**Application number/Title:** 22474 - Genetic determinants for insulin-dependent type 2 diabetes mellitus

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**Keywords provided by the Applicant PI to describe the research project:**

Genetics, insulin-dependent, diabetes

**Application Lay Summary:**

1a: Type 2 diabetes mellitus (T2D) is a heterogeneous disease caused by different mechanisms, including insulin resistance and pancreatic malfunction. Of the patients diagnosed with T2D, a fair amount of the patients requires insulin analogs shortly (e.g., within 1 year) after diagnoses, which is indicative of a major role for pancreatic malfunction already at the moment of diagnosis. Malfunction of the pancreas results in an insulin-dependent T2D phenotype. In this project, we will investigate genetic determinants for insulin-dependent type 2 diabetes mellitus as defined by the use of insulin analogs within 1 year after diagnosis.

1b: The prevalence and incidence of type 2 diabetes mellitus is increasing. After diagnosis, patients with type 2 diabetes are often prescribed oral glucose-lowering drugs, but treatment response is often insufficient or associated with serious adverse drug reactions. A better understanding of the pathophysiological mechanisms present in the patient is pivotal to select the right treatment with a high probability of success. In the proposed project, we will use genetic analyses to determine whether there are different pathophysiological mechanisms involved in patients that do or do not start insulin analogs shortly after diagnosis of type 2 diabetes mellitus.

1c: We will conduct a Genome-Wide association study on the following outcomes:

- Type 2 diabetes mellitus; all patients
- Type 2 diabetes mellitus; those that start insulin analogs shortly after diagnosis
Type 2 diabetes mellitus; those that don’t start insulin analogs shortly after diagnosis

Using publically available bioinformatics tools, we will conduct pathway analyses to determine which pathways and processes are underlying the two different phenotypes. Furthermore, we will use this data to determine whether different risk factors (e.g., body mass index) are also causal risk factors for both subtypes of type 2 diabetes mellitus using Mendelian Randomization.

1d: For the present study, we will use all participants from the UK Biobank with data on diagnosis of type 2 diabetes mellitus (together with data on whether or not they use insulin analogs within 1 year after diagnosis) and genotyped data (imputed). For the present study we will exclude participants aged 40 years and younger to exclude cases of type 1 diabetes mellitus as much as possible. Genotyped data will be available for the full cohort in the first quarter of 2017.