An inflammatory serum metabolomic signature predicts response to vedolizumab treatment in people with Crohn's Disease

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On behalf of the EPIC-Pioneer consortium

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Background:
While Vedolizumab (VDZ) is an established treatment for Crohn's disease (CD), two thirds of patients do not respond. Thus, there remains a clinical need for biomarkers that predict response, pre-treatment. Metabolomic profiling is a rapidly growing field in biomarker discovery and can distinguish between active and quiescent inflammatory bowel diseases. In this study, we sought to identify a metabolic signature able to predict response to VDZ at baseline.

Methods:
Prospective serum samples from 62 CD patients before (baseline) and at post-treatment follow-up (FU) (median 30 weeks, IQR 27-35) were analyzed. Patients were stratified into n=35 responders (R) and n=27 non-responders (NR) using endoscopic (≥50% reduction in SES-CD score), clinical (≥3 point drop in HBI or HBI $\leq$4, no systemic steroids), and/or biochemical assessments (≥50% reduction in C-reactive protein (CRP) and fecal calprotectin (fCal) or a basal CRP $\leq$5 g/mL and fecal calprotectin $\leq$250 μg/g). Untargeted metabolomic profiling was carried out using high-resolution nuclear magnetic resonance (NMR) spectroscopy. Significant differences in metabolite signatures were identified by orthogonal partial least squares discriminant analysis (OPLS-DA). Model accuracy (acc.) was assessed by external 10-fold cross-validation (CV), permutation testing, and validated on an independent test set.

Results:
Bowel preparation required prior to endoscopy assessment had a significant impact on the serum metabolite profile (CV acc. 77±4%, acc. n=10 independent test set 80%, KS test p-value < 0.001) and so these samples were excluded from further analysis. This reduced the cohort size to 19 baseline (12R/7NR) and 25 FU (16R/9NR). The metabolite profiles at baseline and FU were indistinguishable (KS test p-value > 0.05) suggesting the metabolome was stable over FU. However, high (>300 μg/g) fCal values were associated with elevated N-acetyl-glycoprotein (GlycA), a known inflammatory marker, elevated serum glucose concentrations along with decreased serum lipoprotein and lactate levels (CV acc. 74±3%, acc. n=10 independent test set 100%, KS test p-value < 0.001). This, same metabolite signature predicts VDZ response (CV acc. 61±5%, acc. n=6 independent test set 83%, KS test p-value < 0.001) with responders exhibiting increased metabolic inflammation at baseline.

Conclusion: Here, we identify an inflammatory metabolic signature which is associated with fCal levels which predicts response to VDZ. Work to confirm these findings in a larger prospective cohort and extend this method to investigate infliximab, adalimumab and ustekinumab treated patients, as part of the EPIC Pioneer study, is ongoing.

Disclosure: Nothing to disclose.

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Max 4 figures including tables (example of pictures from baseline):

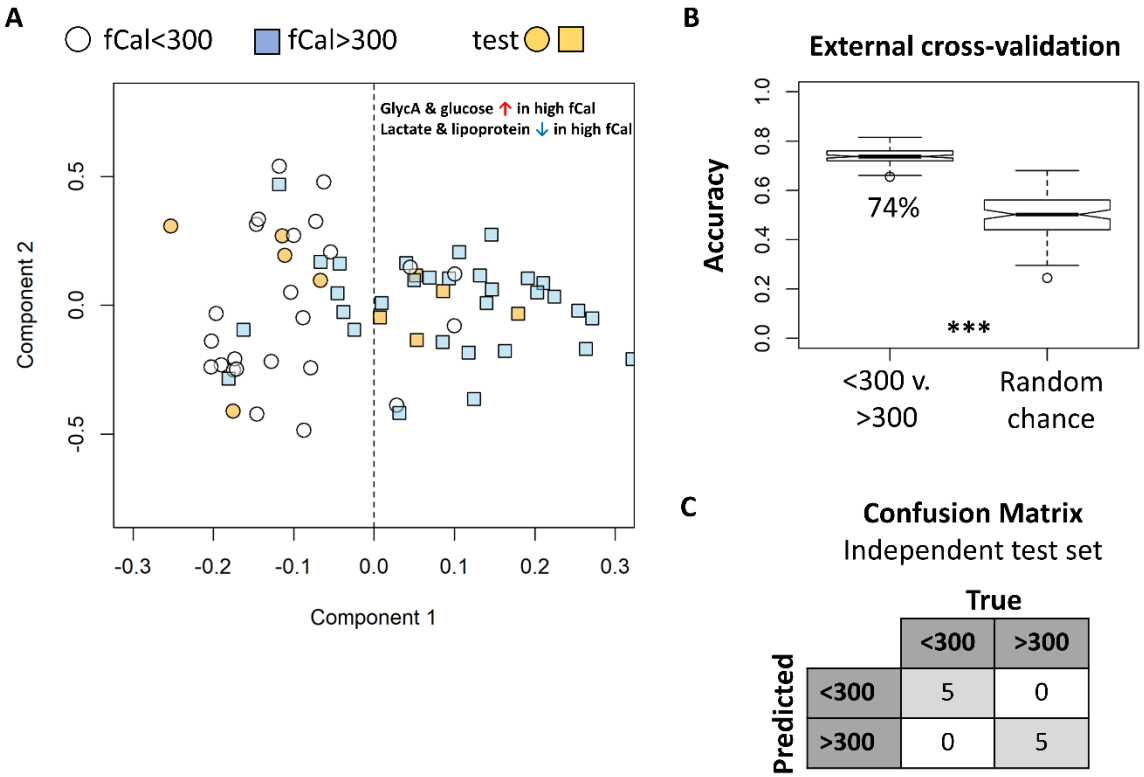

Figure 1. OPLS-DA identifies an inflammatory metabolite signature in CD. A) Representative OPLS-DA scores plot illustrating separation between high fCal (>300 µg/g, blue square) and low fCal (<300 µg/g, white circle) metabolite profiles with the predicted scores of the independent test set (yellow circle and squares) which were not used in model training or cross-validation. B) Results of the external cross-validation with repetition and permutation test. KS-test p-values < 0.001 are represented by ***. C) A confusion matrix of the true and predicted values of the independent test set. Model accuracy on this set was 100%.

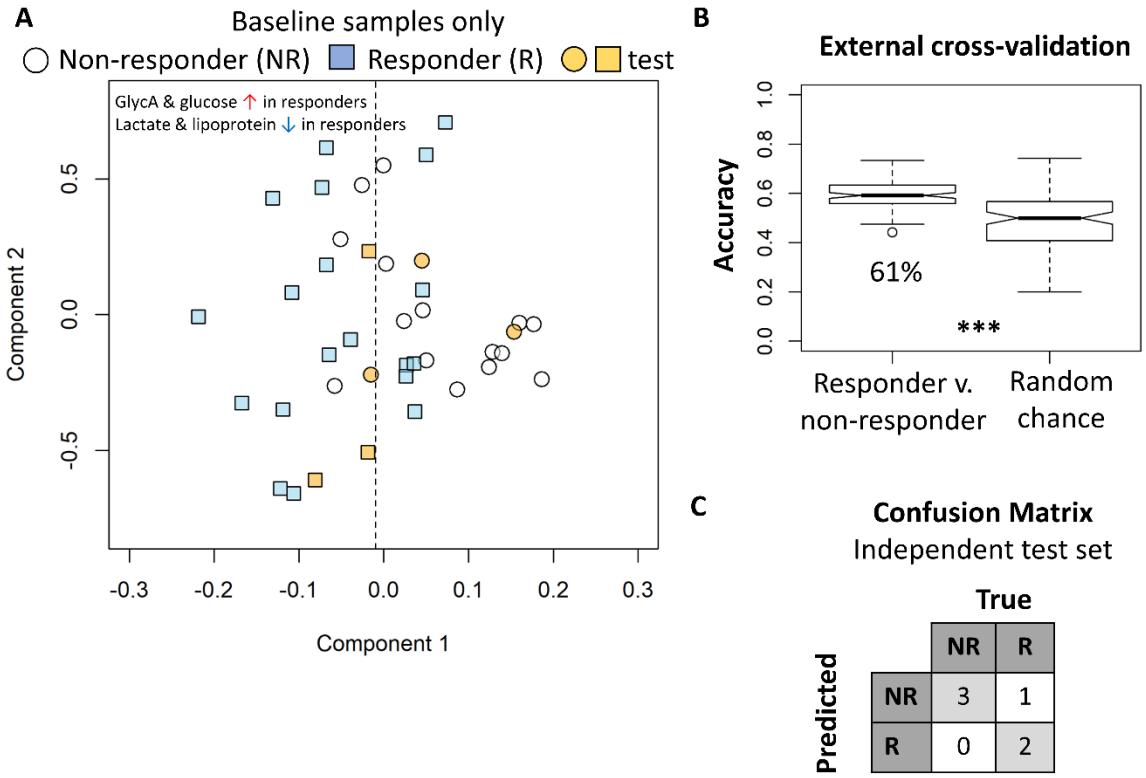

Figure 2. OPLS-DA predicts VDZ response at baseline. A) Representative OPLS-DA scores plot illustrating separation between non-responder (NR, white circle) and responder (R, blue square) metabolite profiles with the predicted scores of the independent test set (yellow circle and squares) which were not used in model training or cross-validation. B) Results of the external cross-validation with repetition and permutation test. KS-test p-values < 0.001 are represented by ***. C) A confusion matrix of the true and predicted values of the independent test set. Model accuracy on this set was 83%.