

The young side of
LYMPHOMA

gli under 40 a confronto

Reggio Emilia, Hotel Mercure Astoria
2-3 ottobre 2026

**Insights sul ruolo del microbiota
nei linfomi**

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Disclosures of Paola Ghione

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Regeneron			X			X	
ADC Therapeutics			X			X	
Genmab			X			X	
Merck		Spouse					
NIH	X						
LRF	X						

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Memorial Sloan Kettering
Cancer Center

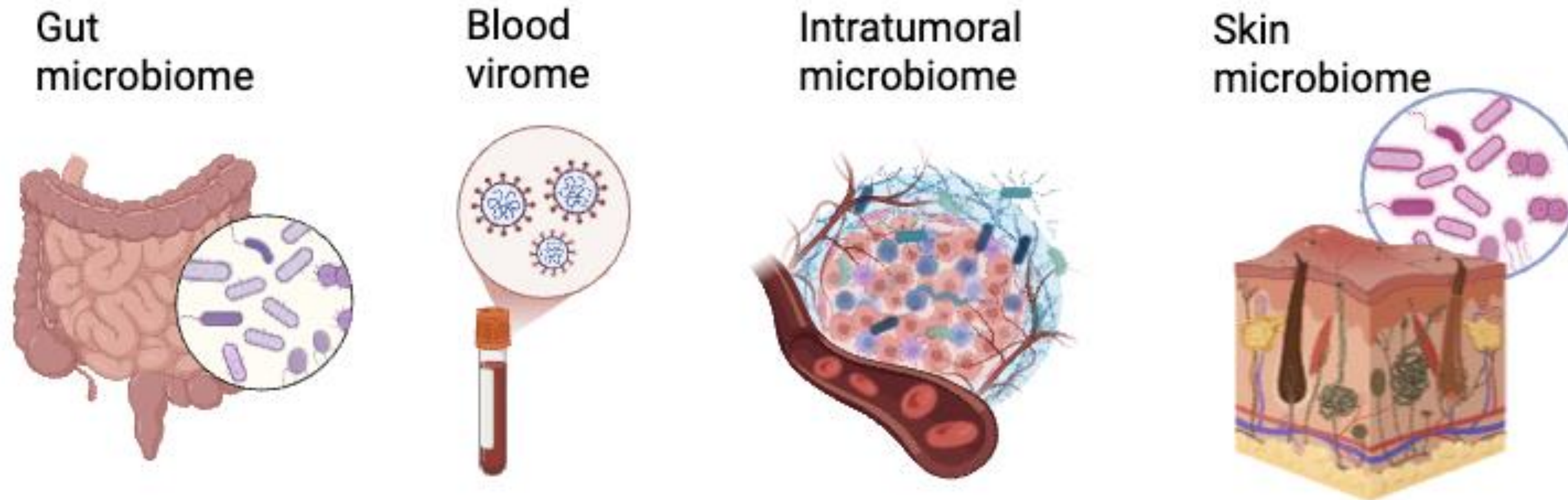
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Role and types of microbiome studied in cancer

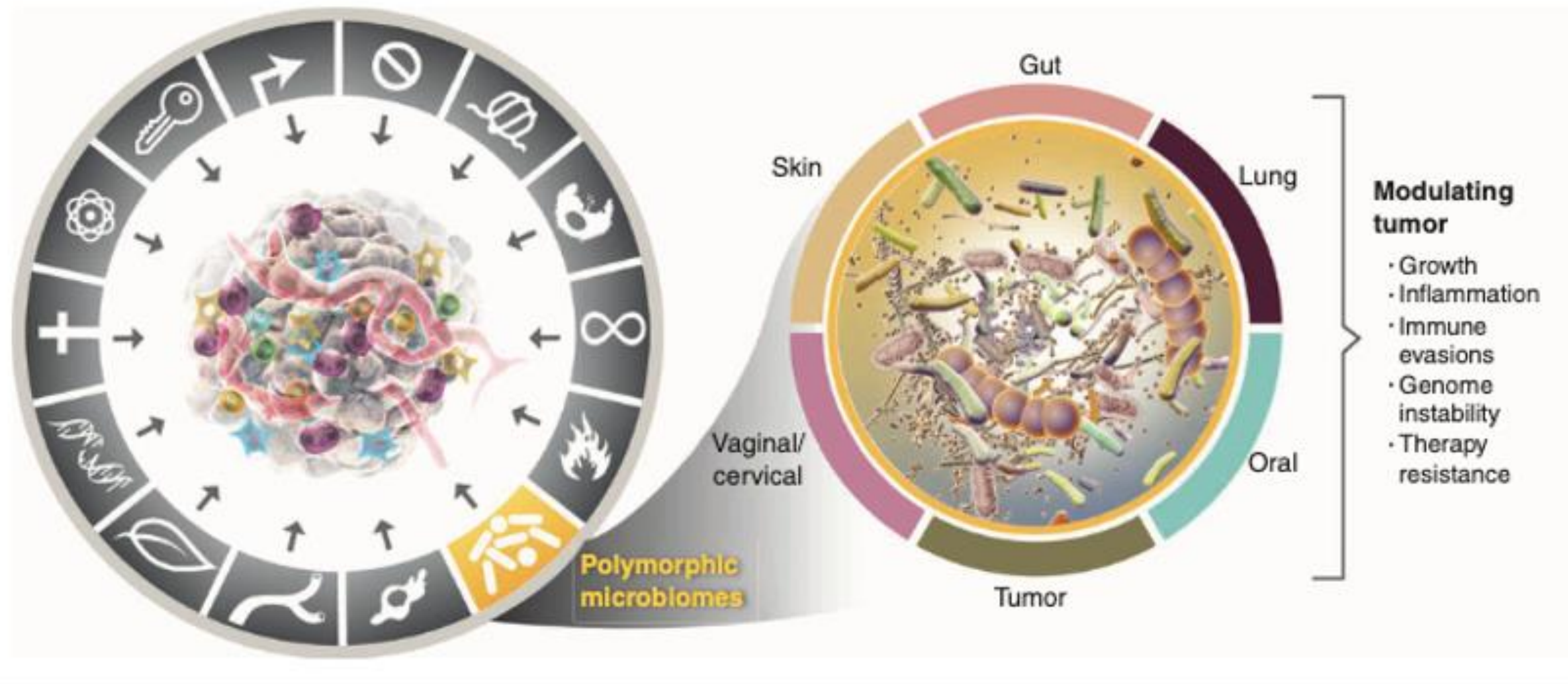
A population-attributable fraction of 15%-20% of all cancers worldwide is related to infectious agents

Strong epidemiologic links exist between infection by *Helicobacter pylori*, EBV, HTLV₁, and specific lymphoma subtypes

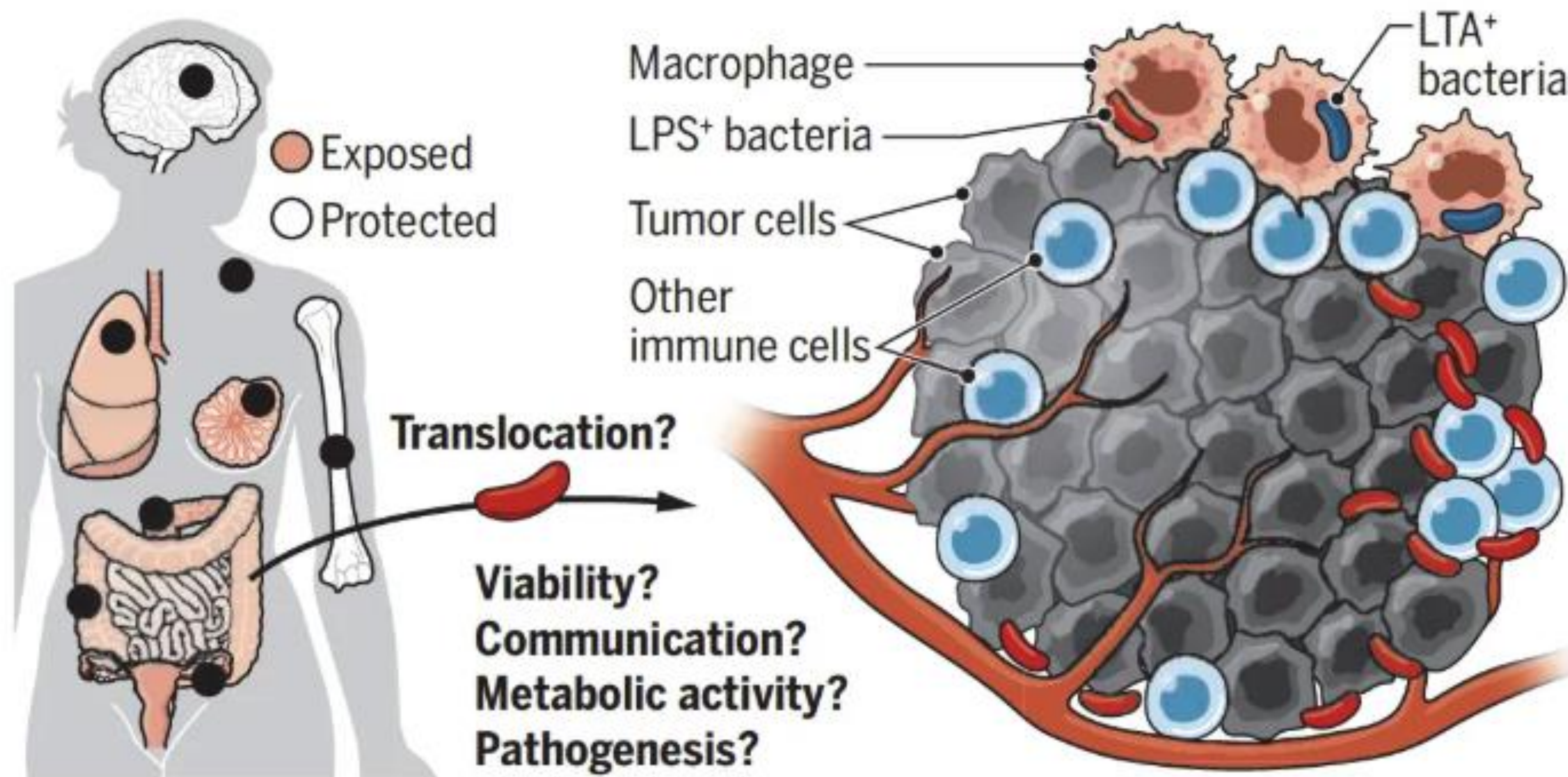
In solid tumors, bacteria are prevalent in niches of immune evasion, where T-cell function is suppressed



The microbiome – the community of microorganisms found in barrier tissues and in the tumor mass – a new “Hallmark of Cancer”



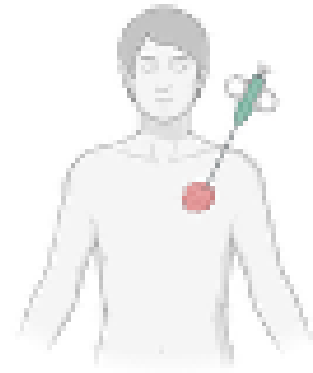
In solid tumors, intratumoral bacteria have been detected in mucosal (exposed, barrier) body sites and protected sites.



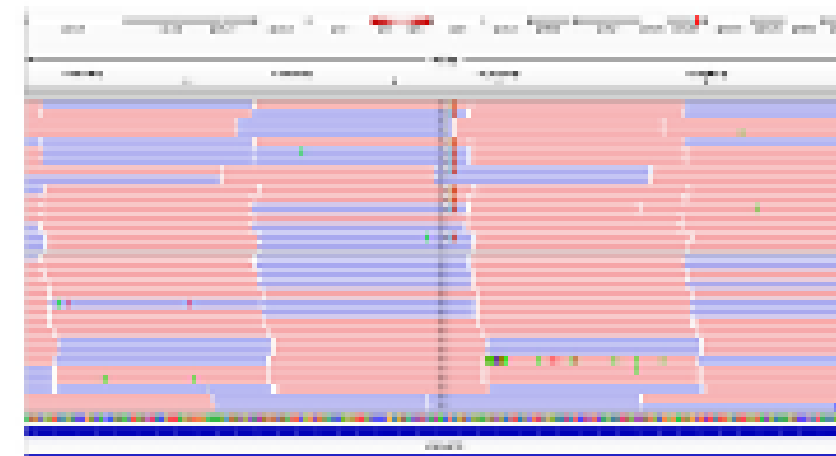
- Can intratumoral microorganisms be detected also in lymphoma?
- Is their presence associated with outcome?

Intratumoral Microbiome Signature (IMS) analysis

Lymphoma biopsy



MSK-IMPACT sequencing



Tumor DNA

Genomic DNA

Non-human DNA

Genomic DNA

Non-human DNA

Sequencing reads

FastQ

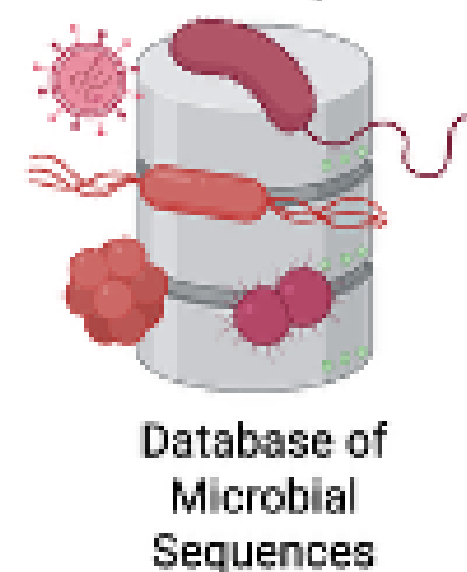
Read alignment

Human reference genome GRCh37 (hg19)

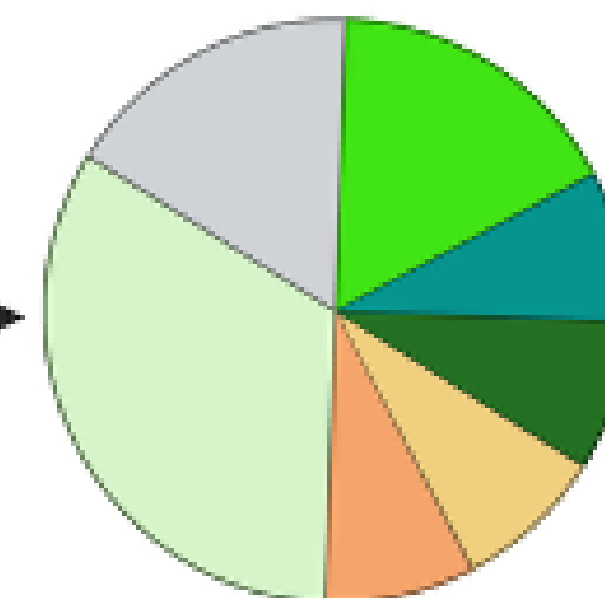
Soft-clipped reads

BLASTn align to microbial genomes

Unmapped reads



QC and Quantify Results

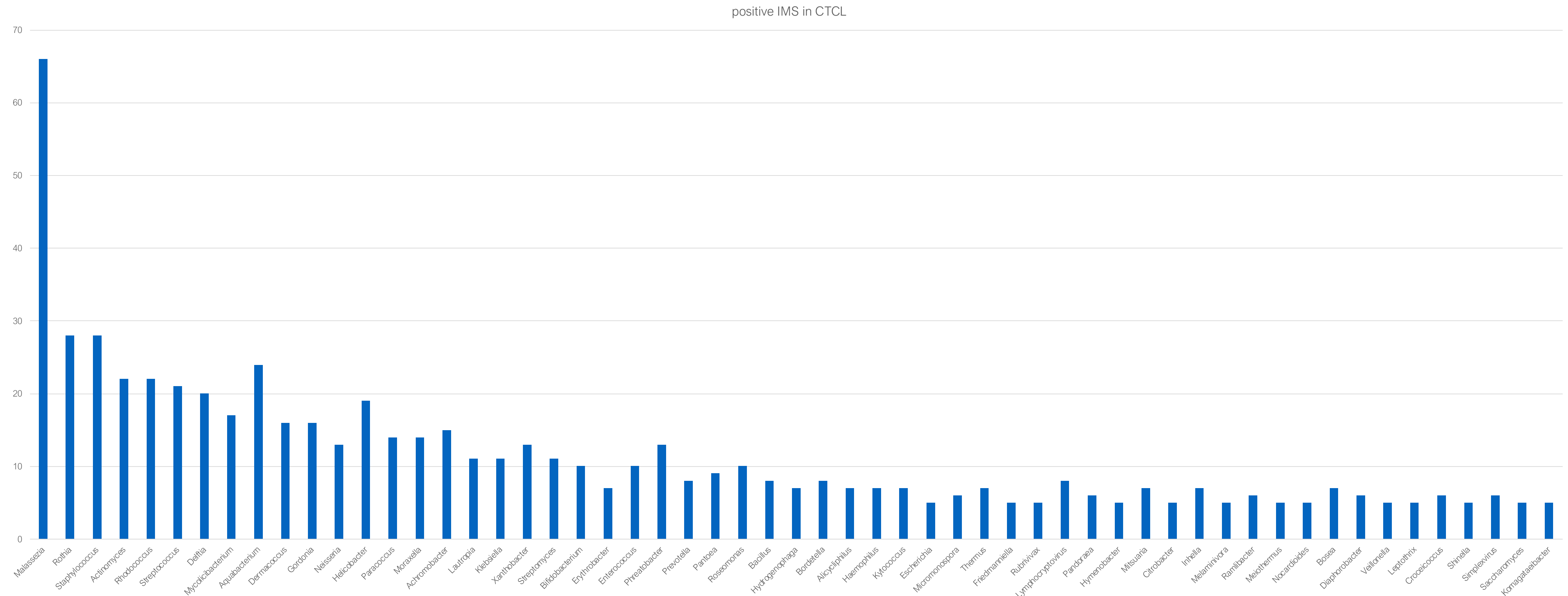


- Bacterial DNA.1
- Bacterial DNA.2
- Bacterial DNA.3
- Viral DNA.1
- Viral DNA.2
- Other microbial reads
- Contaminants

Bioinformatic pipeline re-analyzing NGS data

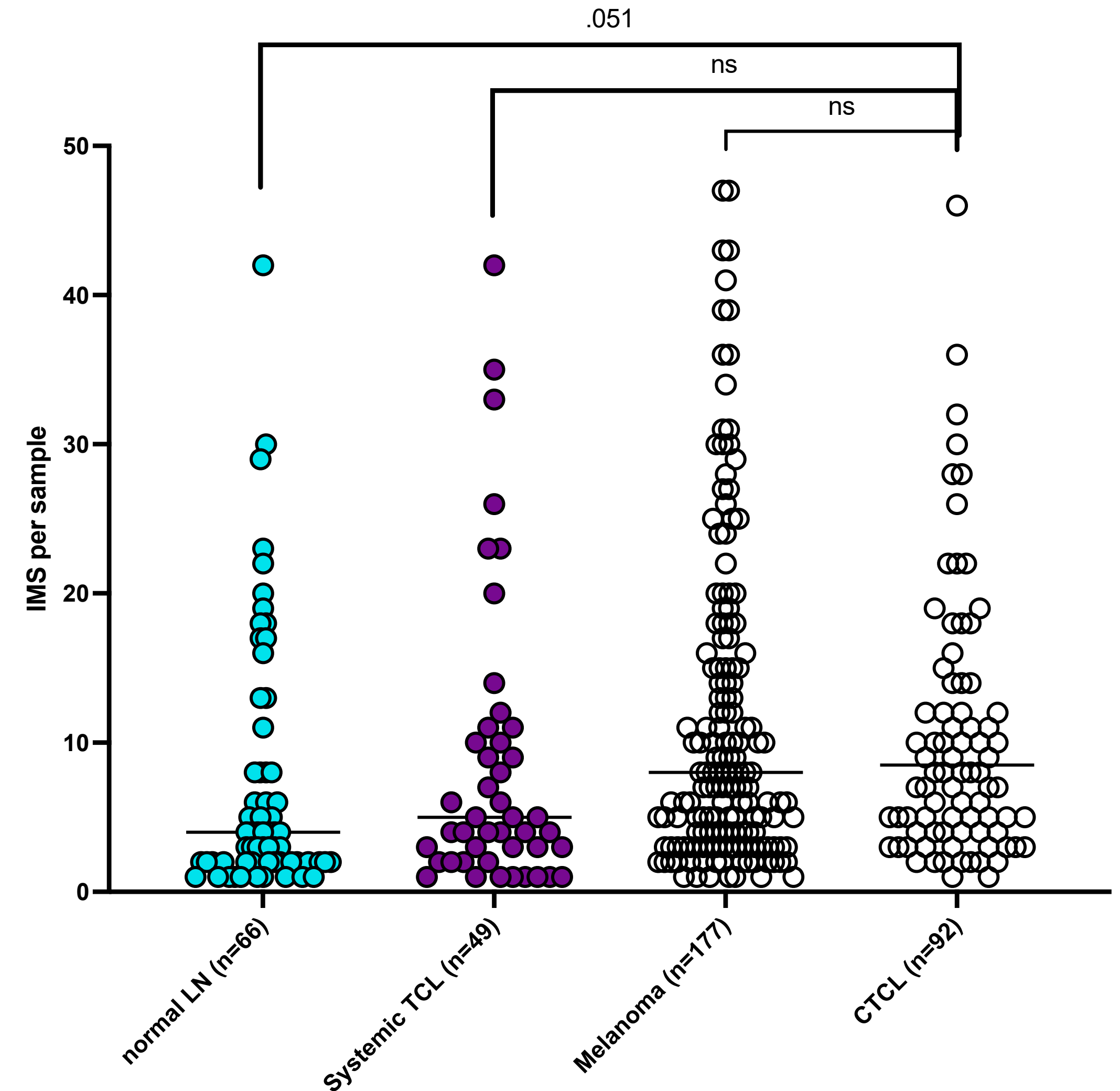
Analysis on 93 CTCL patients with samples with MSKCC diagnosis

Intratumoral Microbiome Signatures (IMS) detected in > 10% of the CTCL samples



Lymphoma vs LN controls - IMS frequency

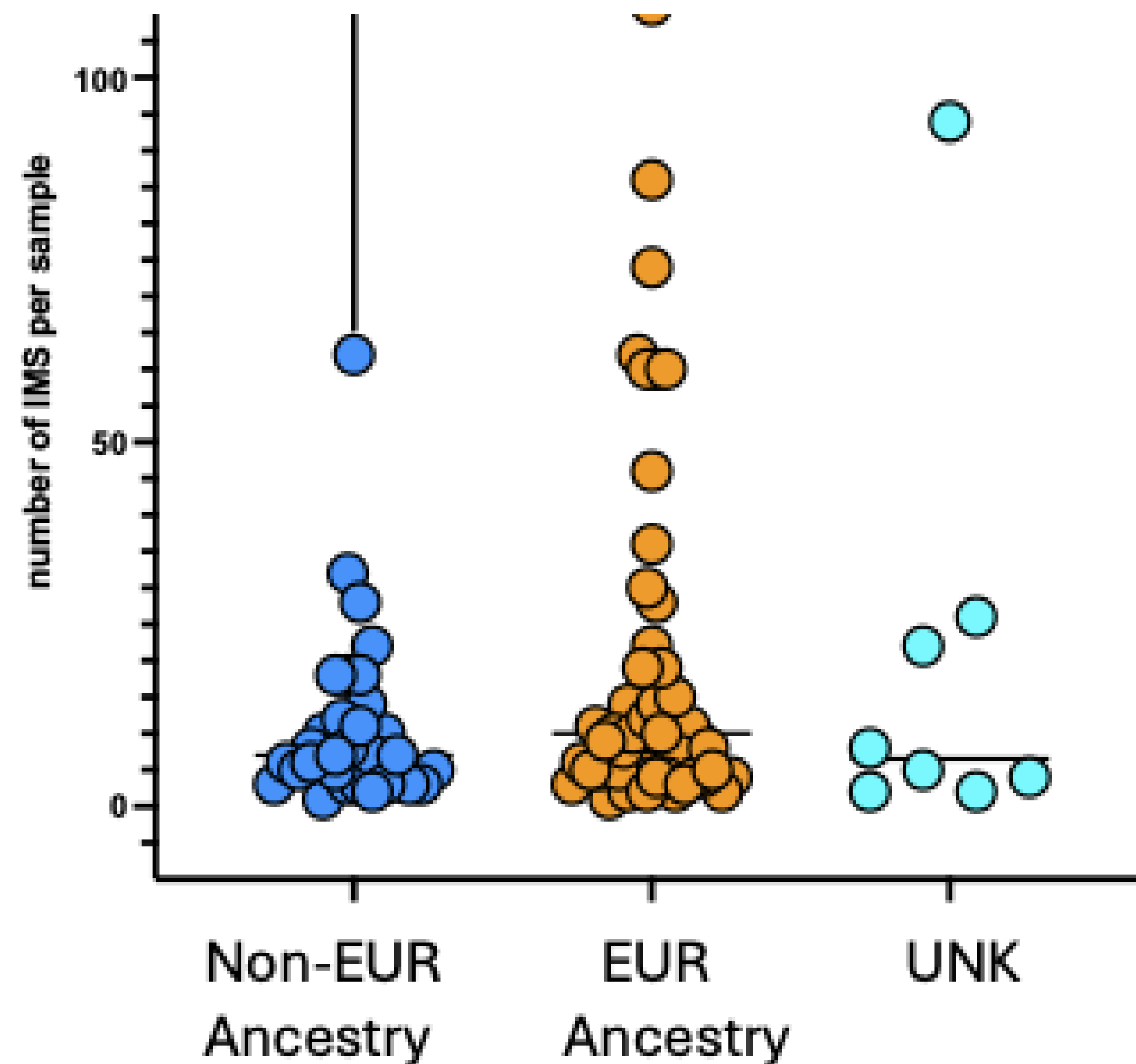
CTCL top 10%	CTCL	Melanoma	CTCL vs Mel (Fisher Exact test)	Systemic TCL	CTCL vs TCL (fisher exact test)
Malassezia			p=ns		p=ns
Rothia			p=ns		p=ns
Staphylococcus	23%	17%	p=.25	31%	p=.32
Actinomyces			p=ns	0	p<.05
Rhodococcus			p=ns		p=ns
Streptococcus	23%	21%	p=.75	33%	p=.23
Delftia			p=ns		p=ns
Mycolicibacterium			p=ns		p=ns
Aquabacterium	24%	8%	p=.0005	0	p<.05
Dermacoccus			p=ns		p=ns
Gordonia			p=ns		p=ns
Neisseria			p=ns		p=ns
Helicobacter	19%	9%	p=.011	0	p<.05
Paracoccus			p=ns		p=ns
Moraxella			p=ns	0	p<.05
Achromobacter			p=ns		p=ns
Lautropia	12%	9%	p=.39	0	p<.05
Klebsiella			p=ns		p=ns
Xanthobacter	14%	8%	p=.13	8%	p=.42
Streptomyces			p=ns		p=ns
Bifidobacterium	10%	5%	p=.19	10%	p=ns
Enterococcus			p=ns	0	p<.05
Phreatobacter	10%	6%	p=ns	0	p<.05
Roseomonas	10%	8%	p=ns	0	p<.05



Ghione P, WCCL 2026

Ghione P, 18-ICML

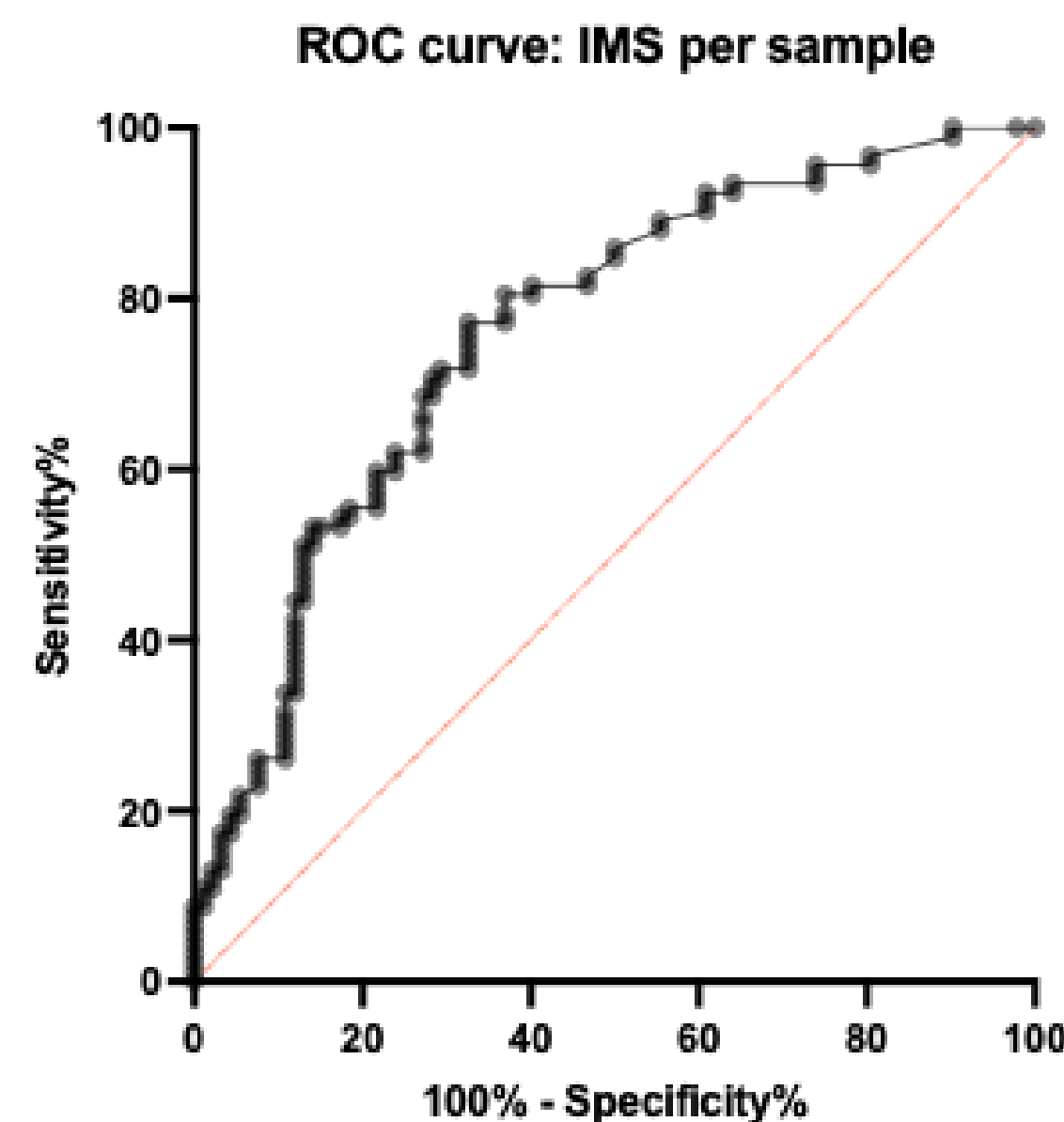
A low #IMS/sample was associated with non-European ancestry



- Ancestral annotation was inferred using NGS (MSK-IMPACT) by Dr Pararajalingam (Dr Elenitoba-Johnson lab)

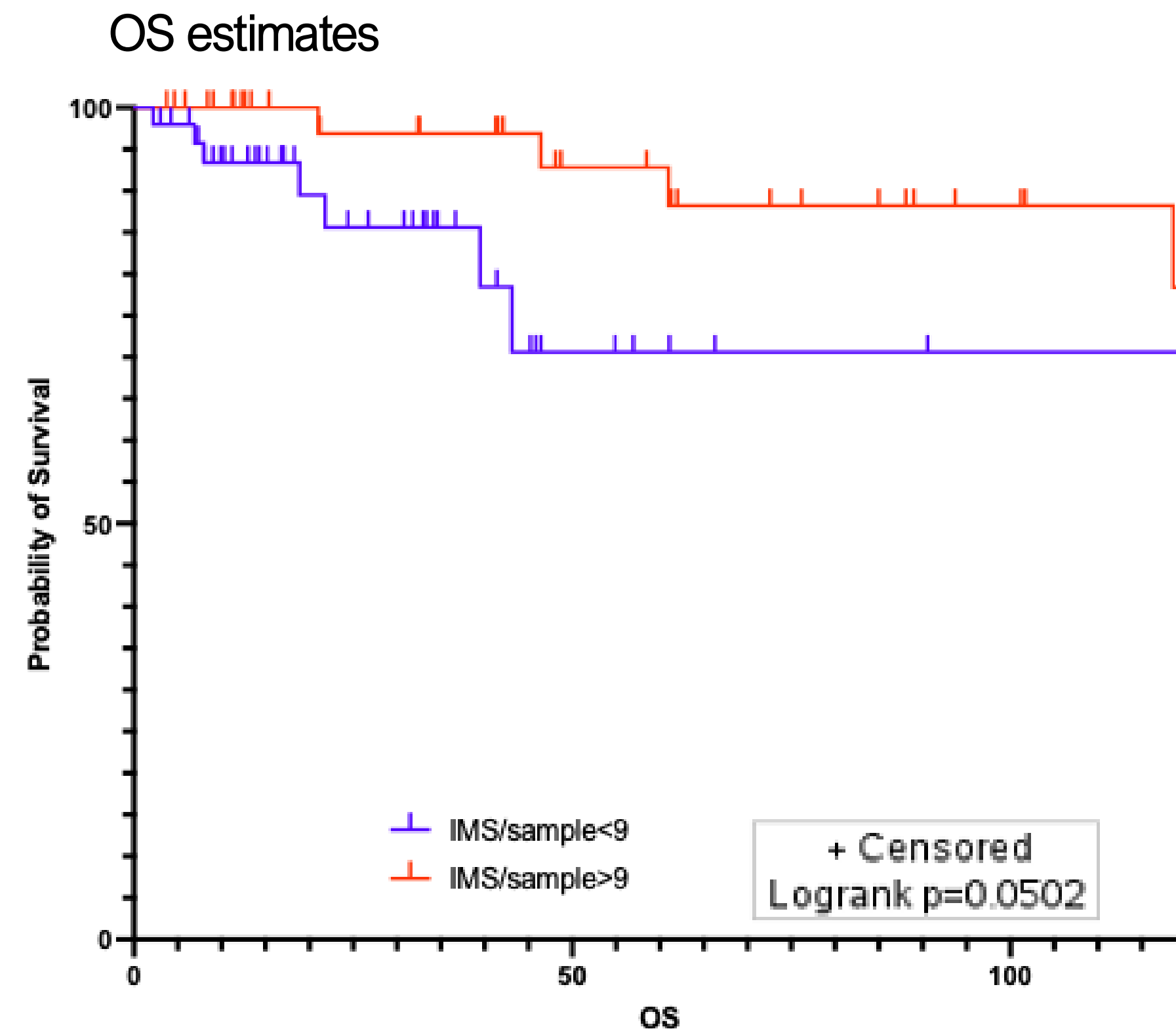
A low # IMS/sample was associated with worse OS

The best cut-off for the # IMS/sample was calculated with the ROC curve



AUC 0.8

Best cut off 9

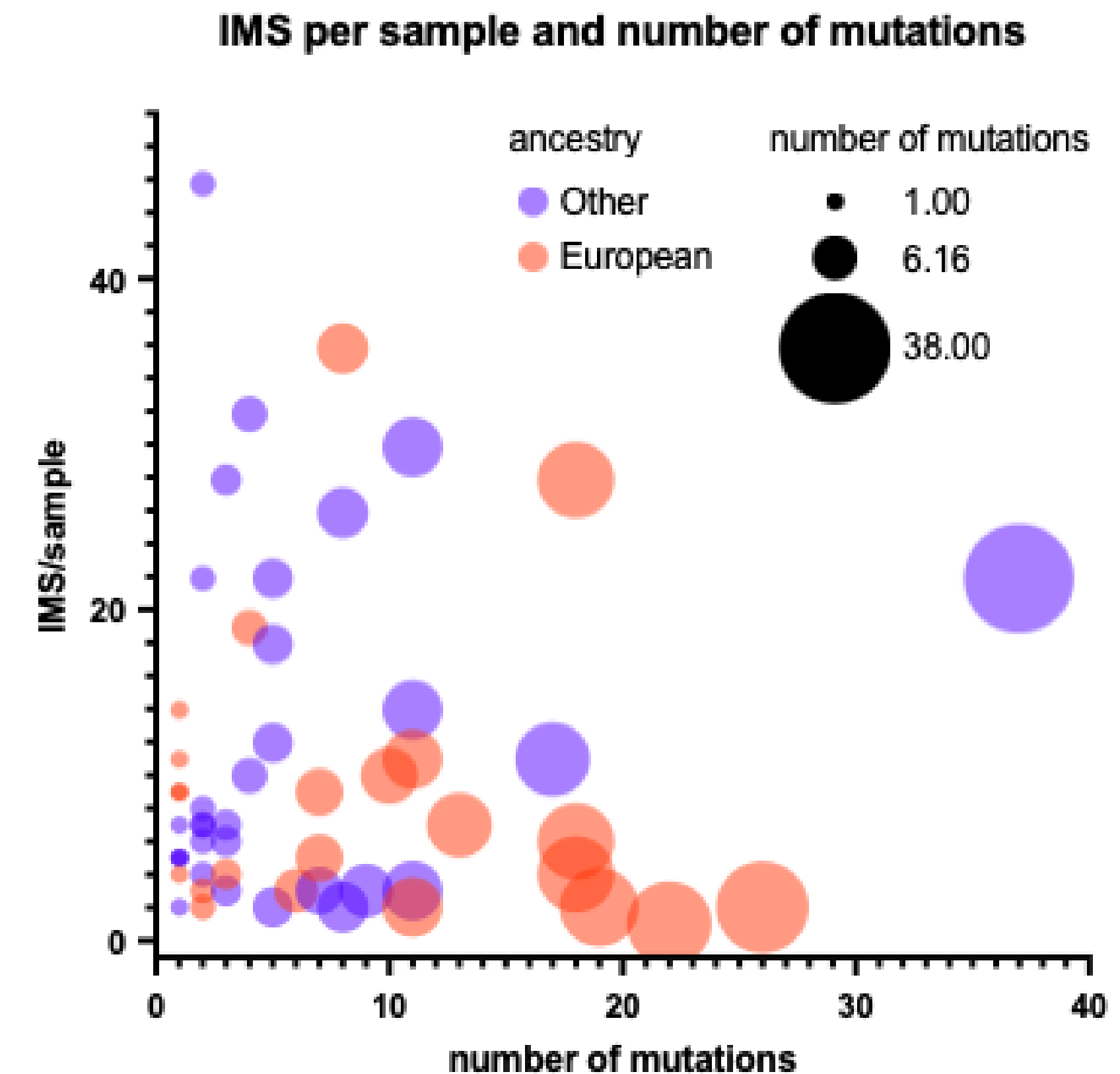


#IMS/sample was associated with JAK/STAT pathway mutations

AND the number of IMS per sample was not related to the number of mutations per sample

gene	High IMS+	Low IMS+	High IMS-	Low IMS-
JAK2	4	6	42	40
JAK1	0	4	46	42
JAK3	2	4	44	42
STAT5B	0	1	46	45
STAT6	0	1	46	45
STAT5A	2	0	44	46
JAK2 structural variants	5	8	17	17
SOCS1	2	7	44	39
Total	15	31	329	316

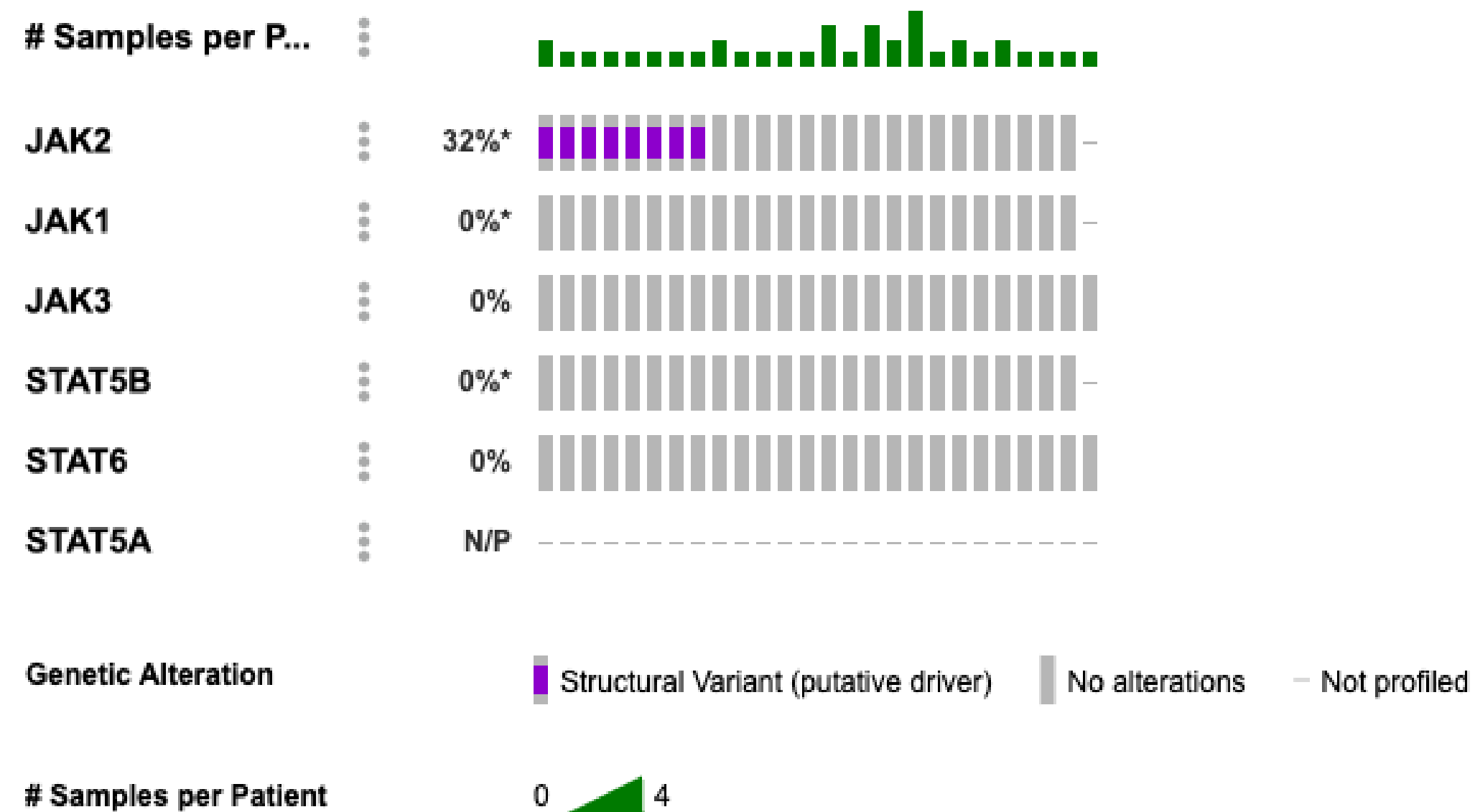
p=.016



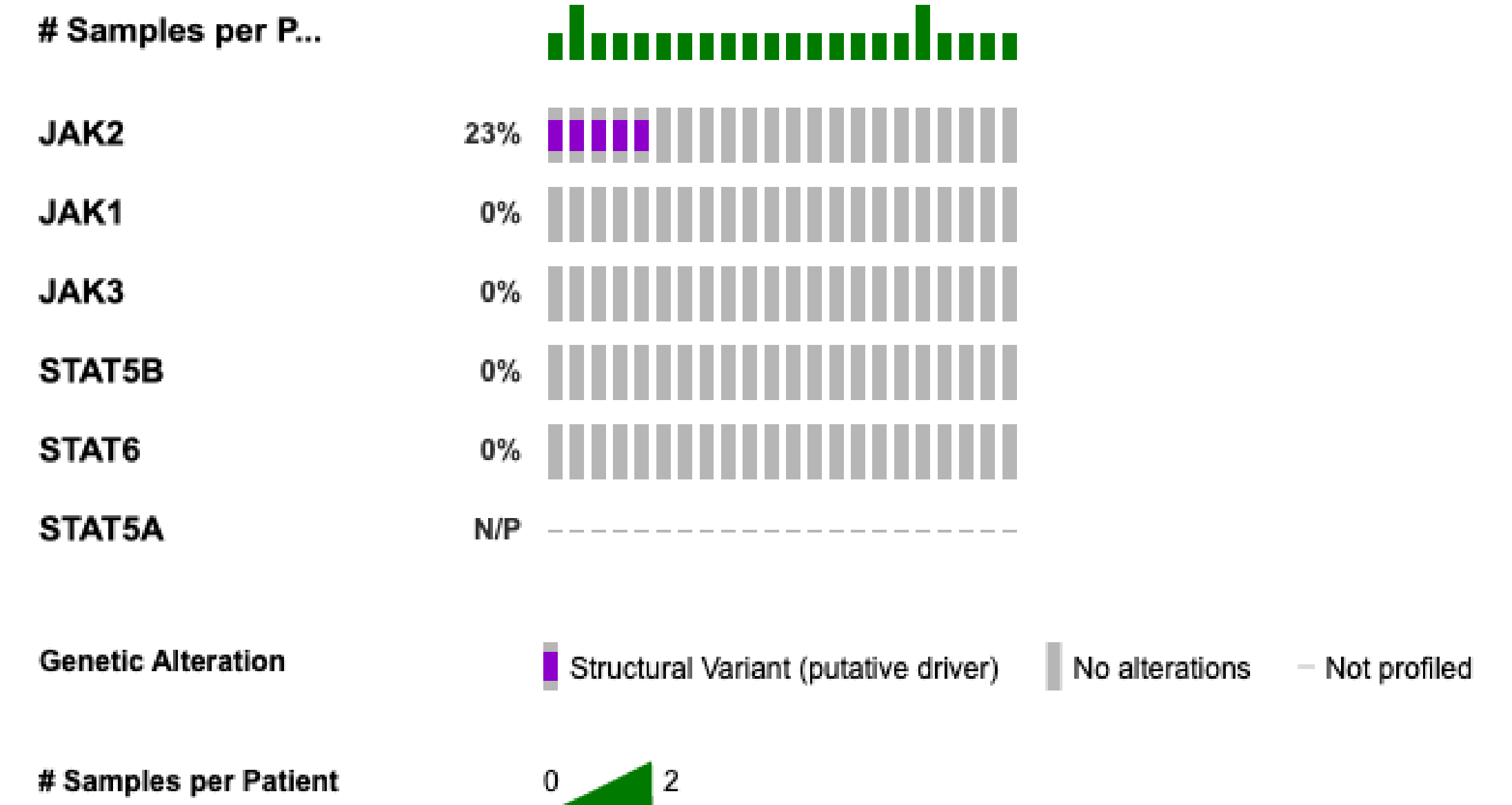
Fusions were analyzed with MSK-ARCHER and showed a similar trend of increased presence in patients with low IMS

ARCHER - Fusions

IMS low



IMS high



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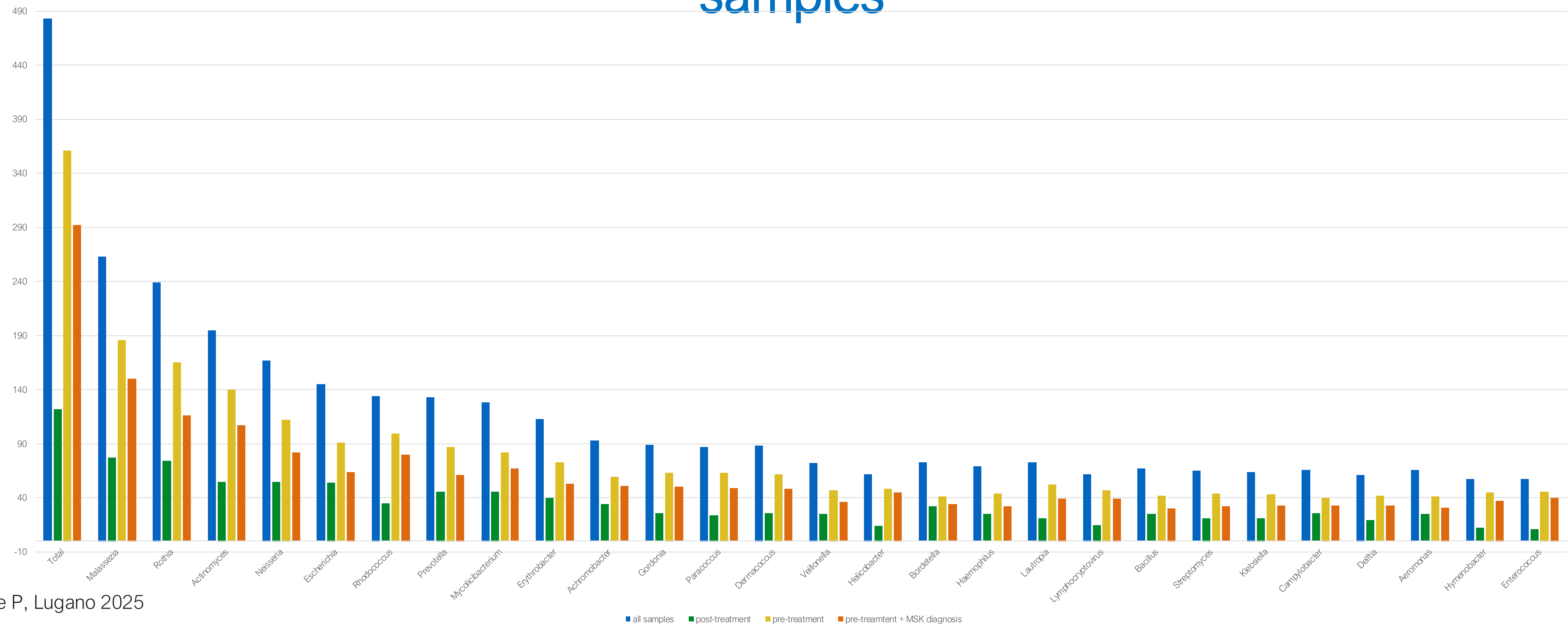
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Analysis on 266 patients with pre-treatment samples with MSKCC diagnosis and first line treatment at MSKCC

VS

71 normal LN analyzed with IMPACT-Heme and microbiome pipeline

Intratumoral Microbiome Signatures (IMS) detected in > 10% of the DLBCL samples



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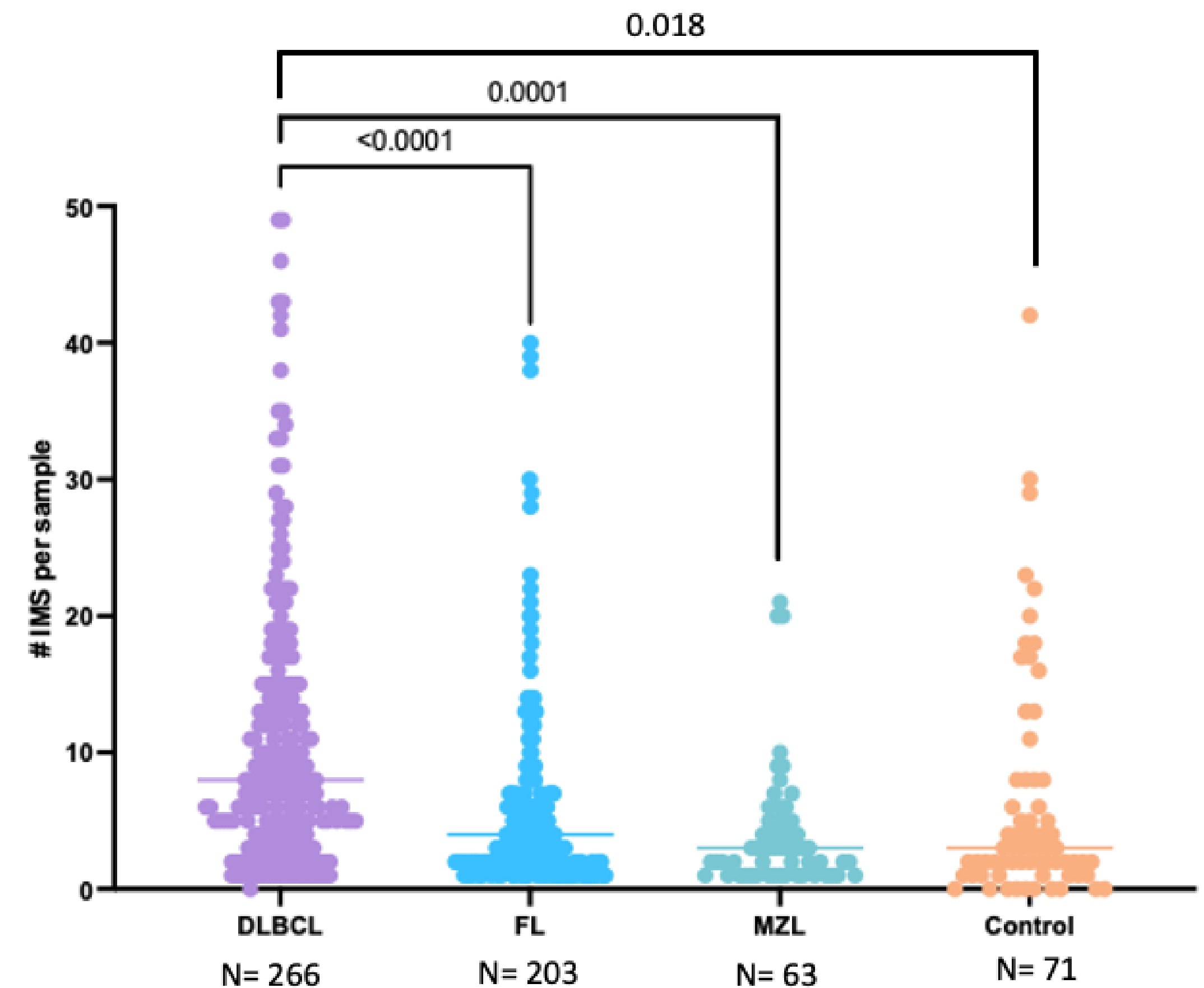
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microorganism	Percent positive (cases)	Percent positive (controls)	p (Fisher's Exact test)
Malassezia	136/266 (51%)	32/71 (45%)	.42
Rothia	135/266 (50%)	17/71 (24%)	.07
Actinomyces	117/266 (44%)	13/71 (18%)	.001
Neisseria	93/266 (35%)	13/71 (18%)	.01
Rhodococcus	79/266 (30%)	8/71 (11%)	.002
Escherichia	78/266 (29%)	2/71 (3%)	.0001
Prevotella	72/266 (27%)	11/71 (15%)	.045
Mycolicibacterium	66/266 (25%)	7/71 (10%)	.006
Paracoccus	50/266 (19%)	9/71 (12%)	.31
Achromobacter	45/266 (17%)	8/71 (11%)	.28
Enterococcus	42/266 (16%)	9/71 (12%)	.58
Delftia	35/266 (13%)	9/71 (12%)	.9

Lymphoma vs LN controls - IMS frequency



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Clinical variables potentially impacting on outcome (fisher/chi2)

Var (n=266)	Frequency	EOT response
Age at diagnosis (> 60 years)	152 (57%)	CR (>60) 74% vs 83% p=ns
Sex (male)	147 (55%)	CR (M) 76% vs 81% p=ns
IPI (0-2)*	128 (49%)	CR (L) 86% vs 70% p=.0031
B-symptoms (yes)**	57 (26.4%)	CR (Y) 72% vs 78% p=ns
Histology		p=ns
GCB	96 (44%)	CR 82%
Non-GC	83 (38%)	CR 75%
Not eval	38 (17%)	CR 97%
HGBCL (yes)	49 (18%)	CR (Y) 61% vs 82% p=.012

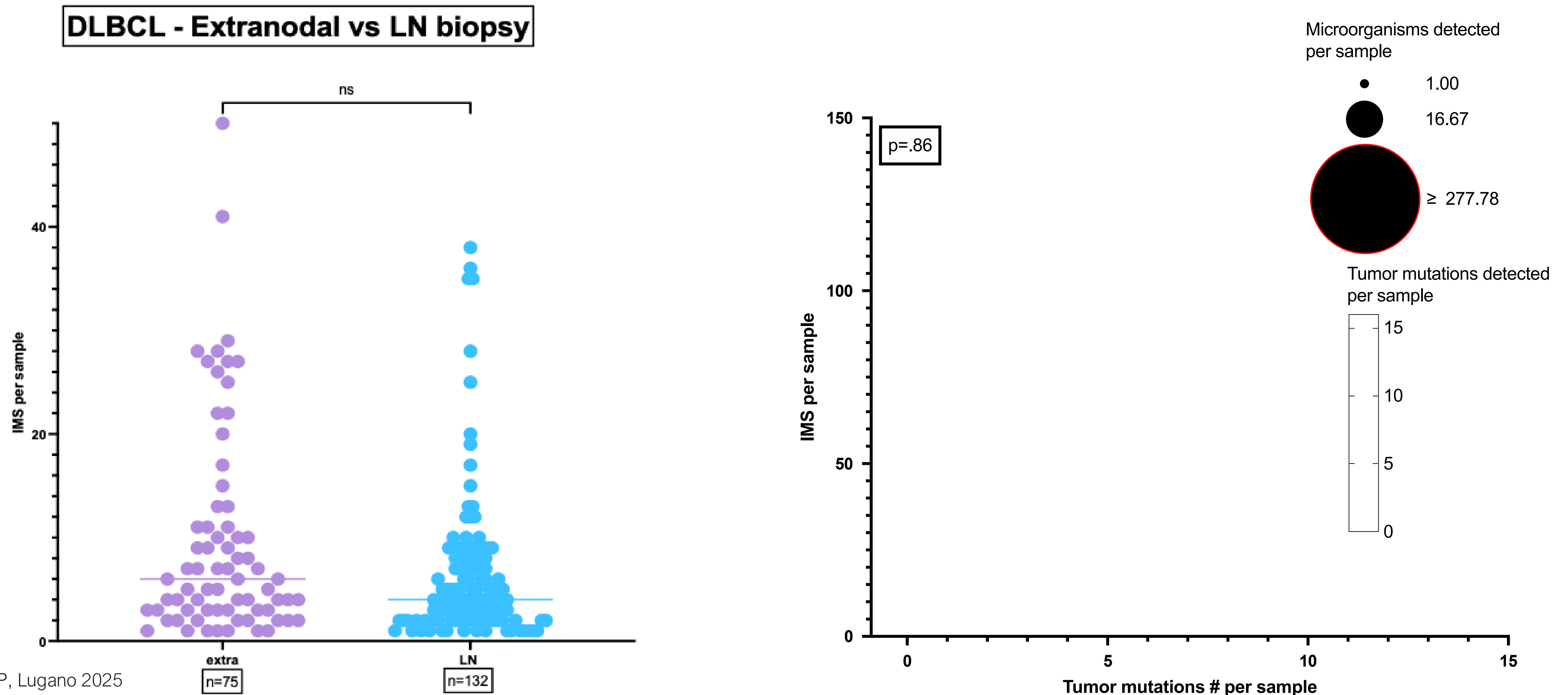
*Missing = 4

**Missing = 50

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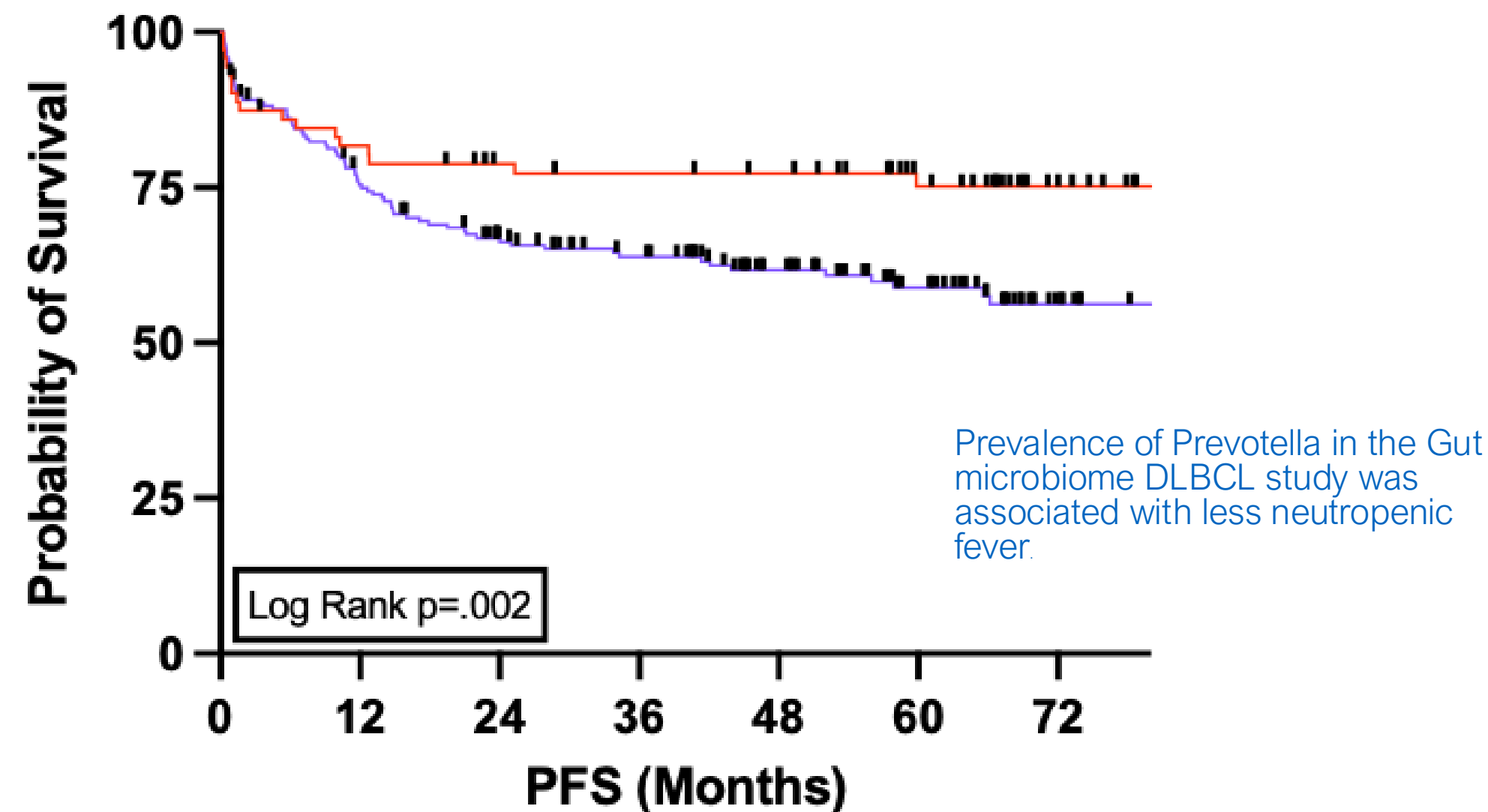
IMS per sample is not associated with biopsy location or number of tumor mutations

Potential confounders in the analysis were carefully considered



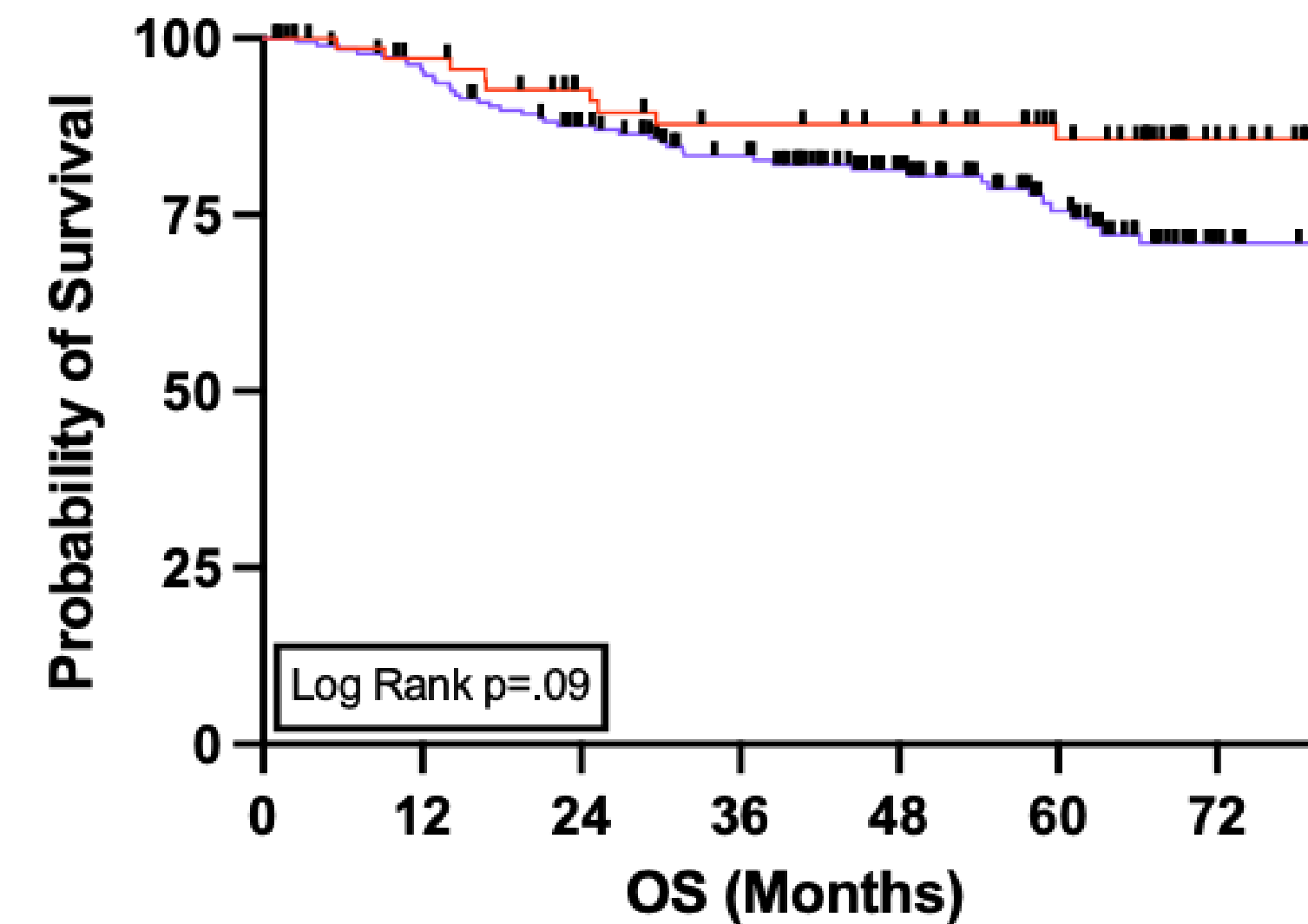
IMS Prevotella detection - PFS and OS

PFS - DLBCL prevotella



Prevotella pos	72	58	52	50	48	37	22
Prevotella neg	194	142	115	100	77	54	30

OS - DLBCL prevotella



Prevotella pos	72	68	58	54	51	40	23
Prevotella neg	194	178	152	132	101	72	40

PFS – COX regression analysis, Maximum Likelihood Estimate

Variable	p (ChiSq)	Hazard Ratio	95% HR confidence interval	
Prevotella	.048	0.586	0.345	0.996
IPI (good)	.125	0.710	0.459	1.100
HGBCL	.096	1.534	0.926	2.541
Age (bin)	.002	2.105	1.307	3.390

OS – COX regression analysis, Maximum Likelihood Estimate

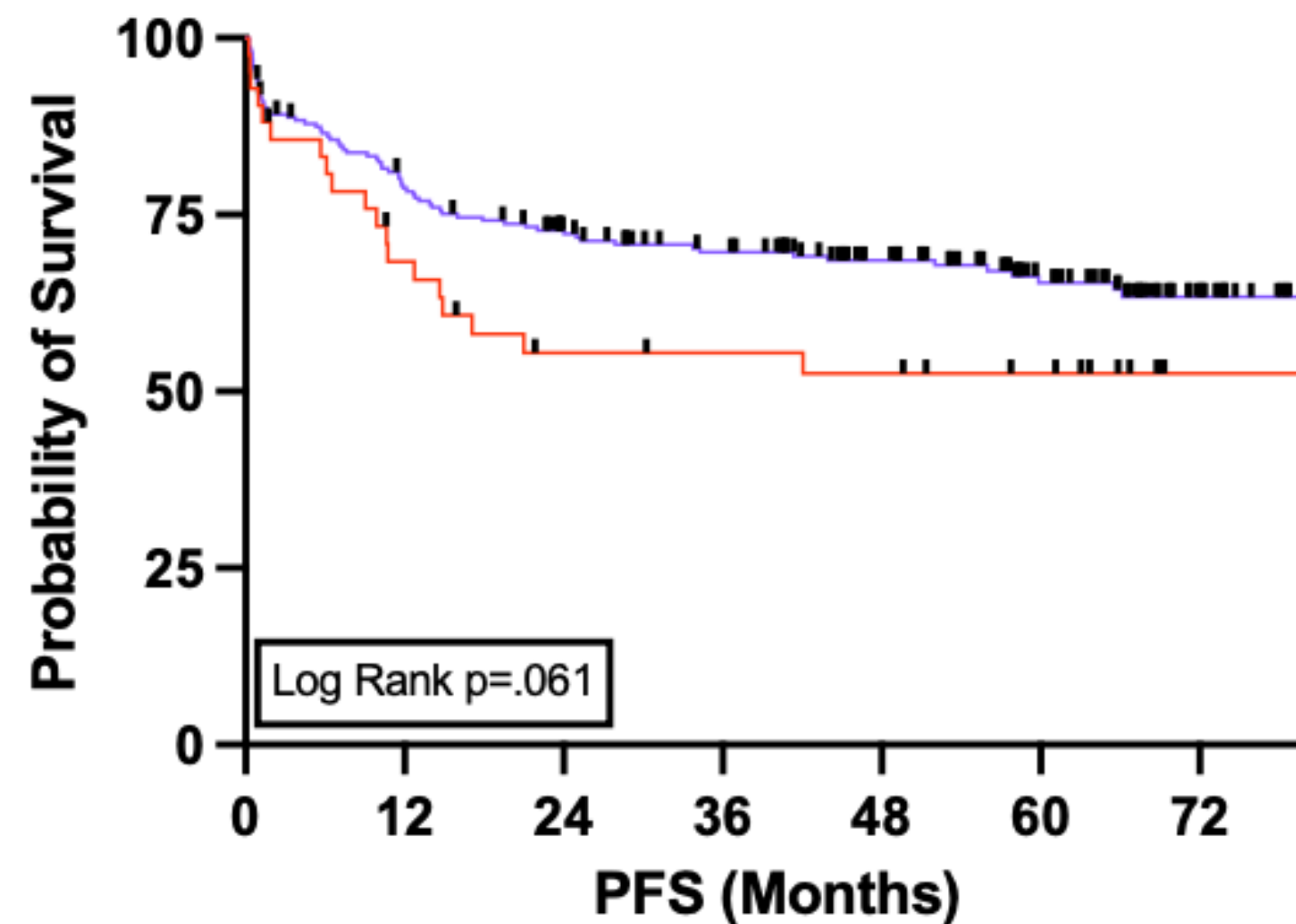
Variable	p (ChiSq)	Hazard Ratio	95% HR confidence interval	
Prevotella	.075	0.535	0.268	1.067
IPI (good)	.613	0.862	0.486	1.530
HGBCL	.126	1.673	0.865	3.235
Age (bin)	.0001	5.351	2.461	11.63

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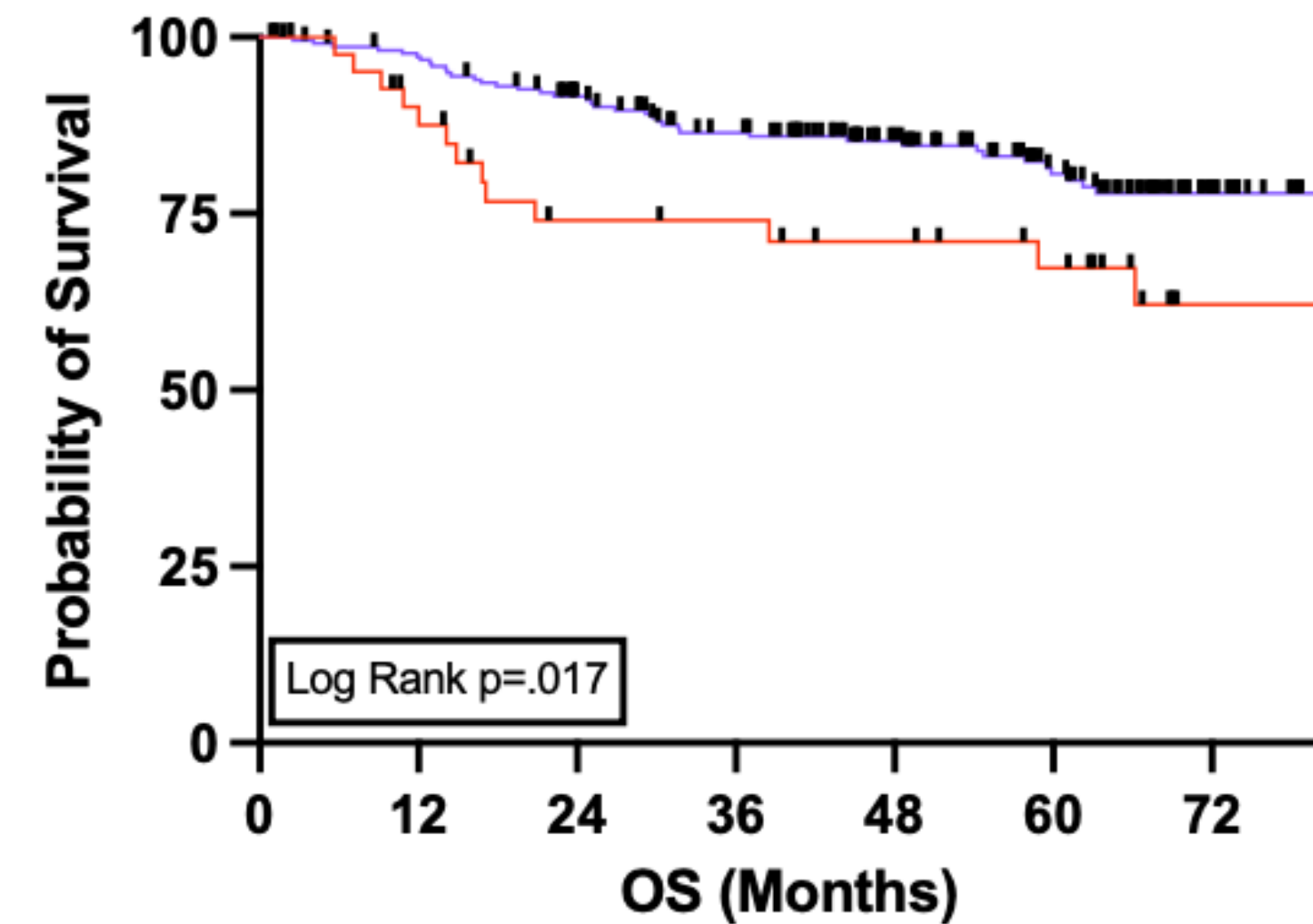
Enterococcus detection - PFS and OS

PFS - DLBCL enterococcus



Enterococcus pos	42	28	21	20	19	16	8
Enterococcus neg	224	172	146	130	106	75	45

OS - DLBCL enterococcus



Enterococcus pos	42	35	27	26	23	19	9
Enterococcus neg	224	210	183	160	129	93	55

PFS – COX regression analysis, Maximum Likelihood Est

Variable	p (ChiSq)	Hazard Ratio	95% HR confidence interval	
Enterococcus	.061	1.632	0.978	2.722
IPI (good)	.109	0.700	0.453	1.084
HGBCL	.048	1.672	1.003	2.787
Age (bin)	.002	2.097	1.304	3.372

OS – COX regression analysis, Maximum Likelihood Est

Variable	p (ChiSq)	Hazard Ratio	95% HR confidence interval	
Enterococcus	.033	1.955	1.056	3.618
IPI (good)	.592	0.854	0.479	1.522
HGBCL	.083	1.802	0.925	3.511
Age (bin)	.0001	5.052	2.322	10.99

Conclusions:

- Gut dysbiosis is known to influence response to treatment and infectious complications in CTCL, other microbiome modalities might unveil other important messages
- A low #IMS/Sample seems to be related to non-EU ancestry, detection of mutations in the JAK/STAT pathway and overall worse survival
- Intratumoral microbiome might potentially influence the lymphoma TME and response to therapy □ ongoing work to verify presence of IMSs and spatial/qualitative relationship to microbiome niches
- *Prevotella* and *enterococcus* IMS associated with PFS/OS and not to specific pathology/prognostic factors at diagnosis
- Do IMSs co-localize in specific niches of the microenvironment? How does the presence of IMSs relate to changes in the tumor microenvironment? → ongoing work to verify presence of IMSs and spatial/qualitative relationship to microbiome niches
- Potential interventions in lymphoma to tackle the microenvironment?

Thank you!!



Patients and families

Bioinformatics

- Chad Vanderbilt

Pathology

- Megan Lim
- Melissa Pulitzer
- Kojo Elenitoba-Johnson
- Prasath Pararajalingam

Dermatology

- **Shamir Geller**
- **Cesar Virgen**
- Viviane Liao

Statistics supervision

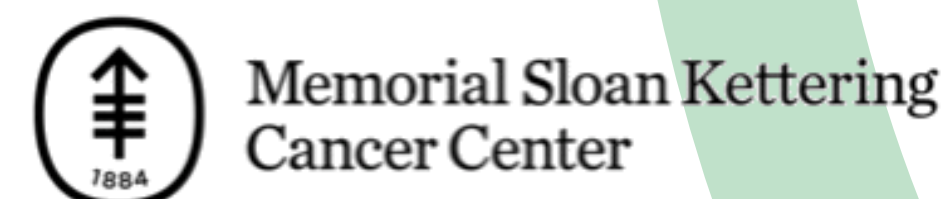
- **Fei Teng**

Microbiome

- **Johnatan Peled**

Lymphoma database team

- **Rita Tavarozzi**
- **Nivetha Ganesan**



Lymphoma

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- Marcel Smith
- Theresa Davey
- Alicia Assini
- Angela Gibaldi
- Mackenzie Maloney

- **Gilles Salles**
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- Andrew Intlekofer
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- Ariela Noy
- Lia Palomba
- Pallawi Torka