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Title of project: Partitioning the genetic risk of type 2 diabetes using multimodal single-cell sequencing of the gastrointestinal tract

ABSTRACT
The gastrointestinal (GI) tract is a complex organ with a profound impact on human health and metabolism. The GI-tract is located at the junction between the gut microbiome and the gut-brain axis, which links intestinal function to the higher cognitive centers resulting in changes in appetite and behavior. Due the complex regionality and cellular composition of the GI tract, it is largely unknown to what extent genetics plays a role in metabolic diseases mediated by the GI tract, including Type 2 Diabetes (T2D) Genome Wide Association Studies (GWASs) have identified thousands of DNA sequence variants associated with an increased risk of T2D. However, the function of most of these DNA variants remain unknown, as it is difficult based on genetic data alone to determine in what cell type a given DNA sequence variant has an effect and what genes it might implicate. To rectify this gap in our knowledge, we will generate a catalogue of all cell types and their activity in the GI tract using multiple single-cell sequencing assays performed on human biopsies from multiple locations in the intestine. We will use this multimodal, single-cell level catalogue to partition T2D data into cell type-specific signals. The use of this will be twofold: It will allow us to better understand the biological context of each individual DNA sequence variant, and thereby better prioritize candidate genes for interventions. Furthermore, by jointly analyzing all DNA sequence variants together we will be able to calculate cell type-specific overall genetic risk scores for each individual patient. We will use this to improve and explore subtyping of patients at risk of developing T2D, with the ultimate goal to improve clinical care.