

Advances in the Diagnosis of Periprosthetic Joint Infection

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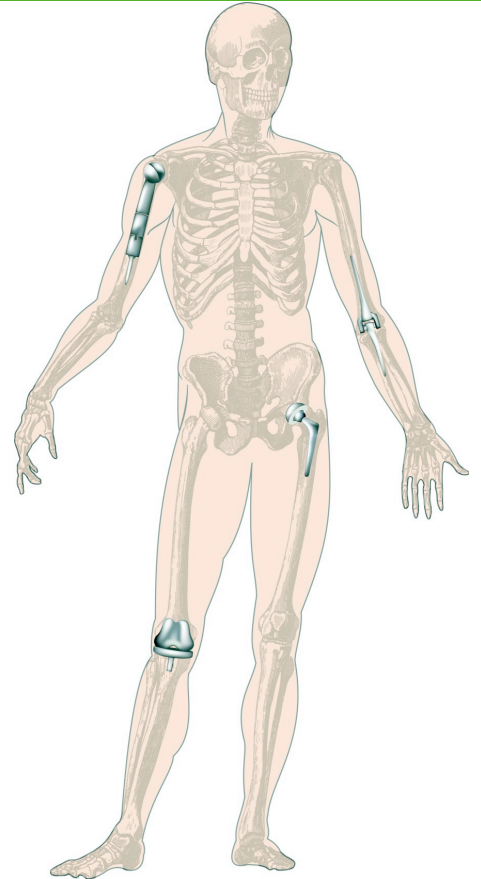
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Déclaration d'intérêts

- **Contracted Research: ContraFect, TenNor Therapeutics Limited, and BioFire**
- **Consultant: Curetis, PathoQuest, Selux Diagnostics, 1928 Diagnostics, PhAST, Torus Biosystems, Day Zero Diagnostics, Mammoth Biosciences, CARB-X, Qvella, Netflix**
- **Mayo Clinic and I have a relationship with Adaptive Phage Therapeutics and Pathogenomix**
- **Patents: *Bordetella pertussis/parapertussis* PCR; device/method for sonication; anti-biofilm substance**

Outline

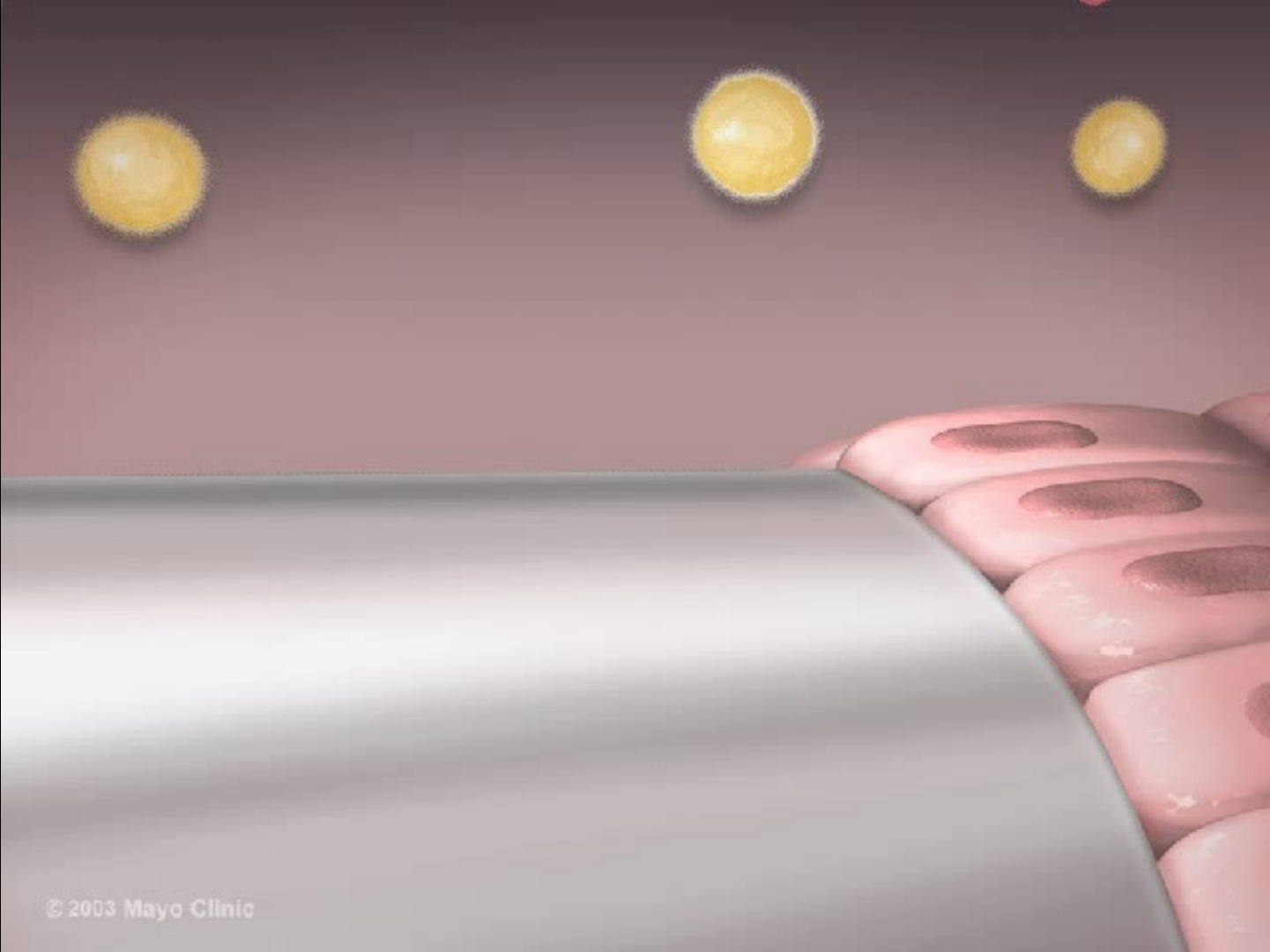


- **The challenge**
- **Biomarker-based diagnostics**
- **Culture-based diagnostics**
- **Molecular diagnostics**

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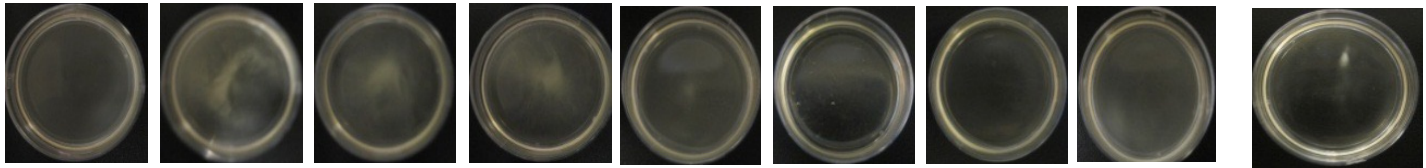




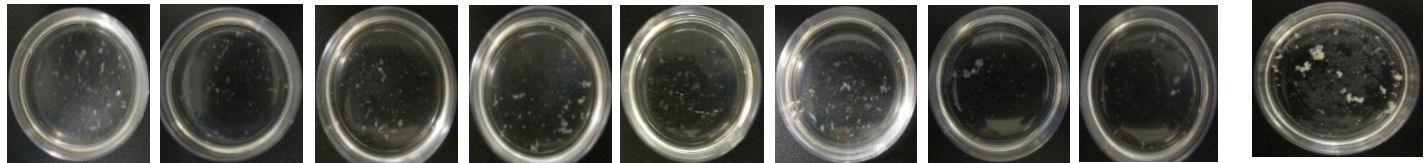
Biofilm-Like Aggregation - Synovial Fluid



Trypticase
Soy Broth



Synovial
Fluid



RP62A-7073

IDRL-8873

IDRL-8933

IDRL-8934

IDRL-8864

IDRL-8866

IDRL-8849

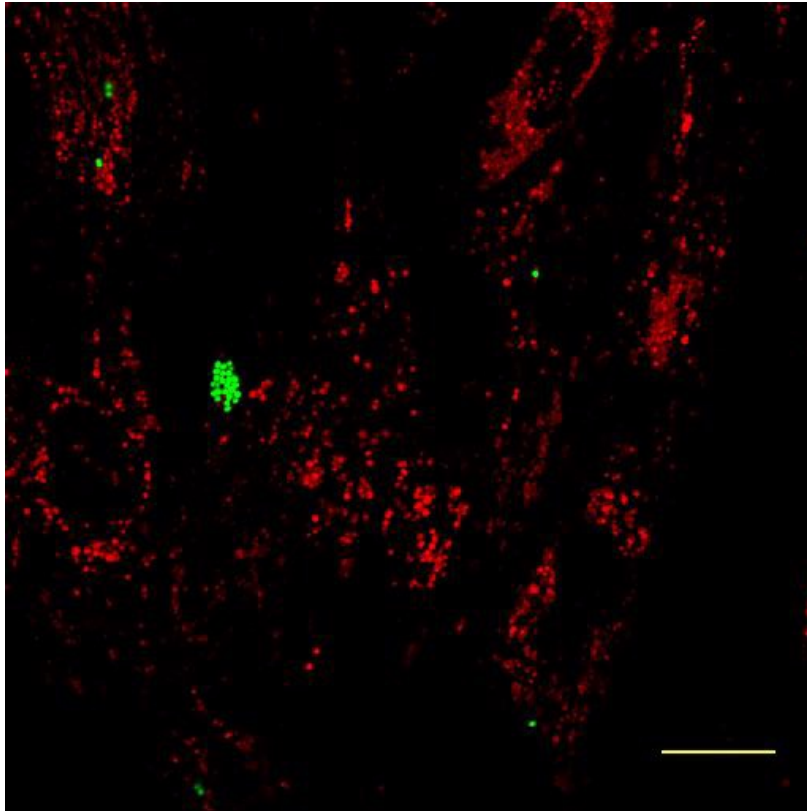
IDRL-8850

USA 300

Staphylococcus epidermidis

Staphylococcus aureus

Intracellular Survival/Growth



Human fibroblasts infected with *Staphylococcus aureus* USA300-GFP

Lysosomes visualized with LAMP-2 antibody with Alexa Fluor 594

Images collected starting 4 hours post infection.
One image acquired every 10 minutes for 4 hours

Microbiology of Hip and Knee Periprosthetic Infection



Microorganism	Total <i>n</i> = 2067 <i>n</i> (%)	Early <i>n</i> = 442, <i>n</i> (%)	Delayed <i>n</i> = 305 <i>n</i> (%)	Late <i>n</i> = 1320 <i>n</i> (%)
Aerobic Gram-positive bacteria:	1698 (82)	372 (84)	260 (85)	1066 (81)
Coagulase-neg <i>Staphylococcus</i> species	761 (37)	165 (37)	115 (38)	481 (36)
<i>Staphylococcus aureus</i> complex	497 (24)	140 (32)	79 (26)	278 (21)
<i>Staphylococcus lugdunensis</i>	77 (4)	7 (2)	13 (4)	57 (4)
<i>Streptococcus</i> species	287 (14)	36 (8)	48 (16)	203 (15)
<i>Enterococcus</i> species	155 (8)	38 (9)	20 (7)	97 (7)
<i>Corynebacterium</i> species	105 (5)	32 (7)	16 (5)	57 (4)
Aerobic Gram-negative bacteria:	222 (11)	57 (13)	43 (14)	122 (9)
Enterobacterales	143 (7)	32 (7)	28 (9)	83 (6)
<i>Pseudomonas</i> species	64 (3)	16 (4)	14 (5)	34 (3)
Anaerobic bacteria:	262 (13)	72 (16)	35 (11)	155 (12)
<i>Cutibacterium</i> species	164 (8)	45 (10)	20 (7)	99 (8)
Other anaerobic bacteria	108 (5)	29 (7)	20 (7)	59 (4)
Fungi	65 (3)	9 (2)	15 (5)	41 (3)
Mycobacteria	12 (0.5)	3 (0.7)	6 (2)	3 (0.2)

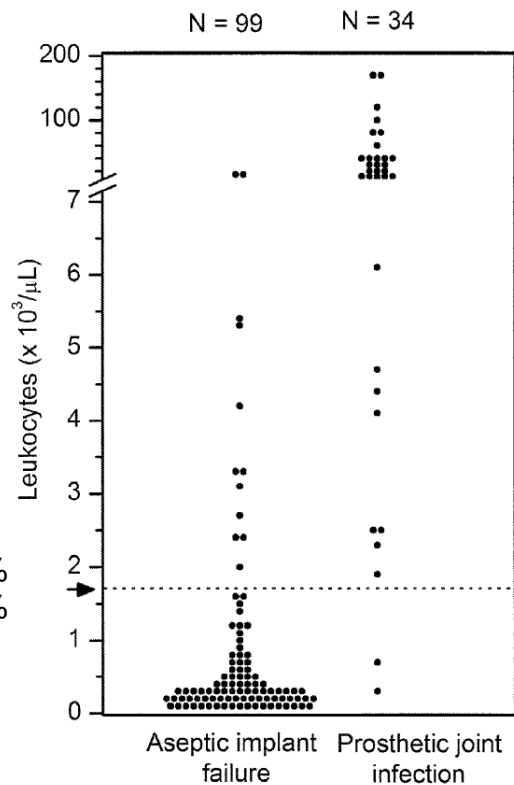
Tai et al. Clin Microbiol Infect
2022;28:255-9

Outline

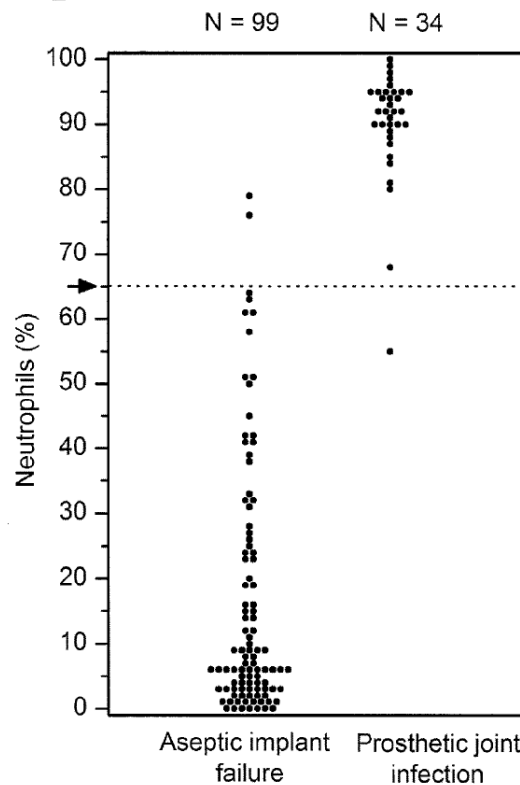
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Synovial Fluid Leukocyte/%Neutrophils



Sensitivity, 94%
Specificity, 88%



Sensitivity, 97%
Specificity, 98%

Synovial Fluid Leukocyte Esterase

Study	Hip/Knee Arthroplasties	Sensitivity (%)	Specificity (%)
Parvizi et al. (2011, Chemstrip 7 urine test strip)	0/108	81	100
Shafafy et al. (2015, Multistix 8 SG)	30/79	81	93
Koh et al. (2017, multiple)	0/60	84	100
Sharma et al. (2020, Siemens Multistix 10 SG)	14/93	90	84
Sharma et al. (2020, Chemstrip 10 MD)	14/93	81	95



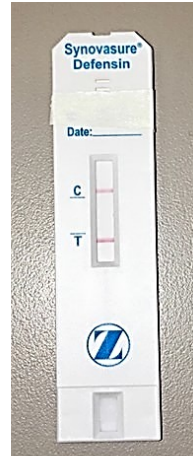
Sharma et al. J Orthop Res 2020;38:2264-74
 AAOS. www.aaos.org/pjguideline. 2019
 Moderate ***

Synovial Fluid C-Reactive Protein

Study		Hip/Knee Arthroplasty	Threshold	Sensitivity (%)	Specificity (%)
Vanderstappen et al. (2013)	Preoperative	0/44	2.8 mg/L	91	94
Tetreault et al. (2014)		59/60	6.6 mg/L	88	85
Omar et al. (2015)		89/0	2.5 mg/L	96	93
Sharma et al. (2020)		14/93	5.65 mg/L	80	92
Sousa et al. (2017)	Intraoperative	15/30	6.7 mg/L	78	94

Sharma et al. J Orthop Res 2020;38:2264-74
AAOS. www.aaos.org/pjiguide. 2019
Moderate ***

Synovial Fluid Alpha-Defensin



Assay	Knee/Hip Arthroplasty	Sensitivity (%)	Specificity (%)
ELISA			
Deirmengian et al. (2014)	84/11	100	100
Deirmengian et al. (2015)	43/3	100	100
Deirmengian (2014)	116/33	97	96
Frangiamore et al. (2016)	78*	100*	98*
	38**	67**	97**
Bonanzinga et al. (2017)	65/91	97	97
Kelly et al. (2018)	33/6	82	82
Sigmund et al. (2018)	54/17	85	98
Stone et al. (2018)	121/62	81	96
Deirmengian et al. (2020)	203/102	89	98
Ivy et al. (2021)	106/25	94	97
Lateral Flow			
Bingham et al. (2014)	61**	100	95
Kasperek et al. (2016)	29/11	67	93
Sigmund et al. (2017)	17/30*	69	94
Okroj et al. (2017)	0/26	100	68
Balato et al. (2017)	51/0	88	97
Berger et al. (2017)	85/36	97	97
Suda et al. (2017)	19/11	77	82
Gehrke et al. (2018)	99/96	92	100
Renz et al. (2018)	151/61	84	96
Sigmund et al. (2018)	54/17	77	98
Deirmengian et al. (2020)	203/102	94	95
Ivy et al. (2021)	106/25	91	93

*Analysis of first or single-stage revision;
**Analysis of second-stage revision (i.e., re-implantation)

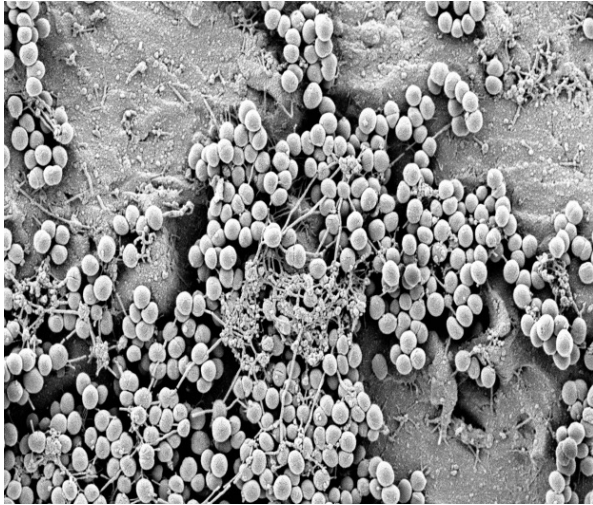
AAOS. 2019
Moderate ***

www.aaos.org/pijguideline

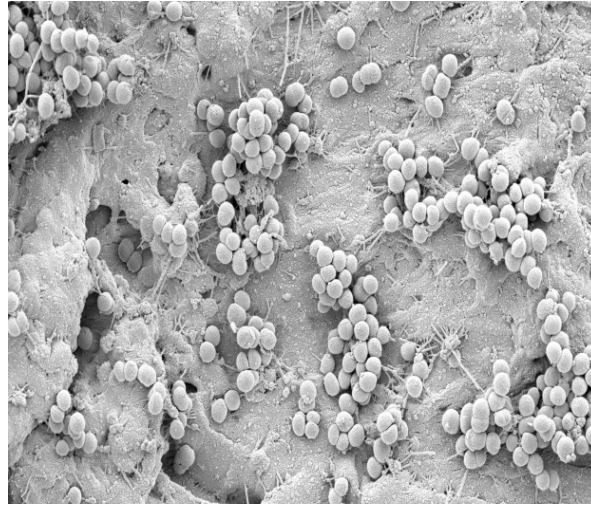
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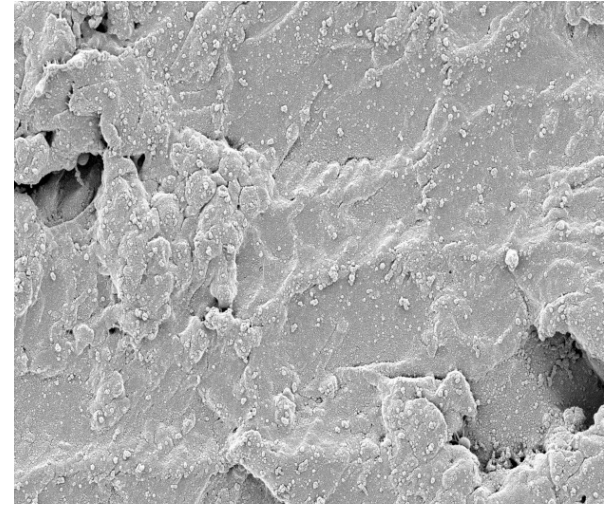
Staphylococcus epidermidis Biofilm (Polycarbonate Coupons)



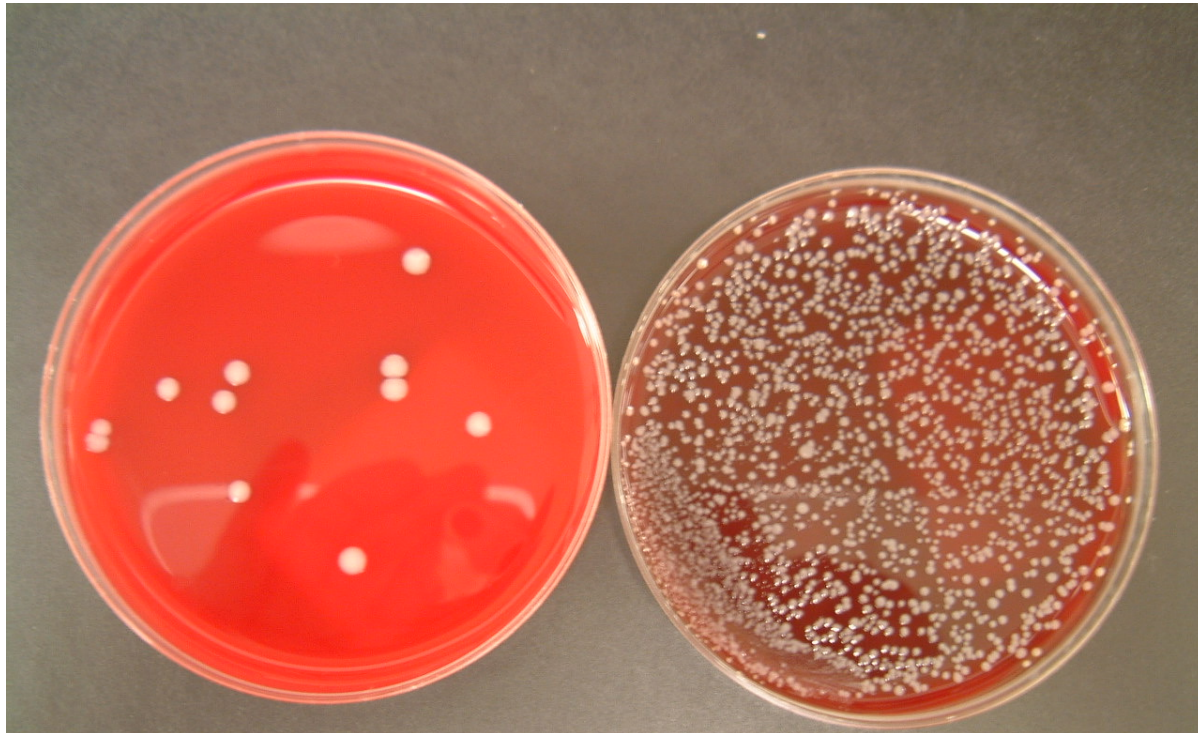
Soaking



Scraping



Sonication



Tissue

Sonicate Fluid

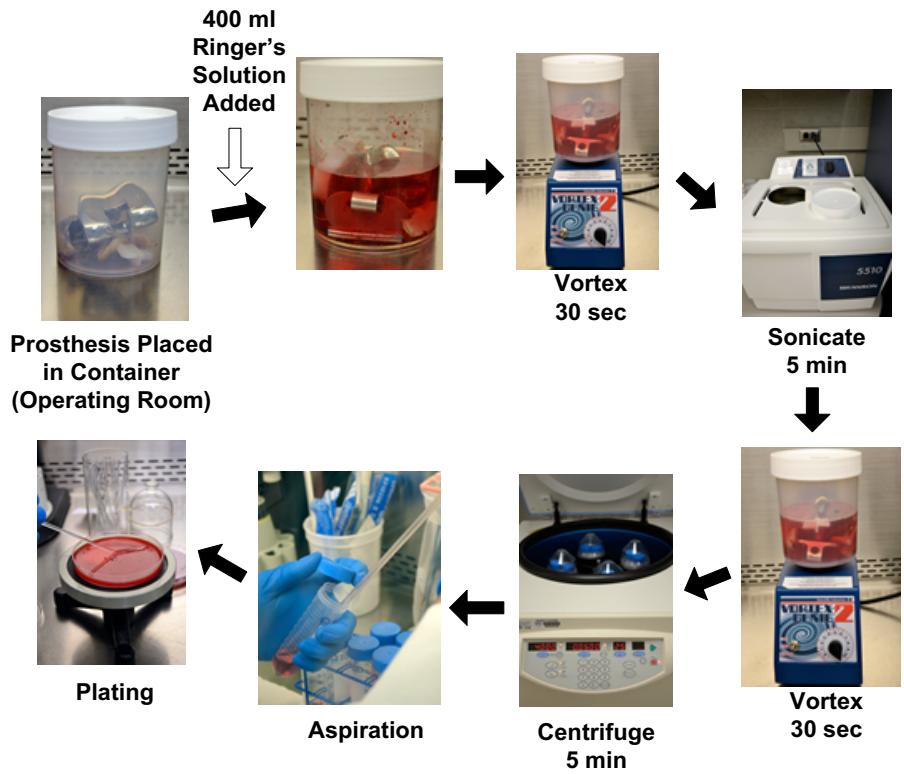
Sonicate Fluid *versus* Tissue Culture

Orthopedic Foreign Body Infection Diagnosis

Implant type		Sonicate fluid	Periimplant tissue	p value	Reference
Hip/knee arthroplasties	Sensitivity	79%	61%	<0.001	Trampuz et al. NEJM 2007;357:654
	Specificity	99%	99%		
Shoulder arthroplasties	Sensitivity	67%	55%	0.046	Piper et al. JCM 2009;47:1878
	Specificity	98%	95%		
Spine implants	Sensitivity	83%	69%	0.07	Carlson et al. Spine 2020;45:E525
	Specificity	92%	94%		
Elbow arthroplasties	Sensitivity	76%	63%	0.11	Flurin et al. JSES 2021;30:1741
	Specificity	100%	94%		
Hip/knee/shoulder arthroplasties, mega-prostheses, osteosyntheses, spine implants	Sensitivity	83%	61%	0.034	Holinka et al. J Orthop Res 2011;29:617
	Specificity	95%	95%		
Hip/knee arthroplasties, tibial inserts, acetabular components, fixation devices, spinal devices, etc.	Sensitivity	90%	67%	<0.001	Puig-Verdie et al. Bone Joint J 2013;95-B(2):244-9
	Specificity	99%	99.5%		
Hip arthroplasties	Sensitivity	75%	69%		Bogut et al. Polish J Microbiol 2014;63:299
	Specificity	97%	100%		
Hip/knee arthroplasties, internal device	Sensitivity	77%	34%	<0.002	Scorzolini et al. New Microbiol 2014;37:321
Fracture fixation implant (plate, screws, spine implant, intramedullary nail)	Sensitivity	90%	57%	<0.001	Yano et al. J Clin Microbiol 2014;52:4176
	Specificity	91%	96%		
Hip/knee/shoulder/elbow arthroplasties	Sensitivity	81%	61%	<0.01	Portillo et al. J Infect 2014;69:35e41
	Specificity	99%	100%		
Hip/knee arthroplasties	Sensitivity	97%	70%	<0.001	Rothenberg et al. Clin Orthop Relat Res 2017;475:1827
	Specificity	90%	97%		
Modular megaprostheses	Sensitivity	91%	52%	0.004	Puchner et al. J Orthop Res 2017
	Specificity	100%	100%		
Hip/knee/other arthroplasties	Sensitivity	47%	68%		Van Diek et al. Acta Orthopaedica, 2018;88;294-299
	Specificity	99%	80%		
Hip/knee arthroplasties	Sensitivity	77%	56%	0.012	Tani et al. Eur J Orthop Surg Trauma 2018;28:51
	Specificity	98%	94%		
Shoulder arthroplasties	Sensitivity	56%	96%		Grosso et al. J Shoulder Elbow Surg 2018;27; 211
	Specificity	99%	75%		
Hip/knee arthroplasties	Sensitivity	93%	67%	0.02	Sebastian et al. J Microbiol Meth 2018;146:51
	Specificity	100%	100%		
Hip/knee/shoulder arthroplasties	Sensitivity	70%	53%	0.001	Prieto-Borja et al. Eur J Clin Microbiol Infect Dis 2018;37;715
	Specificity	98%	91%		
Multiple	Sensitivity	57%	69%		Dudareva et al. J Clin Microbiol 2018 Vol 56:1
	Specificity	94%	97%		
Megaprostheses	Sensitivity	98%	86%	<0.001	Sambri et al. Orthopedics 2019 Vol 42:28
	Specificity	94%	100%		
Spine implants	Sensitivity	94%	66%	0.002	Bürger et al. Eur Spine J 2019 Vol 28;768
	Specificity	99%	96%		
Hip/knee/ankle/elbow arthroplasties	Sensitivity	71%	29%	0.02	Ueda et al. J Arthroplasty 2019 Vol 34:1189
	Specificity	100%	100%		

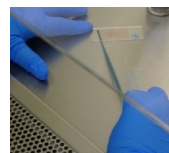
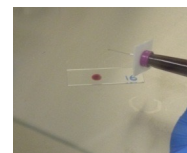


Mayo Clinic Orthopedic Implant Processing



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Periprosthetic Tissue Culture - Blood Culture Bottles



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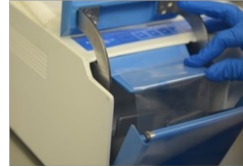
Periprosthetic Tissue Blood Culture Bottle Study



- **Patients undergoing revision arthroplasty, Mayo Clinic, 8/2013–4/2014**
 - 369 subjects - 138 hip, 160 knee, 49 shoulder, 22 elbow arthroplasties
 - 117 (32%) IDSA diagnostic criteria for PJI



Peri-prosthetic tissue sample



Tissue sample homogenized

Conventional Culture Technique:
Homogenate inoculated onto agars and broth



Media manually checked daily for growth and sub-cultured if growth detected

New Technique:
Homogenate inoculated into blood culture bottles and placed onto the semi-automated machine



Bottles continuously monitored for growth and sub-cultured if flagged positive



Blood Culture Bottle Study

Bayesian Latent Class Modeling



Media Combination	Sensitivity	Specificity
Aerobic and anaerobic agars	48.9	99.7
Aerobic and anaerobic agars and thioglycollate broth	62.6	98.1
Aerobic and anaerobic blood culture bottles	92.1	99.7
Aerobic and anaerobic blood culture bottles and thioglycollate broth	92.1	98.8
Aerobic and anaerobic blood culture bottles and aerobic agar	94.6	99.7
Aerobic and anaerobic blood culture bottles and anaerobic agar	96.8	99.8
Aerobic and anaerobic blood culture bottles and aerobic and anaerobic agars	99.1	99.7
All media combined	99.1	97.3

Peel et al. mBio 2016;7:e01776

Tissue Cultures in Blood Culture Bottles

Laboratory Staff Time



Periprosthetic Tissue Culture



- **499 consecutive patients undergoing revision arthroplasty (August 2013 through April 2014)**
- **1,437 periprosthetic tissue samples**
- **Conventional culture techniques (aerobic & anaerobic sheep blood agars, thioglycolate broth)**
 - **Greatest accuracy with four specimens (91%; 95% Credible Interval: 77-100%)**
- **Inoculation of tissues into aerobic & anaerobic blood culture bottles**
 - **Greatest accuracy with three specimens (92%; 95% Credible Intervals: 79-100%)**

Tissue Culture in Blood Culture Bottles *versus* Sonication



IDSA PJI criteria as gold standard			Bayesian latent class modeling				
	Subjects with		Sensitivity	Specificity	Prevalence	Sensitivity	Specificity
	PJI	Aseptic failure	% (95% confidence interval)		% (95% credible interval)		
	104	125			37.2 (31.1, 43.5)		
Tissue	69	5	66.4 (56.4, 75.3)	96.0 (90.9, 98.7)		86.3 (78.3, 92.4)	99.6 (97.7, 100.0)
Sonicate fluid	76	0	73.1 (63.5, 81.3)	100.0 (97.1, 100.0)		88.7 (81.0, 94.3)	99.6 (97.7, 100.0)
Combination	80	5	76.9 (67.6, 84.6)	96.0 (90.9, 98.7)		99.1 (95.7, 100.0)	99.5 (97.6, 100.0)

Fungal & Mycobacterial Stains and Cultures Should Not Be Routinely Ordered



- **Hip or knee PJI 2010-2019**
- **2,067 PJI episodes**
 - 3,629 fungal & 2,923 mycobacterial cultures
 - At least one in 56% of episodes (n = 1,157)
- **Test positivity fungal & mycobacterial cultures 5% (n = 179) & 1% (n = 34), respectively**
- **40 true fungal & 8 true mycobacterial PJIs**
- **Blood culture bottle-based cultures 90% sensitive in diagnosing true fungal PJI; 100% sensitive in detecting rapidly growing mycobacteria**
- **Fungal stains in 27 true fungal PJI – 4 positive (15% sensitivity)**
- **No mycobacterial stain positive**

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16S rRNA Gene-based Targeted Metagenomic Sequencing Assay of Synovial Fluid



- **Synovial fluids clinically tested 8/2020-5/2021**
- **Hip, knee, shoulder, elbow arthroplasties**
- **154 patients (36 PJI)**
- **Clinical sensitivity and specificity for PJI diagnosis 69% and 100%, respectively, for targeted metagenomic sequencing; 72% and 100%, respectively, for culture (p=0.74)**
- **Combination of both more sensitive (83%) compared to culture alone (p=0.04)**
- **Targeted metagenomic sequencing led to significant changes in treatment in 4/36 (11%) PJI subjects**

BioFire Joint Infection Panel



Anaerococcus prevotii/vaginalis
Clostridium perfringens
Cutibacterium avidum/granulosum
Enterococcus faecalis
Enterococcus faecium
Fingoldia magna
Parvimonas micra
Peptoniphilus
Peptostreptococcus anaerobius
Staphylococcus aureus
Staphylococcus lugdunensis
Streptococcus spp.
Streptococcus agalactiae
Streptococcus pneumoniae
Streptococcus pyogenes
Bacteroides fragilis
Citrobacter
Enterobacter cloacae complex

Escherichia coli
Haemophilus influenzae
Kingella kingae
Klebsiella aerogenes
Klebsiella pneumoniae group
Morganella morganii
Neisseria gonorrhoeae
Proteus spp.
Pseudomonas aeruginosa
Salmonella spp.
Serratia marcescens
Candida spp.
Candida albicans
IMP, KPC, NDM, OXA-48-like, VIM, CTX-M
mecA/C and MREJ
vanA/B

BioFire Joint Infection Panel



- **60 synovial fluids from patients with knee arthroplasty failure**
- **BioFire Joint Infection panel vs 16S rRNA gene-based targeted metagenomic sequencing vs culture**
- **Case classification - IDSA diagnostic criteria**

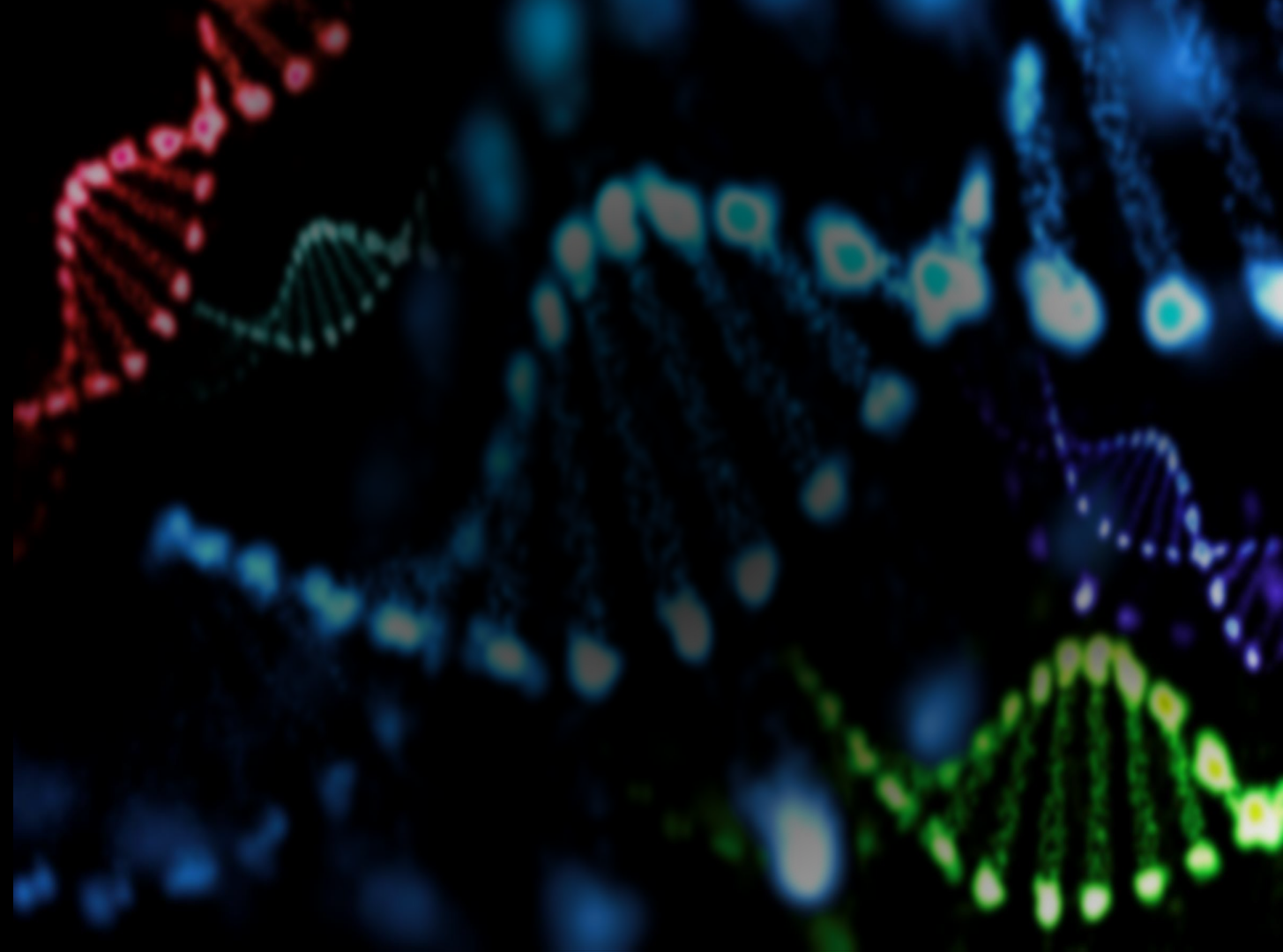
BioFire Joint Infection Panel



Organism-specific findings - culture-positive synovial fluids	Detected/total	
	BioFire	Targeted metagenomic sequencing
On Panel		
<i>Staphylococcus aureus</i>	11/11	12/12
<i>Enterococcus</i> species	1/1	1/1
<i>Staphylococcus lugdunensis</i>	2/2	2/2
<i>Streptococcus salivarius</i> group	0/1	1/1
<i>Streptococcus mitis</i> group	2/2	2/2
Group C <i>Streptococcus</i> species	1/1	1/1
<i>Pseudomonas aeruginosa</i>	1/1	1/1
<i>Serratia marcescens</i>	2/2	2/2
<i>Enterobacter cloacae</i> complex	0/1	1/1
<i>Candida albicans</i>	1/1	0/1
Off Panel		
<i>Staphylococcus epidermidis</i>	0/12	12/12
<i>Corynebacterium striatum</i>	0/1	1/1
<i>Lelliottia</i> species	0/1	1/1
<i>Haemophilus parainfluenzae</i>	0/1	1/1

- **Sensitivity culture-positive PJI - pathogens targeted by JIP**
 - BioFire 95%
 - Targeted metagenomic sequencing 95% (p=1.00)
- **Overall sensitivity**
 - **BioFire 56%**
 - Targeted metagenomic sequencing 93% (p<0.001)
- **Specificity**
 - BioFire 100%
 - Targeted metagenomic sequencing 94%





Sonicate Fluid Shotgun Metagenomic Sequencing



	Samples	Identical Findings	Organisms Not Identified by Metagenomics	New Organisms Detected by Metagenomics
Aseptic Failures	195	188 (96.4%)	N/A	7 (3.6%)
Culture-Positive PJI	115	99 (86.1%)	6 (5.2%)	11 (9.6%)
Culture-Negative PJI	98	55 (56.1%)	N/A	43 (43.9%)

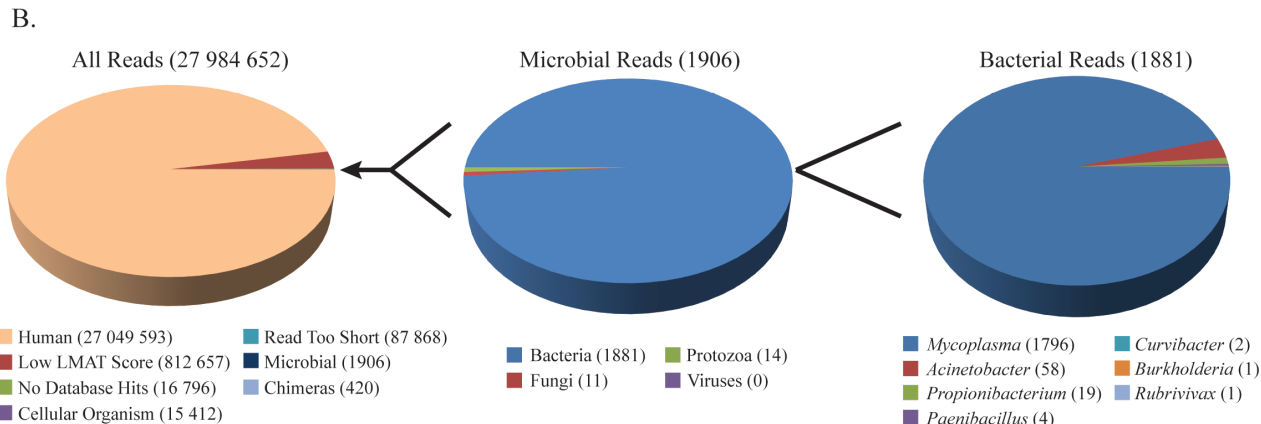
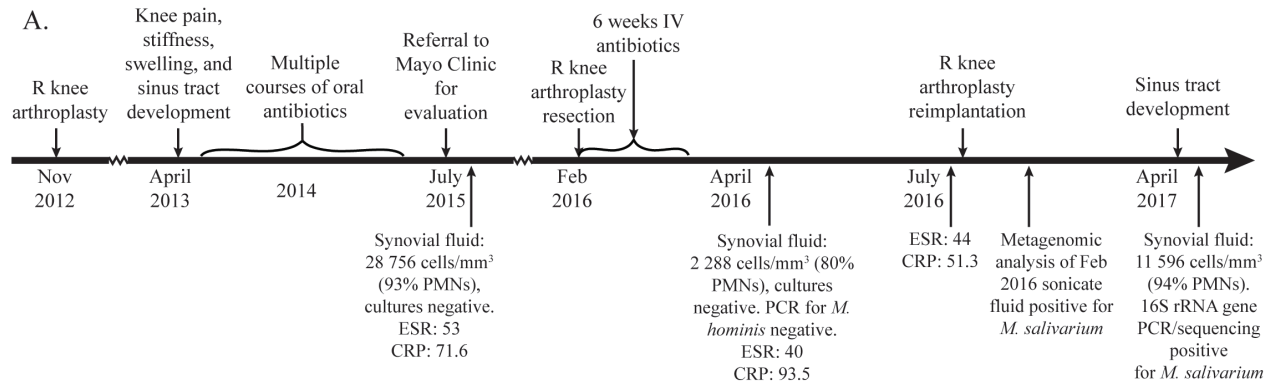


New or Missed Identifications by Shotgun Metagenomics vs. Sonicate Fluid Culture

PJI Organisms Not Detected by Shotgun Metagenomics	<i>Bacillus</i> species <i>Candida albicans</i>	<i>Mycobacterium abscessus</i> <i>Porphyromonas</i> species	<i>Pseudomonas aeruginosa</i> (2)
New Organisms Detected in Aseptic Failures	<i>Cutibacterium acnes</i> (2)	<i>Staphylococcus aureus</i> (3)	<i>Streptococcus sanguinis</i> (2)
New Organisms Detected in Culture-Positive PJIs	<i>Anaerococcus obesiensis</i> <i>Clostridium</i> species <i>Cutibacterium acnes</i> <i>Enterobacter cloacae</i> *	<i>Fingoldia magna</i> (3)* <i>Peptoniphilus harei</i> <i>Prevotella nanciensis</i> <i>Staphylococcus aureus</i>	<i>Staphylococcus epidermidis</i> (6) <i>Staphylococcus lugdunensis</i> (2) <i>Varibaculum cambriense</i>
New Organisms Detected in Culture-Negative PJIs	<i>Anaerococcus urinae</i> <i>Candida albicans</i> (2)* <i>Candida parapsilosis</i> * <i>Clostridium perfringens</i> <i>Corynebacterium pseudogenitalium</i> <i>Cutibacterium acnes</i> <i>Enterococcus faecalis</i> (3)*	<i>Enterobacter cloacae</i> (2)* <i>Facklamia languida</i> <i>Granulicatella adiacens</i> (2)* <i>Mycobacterium bovis</i> BCG* <i>Metamycoplasma salivarium</i> <i>Peptoniphilus</i> species <i>Pasteurella multocida</i> *	<i>Staphylococcus aureus</i> (10)* <i>Staphylococcus epidermidis</i> (5)* <i>Staphylococcus haemolyticus</i> (2)* <i>Staphylococcus lugdunensis</i> <i>Streptococcus agalactiae</i> (4) <i>Streptococcus dysgalactiae</i> (4)* <i>Streptococcus oralis</i> *

* indicates organism identified in cultures other than sonicate fluid

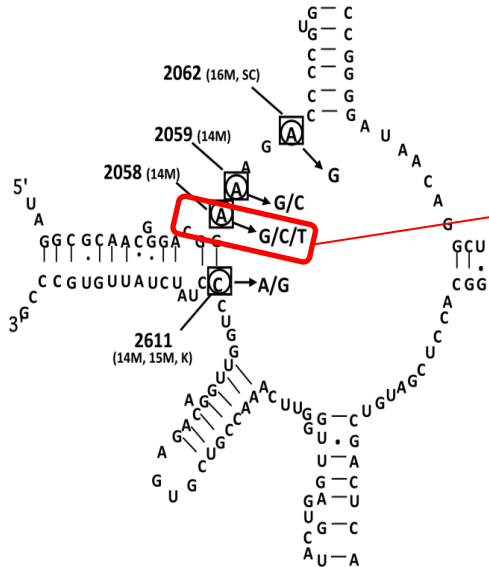
53 yo Man – Right Knee PJI



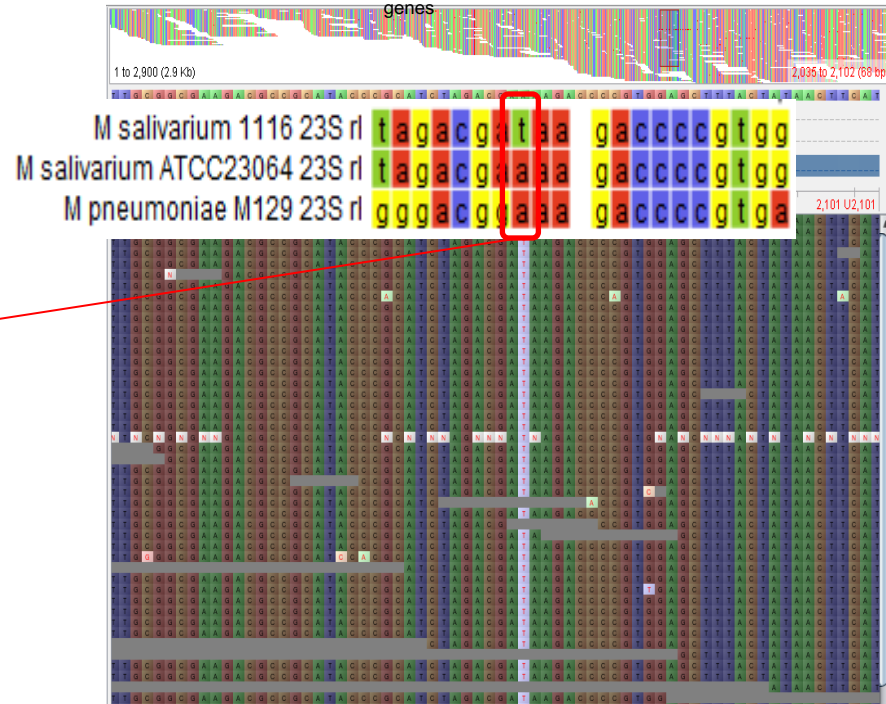
Antibiotic Resistance Prediction

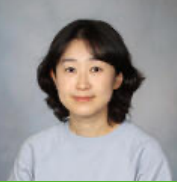


Macrolide resistance-associated mutations in 23S rRNA gene of *M. pneumoniae*



Alignment of case to reference *M. salivarium* and *M. pneumoniae* 23S rRNA genes





- 395 sonicate fluids
 - 208 PJI
 - 187 non-infectious failure
- Targeted metagenomic sequencing detected potential pathogens in 48% of culture-negative PJIs
- No difference between positive percent agreement of targeted (72%) and shotgun (73%) metagenomic sequencing ($P = 0.83$)

Summary

- **The challenge – biofilms, intracellular persistence**
- **Biomarker-based diagnostics**
 - **Interrogation of host response**
- **Culture-based diagnostics**
 - **Aerobic & anaerobic bacterial cultures (no routine fungal or mycobacterial cultures)**
 - **Improved tissue and synovial fluid culture (blood culture bottles)**
 - **Culture arthroplasty-derived materials (biofilms)**
- **Molecular diagnostics**
 - **Generally for challenging cases**
 - **Targeted and shotgun metagenomic sequencing equivalent for PJI**
 - **New multiplex PCR panel just approved by FDA (limited usefulness for PJI 😞)**

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Metagenomic Shotgun Sequencing Synovial Fluid



	Samples	Identical findings	Organisms Not Identified by Shotgun Metagenomics	New Organisms Detected by Shotgun Metagenomics
Aseptic Failures	61	56 (91.8%)	1 (1.6%)	4 (6.6%)
Synovial Fluid Culture-Positive PJs	82	67 (81.7%)	14 (17.1%)	3 (3.7%)
Synovial Fluid Culture-Negative PJs	25	21 (84.0%)	N/A	4 (16.0%)

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Comparison of Three Commercial Tools for Shotgun Metagenomic Sequencing Analysis



	LMAT	CosmosID	One Codex	IDbyDNA
Monomicrobial culture-positive PJIs (13 samples)				
Species detected (13)	12	9 (2*)	9 (3*)	10 (2*)
Additional species detected				
Corroborated	2 (2 samples)	1	2	1
Uncorroborated		1	11 (4 samples)	2 (2 samples)
Polymicrobial samples (3 samples)				
Species detected (11)	10	9	10	10
Additional species detected				
Corroborated	7 (2 samples)	3 (2 samples)	7 (2 samples)	7 (2 samples)
Uncorroborated	0	0	3 (1 sample)	1
Culture-negative PJIs (4 samples)				
Additional species detected				
Corroborated	6 (4 samples)	6 (3 samples)	8 (4 samples)	6 (4 samples)
Uncorroborated	0	0	8 (3 samples)	1
Aseptic failures (4 samples)				
Additional species detected				
Corroborated	0	0	0	0
Uncorroborated	0	0	1	3 (2 samples)

Human Gene Expression in *S. aureus* and *S. epidermidis* PJI

