

# Latent Crohn's Disease Subgroups are Identified by Longitudinal Biomarker Profiles

Precision Medicine Talks (25/08/22)

Nathan Constantine-Cooke



@IBDNathan



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# Background



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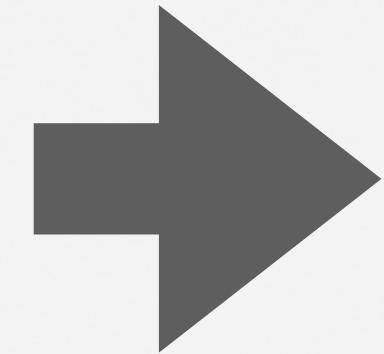
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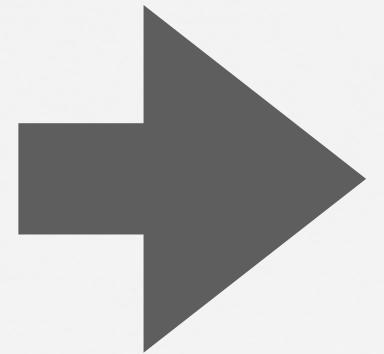
# Crohn's Disease

- An immune-mediated disease affecting 1 in 350 people in the UK
- Causes discontinuous inflammation in any region of the gastrointestinal tract
- Is a progressive disease:

Inflammation



Stricturing



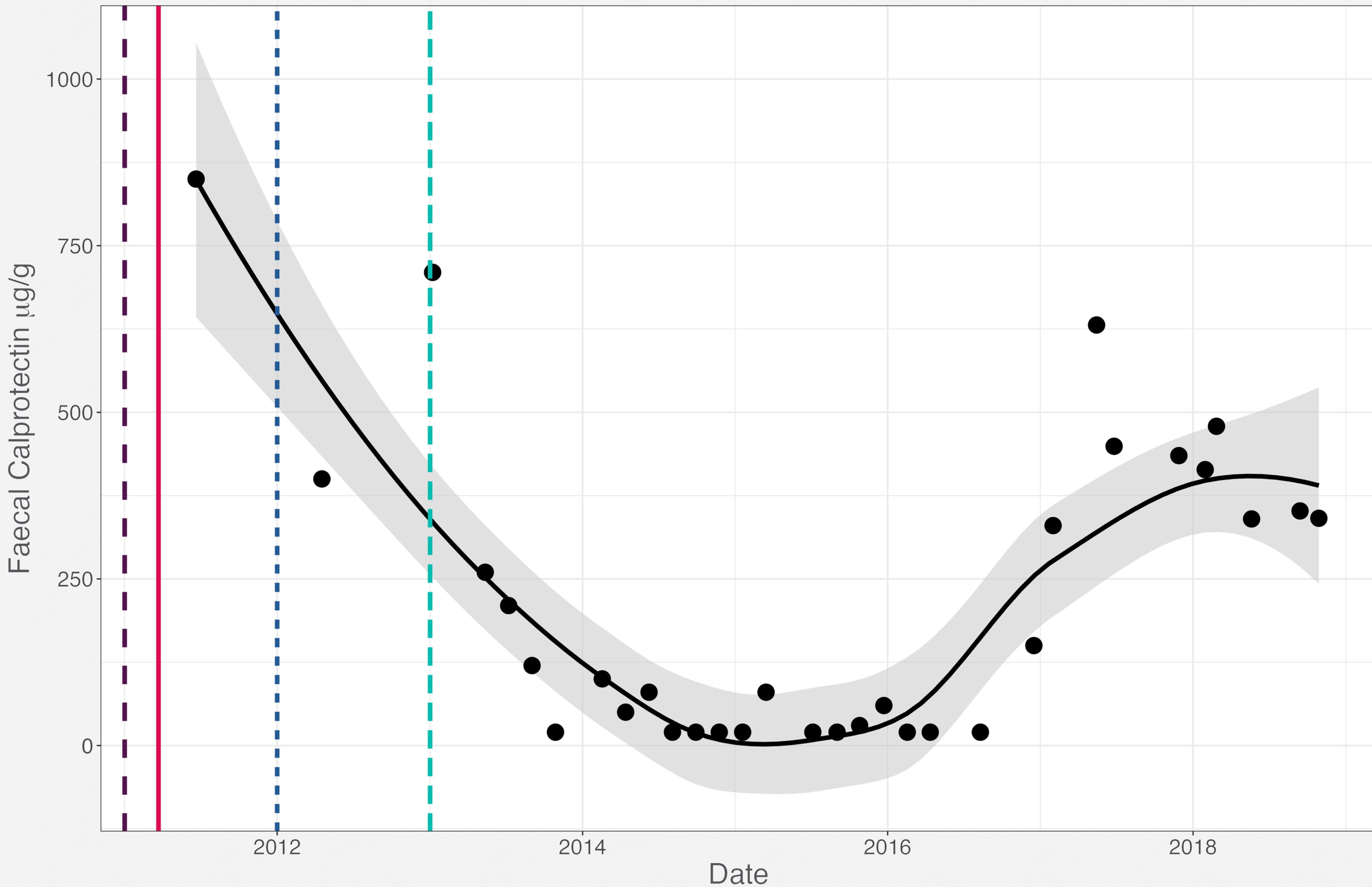
Penetrative



# Monitoring Crohn's disease

- Colonoscopy remains the gold standard for monitoring disease activity.
- However,
  - Colonoscopy is an invasive procedure
  - ... and requires substantial hospital resources.
- As a result, inflammation is regularly monitored using CRP and faecal calprotectin (FCAL).

# Faecal Calprotectin Measurements for PREdiCCt Participant [REDACTED]



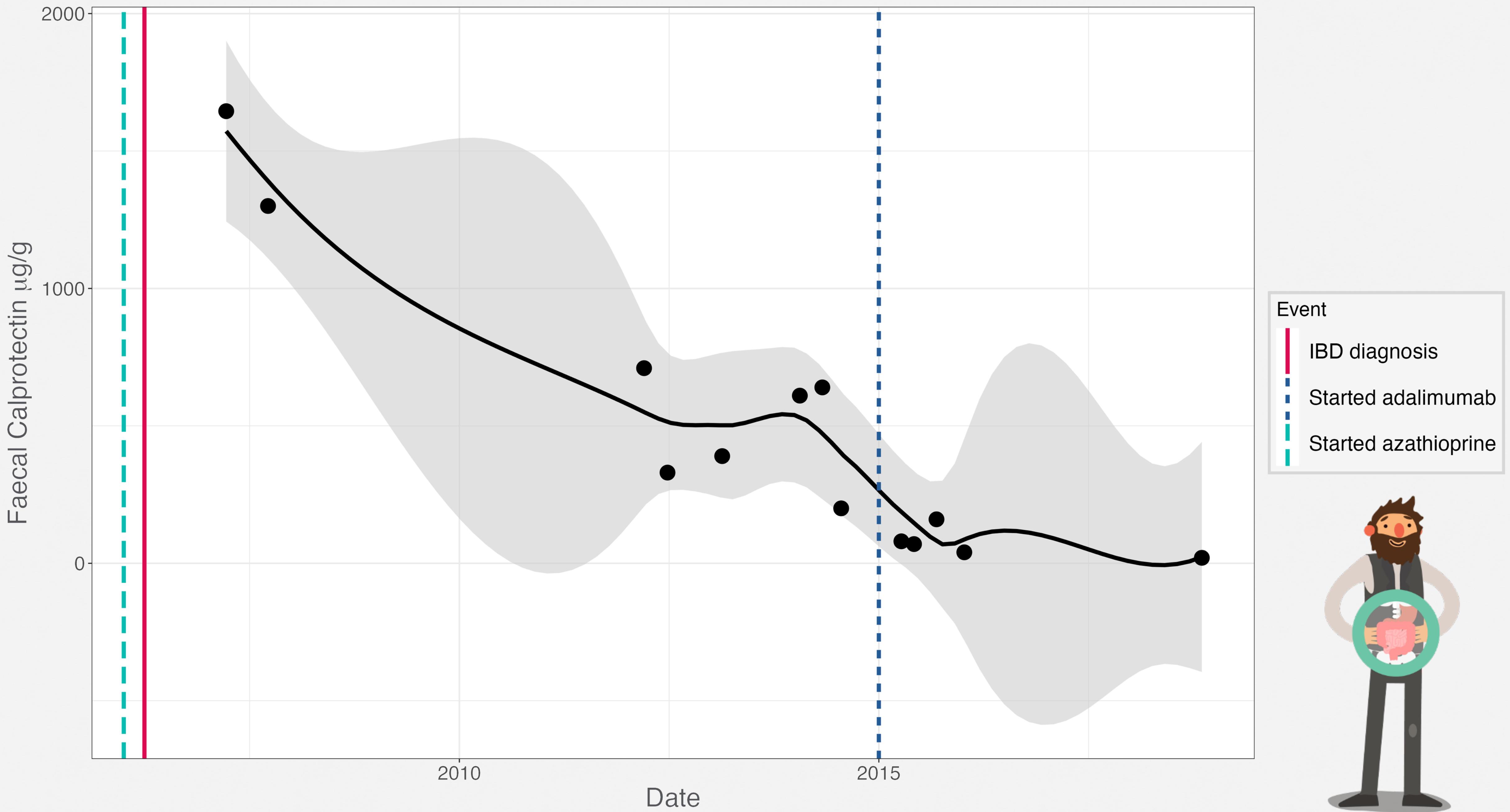
- Event
- IBD diagnosis
  - Started azathioprine
  - Started infliximab
  - Started oral steroids



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# Faecal Calprotectin Measurements for PREdiCCt Participant

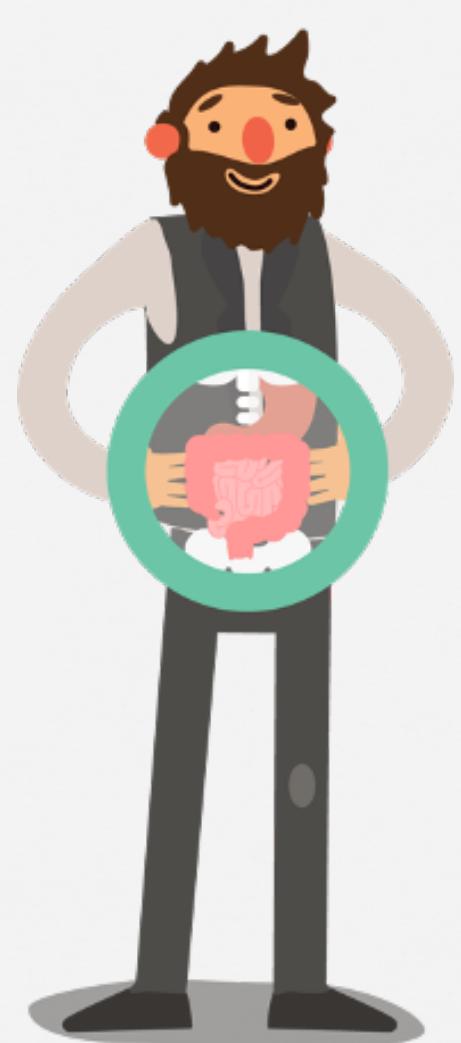


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# Study design



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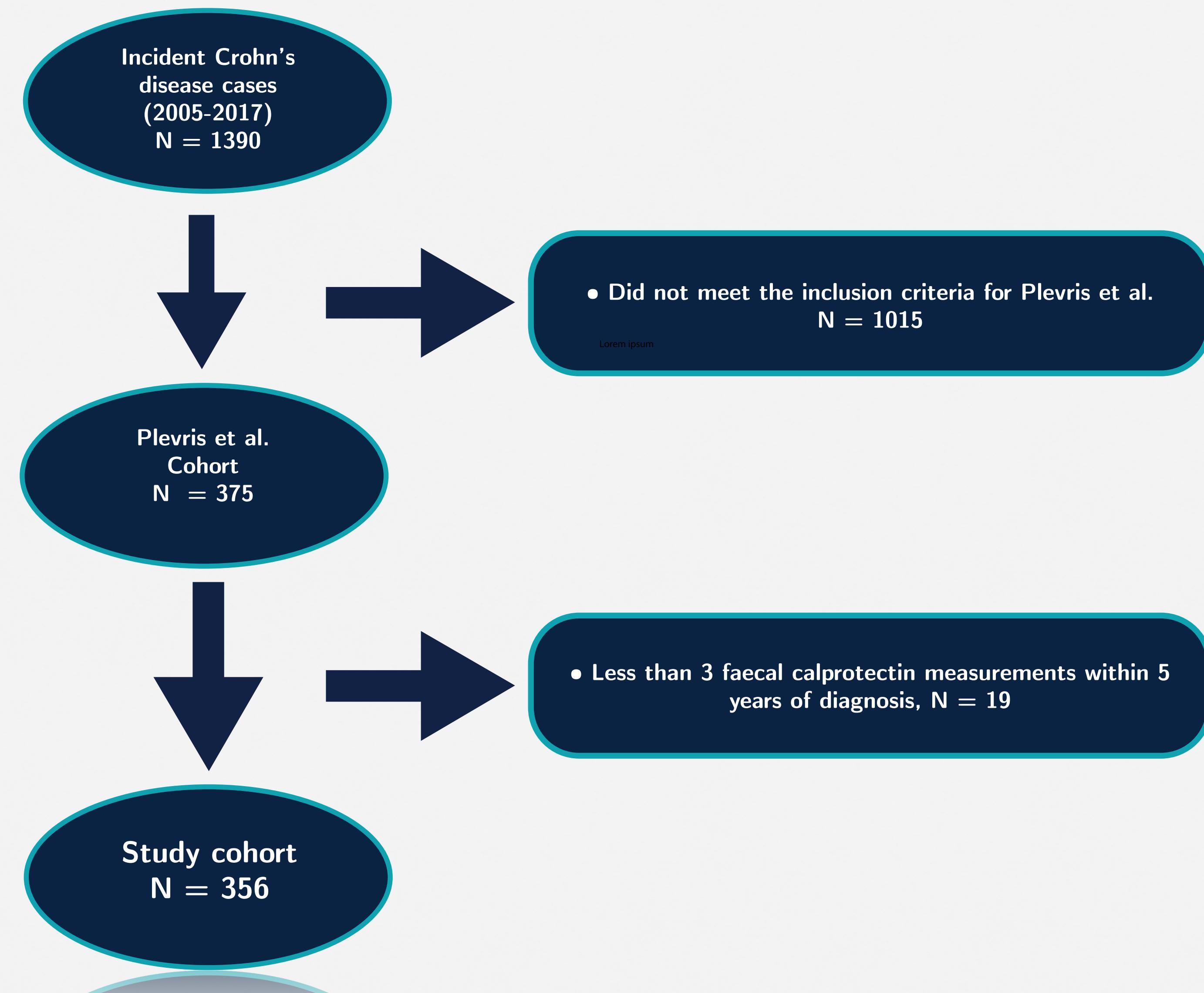
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# Study aims



1. Model FCAL profiles from diagnosis to five years after diagnosis and determine if there are subgroups within the IBD patient population with similar FCAL profiles
2. Determine if membership of these subgroups is associated with a composite end point met if a subject is hospitalised for CD, undergoes resectional surgery, or the progression of disease behaviour.
3. Find if membership of these subgroups are associated with any variables available at diagnosis or treatments prescribed within a year (secondary aim)

# Study inclusion criteria



# Statistical analysis

- Latent class mixed models were used to find classes with shared FCAL trajectories and model these trajectories.
- Log rank tests of Kaplan-Meier curves were used to test for association between class membership and outcomes.
- Chi-squared/Fishers Exact test and ANOVA were used to test for association between class membership and data available at diagnosis.



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# Latent class mixed models

- These models assume a heterogenous population consists of homogenous subgroups
- Combines the features of the linear mixed model with an additional fixed effect component which partitions the population into subpopulations
- Implemented in R via the lcmm package
- Can incorporate natural cubic splines.

$$Y_{ij}|_{c_i=g} = X_{L1i} \left( t_{ij} \right)^\top \beta + X_{L2i} \left( t_{ij} \right)^\top v_g + Z_i \left( t_{ij} \right)^\top u_{ig} + w_i \left( t_{ij} \right) + \epsilon_{ij}$$

# Results



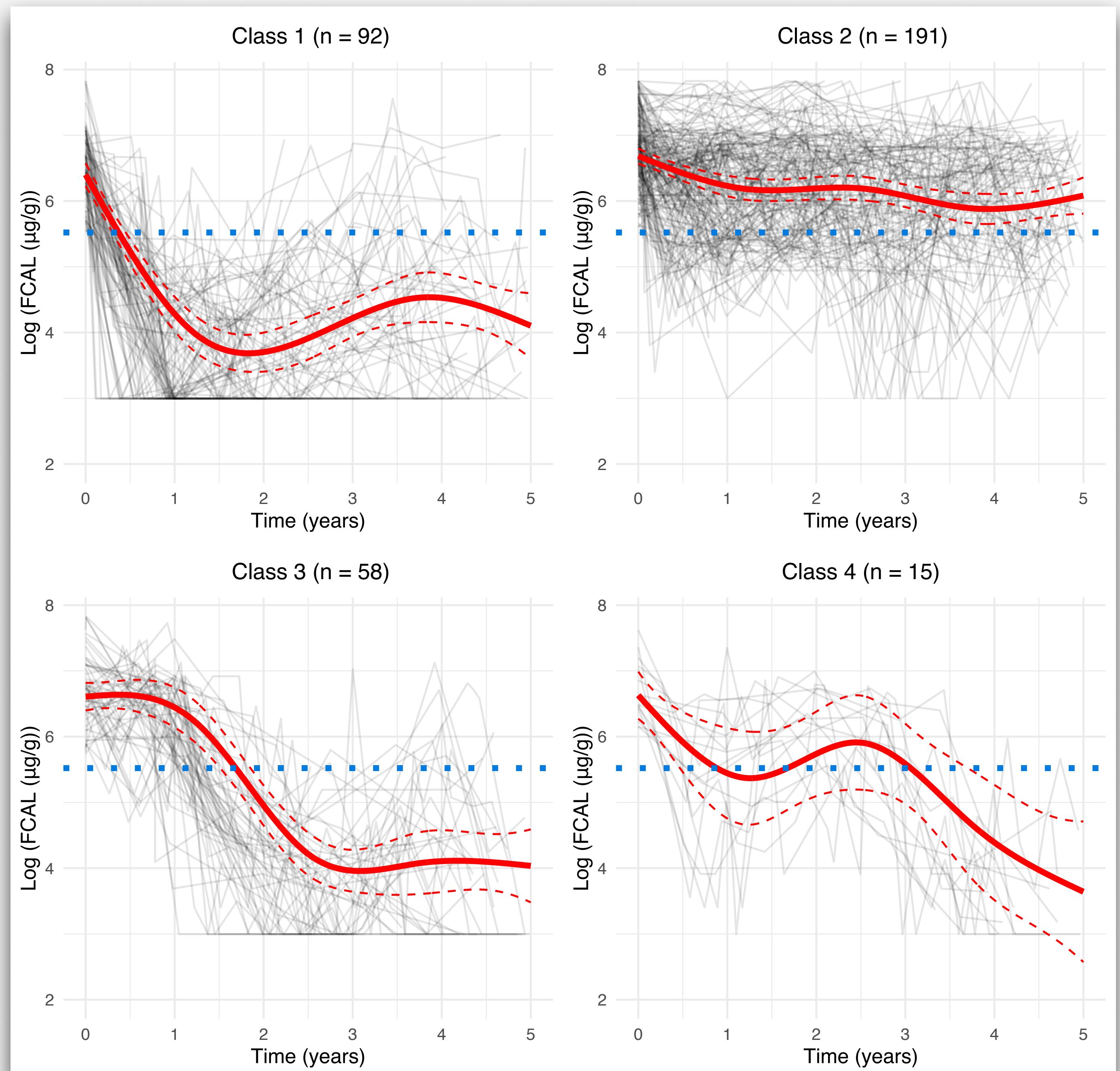
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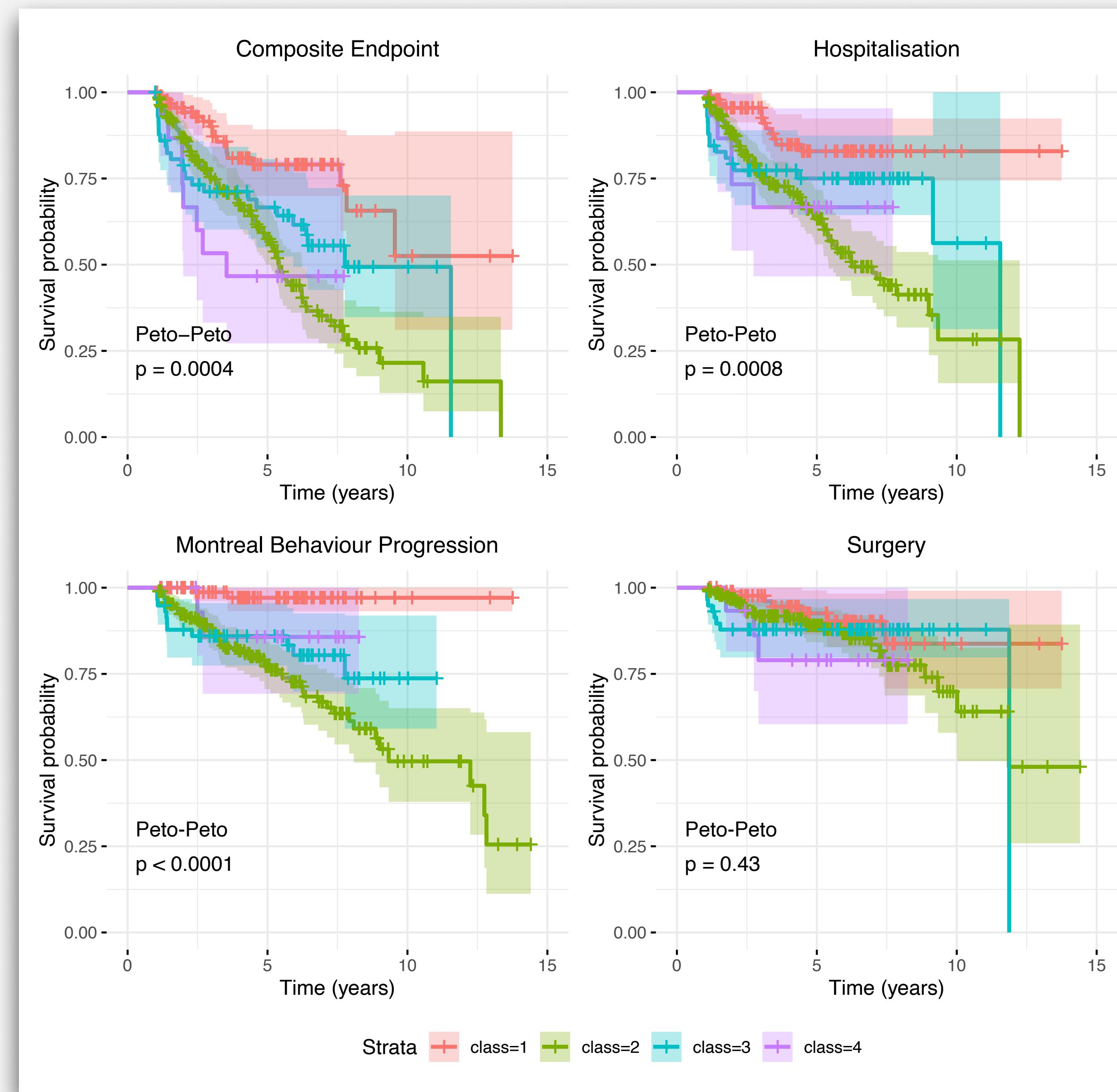
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# Class profiles



# Survival curves for poor disease outcomes stratified by latent class membership



# Significant Associations with Class Membership

- Smoking at diagnosis ( $p = 0.01$ ) and upper gastrointestinal disease ( $p < 0.001$ ) is significantly associated with class membership
- Unable to accurately predict class membership using random forest or multinomial logistic regression (AUC of 0.66 and 0.68 respectively)
- Class membership is associated with early biologic and thioprine prescriptions



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# Discussion



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# Strengths

- We seem to be the first to apply LCMM to FCAL profiles: using a data-driven approach to finding shared disease trajectories.
- We have demonstrated an association with poor disease outcomes.
- We can extend these models to jointly model survival processes: opening the door to dynamic prediction tools.



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# Limitations

- Retrospective study design
- Potential for Inclusion bias
- Observed potential treatment effects require causal inference to truly understand (beyond scope of this study)

# Further work

- Expand to larger cohort size (Lothian IBD Registry + Replication cohort) and use a joint modelling framework allowing dynamic predictions.
- Explore possible associations with class membership and genotypes



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Charlie Lees

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Spyros Siakavellas

Lauranne Derikx

Beatriz Alcalde

Nik Plevris

Phil Jenkinson



## Marioni Group

Riccardo Marioni

