Project Details	
Project Code	MRC21IIREx Oram
Title	Can we predict the future? Predicting type 1 diabetes from birth using mathematical modelling of genetics and biomarkers....
Research Theme	Infection, Immunity & Repair
Summary	This project integrates data science, prediction modelling, genomics and autoantibody measurement to better predict type 1 diabetes. There are emerging interventions that are able to delay onset of type 1 diabetes and this project aims to optimise a prediction model integrating genetic and autoantibody data for a large UK study (the BOX study) to develop a UK type 1 diabetes prediction model.
Description	Type 1 diabetes (T1D) is a common autoimmune disease, resulting from destruction of insulin producing cells in the pancreas. It results in a lifelong requirement for injected insulin and a risk of life threatening and life changing complications. T1D can present at any age, often in early childhood, and is strongly associated with genetic and environmental factors. Development of autoimmunity can commonly be measured years before clinical disease onset by the presence of islet autoantibodies. Professor Gillespie's team are world leaders in the measurement of islet autoantibodies. Professor Oram's group have developed a genetic risk score (GRS) that sums T1D genetic risk into a single variable - currently being tested as a from-birth population prediction tool. Recent immune therapy trials have shown delayed progression to T1D in autoantibody positive children, this has increased interest in the ability to accurately predict which children will develop T1D in the future. Recent work by the PIs (Ferrat..Oram Nature Medicine 2020) has shown that a combined approach integrating genetic, autoantibody and other clinical factors into a combined risk model, can provide accurate prediction of future T1D (ROC AUC ~0.95) from early life. This offers an improved ability to identify who will develop T1D in the future and when this will occur, and could be directly used to identify high risk children for disease prevention therapy, or to develop population based screening strategies. Data for these models has come from studies in the USA and Europe (the TEDDY study and Trialnet Pathway to Prevention), but there are no data from UK studies. In this PhD we plan to validate and further refine cutting-edge diabetes genetic risk scores and prediction models by testing them in the longstanding population-based Bart's Oxford family study (BOX). BOX has been recruiting individuals with T1D and their families since 1985 (>2,737 families and >8000 individuals with autoantibody testing and genotyping, >2000 with T1D and 78 who progressed to T1D during long term follow up). Data are available on islet autoantibody characteristics in children and adults, genetic susceptibility (HLA and SNP typing), family history of diabetes and other autoimmunity. This study has also includes a well characterised group of "Slow Progressors" who have remained diabetes-free for decades despite ongoing islet autoimmunity. The student will 1) generate a T1D genetic risk score and test its discriminative ability for T1D in BOX, 2) test and calibrate a combined T1D prediction model in BOX, 3) Refine the model with additional variables (e.g. autoantibody epitope, titre and affinity, and additional genetic loci) in Trialnet and TEDDY datasets (with >800 additional T1D

	cases) and in BOX, using internal cross validation and externally in collaborating T1D prediction studies. The outcome of this PhD will include training in data science, genomics and genetic risk score generation, multivariable survival modelling using R, islet autoantibody measurement and analysis, and the integration of biomarkers into combined prediction models. It will be directly linked to translation into clinical trials through Professor Dayan's leadership of a UK T1D screening project (with Prof's Oram, Gillespie and collaborators) that is identifying islet autoantibody positive children age 3.5y for enrolment into clinical trials. The project will validate and refine a type 1 diabetes prediction model for the UK population will therefore directly inform type 1 diabetes prediction and intervention studies in the UK.
Supervisory Team	
Lead Supervisor	
Name	Professor Richard Oram
Affiliation	Exeter
College/Faculty	Institute of Biomedical and Clinical Science
Department/School	College of Medicine and Health
Email Address	r.oram@exeter.ac.uk
Co-Supervisor 1	
Name	Professor Kathleen Gillespie
Affiliation	Bristol
College/Faculty	Faculty of Health Sciences
Department/School	Bristol Medical School
Co-Supervisor 2	
Name	Professor Colin Dayan
Affiliation	Cardiff
College/Faculty	Division of Infection and Immunity
Department/School	Cardif
Co-Supervisor 3	
Name	Dr Lauric Ferrat
Affiliation	Exeter
College/Faculty	Institute of Biomedical and Clinical Science
Department/School	Exeter College of Medicine and Health
Co-Supervisor 4	
Name	
Affiliation	
College/Faculty	
Department/School	