

| Project Details |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
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| Project Code    | CMD27Ex Beaumont                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| Title           | Disentangling Diabetes: A Novel Genetic Decomposition Approach                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| Research Theme  | Cardiometabolic Disease                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| Project Type    | Dry lab                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| Summary         | <p>Diabetes is a highly heterogeneous condition, but its clinical management relies heavily on HbA1c – a biomarker affected by distinct pathways: glucose metabolism (glycaemic) and independent red blood cell biology (non-glycaemic). This means that HbA1c can sometimes lead to incorrect management of diabetes. To address this problem, the project will use statistical genetics to untangle these distinct biological pathways. By separating the genetic architecture of glucose from peripheral red blood traits, we will uncover how these independent mechanisms drive diabetes aetiology and long-term complications, ultimately untangling diabetes heterogeneity to understand why different individuals experience different disease outcomes.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| Description     | <p>Type 2 diabetes (T2D) is a chronic condition characterised by high circulating blood glucose. T2D is usually diagnosed and managed using the biomarker glycated haemoglobin (HbA1c). HbA1c reflects average blood glucose levels over the previous 8-12 weeks, but its accurate estimation of glucose levels assumes an average red blood cell (RBC) lifespan of roughly 120 days in all individuals. However, genetic and environmental factors affect RBC lifespan, erythropoiesis, and iron metabolism, which all affect HbA1c accuracy. For example, genetic variants in the G6PD gene lower HbA1c by ~10mmol/mol for a given glucose, delaying T2D diagnosis and increasing complication risk. Uncoupling glycaemic and non-glycaemic components of HbA1c is critical to help generate meaningful thresholds for diabetes diagnosis and management avoiding under-diagnosis and mitigating complications.</p> <p>Genome-wide association studies (GWASs) have identified &gt;200 HbA1c-altering genetic variants, many of which associate with blood glucose levels, or RBC biology, however separating glycaemic from non-glycaemic effects on a genome-wide scale remains challenging. This project will decompose HbA1c genetic effects into separate components, such as glycaemic and non-glycaemic, using state-of-the-art methods such as GWAS-by-subtraction (a method for statistically separating genetic effects on correlated traits). The student will validate their decompositions and use them to understand implications of these pathways, testing the hypothesis that non-glycaemic components confound relationships between HbA1c levels and diabetes complications.</p> <p>While the project plan is initially focussed on partitioning of genetic effects of HbA1c to familiarise the students with the methods, it is designed such that the student will have the freedom to apply these methods to other related cardiometabolic traits (e.g. T2D), matching the expertise of the supervisory team. The student may also choose to use the genetic partitioning of HbA1c to further investigate the effect of different components on diabetes complications.</p> <p>Research Questions</p> |

- Can statistical genetics frameworks effectively separate HbA1c genetics into glycaemic and non-glycaemic components?
- How do these components predict diabetes-related complications and how well can they improve understanding of diabetes complications?
- Can a better understanding of diabetes help to predict the impact of effective interventions for related risk factors (BMI)

#### Aims

##### 1. Model/trait selection

The student will explore and benchmark statistical methods for partitioning genetic associations (e.g. GWAS-by-subtraction, MTAG, c-GWAS). Using summary statistics from the MAGIC consortium (glycaemic traits: fasting/random glucose, fasting insulin, 2-hour glucose), and UK Biobank (blood cell traits: mean corpuscular haemoglobin, RBC and reticulocyte counts, RBC distribution width), the student will evaluate alternative model definitions for decomposing HbA1c genetic components. This work will establish a framework for partitioning glycaemic and non-glycaemic components.

##### 2. Genetic partitioning

Building on the framework established in aim 1, the student will partition genetic components of diabetes traits. These will be evaluated for novel loci against traditional GWAS approaches and compared to previous cluster-based approaches to assess their concordance, and whether they improve biological understanding. Finally, the student will construct polygenic scores (PGS) partitioned by these components and evaluate their performance as predictors of HbA1c, and diabetes traits.

##### 3. Association with diabetes diagnosis and complications

The student will examine associations of T2D, microvascular (e.g. damage to nerves, eyes) and macrovascular (e.g. stroke, heart attack) complications, with components-partitioned PGSs, comparing performance against T2D genetic clusters, and investigate effects on timing of diabetes diagnosis. Techniques such as Multivariable Mendelian Randomisation (MVMR) will be used to examine causality of glycaemic and non-glycaemic components on diabetes complications.

To elucidate intermediate mechanisms driving these components, the student will also integrate proteomic and metabolomic data, available through supervisor Timpson, to triangulate molecular evidence for the impact of key exposures/mediating traits such as adiposity. Treating these molecular traits as intermediate phenotypes will map downstream pathways specific to glycaemic versus non-glycaemic architectures. This multi-omics framework will be cross-referenced with drug-targets, identifying potential opportunities for drug repositioning or predicting off-target mechanism effects.

#### Expected impact and clinical implications

By disentangling HbA1c's glycaemic and non-glycaemic components, the project will improve understanding of how they relate to diabetes management. For example, while diabetes relates to glucose, it is possible that non-glycaemic factors influencing HbA1c affect diabetes complications (e.g. cardiovascular events). This would help understand why some individuals with apparent "good diabetes control" (lower

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|                             | <p>HbA1c levels) may still develop complications while others with higher HbA1c values (“poor control”) do not.</p> <p>The outcome of this project can inform parallel efforts led by co-supervisor Barroso (Wellcome Discovery Award) to develop more personalised HbA1c diabetes diagnosis and monitoring thresholds. Integrating individual genotype, age, and sex could provide personalised thresholds which better reflect glycaemia, avoiding current problems of over- or under-diagnosis and treatment. It will play to the strengths of the full supervisory team, including co-supervisor Timpson whose background is in population-based genetic association studies and the application of applied genetic epidemiology, causal inference and in the assessment of the broader implications of mediator (in this case weight) management.</p> |
| Can be completed part time? | Yes                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| Supervisory Team            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| Lead Supervisor             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| Name                        | Dr Robin Beaumont                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| Affiliation                 | Exeter                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| College/Faculty             | College of Medicine and Health                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| Department/School           | Health and Life Sciences                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
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| Co-Supervisor 1             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| Name                        | Professor Inês Barroso                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| Affiliation                 | Exeter                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| College/Faculty             | College of Medicine and Health                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| Department/School           | Health and Life Sciences                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| Co-Supervisor 2             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| Name                        | Dr Camlia Armirola-Ricaurte                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| Affiliation                 | Exeter                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| College/Faculty             | College of Medicine and Health                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| Department/School           | Health and Life Sciences                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| Co-Supervisor 3             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| Name                        | Professor Nicholas Timpson                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| Affiliation                 | Bristol                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| College/Faculty             | Health and Life Sciences                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| Department/School           | Bristol Medical School                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |