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Review article

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Gut OncoMicrobiome Signatures (GOMS) as next-generation biomarkers for cancer immunotherapy

Gut OncoMicrobiome Signatures (GOMS) as next-generation biomarkers for cancer immunotherapy

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Supplementary files

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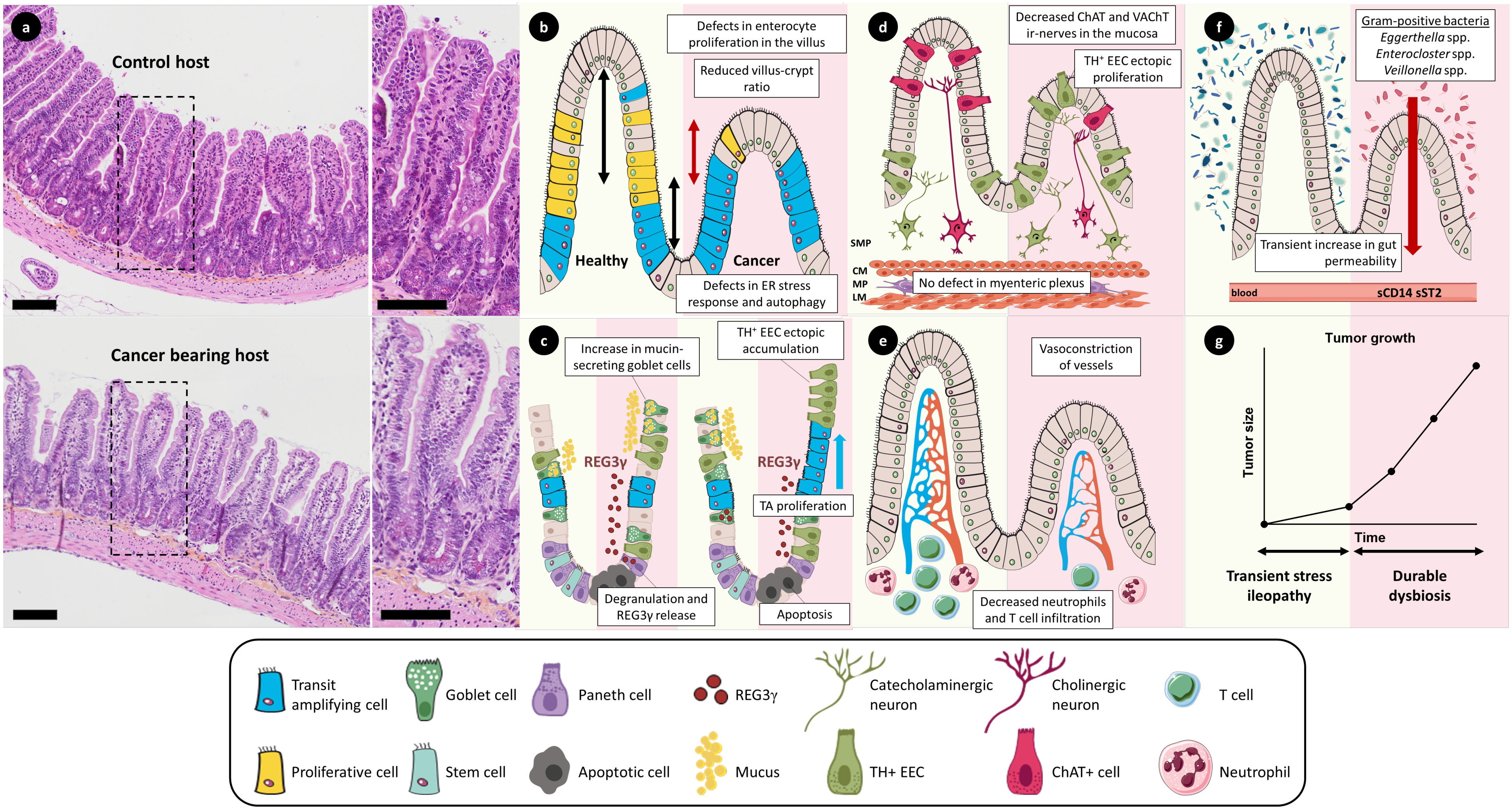

Supplementary FIG. 1 | Microscopic and cellular description of the cancer-induced stress ileopathy.
A-G. Proposed scenario of stress ileopathy induced during a tumorigenic process. Experimental demonstration in cancer bearing mice that tumour inoculation might trigger crypt apoptosis, activation of secretory cells, ectopic proliferation of tyrosine hydroxylase positive and enteroendocrine cells (TH^+ EEC) resulting in a disbalance between cholinergic and adrenergic signalling promoting a transient ileal mucosa atrophy but a protracted intestinal dysbiosis dominated by vancomycin-sensitive species belonging to the *Enterocloster* genus. Micrograph pictures of HE stained ileal tissues showing patchy abrasion of ileal villosities 7–10 days after tumour implantation in C57BL/6 mice.
Bar scale: 100 µm. ChAT, choline acetyltransferase; CM, circular muscle; EEC, enteroendocrine cell; ER, endoplasmic reticulum; ir-nerves, immunoreactive nerves; LM, longitudinal muscle; MP, myenteric plexus; REG3γ, Regenerating islet-derived protein 3 gamma; sCD14, soluble CD14; SMP, submucosal plexus; ST2, soluble interleukin-1 receptor-like 1; TA, transit amplifying cells; TH, tyrosine hydroxylase; VAChT, vesicular acetylcholine transporter.
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Legends for Supplementary Tables

Supplementary TABLE 1 | Pan-disease or pan-cancer GOMS versus healthy metagenomes and alignment with the proposed meta-analysis.

This table aims at aligning bacteria composing the core gut microbiome (according to Dutch Microbiome Project; Gacesa et al.)[22], the health-related microbiome (according to Gacesa et al., Yonekura et al.)[22,24] and faecal bacterial taxa with relative over-representation across various diseases or in patients with cancer regardless of histotypes (according to Gacesa et al., Yonekura et al.)[22,24]. The right columns aligned bacteria significantly retained in the meta-analysis comparing individuals with and without cancer (FIG. 2). The assessment of the effect of immune-checkpoint inhibitors on the intestinal taxonomic composition is currently underway and therefore cannot be provided in this table[173,174]. GOMS, Gut OncoMicrobiome signatures.

Supplementary TABLE 2 | Cohort description for the meta-analysis comparing GOMS in individuals with and without cancer.

Refer to FIG. 2. GOMS, Gut OncoMicrobiome signatures.

Supplementary TABLE 3 | Detailed results of pan-cancer GOMS presented in FIG. 2.

We implemented a Bayesian multinomial logistic-normal linear regression model called Pibble from the R package fido, linking covariates that included cancer status, age and gender to compositional overdispersed count data. We transformed taxonomic relative abundances into count values for Pibble via logistic-normal distribution modeling[175]. Log-ratios with 95% credible intervals were calculated for each species-level genome bin (SGB) and each pairwise cancer–control comparison and were supplied to a random effects model via the rem_mv function in the MetaVolcanoR R package (v.1.4.0) using the restricted maximum-likelihood estimator model. We considered only SGBs with 95% credible intervals greater than or less than zero in > 50% of pairwise comparisons and with a rank in at least 6 of 8 cancers (Supplementary Methods). GOMS, Gut OncoMicrobiome signatures.

Supplementary TABLE 4 | GOMS profiles across various cancer types.

We detail the bacteria orders, families and genus and/or species distinguishing individuals with and without cancer across three distinct cancer types for which data are available and have been reported. Only bacterial taxa relatively over-represented (but not under-represented) in faecal samples from patients with cancer (compared with those without) are annotated. Cancer histotype-specific bacteria are not in bold. GOMS, Gut OncoMicrobiome signatures.

Supplementary TABLE 5 | Cohort description and machine learning analysis for responders versus non-responders among patients receiving immune-checkpoint inhibitors.

We applied a leave-one-dataset-out (LODO) approach to the relative abundance of species-level genome bins (SGBs). Cohorts with more than 20 samples were used in the LODO approach and model performance was assessed using the area under the receiver operator (AUC) values. RF global CV: random forest global cross validation (Supplementary Methods). A Random Forest model applied in a LODO setting on a total of 761 patients with cancer receiving immune-checkpoint inhibitors (for whom sex and age were available) built to differentiate patients with objective responses (complete or partial responses) from non-responders (with stable or progressive disease) had a moderate and rather inconsistent predictive power across left-out datasets and a modest predictive power when merging all dataset for a single cross-validation evaluation (AUC 0.71). These results are consistent with individual reports showing that these groups were compositionally distinguishable but with limited overlap of biomarkers across studies. Of note, cohorts of patients with non-small-cell lung cancer or renal cell carcinoma displayed better AUC predictive values than melanoma cohorts.

Supplementary TABLE 6 | Baseline GOMS associated with response rates in the mega-analysis presented in FIG. 3.

This table reports results from the mega-analysis using Pibble models on clr transformed species-level genome bin (SGB)-level relative abundances presented in FIG. 3 (Supplementary Methods). LogRatio, 95% credible interval and taxonomy by family, genus, species and taxon are detailed. This table includes a summary of the results presented in FIG. 3 by family, genus and species levels. GOMS, Gut OncoMicrobiome signatures.

Supplementary TABLE 7 | Baseline GOMS associated with response rates in the meta-analysis presented in FIG. 4.

This table reports results from the meta-analysis using different differential abundance methods adjusting for age and gender to identify species-level genome bins (SGBs) associated with ORR, presented in FIG. 4 (Supplementary Methods). This table includes a summary of the results presented in FIG. 4 by family, genus and species levels. GOMS, Gut OncoMicrobiome signatures.

Supplementary TABLE 8 | Relationships between cancer-associated bacteria relevant for clinical outcome and confounding factors.

The bacteria retained as significant in the meta-analysis and mega-analysis presented in FIGS 2–3 and Supplementary TABLES 2–3 and 6–7 were highlighted according to their reported association with confounding factors in cancer (FIG. 1). PubMed-related searches as of October 2022 of stool shotgun metagenomics-defined taxonomic composition in various confounding factors of cancer, listed above. Red boxes, increased relative abundance of the metagenomic sequence (MGS); blue boxes, decreased relative abundance of the MGS; purple boxes, increased or decreased relative abundance of the MGS.

Supplementary TABLE 1 | Pan-disease or pan-cancer GOMS versus healthy metagenomes and alignment with the proposed meta-analysis.

Order	Family	Genus (Species)	Core gut microbiome	ref	Health	ref	Pan-disease	ref	Pan-Cancer	ref	Health (Meta-analysis)	ref	Pan-Cancer (Meta-analysis)	ref
Acidaminococcales	*Acidaminococcaceae*	*Acidaminococcus (A. fermentans)*							x	Yonekura, S. et al.				
Bifidobacteriales	*Bifidobacteriaceae*	*Aeriscardovia (A. aeriphila)*			x	Yonekura, S. et al.								
Bacteroidales	*Rikenellaceae*	*Alistipes (A. onderdonkii, A. putredinis, A. shahii)*	x	Gacesa, R. et al.										
Bacteroidales	*Rikenellaceae*	*Alistipes (A. senegalensis, A. shahii, A. communis (Bacteroidales bacterium ph8))*			x	Gacesa, R. et al.								
Eubacteriales	*Lachnospiraceae*	*Anaerobutyricum (A. hallii)*			x	Yonekura, S. et al.								
Eubacteriales	*Lachnospiraceae*	*Anaerostipes (A. hadrus)*			x	Yonekura, S. et al.								
Eubacteriales	*Oscillospiraceae*	*Anaerotruncus (A. colihominis, A. sp.)*					x	Gacesa, R. et al.	x	Yonekura, S. et al.			x	Figure 2
Bacteroidales	*Bacteroidaceae*	*Bacteroides (B. galacturonicus)*			x	Yonekura, S. et al.								
Bacteroidales	*Bacteroidaceae*	*Bacteroides (B. uniformis, B. vulgatus)*	x	Gacesa, R. et al.										
Bacteroidales	*Barnesiellaceae*	*Barnesiella (B. intestinihominis)*			x	Gacesa, R. et al.								
Bifidobacteriales	*Bifidobacteriaceae*	*Bifidobacterium (B. adolescentis, B. pseudocatenulatum)*			x	Gacesa, R. et al., Yonekura, S. et al.								
Bifidobacteriales	*Bifidobacteriaceae*	*Bifidobacterium (B. dentium)*					x	Gacesa, R. et al.	x	Yonekura, S. et al.			x	Figure 2
Desulfovibrionales	*Desulfovibrionaceae*	*Bilophila (B. wadsworthia)*							x	Yonekura, S. et al.				
Eubacteriales	*Clostridiaceae*	*Butyricicoccus (B. sp. AM29-23AC)*									x	Figure 2		
Bacteroidales	*Odoribacteraceae*	*Butyricimonas (B. synergistica, B. virosa)*							x	Yonekura, S. et al.				
Eubacteriales	*Lachnospiraceae*	*Butyrivibrio (B. crossotus)*			x	Gacesa, R. et al.								
Campylobacterales	*Campylobacteraceae*	*Campylobacter (C. gracilis)*							x	Yonekura, S. et al.				
Clostridiales	*Clostridia*	*Candidatus Pararuminococcus (CP. gallinarum)*											x	Figure 2
Clostridiales	*Clostridia*	*Candidatus Schneewindia (CS. gallinarum)*											x	Figure 2
Eubacteriales	*Clostridiaceae*	*Clostridium (C. bolteae CAG:59, C. sp. CAG:58, sp. CAG:242)*							x	Yonekura, S. et al.				
Eubacteriales	*Clostridiaceae*	*Clostridium (C. sp. AF34-13, C. sp. AF34-10BH)*									x	Figure 2		
Eubacteriales	*Oscillospiraceae*	*Clostridium leptum*					x	Gacesa, R. et al.						
Coriobacteriales	*Coriobacteriaceae*	*Collinsella (C. aerofaciens)*			x	Yonekura, S. et al.								
Eubacteriales	*Lachnospiraceae*	*Coprococcus (C. comes)*			x	Yonekura, S. et al.								
Eubacteriales	*Lachnospiraceae*	*Coprococcus (C. eutactus)*									x	Figure 2		
Desulfovibrionales	*Desulfovibrionaceae*	*Desulfovibrio (D. piger)*			x	Gacesa, R. et al.								
Veillonellales	*Veillonellaceae*	*Dialister (D. sp. CAG:357)*			x	Yonekura, S. et al.								
Eubacteriales	*Lachnospiraceae*	*Dorea (D. longicatena)*			x	Gacesa, R. et al., Yonekura, S. et al.								
Eubacteriales	*Oscillospiraceae*	*Dysosmobacter (D. welbionis)*											x	Figure 2
Eggerthellales	*Eggerthellaceae*	*Eggerthella (E. lenta, E. sp.)*					x	Gacesa, R. et al.						
Eubacteriales	*Lachnospiraceae*	*Eisenbergiella (E. massiliensis, E. tayi)*							x	Yonekura, S. et al.			x	Figure 2
Eubacteriales	*Lachnospiraceae*	*Enterocloster (E. asparagiformis, E. bolteae, E. citroniae, E. clostridioformis, E. lavalensis)*					x	Gacesa, R. et al.	x	Yonekura, S. et al.			x	Figure 2
Lactobacillales	*Enterococcaceae*	*Enterococcus (E. faecalis)*											x	Figure 2
Erysipelotrichales	*Erysipelotrichaceae*	*Erysipelatoclostridium (Clostridium innocuum)*											x	Figure 2
Eubacteriales	*Eubacteriaceae*	*Eubacterium (E. ventriosum, E. sp. CAG:274)*			x	Yonekura, S. et al.								
Eubacteriales	*Oscillospiraceae*	*Faecalibacterium (F. prausnitzii)*	x	Gacesa, R. et al.	x	Gacesa, R. et al.								
Tissierellales	*Peptoniphilaceae*	*Finegoldia (F. magna)*			x	Yonekura, S. et al.								
Eubacteriales	*Oscillospiraceae*	*Flavonifractor (F. plautii)*					x	Gacesa, R. et al.						
Eubacteriales	*Lachnospiraceae*	*Fusicatenibacter (F. saccharivorans)*			x	Yonekura, S. et al.								
Enterobacterales	*Hafniaceae*	*Hafnia (H. alvei)*							x	Yonekura, S. et al.				
Eubacteriales	*Oscillospiraceae*	*Harryflintia (H. acetispora)*							x	Yonekura, S. et al.				
Erysipelotrichales	*Erysipelotrichaceae*	*Holdemania (H. filiformis)*					x	Gacesa, R. et al.						
Eubacteriales	*Clostridiaceae*	*Hungatella (H. hathewayi)*					x	Gacesa, R. et al.					x	Figure 2
Eubacteriales	*Oscillospiraceae*	*Hydrogeniiclostridium (H. mannosilyticum)*											x	Figure 2
Eubacteriales	*Eubacteriales*	*Intestinimonas (I. butyriciproducens)*							x	Yonekura, S. et al.			x	Figure 2
Eubacteriales	*Lachnospiraceae*	*Lachnoclostridium (Clostridium scindens, L. sp. An138)*											x	Figure 2
Eubacteriales	*Lachnospiraceae*	*Lachnoclostridium (Clostridium symbiosum)*							x	Yonekura, S. et al.				
Eubacteriales	*Lachnospiraceae*	*Lachnospira (L. eligens, L. pectinoschiza, L. sp. NSJ-43)*			x	Yonekura, S. et al.					x	Figure 2		
Eubacteriales	*Lachnospiraceae*	*Lachnospiraceae (Eubacterium rectale)*	x	Gacesa, R. et al.	x	Yonekura, S. et al.								
Lactobacillales	*Lactobacillaceae*	*Lactobacillus (L. rogosae)*			x	Yonekura, S. et al.								
Eubacteriales	*Oscillospiraceae*	*Lawsonibacter (L. asaccharolyticus)*							x	Yonekura, S. et al.				
Lactobacillales	*Lactobacillaceae*	*Ligilactobacillus (L. ruminis)*			x	Yonekura, S. et al.								
Eubacteriales	*Lachnospiraceae*	*Mediterraneibacter (Ruminococcus gnavus, R. torques)*			x	Yonekura, S. et al.	x	Gacesa, R. et al.					x	Figure 2
Eubacteriales	*Lachnospiraceae*	*Merdimonas (Merdimonas faecis)*											x	Figure 2
Eubacteriales	*Oscillospiraceae*	*Oscillibacter (Oscillibacter sp.)*	x	Gacesa, R. et al.			x	Gacesa, R. et al.			x	Figure 2		
Bacteroidales	*Prevotellaceae*	*Paraprevotella (P. clara, P. sp.)*			x	Gacesa, R. et al.								
Bacteroidales	*Prevotellaceae*	*Prevotella (P. copri, P. stercorea, P. sp. CAG:520)*			x	Gacesa, R. et al., Yonekura, S. et al.								
Eubacteriales	*Oscillospiraceae*	*Pseudoflavonifractor (P. capillosus, P. sp.)*					x	Gacesa, R. et al.					x	Figure 2
Eubacteriales	*Lachnospiraceae*	*Roseburia (R. faecis, R. sp. CAG:471)*			x	Yonekura, S. et al.								
Eubacteriales	*Lachnospiraceae*	*Roseburia (R. hominis)*									x	Figure 2		
Eubacteriales	*Oscillospiraceae*	*Ruthenibacterium (R. lactatiformans)*							x	Yonekura, S. et al.			x	Figure 2
Lactobacillales	*Streptococcaceae*	*Streptococcus (S. parasanguinis, S. salivarius)*					x	Gacesa, R. et al.						
Eubacteriales	*Oscillospiraceae*	*Subdoligranulum sp.*	x	Gacesa, R. et al.	x	Gacesa, R. et al.								
Erysipelotrichales	*Turicibacteraceae*	*Turicibacter (T. sanguinis)*			x	Yonekura, S. et al.								
Oscillospiraceae	*Faecalibacterium*	*unclassified Faecalibacterium (Faecalibacterium sp.)*									x	Figure 2		
Eubacteriales	*Lachnospiraceae*	*unclassified Lachnospira (Lachnospiraceae bacterium)*					x	Gacesa, R. et al.			x	Figure 2		
Eubacteriales	*Oscillospiraceae*	*unclassified Oscillospiraceae (Oscillospiraceae bacterium)*									x	Figure 2	x	Figure 2
Eubacteriales	*Oscillospiraceae*	*unclassified Oscillospiraceae (Ruminococcaceae bacterium D16)*					x	Gacesa, R. et al.						
Eubacteriales	*Peptococcaceae*	*unclassified Peptococcaceae (Peptococcaceae bacterium)*									x	Figure 2		
Veillonellales	*Veillonellaceae*	*Veillonella (V. parvula)*					x	Gacesa, R. et al.						

Supplementary TABLE 2 | Cohort description for the meta-analysis comparing GOMS in individuals with and without cancer.

Study Name	Cancer	Number of patients	Cohort name	Country	PubMedID	in cMD
Terrisse et al., JITC., 2022	Prostate Cancer	33	Oncobiotics	France	35296557	no
Pernigoni et al., Science., 2021	Prostate Cancer	74		Switzerland/UK	34618582	no
Terrisse et al., Cell Death & Diff., 2021	Breast Cancer	35	CANTO	France	33963313	no
Derosa et al., Nature Med., 2022	Lung Cancer	338	Lung Oncobiotics	France	35115705	no
Routy et al., Science., 2018	Lung Cancer	65		France	29097494	no
Yonekura et al., Cancer Discovery., 2022	Ovarian Cancer	29		France	34930787	no
Derosa et al., European Urology., 2020	Kidney Cancer	69		France	32376136	no
Kartal et al., Gut., 2022	Pancreatic Cancer	111		Spain/Germany	35260444	no
Nagata et al., Gastroenterology., 2022	Pancreatic Cancer	43		Japan	35788347	no
Spencer et al., Science., 2021	Melanoma	112		USA	34941392	no
Lee et al., Nature Med., 2022	Melanoma	163	PRIMM	UK/Netherlands/Spain	35228751	yes
McCulloch et al., Nature Med., 2022	Melanoma	94		USA	35228752	no
Gopalakrishnan et al., Science., 2018	Melanoma	24		USA	29097493	yes
Wind et al., Melanoma Research., 2020	Melanoma	20		Netherlands	31990790	yes
Frankel et al., Neoplasia., 2017	Melanoma	37		USA	28923537	yes
Peters et al., Genome Med., 2019	Melanoma	27		USA	31597568	yes
Thomas et al., Nat Med., 2019	Colorectal Cancer	61		Italy	30936548	yes
Wirbel et al., Nat Med., 2019	Colorectal Cancer	60		Germany	30936547	yes
Yu et al., Gut., 2017	Colorectal Cancer	75		China	26408641	yes
Feng et al., Nat Commun., 2015	Colorectal Cancer	46		Austria	25758642	yes
Vogtmann et al., PloS One., 2016	Colorectal Cancer	52		USA	27171425	yes
Zeller et al., Mol Syst Biol., 2014	Colorectal Cancer	53		France	25432777	yes
Yachida et al., Nat Med., 2019	Colorectal Cancer	258		Japan	31171880	yes
Total		**1879**				
Xie et al., Cell Syst., 2016	Healthy Controls	250	Twins UK	UK	27818083	yes
Asnicar et al., Nat Med., 2021	Healthy Controls	1098	PREDICT 1	UK/USA	33432175	yes
Zhernakova et al., Science., 2016	Healthy Controls	1129	LifeLines Deep	Netherlands	27126040	yes
Schirmer et al., Cell., 2016	Healthy Controls	465	Human Functional Genomics Project	Netherlands	27814509	yes
HMP Consortium., Nature., 2012	Healthy Controls	94	HMP 1	USA	22699609	yes
Qin et al., Nature., 2014	Healthy Controls	114		China	25079328	yes
Qin et al., Nature., 2012	Healthy Controls	174		China	23023125	yes
Vieira-Silva et al., Nature., 2020	Healthy Controls	322	MetaCARDIS	Germany/France	32433607	yes
De Filippis et al., Cell Host Microbe., 2019	Healthy Controls	97		Italy	30799264	yes
Keohane et al., Nat Med., 2020	Healthy Controls	117		Ireland	32632193	yes
Dhakan et al., Gigascience., 2019	Healthy Controls	110		India	30698687	yes
Yachida et al., Nat Med., 2019	Healthy Controls	246		Japan	31171880	yes
Nielsen et al., Nat Biotechnol., 2014	Healthy Controls	247	MetaHIT	Denmark/Spain	24997787	yes
Zeevi et al., Cell., 2015	Healthy Controls	878		Israel	26590418	yes
Total		**5341**				

cMD: curatedMetagenomicData

Supplementary TABLE 3 | Detailed results of pan-cancer GOMS presented in FIG. 2 (summary)

Health			Pan-Cancer		
Order	**Family**	**Genus (Species)**	**Order**	**Family**	**Genus (Species)**
Eubacteriales	*Clostridiaceae*	*Butyricicoccus (B. sp. AM29-23AC)*	*Bifidobacteriales*	*Bifidobacteriaceae*	*Bifidobacterium (Bifidobacterium dentium)*
		Clostridium (C. sp. AF34-13, C. sp. AF34-10BH)	*Clostridiales*	*Clostridia*	*Candidatus Pararuminococcus (CP. gallinarum)*
	Lachnospiraceae	*Coprococcus (C. eutactus)*		*Clostridia*	*Candidatus Schneewindia (CS. gallinarum)*
		Lachnospira (L. eligens, L. pectinoschiza, L. sp. NSJ-43)	*Erysipelotrichales*	*Erysipelotrichaceae*	*Erysipelatoclostridium (Clostridium innocuum)*
		Roseburia (R. hominis)	*Eubacteriales*	*Clostridiaceae*	*Hungatella (H. hathewayi)*
		unclassified Lachnospira (Lachnospiraceae bacterium)		*Eubacteriales*	*Intestinimonas (I. butyriciproducens)*
	Oscillospiraceae	*Oscillibacter (Oscillibacter sp. ER4)*		*Lachnospiraceae*	*Eisenbergiella (E. massiliensis, E. tayi)*
		unclassified Oscillospiraceae (Oscillospiraceae bacterium)			*Enterocloster (E. aldensis, E. citroniae, E. clostridioformis, E. lavalensis)*
	Peptococcaceae	*unclassified Peptococcaceae (Peptococcaceae bacterium)*			*Lachnoclostridium (Clostridium scindens, L. sp. An138)*
	Faecalibacterium	*unclassified Faecalibacterium (Faecalibacterium sp.)*			*Mediterraneibacter (Ruminococcus torques)*
					Merdimonas (Merdimonas faecis)
				Oscillospiraceae	*Anaerotruncus (A. colihominis)*
					Dysosmobacter (D. welbionis)
					Hydrogeniiclostridium (H. mannosilyticum)
					Pseudoflavonifractor (Pseudoflavonifractor sp.)
					Ruthenibacterium (R. lactatiformans)
					unclassified Oscillospiraceae (Oscillospiraceae bacterium)
			Lactobacillales	*Enterococcaceae*	*Enterococcus (E. faecalis)*

Supplementary TABLE 4 | GOMS profiles across various cancer types.

Order	Family	Genus (Species)	Breast cancer	ref	Pancreatic ductal carcinoma	ref	Colorectal cancer	ref
Acidaminococcales	*Acidaminococcaceae*	*Acidaminococcus (A. fermentans)*	x	Yonekura, S. et al.			x	Yonekura, S. et al.
Actinomycetales	*Actinomycetaceae*	*Actinomyces (A. graevenitzii, A. sp. ICM39)*			x	Nagata, N. et al.	x	Thomas, A. M. et al.
Bacteroidales	*Rikenellaceae*	*Alistipes (A. indistinctus, A. putredinis, A. shahii, A. sp. CAG:831, A. communis (Bacteroidales bacterium ph8))*	x	Terrisse, S. et al., Yonekura, S. et al.			x	Yonekura, S. et al.
Bifidobacteriales	*Bifidobacteriaceae*	*Alloscardovia (A. omnicolens)*			x	Kartal, E. et al.		
Tissierellales	*Peptoniphilaceae*	*Anaerococcus (A. obesiensis, A. vaginalis)*					x	Wirbel, J. et al.
Eubacteriales	*Oscillospiraceae*	*Anaerotruncus (A. colihominis)*	x	Yonekura, S. et al.			x	Thomas, A. M. et al., Yonekura, S. et al.
Bacteroidales	*Bacteroidaceae*	***Bacteroides (B. finegoldii, B. fragilis, B. nordii, B. ovatus, B. sp. 43_108, B. sp. CAG:633, B. sp. CAG:661, B. thetaiotaomicron, B.uniformis))***	x	Terrisse, S. et al., Yonekura, S. et al.	x	Kartal, E. et al.	x	Yonekura, S. et al.
Bacteroidales	*Bacteroidaceae*	*Bacteroides (B. fragilis)*	x	Terrisse, S. et al.				
Bacteroidales	*Barnesiellaceae*	*Barnesiella (B. intestinihominis)*	x	Terrisse, S. et al.				
Bifidobacteriales	*Bifidobacteriaceae*	*Bifidobacterium (B. dentium)*	x	Yonekura, S. et al.			x	Yonekura, S. et al.
Desulfovibrionales	*Desulfovibrionaceae*	*Bilophila (B. wadsworthia)*	x	Terrisse, S. et al., Yonekura, S. et al.			x	Yonekura, S. et al.
Bacteroidales	*Odoribacteraceae*	*Butyricimonas (B. synergistica, B. virosa)*	x	Yonekura, S. et al.			x	Yonekura, S. et al.
Eubacteriales	*Lachnospiraceae*	*Butyrivibrio (B. crossotus)*			x	Kartal, E. et al.		
Campylobacterales	*Campylobacteraceae*	*Campylobacter (C. gracilis)*	x	Yonekura, S. et al.			x	Yonekura, S. et al.
Eggerthellales	*Eggerthellaceae*	*Eggerthella (E. lenta)*	x	Yonekura, S. et al.			x	Yonekura, S. et al.
Eubacteriales	*Lachnospiraceae*	*Eisenbergiella (E. massiliensis, E. tayi)*	x	Yonekura, S. et al.			x	Yonekura, S. et al.
Eubacteriales	*Lachnospiraceae*	***Enterocloster (E. aldenensis , E. asparagiformis , E. bolteae, E. citroniae, E. clostridioformis, E. lavalensis)***	x	Terrisse, S. et al., Yonekura, S. et al.	x	Nagata, N. et al.	x	Wirbel, J. et al., Yonekura, S. et al.
Lactobacillales	*Enterococcaceae*	*Enterococcus (E. faecalis, E. durans)*	x	Yonekura, S. et al.			x	Yonekura, S. et al.
Enterobacterales	*Enterobacteriaceae*	*Escherichia (E. coli)*	x	Yonekura, S. et al.			x	Thomas, A. M. et al., Yonekura, S. et al.
Eubacteriales	*Eubacteriaceae*	*Eubacterium (E. sp. CAG:180)*	x	Yonekura, S. et al.			x	Yonekura, S. et al.
Eubacteriales	*Oscillospiraceae*	*Faecalibacterium (F. prausnitzii)*	x	Terrisse, S. et al.				
Eubacteriales	*Oscillospiraceae*	*Flavonifractor (F. plautii, F. sp. An100)*	x	Yonekura, S. et al.			x	Yonekura, S. et al.
Fusobacteriales	*Fusobacteriaceae*	*Fusobacterium (F. nucleatum subsp. animalis, nucleatum, vincentii, F. sp. oral taxon 370)*					x	Thomas, A. M. et al., Wirbel, J. et al.
Bacillales	*Bacillales Family XI.*	*Gemella (G. morbillorum)*					x	Thomas, A. M. et al., Wirbel, J. et al.
Enterobacterales	*Hafniaceae*	*Hafnia (H. alvei, H. paralvei)*	x	Yonekura, S. et al.			x	Yonekura, S. et al.
Eubacteriales	*Oscillospiraceae*	*Harryflintia (H. acetispora)*	x	Yonekura, S. et al.			x	Yonekura, S. et al.
Eubacteriales	*Clostridiaceae*	***Hungatella (H. hathewayi)***	x	Yonekura, S. et al.	x	Nagata, N. et al.	x	Wirbel, J. et al., Yonekura, S. et al.
Eubacteriales	*Eubacteriaceae*	*Intestinimonas (I. butyriciproducens)*	x	Yonekura, S. et al.			x	Yonekura, S. et al.
Enterobacterales	*Enterobacteriaceae*	*Klebsiella (K. pneumoniae)*	x	Terrisse, S. et al.				
Eubacteriales	*Lachnospiraceae*	*Lachnoclostridium (Clostridium symbiosum)*			x	Nagata, N. et al.	x	Thomas, A. M. et al., Wirbel, J. et al., Yonekura, S. et al.
Eubacteriales	*Lachnospiraceae*	*Lachnospira (L. eligens)*	x	Terrisse, S. et al.				
Eubacteriales	*Oscillospiraceae*	*Lawsonibacter (L. asaccharolyticus)*	x	Yonekura, S. et al.			x	Yonekura, S. et al.
Eubacteriales	*Lachnospiraceae*	*Mediterraneibacter (Ruminococcus torques)*					x	Wirbel, J. et al.
Methanobacteriales	*Methanobacteriaceae*	*Methanobrevibacter (M. smithii)*			x	Kartal, E. et al.		
Enterobacterales	*Morganellaceae*	*Morganella (M. morganii)*	x	Yonekura, S. et al.			x	Yonekura, S. et al.
Bacteroidales	*Odoribacteraceae*	*Odoribacter (O. splanchnicus)*	x	Terrisse, S. et al., Yonekura, S. et al.				
Coriobacteriales	*Atopobiaceae*	*Olsenella (O. uli)*	x	Yonekura, S. et al.			x	Yonekura, S. et al.
Eubacteriales	*Oscillospiraceae*	*Oscillospiraceae incertae sedis (Clostridium leptum)*					x	Thomas, A. M. et al.
Bacteroidales	*Tannerellaceae*	*Parabacteroides (P. distasonis, P. merdae)*	x	Terrisse, S. et al., Yonekura, S. et al.			x	Yonekura, S. et al.
Tissierellales	*Peptoniphilaceae*	*Parvimonas (P. micra , P. sp.)*					x	Thomas, A. M. et al., Wirbel, J. et al.
Eubacteriales	*Peptostreptococcaceae*	*Peptostreptococcus (P. anaerobius, P. stomatis)*					x	Thomas, A. M. et al., Wirbel, J. et al.
Acidaminococcales	*Acidaminococcaceae*	*Phascolarctobacterium (P. sp. CAG:266)*	x	Yonekura, S. et al.			x	Yonekura, S. et al.
Bacteroidales	*Bacteroidaceae*	*Phocaeicola (P. barnesiae)*	x	Terrisse, S. et al.				
Bacteroidales	*Porphyromonadaceae*	*Porphyromonas (P. asaccharolytica, P. somerae, P. uenonis)*					x	Thomas, A. M. et al., Wirbel, J. et al.
Bacteroidales	*Prevotellaceae*	***Prevotella (P. copri, P. intermedia, P. nigrescens, P. sp. CAG:617, P. sp.)***	x	Terrisse, S. et al., Yonekura, S. et al.	x	Kartal, E. et al.	x	Thomas, A. M. et al., Wirbel, J. et al., Yonekura, S. et al.
Enterobacterales	*Morganellaceae*	*Proteus (P. mirabilis)*	x	Yonekura, S. et al.			x	Yonekura, S. et al.
Eubacteriales	*Lachnospiraceae*	*Roseburia (R. intestinalis)*	x	Terrisse, S. et al.				
Eubacteriales	*Oscillospiraceae*	*Ruthenibacterium (R. lactatiformans)*	x	Yonekura, S. et al.			x	Yonekura, S. et al.
Bacteroidales	*Porphyromonadaceae*	*Sanguibacteroides (S. justesenii)*	x	Yonekura, S. et al.			x	Yonekura, S. et al.
Erysipelotrichales	*Erysipelotrichaceae*	*Solobacterium (S. moorei)*					x	Wirbel, J. et al.
Lactobacillales	*Streptococcaceae*	*Streptococcus (S. anginosus, S. oralis, S. vestibularis)*			x	Nagata, N. et al.		
Lactobacillales	*Streptococcaceae*	*Streptococcus (S. parasanguinis)*					x	Thomas, A. M. et al.
Eubacteriales	*Oscillospiraceae*	*Subdoligranulum (S. sp. 4_3_54A2FAA)*					x	Wirbel, J. et al.
Burkholderiales	*Sutterellaceae*	*Sutterella (S. wadsworthensis)*			x	Nagata, N. et al.		
Desulfovibrionales	*Desulfovibrionaceae*	*unclassified Desulfovibrionaceae (D. bacterium)*	x	Yonekura, S. et al.			x	Yonekura, S. et al.

Eubacteriales	*Lachnospiraceae*	*unclassified Lachnospiraceae (L. bacterium 3_1_57FAA_CT1)*					x	Thomas, A. M. et al.
Eubacteriales	*Oscillospiraceae*	*unclassified Oscillospiraceae (Ruminococcaceae bacterium D16, D5)*	x	Terrisse, S. et al., Yonekura, S. et al.			x	Yonekura, S. et al.
Veillonellales	*Veillonellaceae*	*Veillonella (V. atypica, V. dispar, V. parvula)*			x	Kartal, E. et al., Nagata, N. et al.		

Supplementary TABLE 5 | Cohort description and machine learning analysis for responders versus non-responders among patients receiving immune-checkpoint inhibitors.

Cohort	Cancer	ICI	NR	R	Total	RF	LASSO	Reference	Country	PubMedID	in cMD
						LODO AUC	**LODO AUC**				
FrankelAE_2017	Melanoma	CTLA-4 + PD-1	20	17	**37**	0.66	0.55	Frankel et al., Neoplasia., 2017	USA	28923537	yes
GopalakrishnanaV_2018	Melanoma	PD-1	13	10	**23**	0.58	0.62	Gopalakrishnan et al., Science., 2018	USA	29097493	yes
Manchester_LeeK_2022	Melanoma	CTLA-4 + PD-1	15	10	**25**	0.73	0.52	Lee et al., Nature Med., 2022	UK	35228751	yes
McCullochJA_2022	Melanoma	PD-1	35	59	**94**	0.53	0.52	McCulloch et al., Nature Med., 2022	USA	35228752	no
PRIMM-NL_LeeK_2022	Melanoma	CTLA-4 + PD-1	33	22	**55**	0.62	0.57	Lee et al., Nature Med., 2022	Netherlands	35228751	yes
PRIMM-UK_LeeK_2022	Melanoma	CTLA-4 + PD-1	32	23	**55**	0.49	0.42	Lee et al., Nature Med., 2022	UK	35228751	yes
DerosaL_2022	NSCLC	PD-1	263	75	**338**	0.70	0.55	Derosa et al., Nature Med., 2022	France	35115705	no
RoutyB_2018_Lung	NSCLC	PD-1	53	12	**65**	0.78	0.70	Routy et al., Science., 2018	France	29097494	no
DerosaL_2020	RCC	PD-1	49	20	**69**	0.65	0.66	Derosa et al., European Urology., 2020	France	32376136	no
		Total	**513**	**248**	**761**	**RF Global CV AUC**					
				Total for Global AUC	**761**	**0.71**					

ICI: Immune checkpoint inhibitors
NR: Non-responder (SD+PD)
R: Responder (CR+PR)
RF: Random Forrest
LASSO: Least Absolute Shrinkage and Selection Operator
AUC: area under the curve
cMD: curatedMetagenomicData

Supplementary TABLE 6 | Baseline GOMS associated with response rates in the mega-analysis presented in FIG. 3 (summary)

R (CR+PR)			NR (SD+PD)		
Order	**Family**	**Genus (Species)**	**Order**	**Family**	**Genus (Species)**
Acidaminococcales	*Acidaminococcaceae*	*Phascolarctobacterium (P. succinatutens)*	*Actinomycetales*	*Actinomycetaceae*	*Actinobaculum (A. sp. oral taxon 183)*
Bacteroidales	*Bacteroidaceae*	*Bacteroides (B. caccae, B. nordii)*			*Actinomyces (A. graevenitzii, A. sp. ICM58, A. sp. oral taxon 448)*
Bifidobacteriales	*Bifidobacteriaceae*	*Bifidobacterium (Bifidobacterium adolescentis)*	*Bacteroidales*	*Bacteroidaceae*	*Bacteroides (B. clarus, B. fragilis)*
Burkholderiales	*Sutterellaceae*	*Sutterella (Sutterella wadsworthensis)*		*Rikenellaceae*	*unclassified Rikenellaceae (Rikenellaceae bacterium)*
Eubacteriales	*Clostridiaceae*	*Clostridium (Clostridium sp. AM22-11AC)*	*Bifidobacteriales*	*Bifidobacteriaceae*	*Scardovia (S. wiggsiae)*
	Eubacteriaceae	*Eubacterium (Eubacterium ventriosum)*	*Coriobacteriales*	*Atopobiaceae*	*Lancefieldella (L. parvula)*
	Lachnospiraceae	*Anaerobutyricum (Anaerobutyricum hallii)*		*Coriobacteriaceae*	*Enorma (E. massiliensis)*
		Anaerostipes (Anaerostipes hadrus)	*Desulfovibrionales*	*Desulfovibrionaceae*	*Bilophila (B. wadsworthia)*
		Blautia (B. faecis, B. wexlerae, B. sp. MSK.20.85)	*Eggerthellales*	*Eggerthellaceae*	*Eggerthella (E. lenta)*
		Coprococcus (Coprococcus eutactus)	*Enterobacterales*	*Enterobacteriaceae*	*Escherichia (E.coli)*
		Dorea (D. formicigenerans, D. sp. AF24-7LB)	*Erysipelotrichales*	*Erysipelotrichaceae*	*Erysipelatoclostridium (E. ramosum, Clostridium innocuum, Clostridium saccharogumia)*
		Fusicatenibacter (Fusicatenibacter saccharivorans)			*Faecalitalea (F. cylindroides)*
		Lachnospira (Lachnospira eligens)			*Massilicoli (M. timonensis)*
		Lachnospiraceae_unclassified (Eubacterium rectale, L. bacterium)	*Eubacteriales*	*Christensenellaceae*	*Christensenella (C. sp. Marseille-P3954, C. bacterium NSJ-53)*
		Mediterraneibacter (Mediterraneibacter butyricigenes)		*Clostridiaceae*	*Hungatella (H. hathewayi)*
		Mediterraneibacter (Ruminococcus torques)		*Lachnospiraceae*	*Eisenbergiella (E. tayi)*
		Roseburia (Roseburia faecis, R. intestinalis, R. inulinivorans)			*Enterocloster (E. aldensis, E. bolteae, E. lavalensis)*
	Oscillospiraceae	*Faecalibacterium (Faecalibacterium prausnitzii)*			*Faecalicatena (F. fissicatena)*
		Ruminococcus (R. bicirculans, R. sp. NSJ-71)			*Lachnoclostridium (Clostridium symbiosum)*
		unclassified Oscillospiraceae (Oscillospiraceae bacterium)			*Lachnoclostridium (L. phocaeense, L. sp. An118, L. bacterium)*
	Peptostreptococcaceae	*Intestinibacter (Intestinibacter bartlettii)*		*Oscillospiraceae*	*Anaerotruncus (A. colihominis, A. massiliensis)*
Verrucomicrobiales	*Akkermansiaceae*	*Akkermansia (Akkermansia muciniphila)*			*Lawsonibacter (Lawsonibacter sp.)*
					Massiliimalia (M. timonensis)
					unclassified Oscillospiraceae (Oscillospiraceae bacterium)
					unclassified Oscillospiraceae (Ruminococcaceae bacterium D5)
				Eubacteriales Family XIII	*Mogibacterium (M. diversum)*
			Lactobacillales	*Enterococcaceae*	*Enterococcus (E. durans)*
				Streptococcaceae	*Streptococcus (S. constellatus, S. cristatus, S. mutans, S. sanguinis)*
			Propionibacteriales	*Propionibacteriaceae*	*Propionibacterium (P. acidifaciens)*
			Veillonellales	*Veillonellaceae*	*Dialister (D. invisus)*
					Veillonella (V. parvula)

R (CR+PR): responder status based on RECIST1.1 criterium (CR: complete response, PR: partial response)

NR (SD+PD): non-responder status based on RECIST1.1 criterium (SD: stable disease, PD: progression disease)

Supplementary TABLE 7 | Baseline GOMS associated with response rates in the meta-analysis presented in FIG. 4 (summary)

R (CR+PR)			NR (SD+PD)		
Order	**Family**	**Genus (Species)**	**Order**	**Family**	**Genus (Species)**
Firmicutes unclassified	*Firmicutes unclassified*	*Firmicutes unclassified (Firmicutes bacterium AF16-15)*	*Actinomycetales*	*Actinomycetaceae*	*Actinomyces (Actinomyces graevenitzii)*
Acidaminococcales	*Acidaminococcaceae*	*Phascolarctobacterium (P. succinatutens)*	*Eggerthellales*	*Eggerthellaceae*	*Eggerthella (Eggerthella lenta)*
Bacteroidales	*Bacteroidaceae*	*Bacteroides (B. nordii)*	*Erysipelotrichales*	*Erysipelotrichaceae*	*Faecalitalea (Faecalitalea cylindroides)*
		Phocaeicola (P. coprophilus)	*Eubacteriales*	*Clostridiaceae*	*Hungatella (Hungatella hathewayi)*
	Prevotellaceae	*Prevotella (P. copri clade A)*		*Lachnospiraceae*	*Enterocloster (Enterocloster bolteae)*
	Rikenellaceae	*Alistipes (A. shahii)*			*Lachnoclostridium (Lachnoclostridium phocaeense)*
Bifidobacteriales	*Bifidobacteriaceae*	*Bifidobacterium (B. adolescentis, B. bifidum)*		*Oscillospiraceae*	*Anaerotruncus (Anaerotruncus massiliensis)*
Clostridia	*Clostridia*	*Candidatus Metalachnospira (CM. gallinarum)*			*unclassified Oscillospiraceae (Ruminococcaceae bacterium, Ruminococcaceae bacterium D5)*
		Candidatus Heritagella (CH.intestinalis)	*Synergistales*	*Synergistaceae*	*Cloacibacillus (Cloacibacillus porcorum)*
Coriobacteriales	*Coriobacteriaceae*	*Collinsella (C. bouchesdurhonensis)*	*Veillonellales*	*Veillonellaceae*	*Dialister (Dialister invisus)*
Eubacteriales	*Eubacteriaceae*	*Eubacterium (E. sp. AM28-29)*			*Veillonella (Veillonella parvula)*
	Eubacteriales	*Intestinimonas (I. timonensis)*			
	Lachnospiraceae	*Anaerobutyricum (A. hallii)*			
		Blautia (B. faecicola)			
		Coprococcus (C. catus, C. eutactus)			
		Lacrimispora (L. celerecrescens)			
		Mediterraneibacter (Ruminococcus torques)			
		Roseburia (R. faecis, R. hominis, R. inulinivorans)			
		unclassified Lachnospiraceae (Eubacterium rectale, L. bacterium)			
		Flavonifractor (Flavonifractor sp. An10)			

	Oscillospiraceae	*Ruminococcus (R. bicirculans, R. sp NSJ 71)*			
	Peptostreptococcaceae	*Intestinibacter (I. bartlettii)*			
Lactobacillales	*Lactobacillaceae*	*Limosilactobacillus (Lactobacillus vaginalis)*			

R (CR+PR): responder status based on RECIST1.1 criterium (CR: complete response, PR: partial response)

NR (SD+PD): non-responder status based on RECIST1.1 criterium (SD: stable disease, PD: progression disease)

Supplementary TABLE 8 | Relationship between cancer-associated bacteria relevant for clinical outcome and confounding factors.

Cat.	Bacteria issued from the Meta and Mega-Analysis	Cancer	Healthy aging	Unhealthy aging	Comorbidities	Obesity	Cachexia & frailty	Diabetes	Lung dysfunctions	Liver dysfunctions	Heart & circulatory failures	Comedications	Antibiotics	Gastrointestinal tract	Anti-inflammatory agents	Antidiabetics	Anti-cancer therapies	Chemotherapy	Hormonotherapy	Protein kinase inhibitors
Cancer and NR	*Anaerotruncus colihominis*	🟥	🟥		🟥			🟥									🟦	🟦		
	Bacteroides clarus				🟥						🟥									
	Bacteroides fragilis		🟥	🟦	🟥	🟥					🟥	🟦	🟦	🟦						
	Bifidobacterium dentium	🟥	🟥		🟪		🟦	🟥	🟥			🟥		🟥		🟥				
	Bilophila wadsworthia	🟥		🟦	🟦					🟦		🟦	🟦		🟦		🟥			🟥
	Clostridium innocuum				🟥				🟥			🟥	🟥	🟥	🟥					
	Clostridium scindens											🟥	🟥							
	Clostridium symbiosum	🟥		🟥													🟥			🟥
	Dialister invisus				🟥							🟦		🟦						
	Eggerthella lenta	🟥	🟪	🟥	🟥				🟥				🟥	🟥	🟥	🟦	🟦	🟦		
	Eisenbergiella massiliensis	🟥										🟥		🟥						
	Eisenbergiella tayi	🟥															🟦	🟦		
	Enterocloster aldenensis	🟥																		
	Enterocloster bolteae	🟥		🟥	🟥			🟥	🟥	🟥	🟥		🟥	🟥		🟦	🟥			🟥
	Enterocloster citroniae	🟥		🟥	🟪	🟦		🟥									🟥			🟥
	Enterocloster clostridioformis	🟥			🟥			🟥			🟥	🟪	🟥	🟥		🟪				
	Enterocloster lavalensis	🟥																		
	Erysipelatoclostridium ramosum				🟪	🟦			🟥	🟥		🟥	🟥							
	Escherichia coli	🟥			🟥			🟥			🟥		🟦	🟥		🟥				
	Faecalicatena fissicatena				🟪	🟦					🟥									
	Faecalitalea cylindroides				🟥				🟥											
	Hungatella hathewayi	🟥		🟥	🟥			🟥		🟥		🟥	🟥				🟥			🟥
	Intestinimonas butyriciproducens	🟥																		
	Lancefieldella parvula				🟥	🟥														
	Ruminococcaceae bacterium D5	🟥	🟥																	
	Ruminococcus torques	🟦		🟥	🟪	🟥		🟥			🟥		🟦	🟥	🟦	🟦	🟥	🟥		
	Ruthenibacterium lactatiformans	🟥																		
	Scardovia wiggsiae				🟥				🟥											
	Streptococcus cristatus			🟥								🟥		🟥						
	Streptococcus mutans		🟥									🟥		🟥						
	Streptococcus sanguinis				🟦		🟦					🟥		🟥						
	Veillonella parvula				🟥				🟥				🟥	🟥		🟦	🟦	🟦		
Control and R	*Akkermansia muciniphila*		🟥	🟦	🟪	🟦	🟥		🟥				🟦	🟥			🟥			🟥
	Alistipes shahii		🟥	🟦	🟦	🟦		🟦			🟦		🟦	🟥			🟥		🟥	🟥
	Anaerobutyricum hallii	🟦	🟦		🟪	🟥				🟦							🟦			🟦
	Anaerostipes hadrus	🟦	🟦		🟪	🟥				🟦	🟥	🟦	🟦	🟦		🟦				
	Bacteroides caccae				🟪	🟦	🟦				🟥									
	Bacteroides nordii				🟪		🟦				🟥									
	Bifidobacterium adolescentis	🟦			🟦	🟦		🟦	🟦				🟦	🟦		🟥	🟦			🟦
	Bifidobacterium bifidum				🟪	🟥	🟦		🟥				🟦	🟥		🟥				
	Blautia wexlerae		🟦		🟥	🟥							🟦	🟦	🟥	🟦				
	Coprococcus catus				🟪				🟥		🟥	🟦	🟦	🟦	🟦		🟦			🟦
	Coprococcus eutactus				🟪				🟦		🟥	🟦	🟦							
	Dorea formicigenerans				🟪	🟥					🟥	🟦	🟦	🟦	🟦		🟥	🟥		
	Eubacterium rectale	🟦	🟦	🟦	🟦			🟦		🟦		🟦	🟦	🟦		🟦	🟦			🟦
	Eubacterium ventriosum	🟦	🟦		🟪						🟥	🟦	🟦	🟦		🟦				
	Faecalibacterium prausnitzii		🟦		🟦	🟦		🟦	🟦	🟦	🟦	🟦	🟦	🟦		🟦	🟥			🟥

Fusicatenibacter saccharivorans	🟦																		
Intestinibacter bartlettii				🟪			🟦	🟥	🟦		🟦				🟦				
Lachnospira eligens		🟦		🟦	🟦			🟦	🟦	🟦		🟦	🟥		🟦	🟥		🟥	🟥
Lachnospira pectinoschiza	🟦			🟥						🟥									
Limosilactobacillus vaginalis											🟥		🟥						
Phascolarctobacterium succinatutens				🟥	🟥						🟦		🟦	🟦					
Phocaeicola coprophilus				🟥						🟥									
Prevotella copri	🟦	🟦		🟪		🟦		🟥		🟦	🟦		🟦			🟦			🟦
Roseburia faecis	🟦			🟥	🟥														
Roseburia hominis			🟦	🟦					🟦	🟦									
Roseburia intestinalis				🟪				🟥	🟦		🟦		🟦		🟦	🟦	🟦		
Roseburia inulinivorans				🟦							🟦	🟦	🟦	🟦	🟦				
Ruminococcus bicirculans				🟥						🟥	🟦	🟦			🟦				
Ruminococcus torques	🟦		🟥	🟪	🟥		🟥			🟥		🟦	🟥	🟦	🟦	🟥	🟥		
Sutterella wadsworthensis				🟦				🟦		🟦									
Ref.	[22, 24, 96]	[21, 176-178]	[9, 179-180]	[22, 64, 181-192]							[25, 44, 192-199]					[25, 26, 44, 200]			
	Yonekura et al.,2020; Gacesa et al.,2022; Park et al.,2022	Li et al., 2022; Rampelli et al.,2020; Wang et al.,2022; Sato et al., 2021	Luan et al., 2020; Ghosh et al., 2020; Zhang et al., 2021	Qin et al., 2014; Liu et al., 2017; Wang et al., 2018; Cui et al., 2018; Crovesy et al., 2020; Bowerman et al., 2020; Calderón-Pérez et al., 2020; Ni et al., 2021; Jiao et al., 2021; Behary et al., 2021; Solé et al., 2021; Nakai et al., 2021; Aasmets et al., 2022; Gacesa et al., 2022							Aasmets et al., 2022 Clooney et al., 2016 Derosa et al., 2020 Imhann et al., 2016 Lin et al., 2021 Nagata et al., 2022 Palleja et al. 2018 Parker et al., 2017 Singh et al., 2022 Vich Vila et al. 2020					Derosa et al., 2020 Li et al., 2021 Nagata et al., 2022 Terrisse et al., 2021			

🟥 Increased in relative abundance
🟦 Decreased in relative abundance
🟪 Increased or decreased in relative abundance

Supplementary Methods

Pan-cancer GOMS meta-analysis (FIG. 2 and Supplementary TABLES 2 and 3)

We performed fecal taxonomic profiling with MetaPhlAn 4[1] on gut samples collected from adult individuals at first collection with corresponding age and gender information from 1,879 patients spanning 8 different cancers comprising 30 cohorts from 23 published studies[2–24] and 5,341 control individuals comprising 17 control cohorts from 14 published studies[13,25–37]. Studies were selected after a PubMed search in the English literature for the following key words: microbiota, microbiome, healthy volunteers, cancer, immune checkpoint inhibitors and metagenomics. Studies with online repository of metagenomics sequences as well as baseline characteristics including cancer histology, age and sex were then included. We excluded 7 studies i) sequencing was performed by 16S rRNA[38–43] or ii) metagenomics was not available online[44]. Twenty-six study-level data and metadata were already present in the curatedMetagenomicData (cMD) R package[45] and for newer, not yet included studies in cMD (11 in total; **Supplementary TABLE 2**), data and metadata were gathered from public repositories such as NCBI's Sequence Read Archive and Biosample repository; as well as in supplementary materials.

We implemented a Bayesian multinomial logistic-normal linear regression model called Pibble from the R package fido[46], linking covariates that included cancer status, age and gender to compositional overdispersed count data. Only SGBs with a prevalence above 5% were kept in each cohort and their relative abundances were transformed into count values for Pibble via logistic-normal distribution modeling[47]. Log-ratios with 95% credible intervals were calculated for each SGB and each pairwise cancer/control comparison and were supplied to a random-effects model via the rem_mv function in the MetaVolcanoR R package (v.1.4.0) using the restricted maximum-likelihood estimator model. For each cancer, only SGBs whose 95% credible interval was greater than or less than zero in >45% of pairwise comparisons were considered for downstream analysis. SGBs were then ranked centering around 0 according to their random effects model p-value and coefficient sign. SGBs without a rank in more than 2 cancers were discarded, and the average rank across cancers was determined using concordant ranks across the different cancers (**FIG. 2 and Supplementary TABLE 3**).

R versus NR GOMS machine learning analysis (Supplementary TABLE 5)

We applied a Leave-one-dataset-out (LODO) approach to CLR (centered log ratio) transformed SGB relative abundances; data from one cohort was set aside as an external validation set, whereas data from the remaining cohorts were pooled together as a single training set, iterating along all the cohorts. Cohorts with more than 20 samples were used in the LODO approach and model performance was assessed using the area under the receiver operator (AUC-ROC) values. We applied two different machine learning models;

i) Random Forest model implemented in the metaML package[48] using an ensemble of 1,000 estimator trees and Shannon entropy to evaluate the quality of a split at each node of a tree. The minimum number of samples per leaf and the number of features per tree were 5 and 30%, respectively.

ii) L1-regularized (Lasso) logistic regression model implemented in the SIAMCAT R package (v.1.6.0)[49]. The lambda parameter was selected to maximise the AUC-ROC under the constraint that the model contained at least five nonzero coefficients (**Supplementary TABLE 5**).

R versus NR GOMS meta and mega analysis (FIG. 3 and 4 and Supplementary TABLES 6 and 7)

We performed fecal taxonomic profiling with MetaPhlAn 4[1] on 808 patients classified as responders (R, n=263) and non-responders (NR, n=545), based on RECIST 1.1, encompassing criteria for objective response rates (R meaning PR and CR, while NR was SD and PD) comprising 12 cohorts from 8 published studies[2–9]. Studies were selected after an initial PubMed search as explained above. Then based on the availability of online data regarding age, gender and RECIST 1.1 classification studies were included. Similar to the pan-cancer data collection process, half of the studies' data and metadata were already present in the curatedMetagenomicData (cMD) R package[45] and the same approach was conducted (as described above).

For mega-analysis, only SGBs with a prevalence above 5% were kept and cohort information was included in the pibble model along with response, age and gender. Only SGBs' log-ratios whose 95% credible intervals were above or below zero were considered (**FIG. 3 and Supplementary TABLE 6**).

For the meta-analysis, an ensemble of differential abundance methods and normalizations (8 in total) were used to estimate fold changes (or log ratios) with their respective confidence intervals between responders and non-responders and supplied to a random-effects model via the rem_mv function in the MetaVolcanoR R package (v.1.4.0) using the restricted maximum-likelihood estimator model. For methods requiring count data (i–v and vii), absolute raw counts were estimated from SGB-level MetaPhlAn 4 relative abundances by multiplying these values by the total number of reads for each sample (**FIG. 4 and Supplementary TABLE 7**).

i. DESeq2 (v.1.30.0)[50] with the poscounts estimator (DESeq2_poscounts);

ii. DESeq2 with the poscounts estimator and a zero-inflated negative binomial model (DESeq2_poscounts_zb), and observational weights were computed using the zinbwave package (v.1.12.0)[51] and supplied to the DESeqDataSet class object to account for zero inflation;

iii. DESeq2 with trimmed mean of *M* values (TMM; DESeq2_TMM), where normalization factors were calculated using TMM normalization, and a negative binomial generalized log-linear model was fit to the read counts of each feature using the glmFit function and the edgeR (v.3.32.0)[52] package;

iv. limma (v3.46.0)[53] with TMM values (limma_voom_TMM) (the limma package includes a voom function that transforms previously normalized counts to log counts per million, estimates a mean–variance relationship and uses this to compute appropriate observational-level weights);

v. limma with TMM values and a zero-inflated negative binomial model (limma_voom_TMM_zb) (to adapt the limma-voom framework to zero inflation, zinbwave weights were multiplied by voom weights);

vi. ANCOM-BC (v.1.0.1)[54], which uses a linear regression framework in log scale and accounts for sampling fraction by introducing a sample-specific bias correction that is estimated from the observed data (we used the same parameters as described in the univariate/multivariate analysis);

vii. Maaslin2 (v.1.4.0)[55], where logit-transformed relative abundances were normalized with total-sum scaling and supplied to the maaslin2 function using the variable of interest as a fixed effect;

viii. Standardized mean differences (relative abundances were arcsine-square root transformed and followed the same procedure as in Thomas et al.[15]);

ix. Pibble (v.1.4.0), a Bayesian multinomial logistic-normal linear regression model from the R package fido[46], linking covariates that included response, age and gender to compositional overdispersed count data.

Data and code availability

Code and data to reproduce the analysis reported in this review can be found in the Github repository: https://github.com/andrewmaltezthomas/NRCO_GOMS

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