



Clinical Metagenomics in Bone and Joint Infections

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Bone and Joint Infections: Proof of Concept Study

($\geq 1 \text{ pg}/\mu\text{L}$ bacterial DNA, $<99\%$ human DNA)

Patient	Samples	Age	Gender	Post-operative infection (type of surgery)	Delay between surgery and infection	Body site	Material involved
A	3	51	M	Yes (material)	<1 month	Ankle	Osteosynthesis
B	2	50	F	No		Clavicle	None
C	3	54	M	Yes (material)	<1 month	Toe	Osteosynthesis
D	1	66	M	Yes (material)	1 and 3 months	Tibia	Osteosynthesis
E	1	61	F	Yes (material)	<1 month	Knee	Total knee prothesis
F	1	63	M	Yes (material)	<1 month	Mandible	Osteosynthesis
G	3	69	M	Yes (bone resection)		Tibia	None
H	2	64	F	No		Sacrum	None
I	2	86	F	Yes (material)	1 and 3 months	Knee	Total knee prothesis
J	2	50	F	No		Tibia	None
K	1	86	F	No	>3 months	Knee	Osteosynthesis
L	1	51	M	Yes (material)	>3 months	Tibia	Osteosynthesis
M	1	87	F	Yes (material)	<1 month	Knee	Total knee prothesis
N	1	60	M	No		Greater trochanter and ischium	None

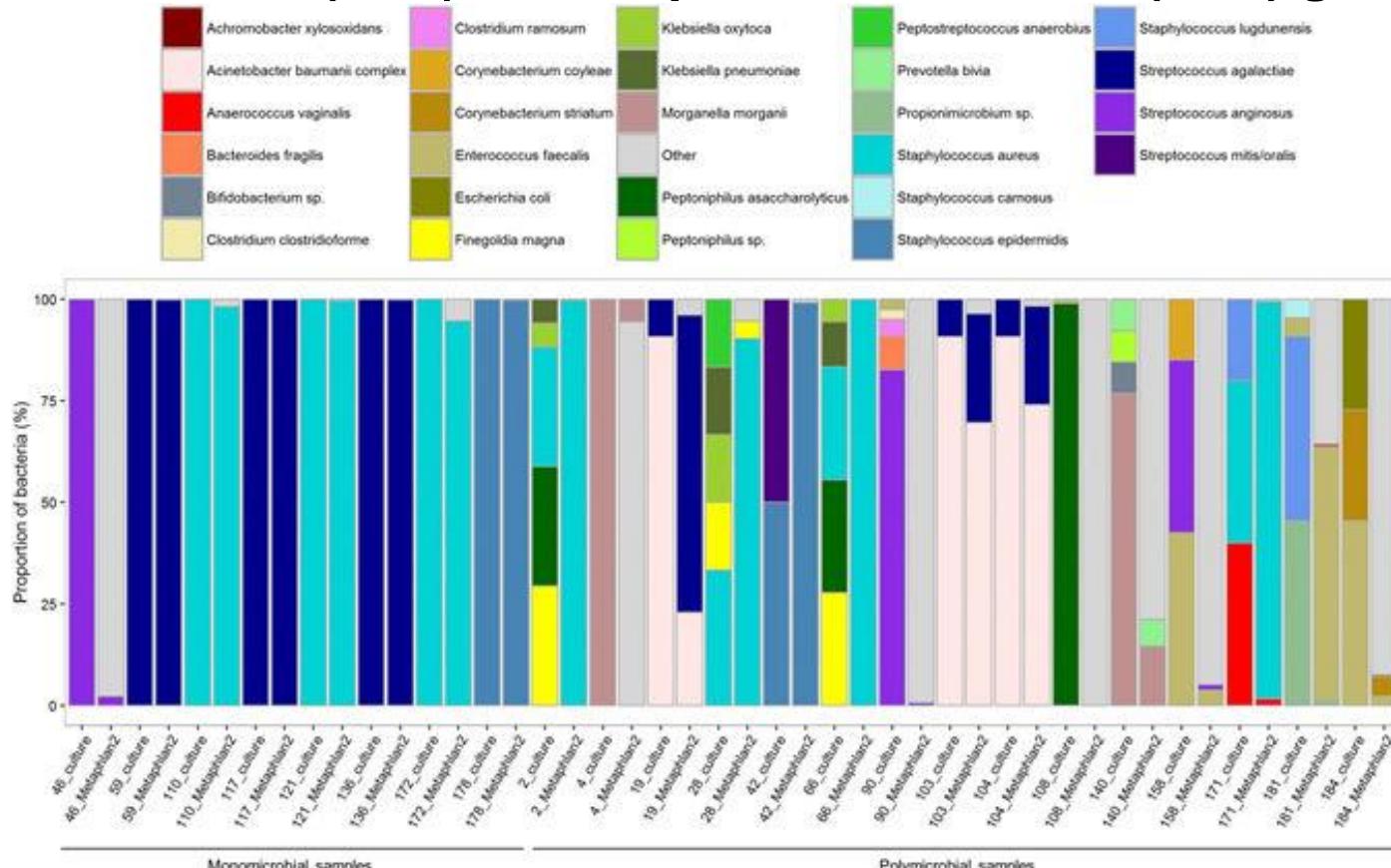
Proportions of Species Recovered In Culture and From Reads (Metaphlan2)

Monomicrobial samples by culture (n = 8)

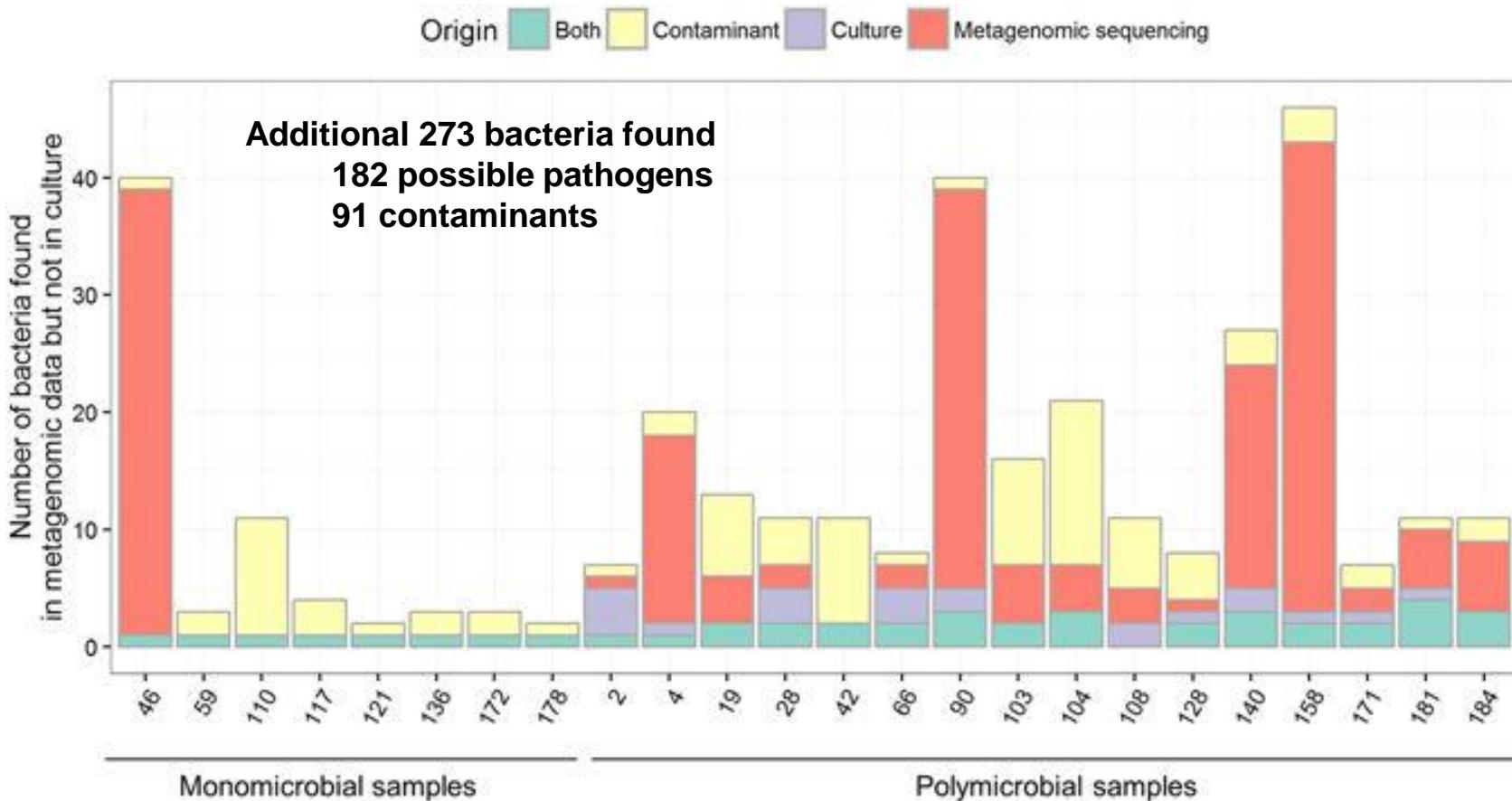
Presence of pathogen confirmed by metagenomics

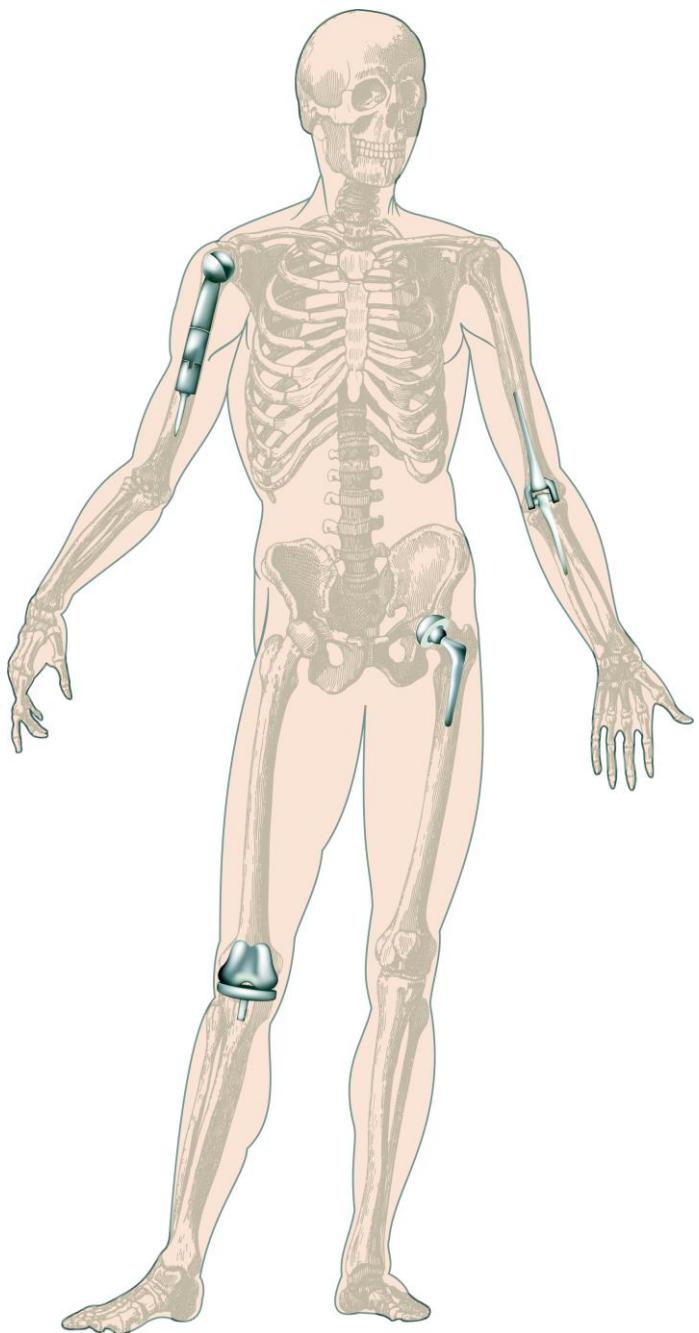
Polymicrobial samples by culture (n = 16)

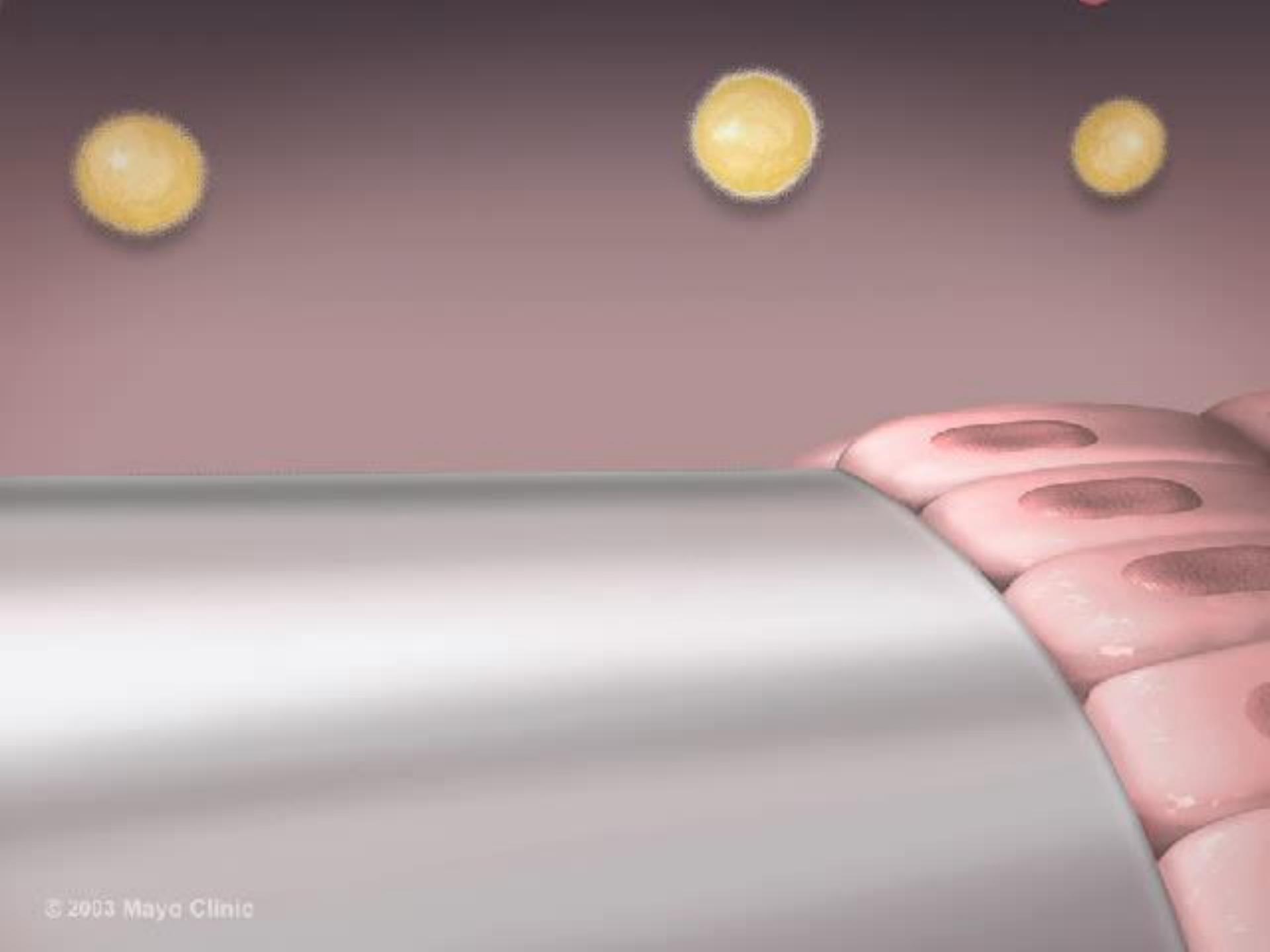
32/55 (58%) found species level, 41/55 (75%) genus level



#Species Found By Culture and Metagenomic Sequencing







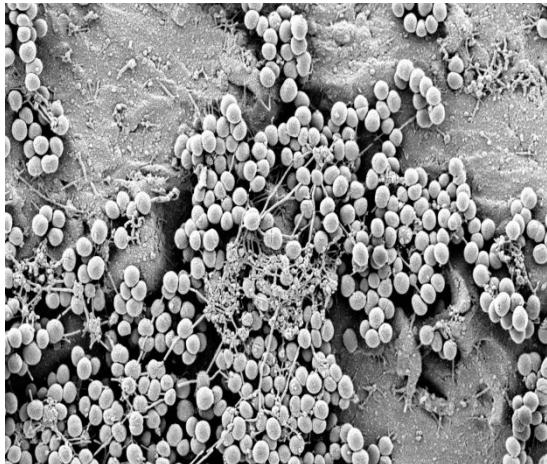
Prosthetic Joint Infection Microbiology

	Hip and Knee		Hip	Knee	Shoulder	Elbow
	All time periods	Early				
Number of joints	2435	637	1979	1427	199	110
<i>Staphylococcus aureus</i>	27	38	13	23	18	42
Coagulase negative staphylococci	27	22	30	23	41	41
<i>Streptococcus</i> species	8	4	6	6	4	4
<i>Enterococcus</i> species	3	10	2	2	3	0
Aerobic gram negative bacilli	9	24	7	5	10	7
Anaerobic bacteria	4	3	9	5		
<i>Cutibacterium acnes</i>					24	1
Other anaerobes					3	0
Culture negative	14	10	7	11	15	5
Polymicrobial	15	31	14	12	16	3
Other	3					

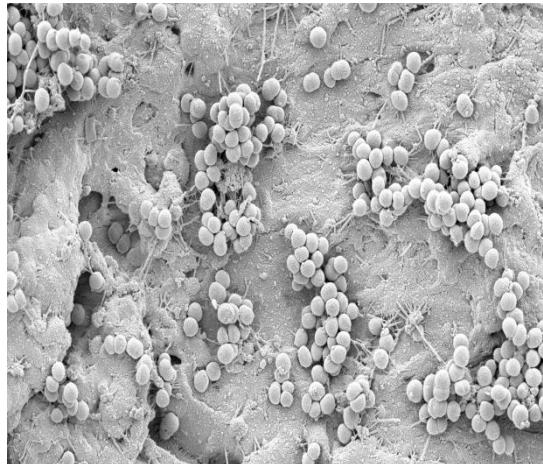
Tande and Patel. Clin Microbiol Rev 2014;27:302



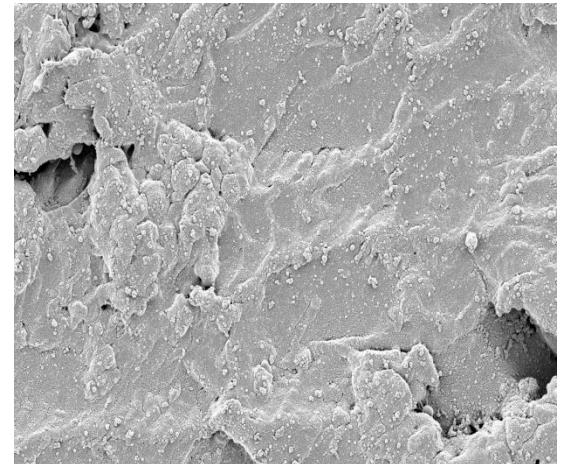
Staphylococcus epidermidis Biofilm on Polycarbonate Coupons Scanning Electron Microscopy



Soaking



Scraping



Sonication

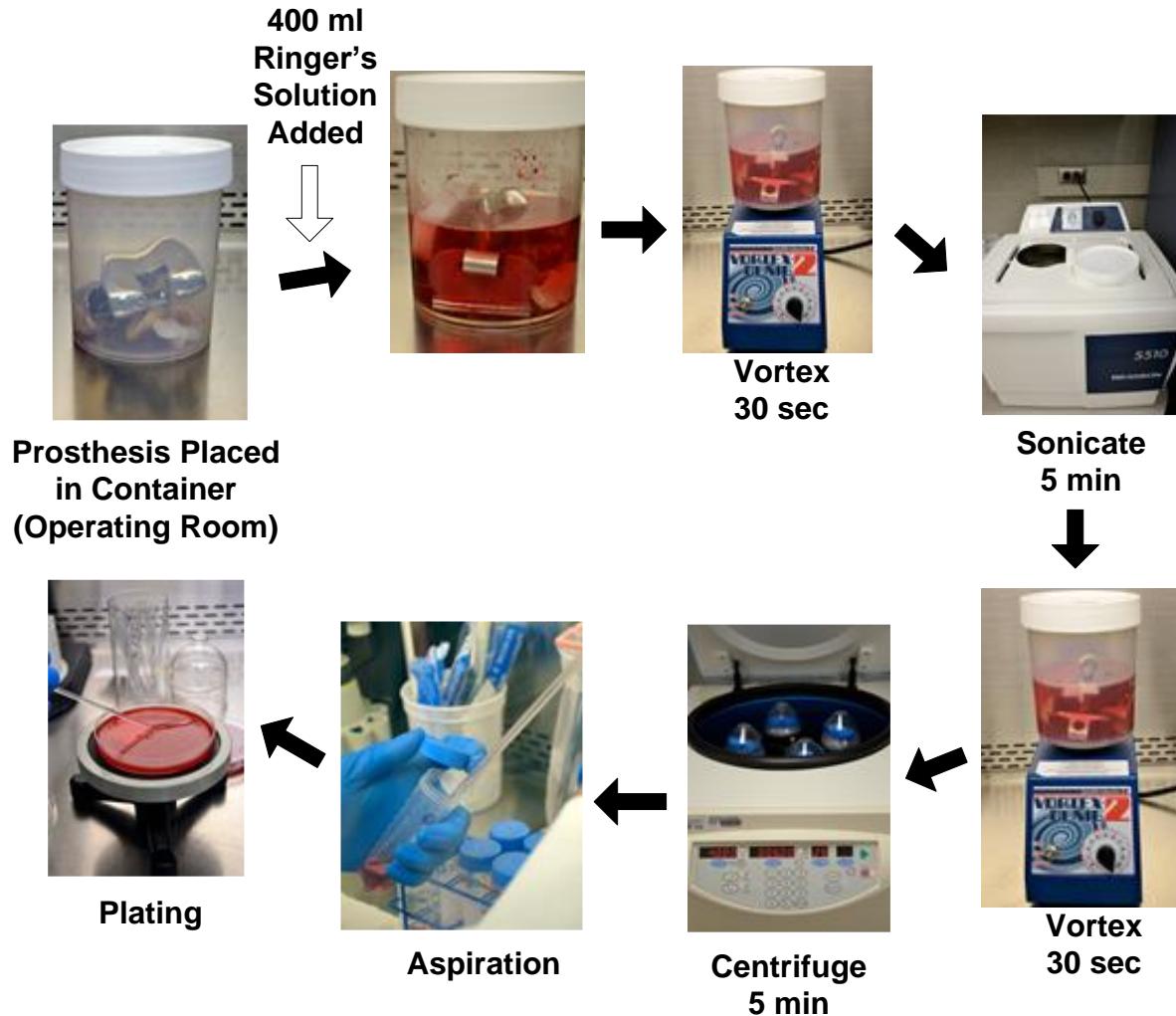


Tissue



Sonicate

Current Orthopedic Implant Processing - Mayo Clinic



Comparison of Sonicate Fluid and Tissue Culture Diagnosis of Orthopedic Foreign Body Infection

Implant type		Sonicate fluid	Periimplant tissue	p value	Reference
Hip/knee arthroplasties	Sensitivity	79%	61%	<0.001	Trampuz et al, NEJM 2007 Vol 357;654
	Specificity	99%	99%		
Shoulder arthroplasties	Sensitivity	67%	55%	0.046	Piper et al, JCM 2009 Vol 47:1878
	Specificity	98%	95%		
Spine implants	Sensitivity	91%	73%	0.046	Sampedro et al, Spine 2010 Vol 25:1218
	Specificity	97%	93%		
Elbow arthroplasties	Sensitivity	89%	55%	0.18	Vergidis et al, JSES 2011 Vol 20;1275
	Specificity	100%	93%		
Hip/knee/shoulder arthroplasties, mega-prostheses, osteosyntheses, spine implants	Sensitivity	83%	61%	0.034	Holinka et al. J Orthop Res 2011 Vol 29:617
	Specificity	95%	95%		
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 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/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 2016
	Specificity	100%	100%		

Sonication and 16S rRNA Gene PCR Hip/Knee Prostheses



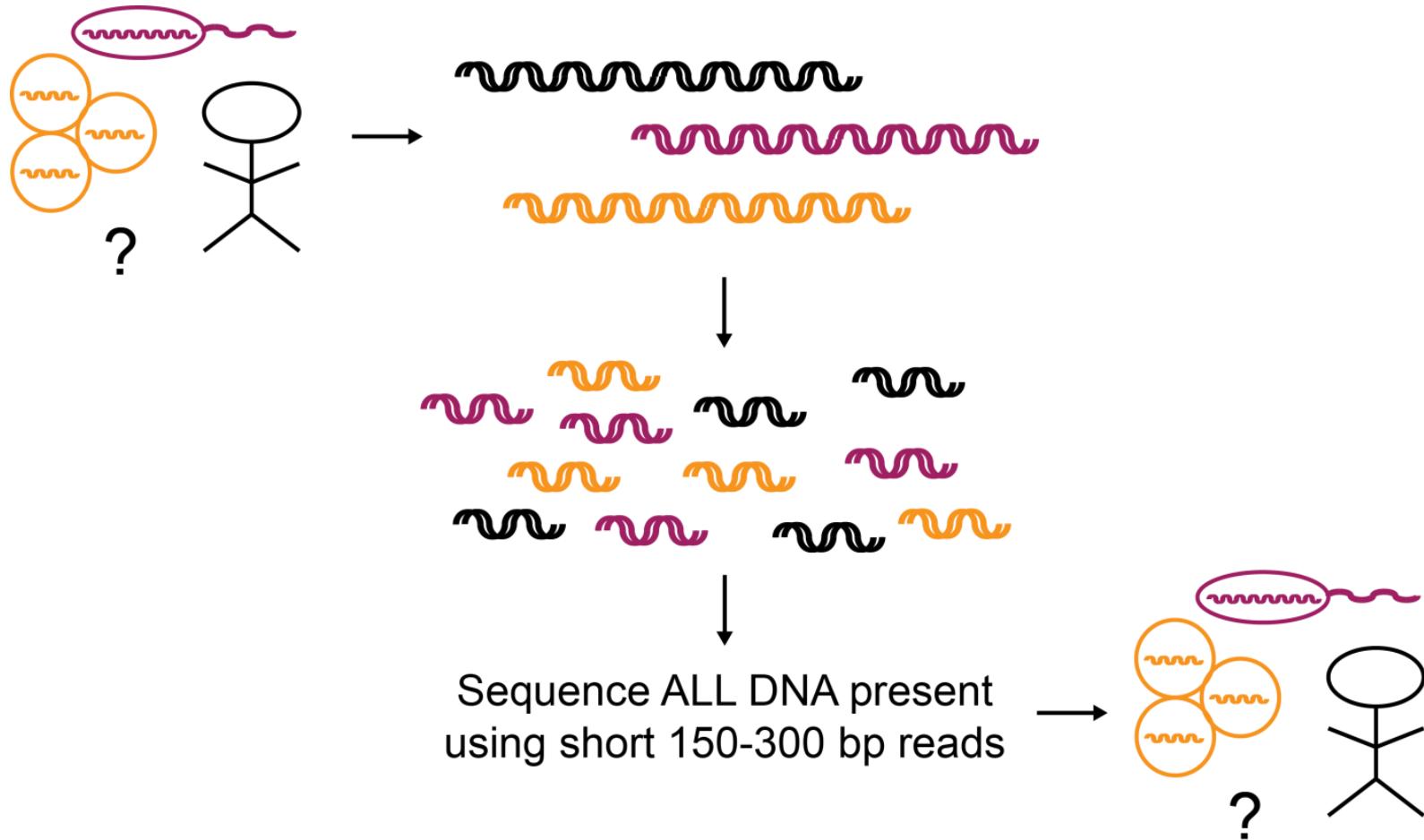
Test	Sensitivity 135 PJI	Specificity 231 Aseptic Failure	Accuracy
	% (95% Confidence Interval)		
Tissue culture	70.4 (64.5-76.3)	98.7 (97.2-100)	88.3 (84.2-92.4)
Sonicate fluid culture	72.6 (66.8-78.4)	98.3 (96.6-100)	88.8 (84.7-92.9)
Sonicate fluid broad-range PCR	70.4 (64.5-76.3)	97.8 (95.9-99.7)	87.7 (83.5-91.9)
Combination of two tests above	83.0 (78.2-87.8)	95.7 (93.1-98.3)	91.0 (87.3-94.7)
Sonicate fluid culture plus PCR	78.5 (73.2-83.8)	97.0 (94.8-99.2)	90.2 (86.4-94.0)
Synovial fluid culture	64.7 (56.5-72.9)	96.9 (93.9-99.9)	84.1 (77.8-90.4)
Sonicate fluid PCR - lower cutoff (CP <27.59 cycles)	80.0 (74.8-85.2)	90.9 (87.2-94.6)	86.8 (82.5-91.3)



Sonication Studies – PJI PCR Panel Hip/Knee Prostheses

Test	Aseptic failure (290)	PJI (144)	Sensitivity	Specificity	PPV	NPV
	No. of patients with positive specimens		% (95% confidence interval)			
Synovial-fluid culture	5/161	59/89	66.3 (55.5-76.0)	96.9 (92.9-99.0)	92.2 (82.7-97.4)	83.9 (77.8-88.8)
Tissue culture						
Any growth	45	119	82.6 (75.4-88.4)	84.5 (79.8-88.5)	72.6 (65.1-79.2)	90.7 (86.6-93.9)
≥2 positive tissues (same organism)	6	101	70.1 (62.0-77.5)	97.9 (95.6-99.2)	94.4 (88.2-97.9)	86.9 (82.7-90.3)
Sonicate fluid culture	5	105	72.9 (64.9-80.0)	98.3 (96.0-99.4)	95.5 (89.7-98.5)	88.0 (83.9-91.3)
Sonicate fluid PCR (10 assay panel)			77.1 (69.3-83.7)	97.9 (95.6-99.2)	94.9 (89.2-98.1)	89.6 (85.7-92.7)
Any positive result	6	111				
<i>Staphylococcus</i> sp	2	75				
<i>S. aureus</i>	0	28				
Coagulase-negative staphylococci	2	47				
<i>Streptococcus</i> sp	3	11				
<i>Enterococcus/Granulicatella/Abiotrophia</i> sp	0	11				
Enterobacteriaceae	1	8				
Gram-positive anaerobic cocci	0	8				
<i>Cutibacterium</i> sp	0	8				
<i>P. aeruginosa</i>	0	5				
<i>Corynebacterium</i> sp	0	4				
<i>C. jeikeium/urealyticum</i>	0	0				
Non- <i>jeikeium</i> sp	0	4				
<i>Proteus</i> sp	0	1				
<i>B. fragilis</i> group	0	0				

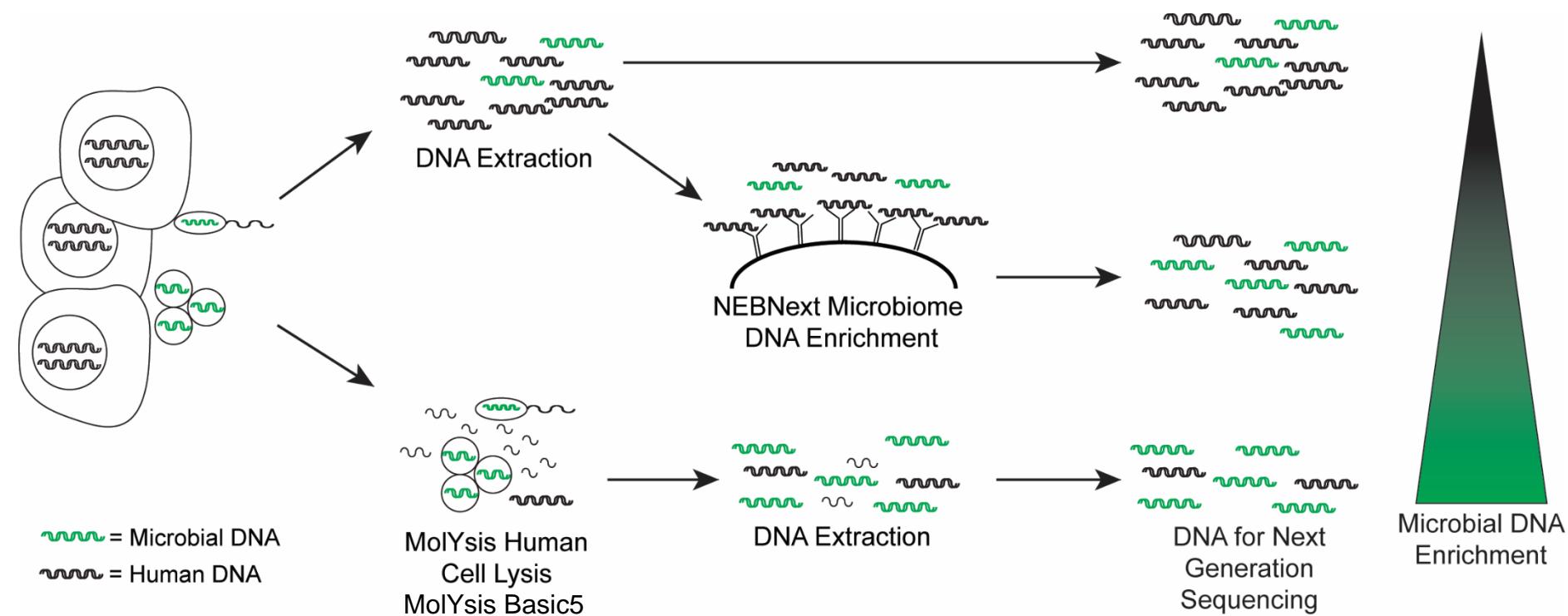
Metagenomic Shotgun Whole Genome Sequencing



Evaluation of Arthroplasty Failure Using Metagenomic Whole Genome Shotgun Sequencing

- **Goals:**
 - **Improve sensitivity**
 - Difficult to culture organisms
 - Fastidious organisms
 - Recent antibiotic exposure
 - Polymicrobial infections
 - Identify subpopulations within species
 - Identify important genes
 - Antibiotic resistance markers
 - Virulence factors

Comparison of Microbial Enrichment Methods Metagenomic Analysis of Arthroplasty Failure



Comparison of Microbial Enrichment Methods Metagenomic Analysis of Arthroplasty Failure

- DNA extraction: **Mobio BIOstic Bacteremia DNA isolation kit**
- Whole genome amplification: **Illustra GenomiPhi V2 kit**
- Amplified DNA purification: **Agencourt AMPure XP beads**
- Paired-end library prep: **NEBNext Ultra DNA Library Prep Kit**
- Sequencing: **Illumina HiSeq 2500 in rapid run mode with 2 x 250 bp reads (multiplexed 6 up to samples/lane)**
- Adapter sequence removal: **Trimmomatic (v0.35)**
- Human & PhiX sequence removal: **BioBloom tools (v2.0.12)**
- Data analysis: **Livermore Metagenomics Analysis Toolkit (LMAT) with kML + Human.v4.14.20.g10.db database**

Comparison of Microbial Enrichment Methods

Metagenomic Analysis of Arthroplasty Failure



	No Enrichment	NEBNext Microbiome DNA Enrichment	MolYsis Enrichment
<i>S. aureus</i> PJI			
% of reads	0.02% (4,158 of 25,609,460)	0.2% (350,625 of 169,981,133)	7.7% (2,286,890 of 29,530,730)
Enrichment factor		13X	481X
<i>S. epidermidis</i> PJI			
% of reads	0.007% (1,682 of 23,606,476)	0.2% (133,680 of 74,544,475)	7.0% (2,268,087 of 32,184,381)
Enrichment factor		25X	986X
<i>E. faecalis</i> PJI			
% of reads	0.006% (1,671 of 26,949,030)	0.5% (497,206 of 94,522,959)	59.4% (16,407,878 of 27,643,294)
Enrichment factor		85X	9,580X



S. aureus PJI

No Enrichment

Read Score	# of Reads	TaxID Taxonomy group
877206	445817	9606 species,Homo sapiens genus,Streptococ
54347.8	29068	1301 cus
25834.1	32491	2759 superkingdom,Eukaryota
9473.81	15978	131567 no rank,cellular organisms species group,Streptococcus
7892.17	4622	671232 anginosus group
4756.18	2901	1279 genus,Staphylococcus species,Staphylococcus
1567.67	1007	1280 aureus
1197.96	755	1338 species,Streptococcus intermedius genus,Pseudomo
843.518	509	286 nas
534.066	346	76860 species,Streptococcus constellatus no rank,Streptococcus tigurinus
367.308	232	1282664 AZ_3a
361.242	530	1 depth=0,taxid=1,ktaxid=1,entries=-1
347.345	228	1282 species,Staphylococcus epidermidis subspecies,Streptococcus
255.733	159	184250 constellatus subsp. pharyngis
252.168	204	1328 species,Streptococcus anginosus no rank,Streptococcus intermedius
223.389	155	857292 F0395 no rank,Streptococcus intermedius
221.627	170	883167 F0413
206.954	130	1248438 no rank,Pseudomonas alcaliphila 34
175.499	102	1743 genus,Propionibacterium
145.828	96	90964 family,Staphylococcaceae no rank,Streptococcus equi subsp.
131.955	141	1051072 zoopelagicus ATCC 35246 species group,Pseudomonas
106.976	75	136841 aeruginosa group no rank,Pseudomonas
79.7075	55	1182590 pseudoalcaligenes CECT 5344 no rank,Streptococcus salivarius
71.3676	49	1074494 M18
71.2256	52	1300 family,Streptococcaceae
70.0294	52	32630 species,synthetic construct species,Streptococcus
69.8811	44	1077464 tigurinus
51.1347	31	101564 species,Pseudomonas alcaliphila no rank,Pseudomonas mendocina
48.2248	35	1390370 EGD-AQ5 phylum,Firmicute
47.8076	86	1239 s

NEBNext Enrichment

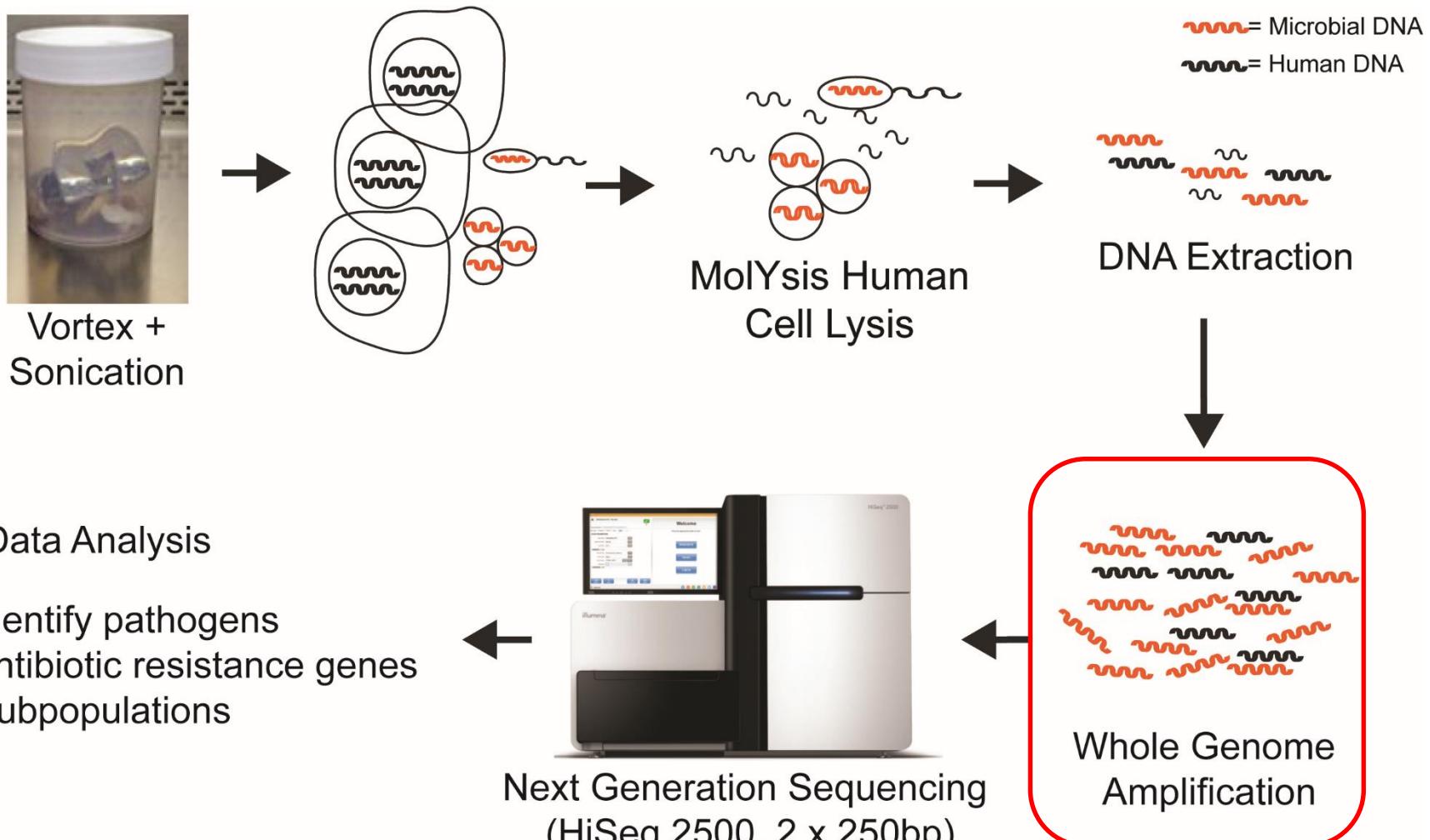
Read Score	# of Reads	TaxID Taxonomy group
8.14E+07	4168479	9606 species,Homo sapiens
	4	genus,Streptococ
807585	1210368	2759superkingdom,Eukaryota
611285	342132	32630species,synthetic construct
580565	336338	1280species,Staphylococcus aureus
268536	481220	131567 no rank,cellular organisms
15809	10833	1279genus,Staphylococcus
13898.3	18574	1depth=0,taxid=1,ktaxid=1,entries=-1
13530.1	9200	286genus,Pseudomonas
2688.34	2762	136843 species group,Pseudomonas fluorescens
1816.09	1388	group no rank,Staphylococcus aureus HIF003_B2N-C
1561.25	959	90964family,Staphylococcaceae
1318.53	776	1743genus,Propionibacterium
1236.36	1069	10003441 species,Staphylococcus aureus plasmid pTZ2162
1226.75	1799	294species,Pseudomonas fluorescens
1029.9	1597	1292037 no rank,Amycolatopsis vancoresmycina DSM 44592
923.909	719	10003448 species,Staphylococcus aureus plasmid pSA1379
645.914	403	463794no rank,Pseudomonas fluorescens BBc6R8
564.99	561	613genus,Serratia
462.127	1310	2superkingdom,Bacteria
408.322	283	1197727species,Pseudomonas sp. Ag1
256.031	204	1284392species,Pseudomonas sp. FH1
230.898	254	543family,Enterobacteriaceae
217.701	156	10003454 species,Staphylococcus aureus plasmid EDINA
203.746	204	317species,Pseudomonas syringae
196.998	215	1239phylum,Firmicutes
181.019	146	68887species,Torque teno virus
178.088	112	1206777species,Pseudomonas sp. Lz4W
154.956	184	1163065species,Pseudomonas sp. CBZ-4
144.54	125	135621family,Pseudomonadaceae
112.687	87	99158species,Hammondia hammondi
109.857	84	1240676species,Pseudomonas sp. PAMC 26793
94.634	63	1301genus,Streptococcus
93.5661	55	1248438no rank,Pseudomonas alcaliphila 34
91.8243	74	80865genus,Delftia
86.2212	81	308865genus,Elizabethkingia
77.866	45	985010species,Pseudomonas sp. TJI-51
74.2086	46	53335genus,Pantoea
69.9358	45	91459species,Methylbacterium sp. B1

MolYsis Enrichment

Read Score	# of Reads	TaxID Taxonomy group
	219358	1280 species,Staphylococcus aureus
3.21E+06	7	9606 species,Homo sapiens
1.26E+06	713346	2759superkingdom,Eukaryota
193781	215573	1279genus,Staphylococcus
96085.8	71730	131567 no rank,cellular organisms
86648.5	93461	no rank,Staphylococcus aureus
17892.4	15986	1156998 HIF003_B2N-C
4970.16	3686	90964 family,Staphylococcaceae
3083.97	2641	10003441 pTZ2162
2110.41	1776	10003448 pSA1379
1768.6	2414	1 depth=0,taxid=1,ktaxid=1,entries=-1
1649.2	1185	32630 species,synthetic construct
958.691	1031	1239 phylum,Firmicutes
867.117	669	10003454 EDINA
716.226	2113	2superkingdom,Bacteria
372.719	290	10003425 pBORa53
307.861	198	286genus,Pseudomonas
200.233	175	68887 species,Torque teno virus
192.236	504	1385 order,Bacillales
99.5046	91	10003460 species,Staphylococcus aureus plasmid
77.8404	173	91061 class,Bacilli
50.2773	45	308865genus,Elizabethkingia
47.0102	71	1282 species,Staphylococcus epidermidis
44.0471	40	1301 genus,Streptococcus
39.0756	22	1743 genus,Propionibacterium
37.8316	24	1248438 no rank,Pseudomonas alcaliphila 34 species group,Pseudomonas aeruginosa
28.2731	18	136841 group no rank,Pseudomonas mendocina EGD-
24.6249	18	1390370 AQ5

Thoendel et al. J Microbiol Methods 2016;127:141–5

Host DNA Depletion Depletes DNA Quantities for Sequencing





Impact of Contaminating DNA in Whole Genome Amplification Kits on PJI Diagnosis

- 8 sonicate fluids, including culture-positive and –negative PJI, and aseptic failure
- Microbial DNA enrichment: MoYsis Basic5 kit
- DNA extraction: MoBio Bacteremia DNA isolation kit
- Whole genome amplification:
 1. Qiagen REPLI-g Single Cell kit (Qiagen, Hilden Germany)
 2. Illustra V2 Genomiphi kit (GE Healthcare Bio-Sciences, Pittsburgh PA)
 3. Illustra Single Cell Genomiphi kit
- Amplified DNA purification: Agencourt AMPure XP beads
- Paired-end library preparation: NEBNext Ultra DNA Library Prep Kit
- Sequencing: Illumina HiSeq 2500 rapid run mode, 2x250 bp reads (multiplexed 6 samples/lane)
- Controls (no WGA) - library preparation with NEBnext Ultra II DNA library Prep Kit (4 samples/lane)
- Illumina adapters removal: Trimmomatic
- Human and PhiX sequences prefiltration: BioBloom tools
- Taxonomic assignment of reads: LMAT with kML + Human.v4.14.20.g10.db database
- Trimming of low-quality reads: Trimmomatic
- Analysis of trimmed reads: MetaPhlan2

Sonicate Fluid Samples Tested and Relative Read Counts (LMAT)

Sample	Site	Microbiology		Qiagen REPLI-g		Illustra Single Cell		Illustra V2	
		Sonicate Fluid	Positive tissue cultures	Total reads		Total reads		Total reads	
				Pathogen reads	Non-pathogen reads	Pathogen reads	Non-pathogen reads	Pathogen reads	Non-pathogen reads
Culture-positive PJI									
980	H	Group C <i>Streptococcus</i> <20 CFUs	1 of 3	27,244,012		36,576,986		25,754,214	
				2,694,906	103	286,577	556	3,075,181	566
982	K	<i>S. epidermidis</i> >100 CFUs	3 of 4	28,320,234		30,284,116		26,508,366	
				3,272,895	591	102,934	203	9,539,147	17,625
986	K	<i>S. aureus</i> <20 CFUs	1 of 5	26,835,306		28,991,289		27,391,148	
				26,397	77,581	424	308	168,046	240,703
996	H	<i>B. fragilis</i> , >100 CFUs	3 of 3	28,388,841		28,745,844		28,904,638	
				155,761	4,853	11,134	1,346	96,154	8,140
1002	K	<i>C. striatum</i> , 51- 100 CFUs	3 of 3	32,165,206		27,925,551		32,338,186	
				536,155	2,594	5,503	422	1,000,810	53,019
Culture-negative PJI									
984	K	Culture negative	0 of 4	31,616,449		26,240,307		36,808,230	
				NA	2,821	NA	305	NA	16,974

Sonicate Fluid Samples Tested and Relative Read Counts (LMAT)

Sample	Site	Microbiology		Qiagen REPLI-g		Illustra Single Cell		Illustra V2	
		Sonicate Fluid	Positive tissue cultures	Total reads		Total reads		Total reads	
				Pathogen reads	Non-pathogen reads	Pathogen reads	Non-pathogen reads	Pathogen reads	Non-pathogen reads
Aseptic Failure									
983	K	Culture negative	0 of 3	32,924,419		29,076,492		32,128,178	
				NA	278	NA	522		45,539
987	K	Anaerobic organism, <20 CFUs	1 of 3, <i>Bacillus</i> species	30,316,155		30,587,175		27,955,363	
				NA	7,628	NA	265	NA	655,417
Controls									
<i>C. glutamicum</i>	NA	NA	NA	28,121,822		28,973,351		26, 986,400	
				26,912,706	2,145	22,276,446	856	26,149,302	1,311
Ringers	NA	NA	NA	27,488,254		29,531,289		27,810,322	
				NA	24,140	NA	3,560	NA	835,014
WGA no template	NA	NA	NA	25,669,747		53,626,034		24,512,662	
				NA	6,695	NA	46,759	NA	7,818,383

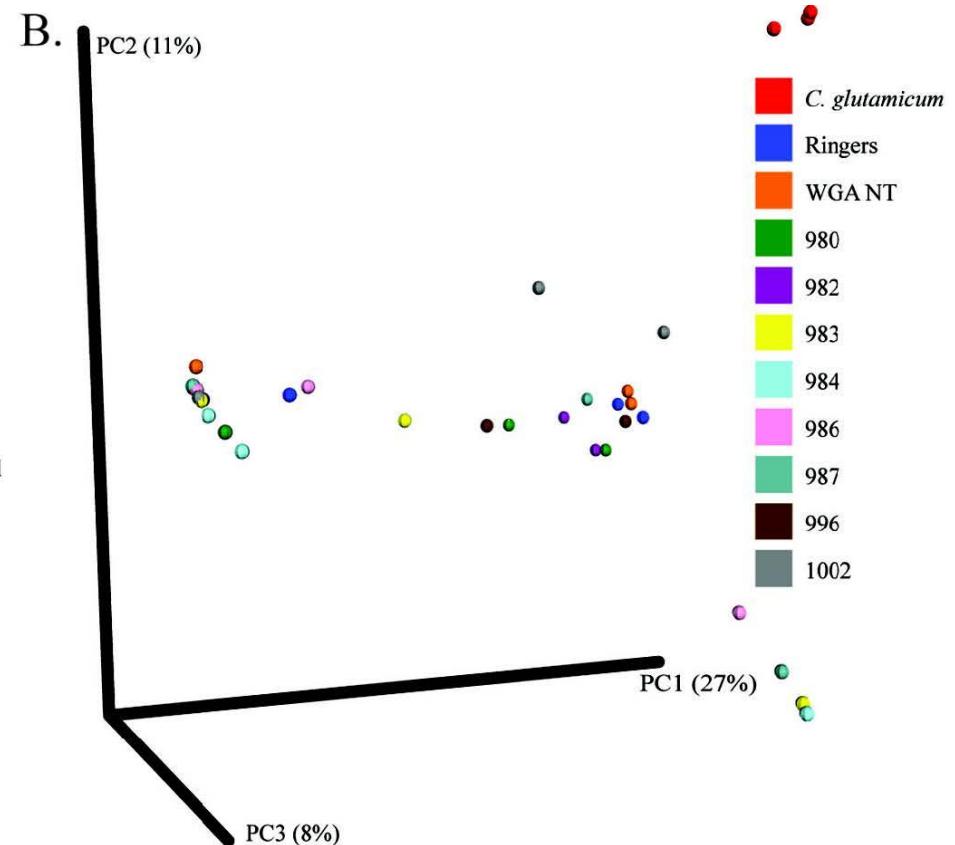
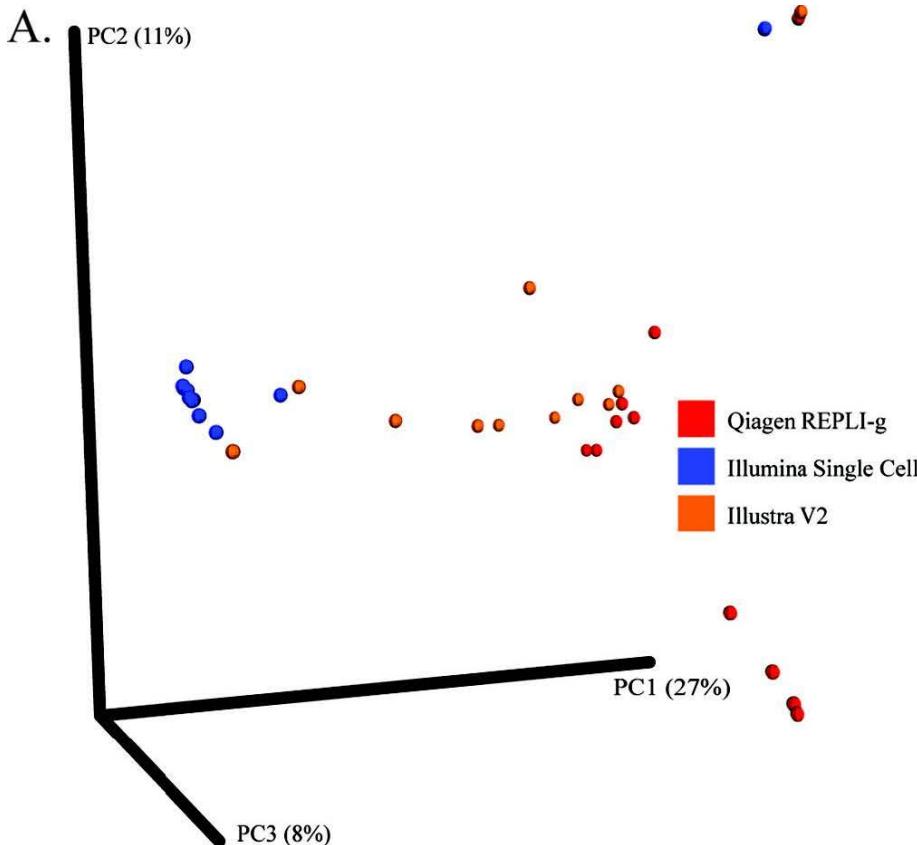
MetaPhlAn2 Identification of Species

Sample	MetaPhlAn2 Identifications			
	Qiagen	Illustra Single-Cell	Illustra V2	No WGA
Culture-positive PJI				
980	<i>S. dysgalactiae</i> Torque teno mini virus 2 Torque teno mini virus 9 Torque teno virus	<i>S. dysgalactiae</i>	<i>S. dysgalactiae</i>	<i>S. dysgalactiae</i>
982	<i>S. epidermidis</i> Mupapillomavirus 1	<i>S. epidermidis</i>	<i>S. epidermidis</i>	<i>S. epidermidis</i>
986	Unclassified Propionibacteriaceae <i>S. aureus</i>	No ID	<i>S. aureus</i> <i>P. alcaliphila</i>	<i>S. aureus</i> <i>C. acnes</i> Unclassified <i>Escherichia</i>
996	<i>B. fragilis</i> Torque teno virus	<i>B. fragilis</i>	<i>B. fragilis</i> Unclassified Pseudomonas Torque Teno Virus	<i>B. fragilis</i>
1002	<i>C. striatum</i>	<i>C. striatum</i>	<i>C. striatum</i> <i>Lactococcus lactis</i> <i>C. acnes</i> <i>P. mendocina</i> <i>P. alcaliphila</i>	<i>C .striatum</i>
Culture-negative PJI				
PJI984	No ID	No ID	Unclassified Pseudomonas	<i>C. acnes</i> Porcine type C oncovirus <i>M. luteus</i> <i>S. maltophilia</i>



β -Diversity by Samples versus WGA Kit

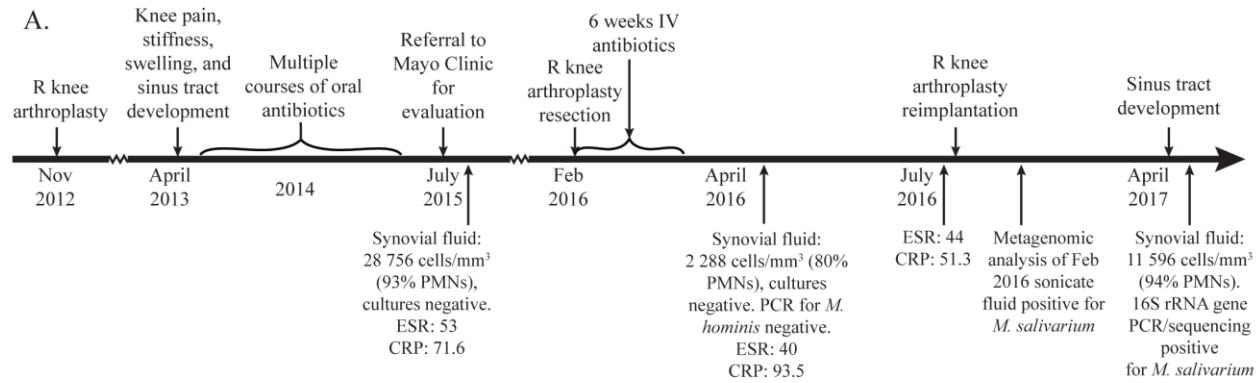
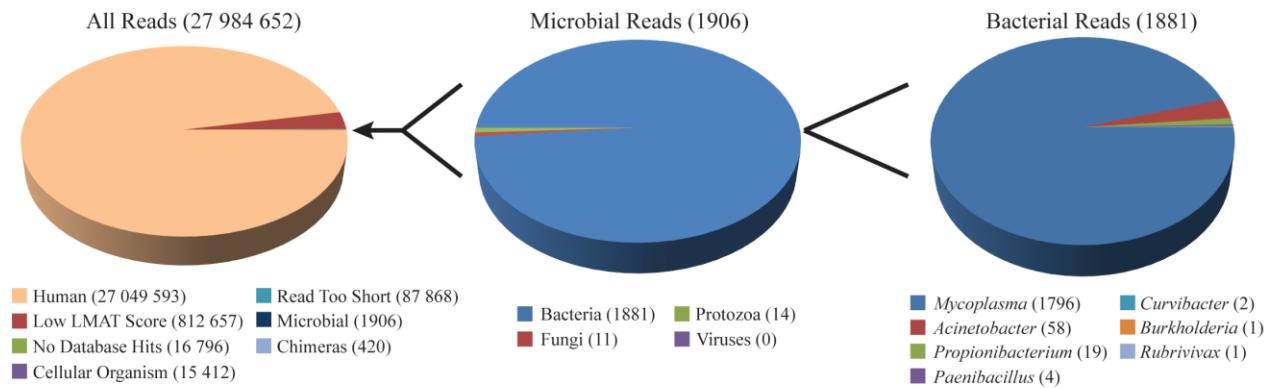
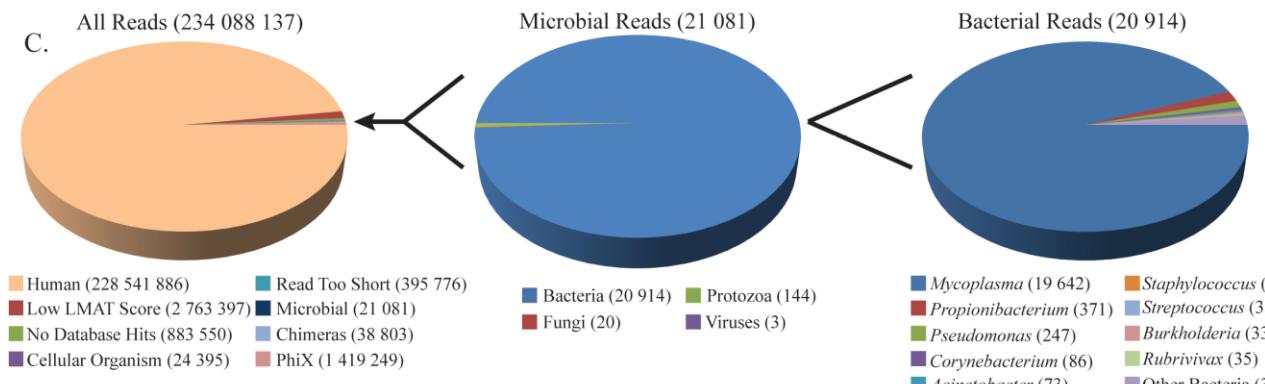
β -diversity of gene content of the samples was determined using QIIME and plotted on a principal coordinate analysis plot. Samples are colored according to the WGA kit used for amplification (A) or by template sample source (B). NT no template.





MAYO CLINIC

53 yo Man – Right Knee PJI

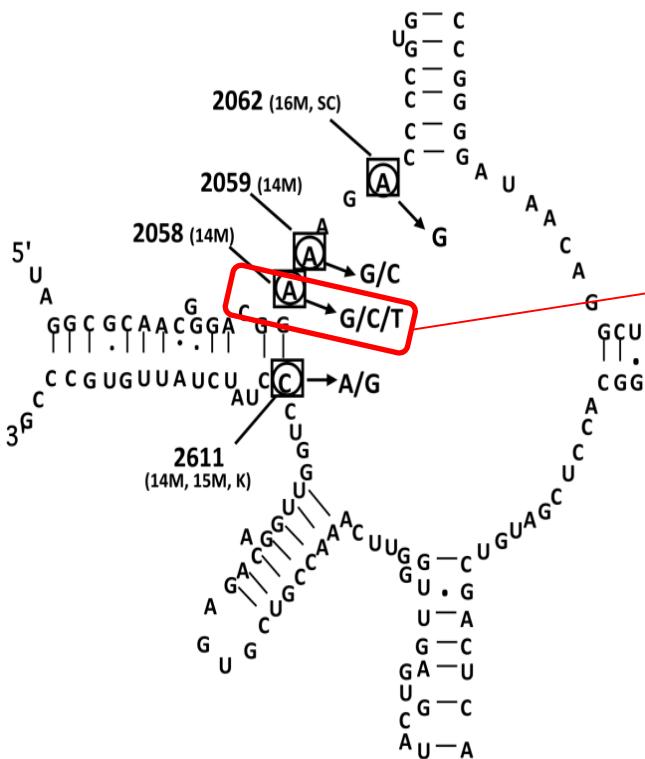
**B.****C.**

Thoendel et al.
Clin Infect Dis
2017;65:332-5.

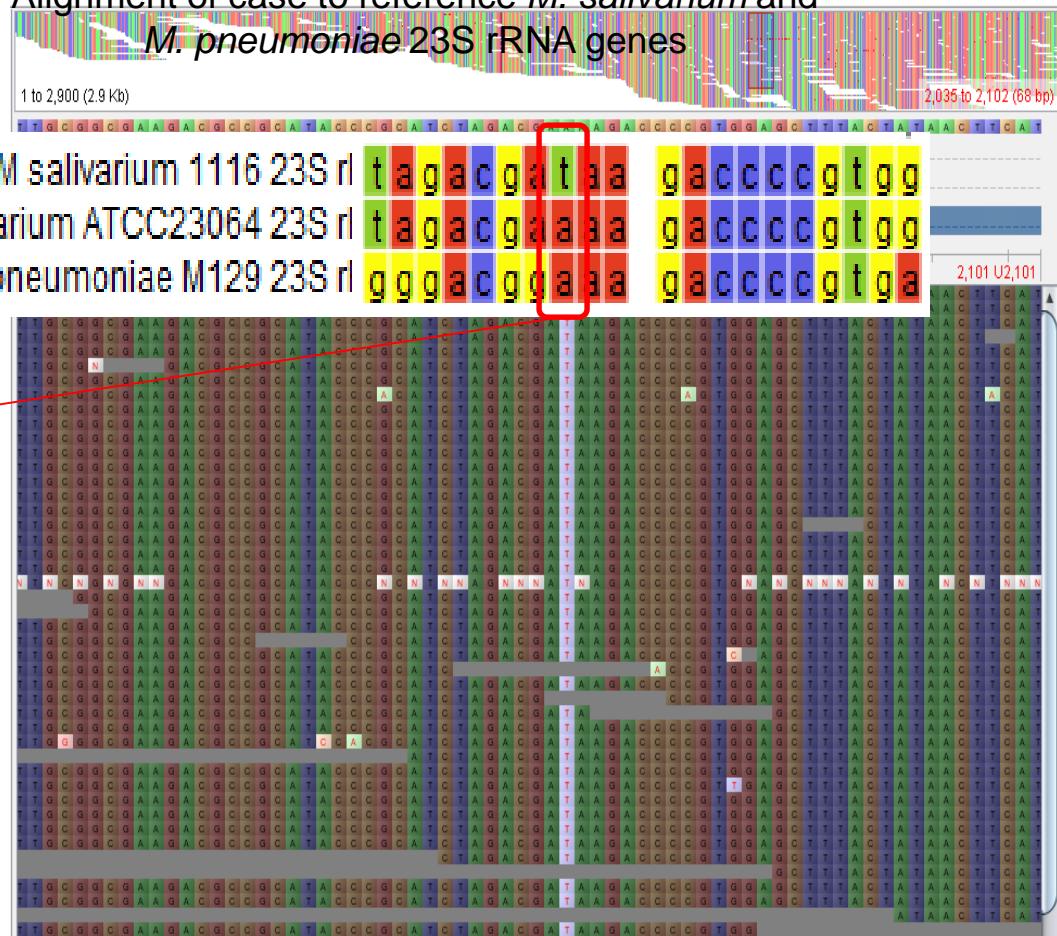
Antibiotic Resistance Prediction



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



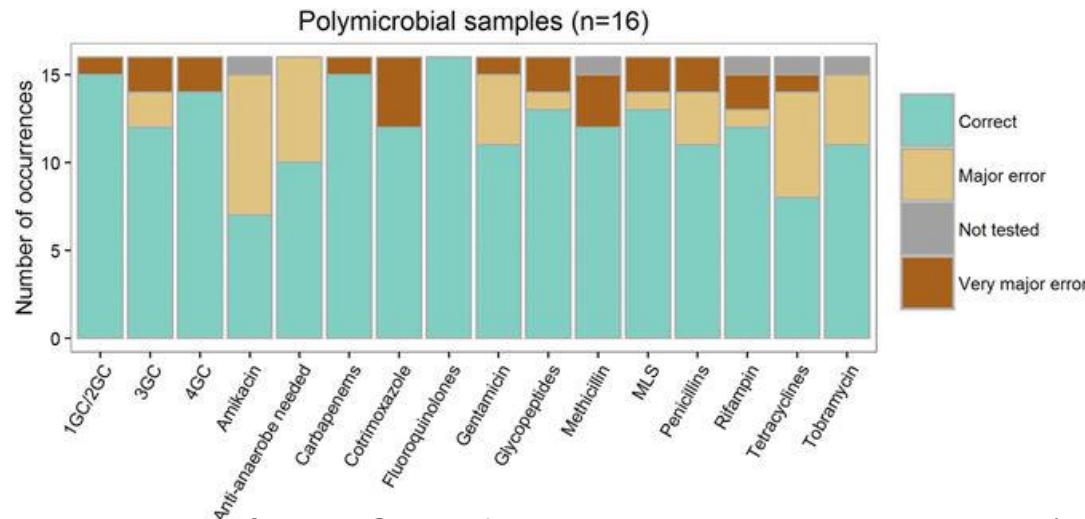
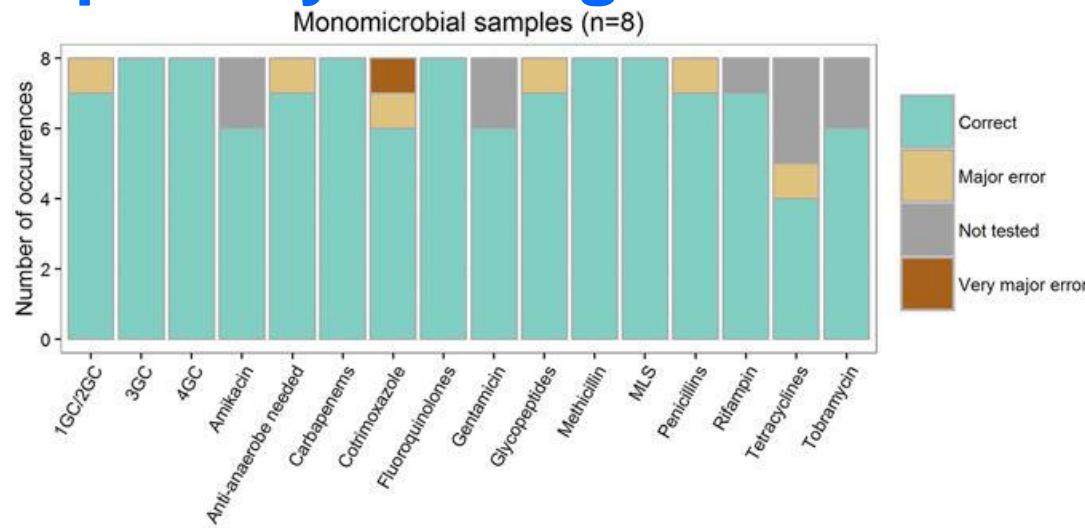
Alignment of case to reference *M. salivarium* and *M. pneumoniae* 23S rRNA genes



Antibiotic Susceptibility From Metagenomic Data versus Culture & Conventional Antibiotic Susceptibility Testing

Correct susceptibility inferred

**94% monomicrobial
77% polymicrobial samples**



Conclusions

- Metagenomic analysis of bone and joint infection promising
 - Culture-negative cases
 - Specimen type matters
 - Need for specific reagents/protocols/bioinformatics tools for bone and joint infection, especially prosthetic joint infection

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