# Explainable Machine Learning to Identify CLL Based on Gut Microbiome Data

Tereza Faitová [1], Ramtin Zargari Marandi[2], Carsten Utoft Niemann[1,3]

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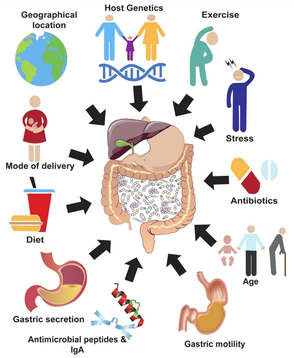
## Introduction




**Gut microbiome**
- is an ecosystem in our guts formed by microbial species
- controls the digestion of food, immune system and CNS

**Gut microbiome composition**
- is mostly comprised of bacteria
- is highly dynamic
- is affected by many factors (see picture)
- rich and diverse microbiome is favorable & health promoting

**Gut microbiome in CLL**
- is less diverse than in healthy individuals
- can affect disease development (shown in TCL1 mice)
- is depleted of short-chain fatty acid producing bacteria

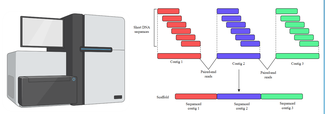
Hypothesis: Gut microbiome of CLL patients is different from microbiomes of other patients

## Materials and Methods

1) Patient and healthy cohorts

2) Feces samples collection

3) Shotgun metagenomic sequencing



4) Cohorts overview, Machine learning, Data analysis

87 CLL | 59 healthy | 165 baseline HSCT | 9 kidney donors | 91 thorax surgery patients

674 gut microbial species abundance, Age & Sex

**Classification model**

Development set
69 (21%) CLL & 259 (79%) no-CLL

Validation set
18 (22%) CLL & 65 (78%) no-CLL

5-fold cross validation & model development

Validation, best model selection & interpretation

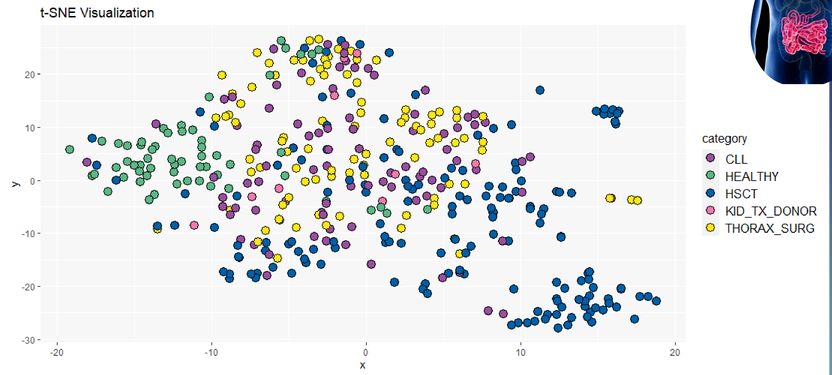
**Statistical analyses**

Alpha & beta diversities

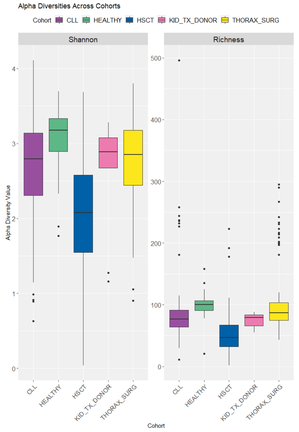
Dimensional reduction

Relative abundance analyses

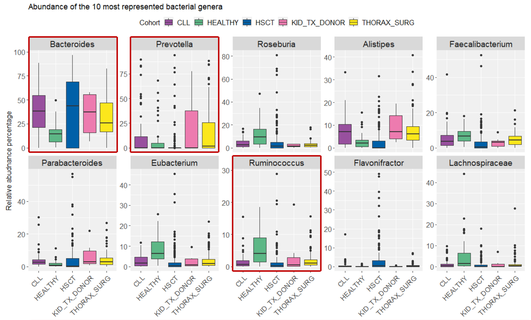
## Results




**t-SNE Visualization**
High dimensional metagenomic data in 2D - t-SNE models pairwise similarities between samples and maps them to 2D space.
Each point = one sample. Color code = cohort. Samples with similar microbial community compositions are closer together.
Underlying patterns revealed:
- no clear clusters, but similarities **within HSCT** and HEALTHY cohorts
- CLL, THORAX_SURG, and KIDNEY DONORS seem to have heterogeneous microbiome compositions

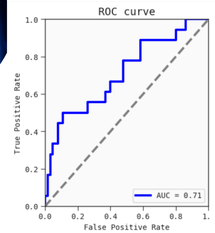


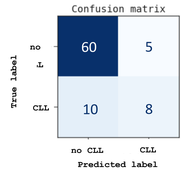

**Richness**:
number of different species present in the community
**Shannon Index**:
considers both species richness and evenness

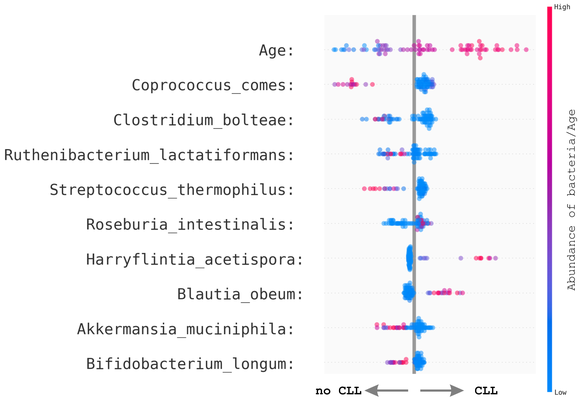



**Alpha diversity** (left)
Shannon diversity: HSCT < CLL < THORAX_SURG < KIDNEY DONORS < HEALTHY
HSCT and HEALTHY cohorts show lowest and highest diversity across metrics, r.
No significant difference in alpha diversity among CLL, THORAX_SURG and KIDNEY DONORS

**Relative abundance of the most abundant genera** (right)
HSCT and CLL are most enriched in *Bacteroides* (enterotype 1), often associated with disease states
HSCT is also significantly enriched in *Flavonifractor*, yet unexplored bacterial genus
HEALTHY are most enriched in *Ruminococcus* (enterotype 2), often described as beneficial
are also enriched in beneficial *Faecalibacterium*, *Lachnospiraceae* and *Eubacterium*
No cohorts were significantly enriched in *Prevotella* (enterotype 3)




Machine learning outcome (LightGBM model):
**ROC curve:** used to evaluate the performance of a binary classification model
**Confusion matrix:** represents how well the model predictions match the actual outcomes
**SHAP plot:**
- illustrates the top contributing features to the identification of CLL - bacterial species and age in our case
- red = higher value, blue = lower value
- interpretation: The higher the age, the higher predicted probability of CLL – positive correlation
  The higher abundance of *Coprococcus comes*, the lower predicted probability of CLL - negative correlation

**Model evaluation:**
- AUC = 0.71; specificity = 0.92, and sensitivity = 0.44 on the validation set
- High specificity = model can classify no-CLL with very high precision (5/65 misclassifications)
- Low sensitivity = model is performing poorly in CLL classification (10/18 misclassifications)

## Conclusion

- CLL microbiomes are different from HEALTHY and HSCT
- CLL microbiomes are less diverse than HEALTHY but more diverse than HSCT.
- CLL and HSCT microbiomes are enriched in *Bacteroides*.
- CLL and HSCT microbiomes are depleted of several beneficial bacteria.
- Our machine learning model is better in classifying **no-CLL** than CLL.

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## Affiliations

1) Department of Hematology, Rigshospitalet, Copenhagen, DK
2) Centre of Excellence for Health, Immunity and Infections (CHIP), Rigshospitalet, Copenhagen, DK
3) Department of Clinical Medicine, University of Copenhagen, DK

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