Assessing Risk and Progression of Prediabetes and Type 2 Diabetes to Enable Disease Modification

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AbbVie, Astra-Zeneca, Boehringer Ingelheim, GSK, Janssen, Lilly, MSD, Novartis, Novo Nordisk, Pfizer, Sanofi, Servier
• **Problem**
  – The incidence of type 2 diabetes (T2D) is increasing at epidemic proportions
  – Declining cellular health in T2D likely begins before glucose levels rise or diagnosis of disease
  – Current T2D therapies focus more on blood glucose control than on improving cellular health or altering the course of the disease
  – Gaps exist to improve feasibility of drug development to restore cellular health and
    • Prevent progression of prediabetes to T2D or to
    • Delay or prevent disease progression in individuals with T2D
Need

• Robust approaches are needed to select the individuals most in need of and most likely to benefit from new potential disease-modifying therapies for clinical trials.

• Validated biomarkers and diagnostic assays are needed to identify individuals with rapidly declining health of cells that function in maintaining blood glucose levels, including insulin-producing pancreatic beta cells and glucose-metabolizing liver, muscle, and fat cells.

• Innovative clinical trial designs are needed to improve the feasibility of drug development for disease-modifying therapies in prediabetes and diabetes.

• Collaboration and dialogue with regulatory and economic experts is needed to advance development of disease-modifying therapies to prevent or delay progression of T2D.
Overall Objectives

Prioritize and/or validate biomarkers (and assays):
To enable prospective selection of subjects with rapid progression from prediabetes to type 2 diabetes and type 2 diabetes subjects with accelerating type 2 diabetes disease progression prioritize and/or validate panels of human biomarkers or assays of

- pancreatic beta cell stress, function, mass, and death (validation and discovery components)
- impaired hepatic, skeletal muscle, and/or adipose cellular functions contributing to progression of insulin resistance (validation and discovery components)

Develop innovative potential regulatory approaches
In collaboration with regulatory experts, including adaptive clinical trial designs, enabling feasible and robust benefit/risk assessments in clinical trials for
- therapeutic intervention in prediabetes to prevent or delay onset of type 2 diabetes
- therapeutic interventions in type 2 diabetes for disease modification to reduce the rate of disease progression

Model short- and long-term economic and public health benefit/risk assessments for
- therapeutic intervention in prediabetes to prevent or delay onset of type 2 diabetes
- therapeutic interventions in type 2 diabetes for disease modification to reduce the rate of disease progression
Overall key deliverables

**Validation and/or discovery of human phenotypes and biomarker panels predictive of rapid declines in**

- Pancreatic beta cell health and function
- Insulin action-targeted hepatic, skeletal muscle, and/or adipose cellular functions to enable prospective identification of  
  a) “rapid progressors” from prediabetes to type 2 diabetes and  
  b) accelerating type 2 diabetes disease progression for patient identification for clinical trial recruitment or therapeutic intervention

**Prioritization and selection of robust phenotypes and biomarker panels that enable feasible prospective patient segmentation/selection, clinical trial design and regulatory paths to assess new therapeutic options for**

- Prevention of progression from prediabetes to type 2 diabetes and  
- Prevention of acceleration of type 2 diabetes disease progression

**Development of new regulatory approaches or standards** enabling innovative and feasible clinical trial designs for disease modification in patients with prediabetes or type 2 diabetes

**Benefit/risk models for public health** and economic impact of therapeutic intervention to prevent or delay progression from prediabetes to type 2 diabetes
• Network of academic basic, translational, clinical research scientists with expertise in
  – biomarker discovery across the range of specified technologies,
  – human pancreatic beta cell, hepatic, muscle, and adipose biology
  – conducting intensive clinical phenotyping of prediabetes and type 2 diabetes patients

• Investigators with expertise in and ability to leverage existing retrospective cohorts and collaborations with ongoing studies of individuals with prediabetes and with type 2 diabetes
  – including clinical phenotype data, biomarker data, longitudinal outcomes data and available biobank biofluids and/or tissues
Suggested project structure

**WP1:** Administration, management, and communications

**WP2:** Data integration, analysis, and informatics

**WP3:** Pancreatic beta cell biomarker prioritization and selection

**WP4:** Insulin action target (liver, muscle, adipose) cell biomarker prioritization and selection

**WP5:** Assays and technologies development

**WP6:** Regulatory consensus for disease modification

**WP7:** Modeling economic and public health impact of disease modification
Further details and timelines

• Indicative project duration: 4 years

• Anticipated Timelines:
  – Currently in consultation process with IMI stakeholders
  – 7th October 2014: Publication of indicative topic text on IMI Website
  – 12th Dec 2014: Launch of call
  – 24th March 2015: Deadline for submission of Expression of Interest