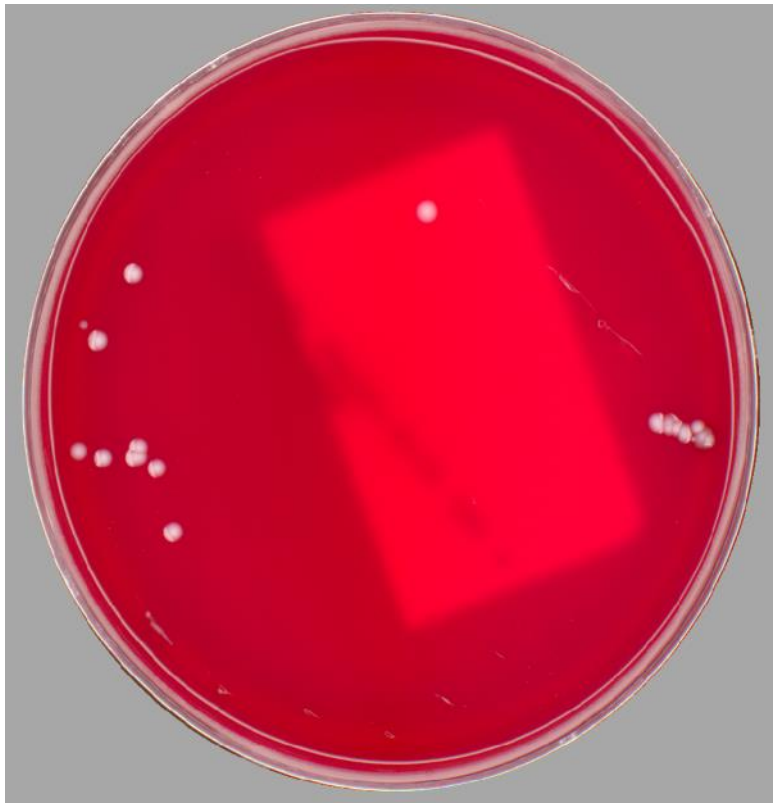
- **Question: What are we asking automation in Urine Culture Review to do?**
  - Identify cases that meet criteria for urine culture work up
  - Identify cases that don't meet criteria for work up
  - Questions?
    - Can it identify cases of no growth and auto-remove from the workflow
    - Can it identify cases $>10^4$ that we can route to the techs
    - Can it identify cases $<10^4$ that we can route to the techs


"Negative Cases
Cases of High Clinical Significance
Cases of Low Clinical Significance
Cases that require our review
No growth cases (Negative)
Negative auto-report
Cases with ≥10⁴ CFU/ml that need our attention (Positive)
Purity in isolation
≤ 2 different colony morphotypes
≥ 3 different colony morphotypes
High Clinical Significance
Prominent or equal representation
Prominent or equal representation
Review for microbiologist
Cases with <10⁴ CFU/ml that need our attention (Positive)
Doubtful Clinical Significance
Swarming growth (proteus)
All Beta-Hemolytic patterns
GNR on MacConkey Plate
Auto review transplant, urology
For Microbiology Review

Examples of the Digital Image Capture and Urine Culture Calling with the APAS



2 morphotypes >10^4 CFU/ml



≥3 morphotypes >10^4 CFU/ml

“swarming” category

APAS : Ability to remove negative cultures from our Urine Culture Workflow

- **QUESTION: What is the Accuracy of the APAS in detecting no growth urine cultures?**

- 6200 clinical specimens
- 1860 cultures removed as true “no growth” cases
- APAS successfully removed 30% of cases from the clinical laboratory workflow

100% Agreement with Manual clincal interpretation

1860/1860

Conclusion:

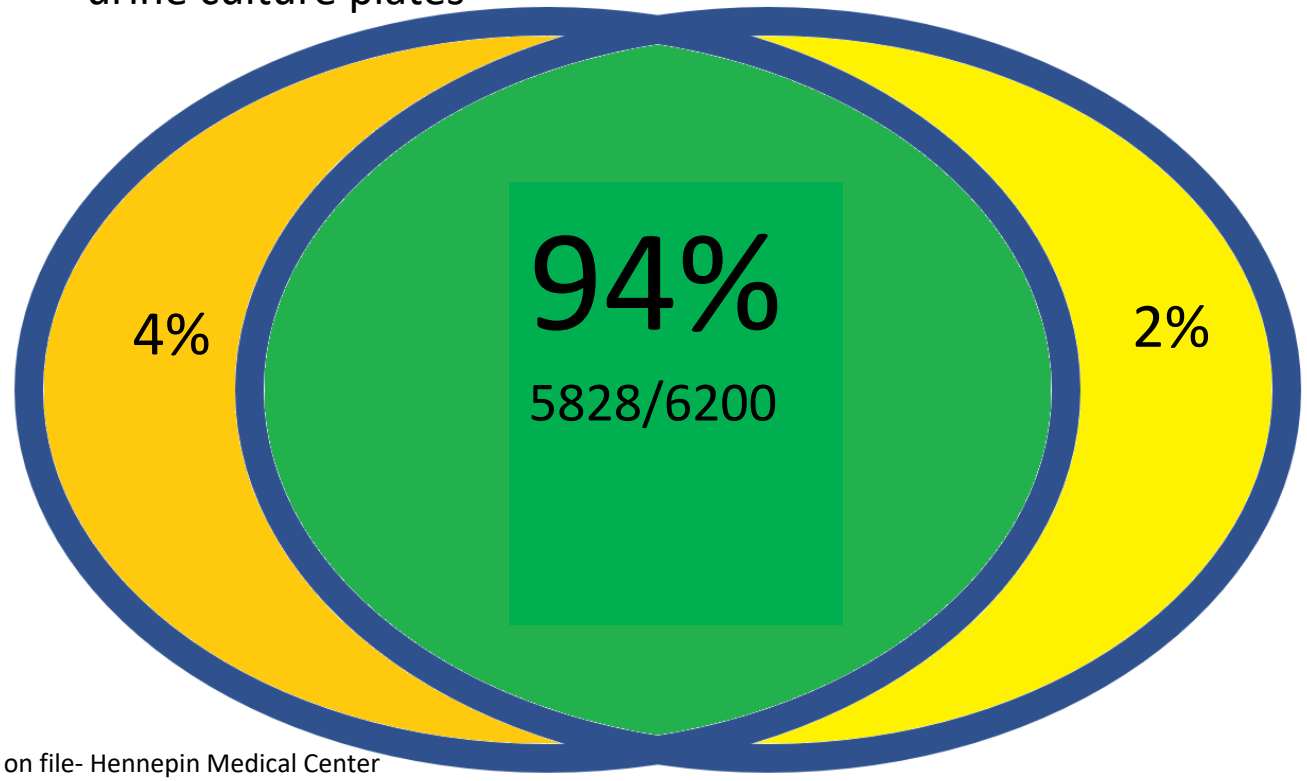
APAS has 100% agreement in reviewing, interpreting, and removing “no growth” urine cultures from clinical practice

Data on file- Hennepin Medical Center

APAS vs Clinical technologist: Ability to detect negative cases and >10^4 CFU/ml quantitated Urine Culture Plates

- **QUESTION: Can APAS correctly innumerate urine culture plates and identify cases for review >10^4**

- 6200 clinical specimens
- APAS detection vs Clinical Technologists bench Read
- Metric of Study = Ability of the APAS to correctly identify >10^4 or <10^4 CFU/mL on quantitated urine culture plates



2% = 125/6200 defect in the media or label misread

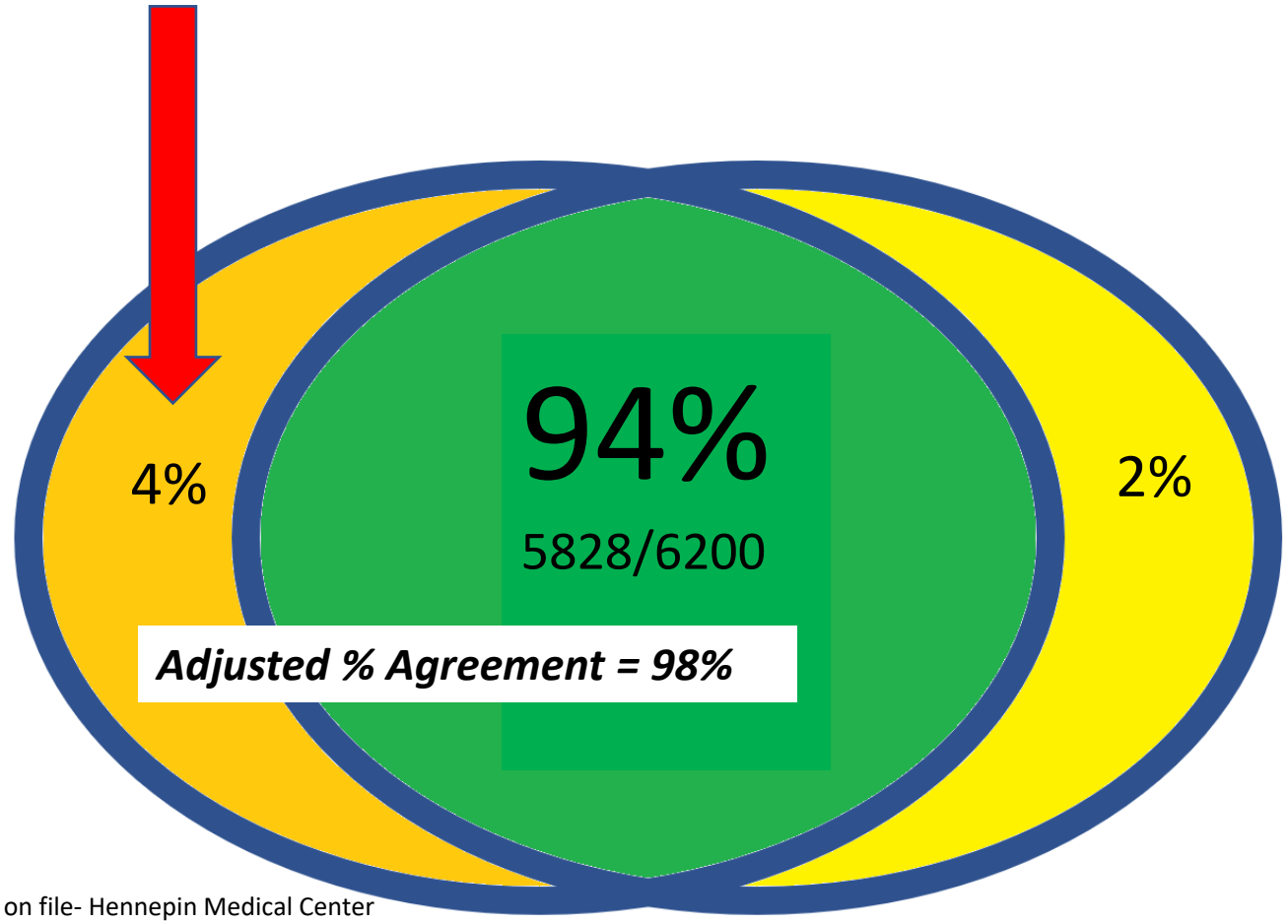
4% = 247/6200 APAS detection of small alpha streptococci not detected by the APAS

Adjusted % agreement = 98%

Data on file- Hennepin Medical Center

Let’s review the 4% of cases

- **QUESTION: What is the impact of the “4%?**



4% = 247/6200 APAS detection of small alpha streptococci not detected by the APAS

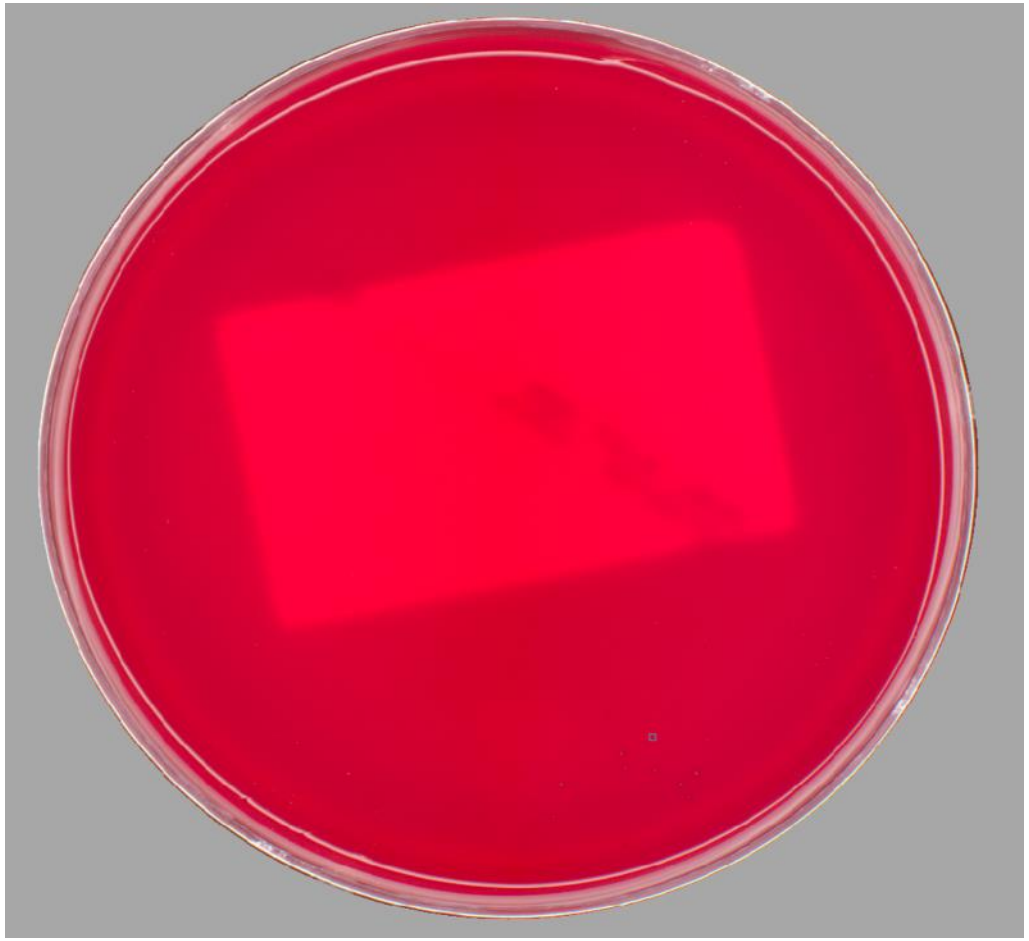
***0.8% of these cases were determined to be clinically reportable as Staphylococcus Saprophyticus**

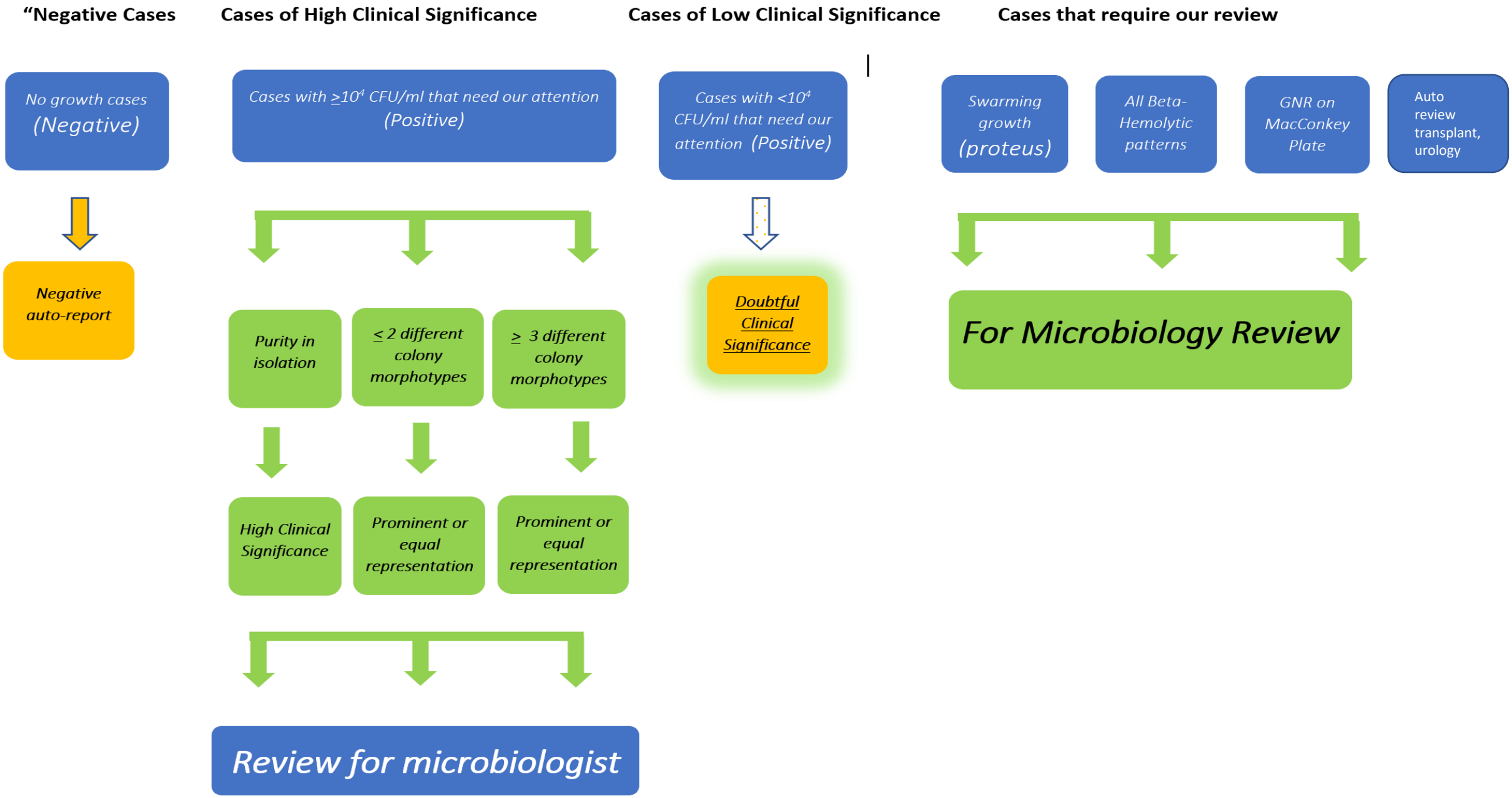
***1.2% of these cases involved detection of non-beta hemolytic GroupB Streptococci in women of child-bearing years at quantitation <10^4 CFU/ml**

***Removing cases involving small colony alpha-Streptococci species from clinical workflow saved 16.4 hrs. of cumulative technologist time (ave 4mins/case)**

Data on file- Hennepin Medical Center

Doubtful Clinical Significance? Can we use this category to auto-verify these cases to remove them from the workflow?

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All Beta-Hemolytic patterns
GNR on MacConkey Plate
Auto review transplant, urology
For Microbiology Review

Hennepin County Medical Center (USA) APAS Urine Culture Reporting

	Reporting Criteria	Impact on Clinical Workflow	Percentage of Clinical Cases
Positive =	* >10(4) cfu/ml &/or and GNR growth on the MacConkey plate * Detection of Beta-hemolysis on Sheep Blood Agar Plate	High priority Cultures	27%
Negative =	no growth	Auto Cleared from the workflow	16.2%
To Technologist Review	= >10(4) cfu/ml and/or swarming on the plate	Review for technologist– low priority	4%
HCMC "doubtful" classification	= <10(3) cfu/ml, no beta-hemolysis, no GNR on the MAC	Review for technologist –low priority	19.7%

Up to 35.9% (16.2% + 19.7%) of cases are auto-cleared by the APAS from the clinical workflow

Data on file- Hennepin Medical Center

What do we do if we use Chromogenic media?

Medium	No. of specimens[a]					Value (% [95% CI])[b]			
	Tested	APAS+ MN+	APAS− MN−	APAS+ MN−	APAS− MN+	PPA	NPA	PPV	NPV
CHROMagar MRSA II	5,913	236	5,525	152	0	100 (96–100)	97.3 (97–97.5)	60.8 (59.3–62.3)	100 (96–100)
CHROMagar Staph aureus	744	133	585	20	6[c]	95.7 (92.7–98.7)	96.7 (94.5–98.9)	86.9 (80.7–93.1)	99 (92–100)

[a]APAS, APAS analytical module; MN, manual reading.

[b]PPA, positive percent agreement; NPA, negative percent agreement; PPV, positive predictive value; NPV, negative predictive value; CI, confidence interval.

[c]Upon rereview, one of these was misidentified by the technologist on manual read and is a true negative.

Strain	No. of specimens with:[a]					
	Pink inoculum[b]	Positive manual read and negative APAS results	Pink colonies	False-positive manual read and negative APAS results	True positive missed by manual read	Agar issues
MRSA	85	0	44	0	5	18
S. aureus	10	5	5	1	5	0

[a]APAS, APAS analytical module.

[b]Pink inoculum was seen more frequently with traditional swab samples than with ESwab samples.

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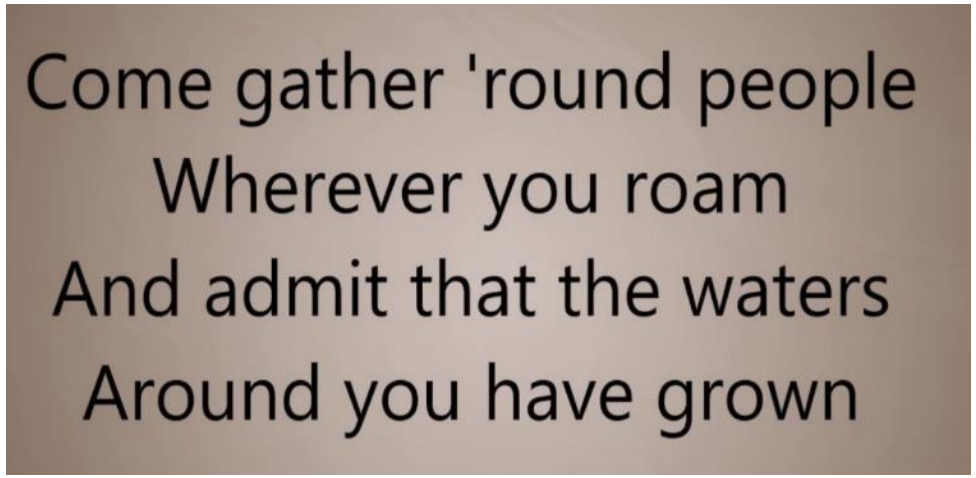
The Waters are Changing



The times they are a-changing.
- Bob Dylan

Conclusions:

1.) Updated tools are needed for microbiology

2.) Automation in the lab can help define the workflow and optimize our talent.

- The APAS system can help stratify our urine culture work
  - Identifying the cases that require review while removing 35% of the cases from the workflow

3.) Automation provides the provision of highly accurate and quicker reporting. Ongoing work to evaluate the impact on workflow and relative value unit savings of this lab automation is occurring

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