**eMERGE Network Proposal for Analysis**

Project/Manuscript Concept Sheet

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| **Reference Number** | NT256 |
| **Submission Date** | September 7th, 2017 |
| **Project Title** | Revealing hidden white blood cell count phenotypes for gene discovery: deep phenotyping with latent class mixed modeling. |
| **Tentative Lead Investigator (first author)** | Taryn O. Hall |
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| **Sites Involved** |  All eMERGE sites |
| **Background / Significance** | White blood cell (WBC) count is a marker of systemic inflammation and immune system health. WBC count varies acutely in response to infection and other environmental exposures, however resting-state WBC may be an indicator of chronic disease risk. Elevated resting WBC count has been associated with metabolic syndrome[(Chao et al. 2014; Pei et al. 2015)](https://paperpile.com/c/JHNnCi/h5kVP%2BciwsU), cardiovascular disease[(Huh et al. 2015; Loimaala et al. 2006)](https://paperpile.com/c/JHNnCi/TVGDI%2BT07yB) and mortality[(Nilsson, Hedberg, and Ohrvik 2014; Ahmadi-Abhari, Luben, and Wareham 2013)](https://paperpile.com/c/JHNnCi/m2r2X%2BhmZ5a)). This may reflect excess inflammation as evidenced by WBC count, or leukocytes may contribute directly to disease [(Coller 2005)](https://paperpile.com/c/JHNnCi/XFaw2).There is evidence that steady-state WBC count is not fixed over time. Longitudinal analysis has shown a U-shaped pattern in WBC counts over the lifespan, with the point of inflection around 60 years old [(Chmielewski et al. 2016)](https://paperpile.com/c/JHNnCi/wxFL). Heterogeneity in WBC count trajectory also exists and some trajectories are associated with morbidity and mortality[(Ruggiero et al. 2007)](https://paperpile.com/c/JHNnCi/gQMs). Because WBC count is also influenced by adiposity, changes in steady-state WBC count may reflect age-related change in body composition. However, in a mouse model, different strains exhibited different WBC count trajectories, indicating these trajectories may be under genetic control [(Telieps et al. 2016)](https://paperpile.com/c/JHNnCi/Y0wuI). Deep phenotyping aims to increase the granularity of a phenotype in hopes that a more precise phenotype will increase the power of a GWAS and lead to more precise and larger effect size estimates[(Manchia et al. 2013)](https://paperpile.com/c/JHNnCi/ut3Rj). Extending a phenotype over time by characterising different patterns in longitudinal data is one strategy to deepen phenotype[(Tracy 2008)](https://paperpile.com/c/JHNnCi/10ciX). Trajectory heterogeneity may be difficult to observe in large, observational datasets using standard statistical methods. Latent class mixed modeling (LCMM) is a method that can identify unobserved heterogeneity in longitudinal data and attempts to classify individuals into groups based on a linear model of repeated measurements over time [(Proust-Lima, Philipps, and Liquet 2017)](https://paperpile.com/c/JHNnCi/v6Nr).  |
| **Outline of Project** | 1. Run LCMM on WBC counts repeated measures to identify latent, trajectory-based phenotypes (already completed)2. Move latent phenotype forward to GWAS with imputed data for gene discovery (already completed)3. Draft manuscript (in the process)4. Publish |
| **Desired****Variables (essential for analysis****indicated by \*)** | **Phenotypes:**1. Repeated measures of WBC counts\* and differential already collected in eMERGE I and stored at UW.

**Covariates:**Demographic: Height, weight (at visit), sex, self-identified race and age at event\*. |
| **Desired data** |  |
| **Planned Statistical Analyses** | 1. Run LCMM to discover latent trajectory based phenotype2. GWAS with identified latent phenotypes as a logistic regression analyses.  |
| **Ethical considerations** |  There are no physical risks involved. |
| **Target Journal** | Genes and Immunity |
| **Milestones\*\*** | Construct latent phenotype using LCMMGWAS with latent phenotype and imputed dataDraft manuscriptPublish  |

**\*\*** This section should include: Timeline for completion of project, including approval, project duration, first and second draft of the paper and submission.



Image 1: Latent trajectory phenotypes revealed by LCMM 

Image 2: GWAS (all ancestry) of latent phenotypes using imputed genetic dataset

References

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