SUMMIT

Surrogate markers for micro- and macro-vascular hard endpoints for innovative diabetic tools

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Leif Groop, Lund University
IDF Regions and Global Projections for the Number of People with Diabetes (20-79 years), 2010-2030

<table>
<thead>
<tr>
<th>REGION</th>
<th>2010 Millions</th>
<th>2030 Millions</th>
<th>INCREASE %</th>
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</thead>
<tbody>
<tr>
<td>Africa</td>
<td>12.1</td>
<td>23.9</td>
<td>98%</td>
</tr>
<tr>
<td>Middle East and North Africa</td>
<td>26.6</td>
<td>51.7</td>
<td>94%</td>
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<tr>
<td>South-East Asia</td>
<td>58.7</td>
<td>101.0</td>
<td>72%</td>
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<tr>
<td>South and Central America</td>
<td>18.0</td>
<td>29.6</td>
<td>65%</td>
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<tr>
<td>Western Pacific</td>
<td>76.7</td>
<td>112.8</td>
<td>47%</td>
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<tr>
<td>North America and Caribbean</td>
<td>37.4</td>
<td>53.2</td>
<td>42%</td>
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<tr>
<td>Europe</td>
<td>55.2</td>
<td>66.2</td>
<td>20%</td>
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<tr>
<td>World</td>
<td>284.6</td>
<td>438.4</td>
<td>54%</td>
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</table>
Prevalence (%) Estimates of Diabetes (20-79 years), 2010
Prevalence (%) Estimates of Diabetes (20-79 years), 2030
Key defects in diabetes

Hyperglycemia

Muscle
EVERY 24 HOURS

- New Cases – 4,100
- Deaths – 810
- Amputations – 230
- Kidney Failure – 120
- Blindness - 55

Diabetic Complications

Diabetic nephropathy
About 30% of T1D and T2D patients develop DN. This is characterized by a progressive decline of kidney function leading to ESDR with need for dialysis or transplantation.

Diabetic retinopathy
Affects most patients with DM to some degree and 2% will become blind. There is visual impairment in most of the patients.

Cardiovascular Diseases
Up to 75% of all deaths in T2D are due to CVD. T1D patients have a 4 to 7 fold risk of major CVD, T2D patients a 2 – 4 fold risk for a development of MI, stroke or peripheral arterial diseases.
Diabetic Complications

There is a high therapeutic need for new treatments of diabetic complications beyond glucose lowering therapies.

Clinical trials to show benefit of such therapies are large, long-lasting and costly.

The key goal and deliverable of SUMMIT is the development of ways, technologies and tools to make clinical trials testing of novel medications in diabetic complications shorter and more focused.
Identify susceptibility markers predicting diabetic complications.

Identify genetic markers/biomarkers/non invasive markers that can be used to
a) collect patients at high risk of complications
b) monitor progression, reduction or prevention of complications
c) serve as useful surrogate endpoints in clinical trials

Acceptable by regulatory agencies (EMA, FDA)

Develop animal models, novel imaging technologies, data mining and in silico modeling tools.
SUMMIT – How we do it

Will focus on DN, DR and CVD complications in T1D and T2D patients.

The project is divided in three phases:

1. Discovery of novel genetic and biomarkers for diabetic complications (existing biosamples) 18 months.
2. Validation of these biomarkers in appropriate cohorts (years 2 – 3).
3. Translation of these findings into clinically relevant settings. Predict and monitor progression of complications (years 4 – 5).
SUMMIT - A Multifacet Approach

WP1 Genetic Markers
WP2 Biomarker Discovery
WP3 New Imaging Technologies
WP4 Animal Models
WP5 Data Mining & \textit{In silico} modeling

Existing Animal Models
Patient overlap between WPs 1, 2 & 3

Data from Bioinformatic & Bibliometric Resources

Management & Coordination
Administration
Training
Dissemination
Expected benefit to patients

• Early identification of patients at risk of developing diabetic complications allows implementation of aggressive treatment and preventive measures

• Faster development of drugs targeted on prevention and treatment of diabetic complications
Added value of the consortium

- Joint forces and resources of some of the best experts in the world in the field of diabetic complications provide an unprecedented possibility to generate new knowledge that can change the field
  - Broad **access** to unique biobanks, drug trials, knowledge
  - Combined **expertise** to overcome bottlenecks in diabetic complications research (genetic and biomarkers, imaging technologies, animal models, in silico modeling and data mining)
  - Increased **efficiency** and synergies through targeted interrelation and cross-fertilization between the different work packages (work packages feed into each other)

- New collaboration between scientists from academia and pharmaceutical companies will improve the European research area
Added value of the consortium

- **Academic Partners:**
  - Intensified networking through new collaborations
  - Aligned research efforts and new funding schemes enable projects with high impact on patients needs

- **EFPIA partners:**
  - Intensified exchange with the scientific community and new collaborations
  - Better alignment of public research and needs for drug development

- **Patients:**
  - Individualized medicine
  - Faster access to new and better treatment
What is genetics for?

- Find causal genetic variants
- New biological insights relevant to T2D in general
- Better measures of individual aetiology
- Clinical advances for “everyone”
  - New therapeutic targets
  - New biomarkers
  - New preventative measures
- Personalized medicine
  - Prognostics
  - Diagnostics
  - Therapeutic optimisation

SUMMIT
surrogates markers for macro- and micro-vascular hard endpoints for innovative diabetes tools
Results/achievements so far

- ~ 40 cohorts with large numbers of patients with T1D and T2D available in the consortium

<table>
<thead>
<tr>
<th>Partner</th>
<th>Project name</th>
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<tr>
<td>ULUND</td>
<td>Botnia</td>
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<tr>
<td></td>
<td>Diabetes Registry</td>
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<td></td>
<td>Malmö Preventive Project</td>
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<td>Malmö Diet &amp; Cancer</td>
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<td>Nordi</td>
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<td>KHD</td>
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<td>MES</td>
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<td>Procardis</td>
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<td>Improve</td>
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<td>Greater Stockholm Area</td>
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<td>DIGAMI</td>
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<td>MONICA/KORA Augsburg</td>
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<td>KORA DM</td>
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<td>MN</td>
<td>BENEDICT</td>
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<td>DEMAND</td>
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<td>UCAM</td>
<td>Nephropathy Family Study</td>
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<td>UK GRID</td>
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<td>Oxford Regional Prospective Study</td>
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<td>Adolescent statins intervention</td>
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<td>UNIHDUN</td>
<td>EuroDiab</td>
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<td>Coronary artery calcification study</td>
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<td>The Wellcome Trust Functional Genomics UK Collection for T2D</td>
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<td>DARE</td>
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<td>Y2T2D</td>
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- Project names corresponding to the partners listed above.
Results/achievements so far

- Access to further cohorts through other consortia
- Relevant numbers of patients with and without DN, DR and CVD
- Samples for DNA, plasma, serum and urine as well as RNA from lymphocytes and tissue (kidney, vascular wall)
- GWAS data for several cohorts existing
- Phenotype definitions
- Patients/samples ready for first projects
Results/achievements so far

- **WP 1**: First studies to identify genetic markers which can predict diabetic nephropathy
- **WP 2**: First panel of biomarkers to be tested for their ability to predict diabetic complications
- **WP 3**: Development of novel imaging techniques to detect early atherosclerosis (virtual histology) and diabetic eye disease
- **WP 4**: Evaluation of existing animal models, first animal model to be used for studies on diabetic complications
- **WP 5**: In silico work to prioritize which genetic markers and biomarkers should be taken from discovery to validation, first version of a disease ontology of diabetic complications
- **WP 6**: Meetings: Kick-off, steering committee, executive board, webpage under construction, logo, contacts and communication
Gene score of variants in lipid genes can replace lipid measurements in predicting cardiovascular outcomes

Kathiresan S, Orho-Melander M, Melander O et al
Consecutive series of the same coronary plaque. In the histology images black is calcium, strong magenta is fibrous tissue and light pink is the core. In the Virtual Histology® 4 different categories of tissues are seen: fibrous tissue (green), fibro-fatty (greenish yellow), necrotic core (red) and calcium in white. In the IVUS, P is the probe inside the lumen, in grey are the fibrotic regions, in white (more echogenic) calcium and in dark, echolucent is the core.
SUMMIT-Consortium

- 24 Partners
- 18 academic centers (Sweden, Finland, GB, Italy, Germany)
- 1 SME (Finland)
- 4 pharmaceutical companies (Germany, Switzerland, GB)

- EFPIA: ~10 million EURO
- IMI JU: ~14 million EURO
- Total costs: 28.5 million EURO

- Start: November 1, 2010
- Duration: 5 years

- Excellent scientific and geographical coverage
- High challenge to coordinate and manage SUMMIT
Participants

**Academia/public sector:**
- Lund University
- Karolinska Institute
- Helmholtz Zentrum Munich,
- Instituto di Ricerche Farmacologiche “Mario Negri”
- The University of Cambridge
- University of Dundee
- The University of Exeter
- Goeteborgs Universitet
- Folkhälsan, Helsinki
- The National Institute for Health and Welfare, Finland
- University of Eastern Finland
- The University of Oxford
- Università degli Studi di Padova
- Università degli Studi di Pavia
- Università di Pisa
- Università Cattolica del Sacro Cuore, Rome
- University of Turku
- University of Edinburgh

**EFPIA:**
- Boehringer Ingelheim
- Astra Zeneca
- Eli Lilly
- Hoffmann-La Roche

**Small and medium sized enterprizes (SME):**
- Biocomputing Platforms Ltd Oy
SUMMIT-Contact

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