

# Gut microbiome composition associates with clinical response to immune checkpoint inhibitor (ICI) therapy across multiple patient cohorts

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## Abstract

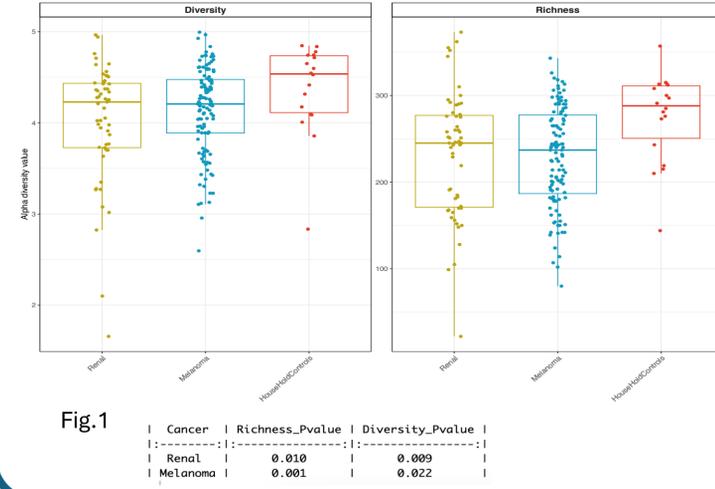
**Background:** The gut microbiome composition has been reported to influence response to ICIs. However, clinical application is limited because to date, most studies have focused on single patient cohorts and generated inconsistent cross-cohort findings. The MITRE (Microbiome Immunotherapy Toxicity and Response Evaluation, NCT04107168, PMID: 35073853) UK multicentre study is recruiting patients receiving standard of care ICIs for various indications. Stool, blood and tissue samples are being collected and correlated with treatment outcomes.

**Method:** An interim analysis of 171 patients and 18 household controls (HHCs) was undertaken. Stool samples collected prior to starting ICI and on treatment were subjected to metagenomic sequencing. Microbiome taxonomic data was correlated with treatment efficacy: response was defined for advanced disease as 6month progression-free survival using RECIST 1.1 criteria and for adjuvant patients as 12month recurrence-free survival.

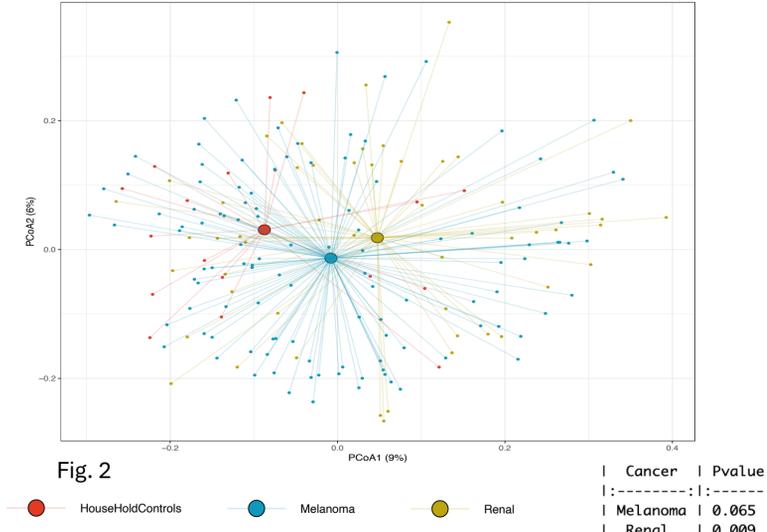
**Results:** Cancer patients had less rich (melanoma p=0.001, renal p=0.01) and less diverse (melanoma p=0.022, renal=0.009) pretreatment microbiomes compared to HHCs. The microbial composition also differed between HHCs and melanoma (p=0.065) and renal (p=0.009) cohorts. The microbiome of ICI responders was more similar to HHCs than non-responders, especially in cohorts 2 and 4. Microbiome composition changed during the first 12 weeks of treatment. The greatest shifts were noted in cohorts 2 and 3, which were also associated with highest incidence of diarrhoea/colitis. Machine learning models identified microbiome taxonomic signatures predictive for response (ROC curve AUC>0.7), the pre-treatment microbiome of patients was associated with response for all cohorts except cohort 3.

**Conclusions:** Microbiome associations consistent across multiple ICI-treated patient cohorts has potential for clinical utility, both as a predictive biomarker and as a novel target for intervention<sup>1</sup>.

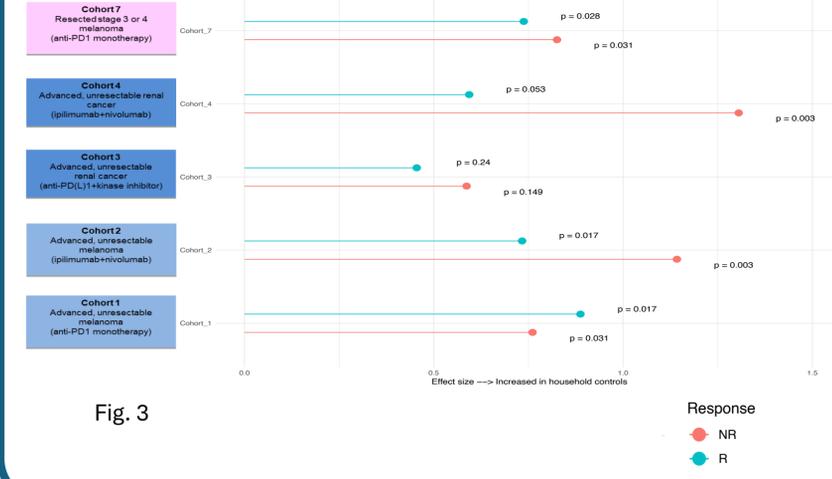
## Cancer patients had less diverse microbiomes compared with household controls



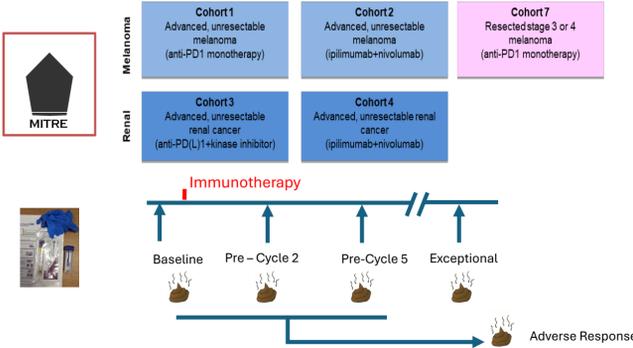
## Microbial communities differed between household controls and melanoma and renal cancer patients



## Non-responders in most cohorts were more different to household controls than responders – especially cohorts 2 and 4

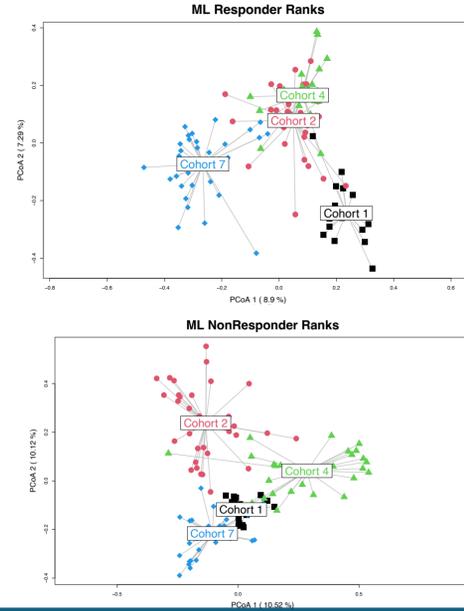


## MITRE: Microbiome Immunotherapy Toxicity and Response Evaluation

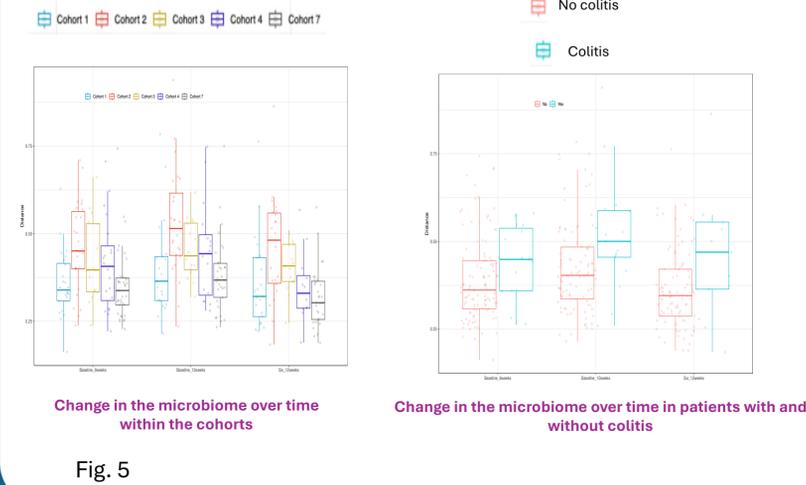


Cohort	Cancer	Treatment	Cohort size	Response rate
1	Advanced, unresectable melanoma	Anti-PD1	27	64%
2		Anti-PD1 and Anti-CTLA4	40	59%
3	Advanced, unresectable renal cancer	Anti-PD-(L)1 + TKI	24	65%
4		Anti-PD1 and Anti-CTLA4	31	59%
7	Resected stage 3 or 4 melanoma	Anti-PD1	49	70%
-	Household controls	None	18	--

## The “Good bacteria” in the microbiome signature of cohort 2 and 4 were more similar than the other cohorts. This was not seen when looking at non-responder associated species in the microbiome signatures



## The structure of the microbiome changed over time in cancer patients. Cohorts 2 and 3 changed the most, with cohort 4 also varying. Colitis was most common in cohort 2, 3 and 4 (33%, 17% & 14%). The structure of the microbiome changed more in patients with colitis than without



## ROC curves for a Microbiome response signature were created, after taking into account potential confounders. Machine learning models built to predict response achieved good performance (AUCs ≥ 0.70) for the “immunotherapy only” cohorts. There was no association seen with cohort 3 (anti-PD-1 + TKI)

