



Innovative Medicines Initiative

## SUMMIT

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

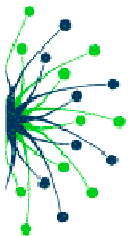
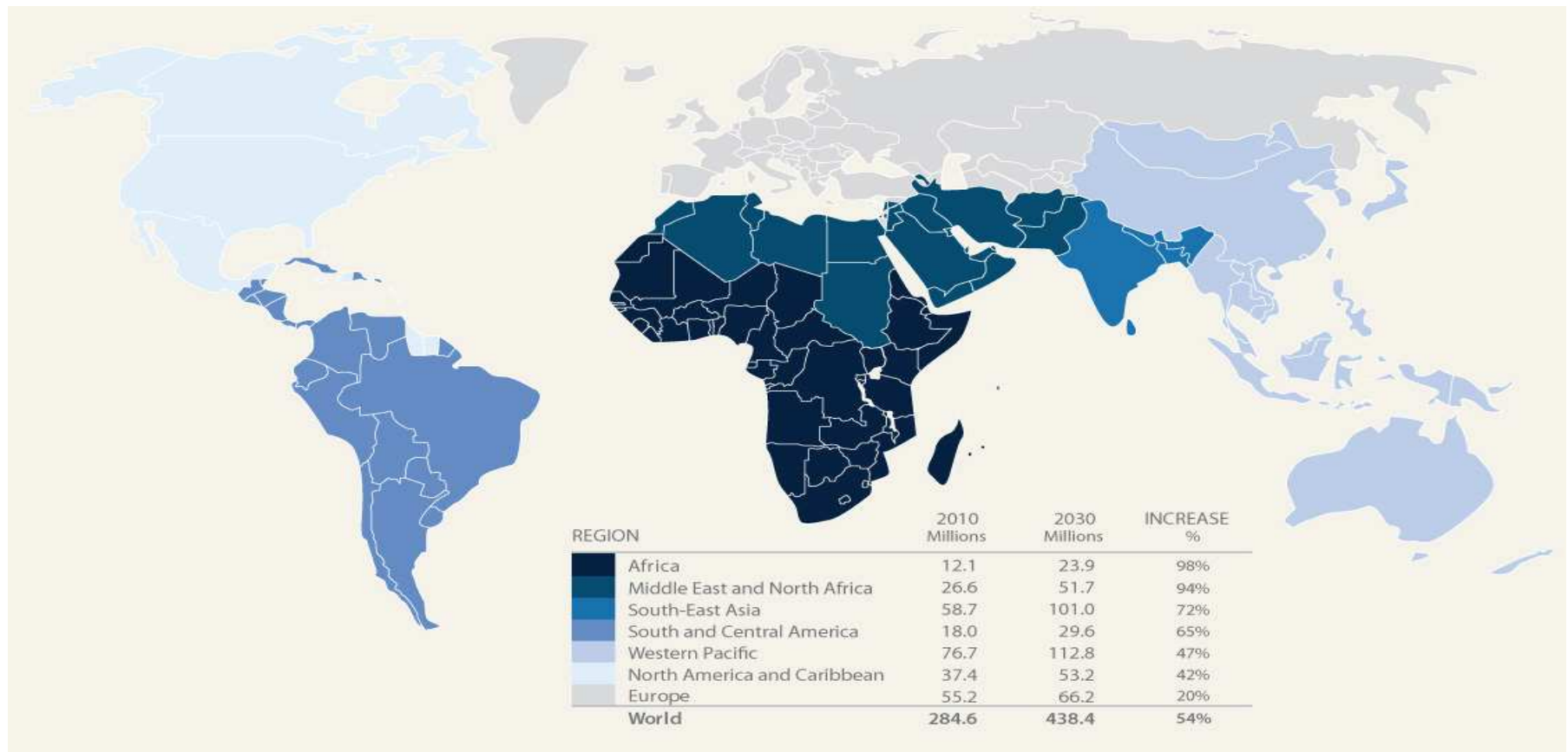


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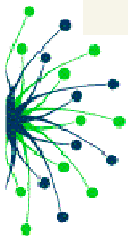
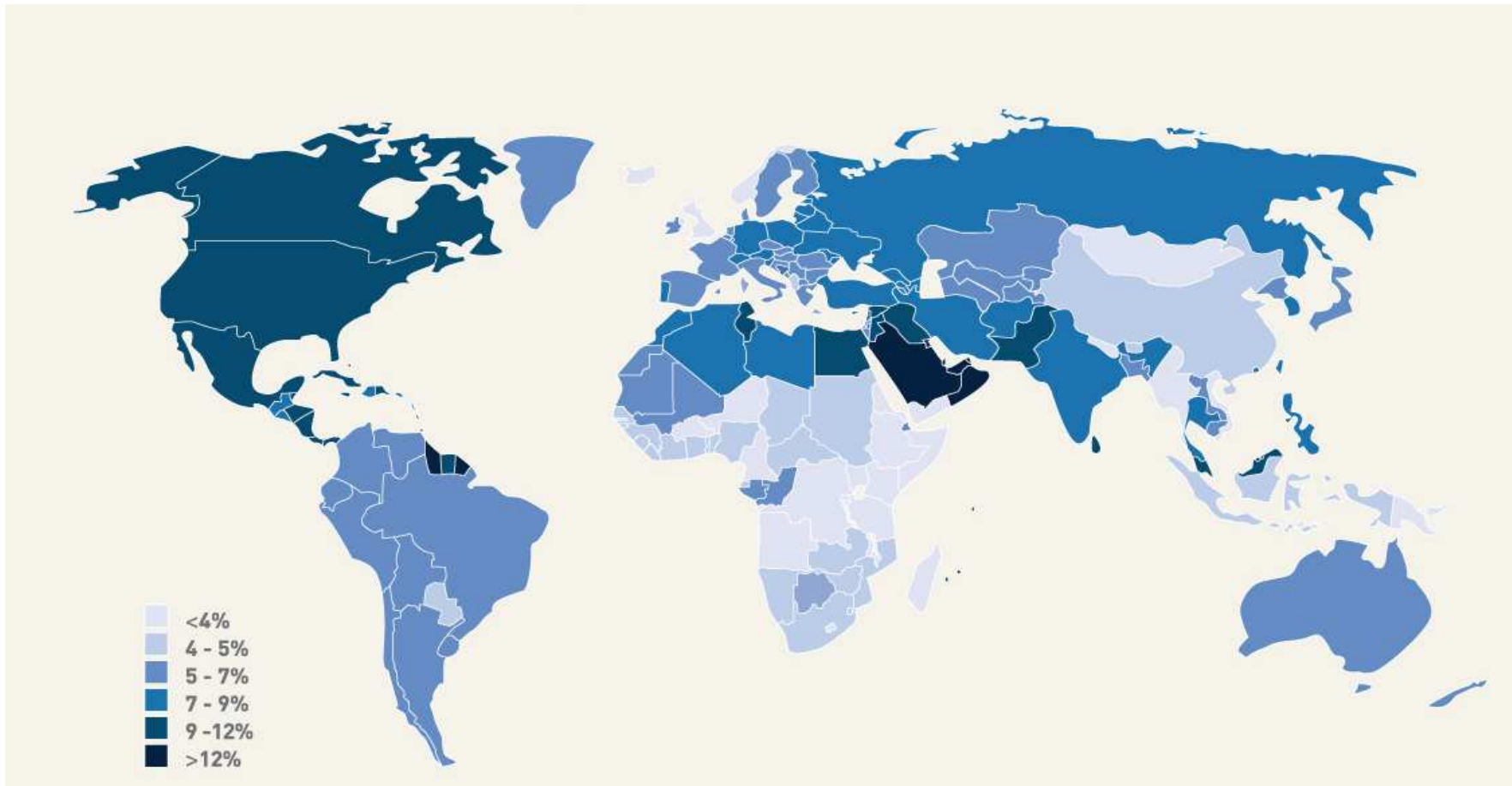
Michael Mark, Boehringer-Ingelheim  
Leif Groop, Lund University

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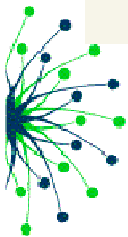
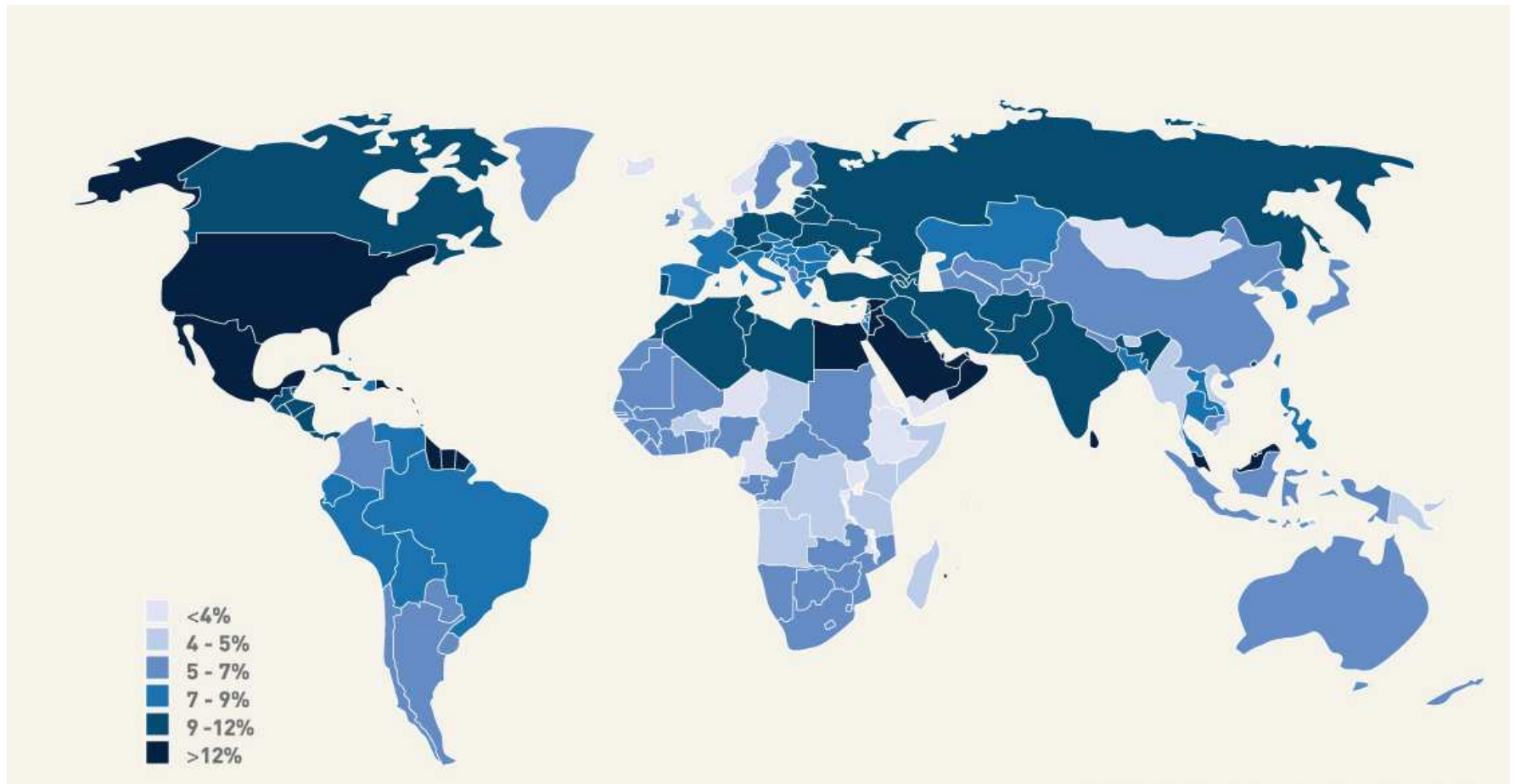
# IDF Regions and Global Projections for the Number of People with Diabetes (20-79 years), 2010-2030



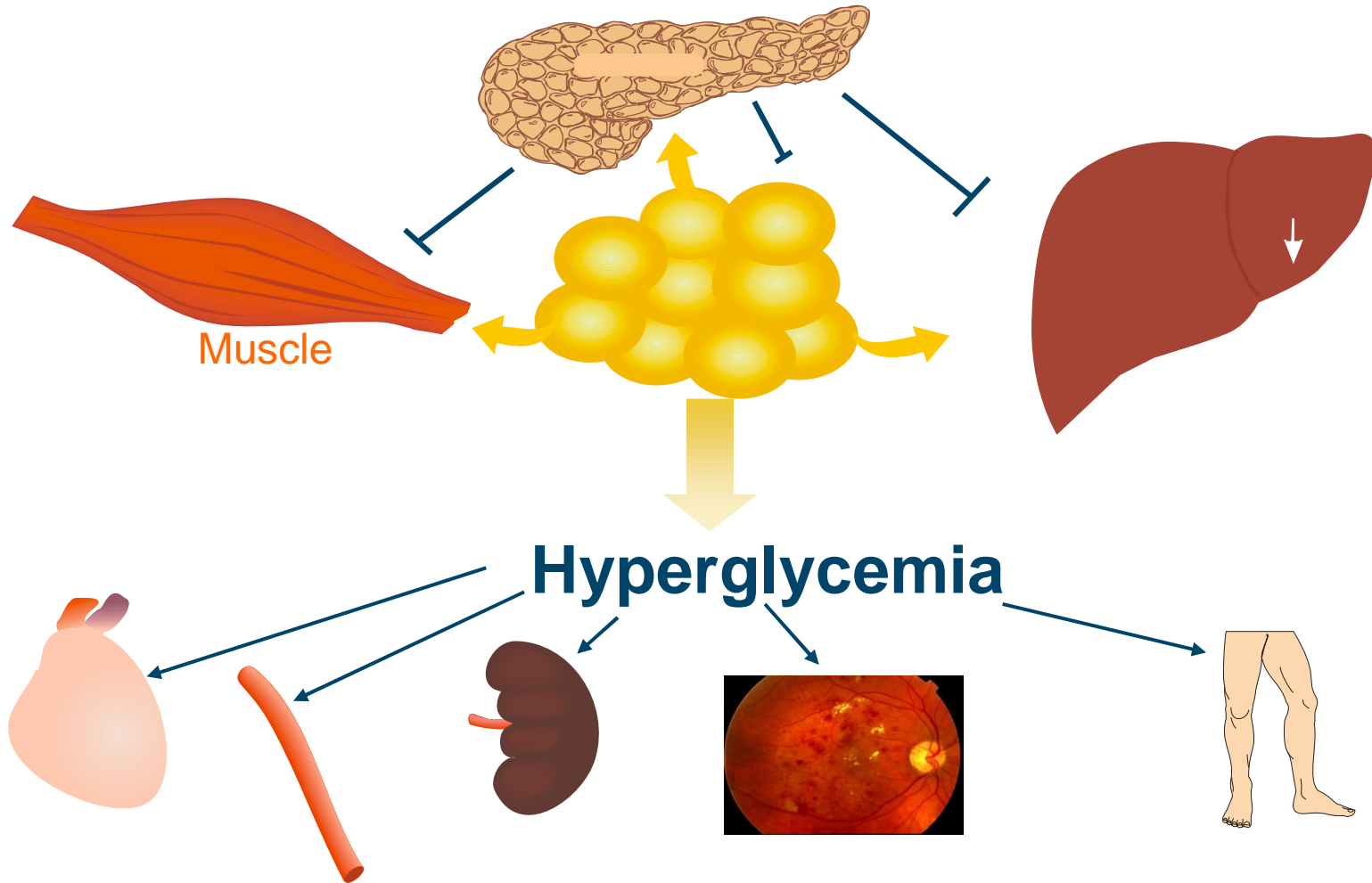
# Prevalence (%) Estimates of Diabetes (20-79 years), 2010



# Prevalence (%) Estimates of Diabetes (20-79 years), 2030



# Key defects in diabetes



# EVERY 24 HOURS

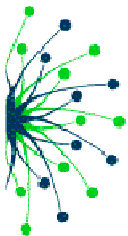
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- New Cases – 4,100
- Deaths – 810
- Amputations – 230
- Kidney Failure – 120
- Blindness - 55



*Derived from NIDDK, National Diabetes Statistics fact sheet. HHS, NIH, 2005.*





# Diabetic Complications

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## Diabetic nephropathy

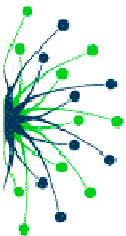
About 30% of T1D and T2D patients develop DN. This is characterized by a progressive decline of kidney function leading to ESDR with need for dialysis or transplantation.

## 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

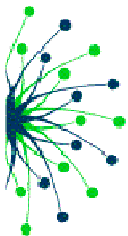
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There is a high therapeutic need for new treatments of diabetic complications beyond glucose lowering therapies.

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.





# SUMMIT- Expected Outcomes

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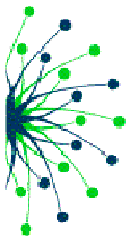
Identify susceptibility markers predicting diabetic complications.

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

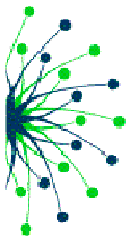
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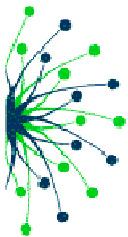
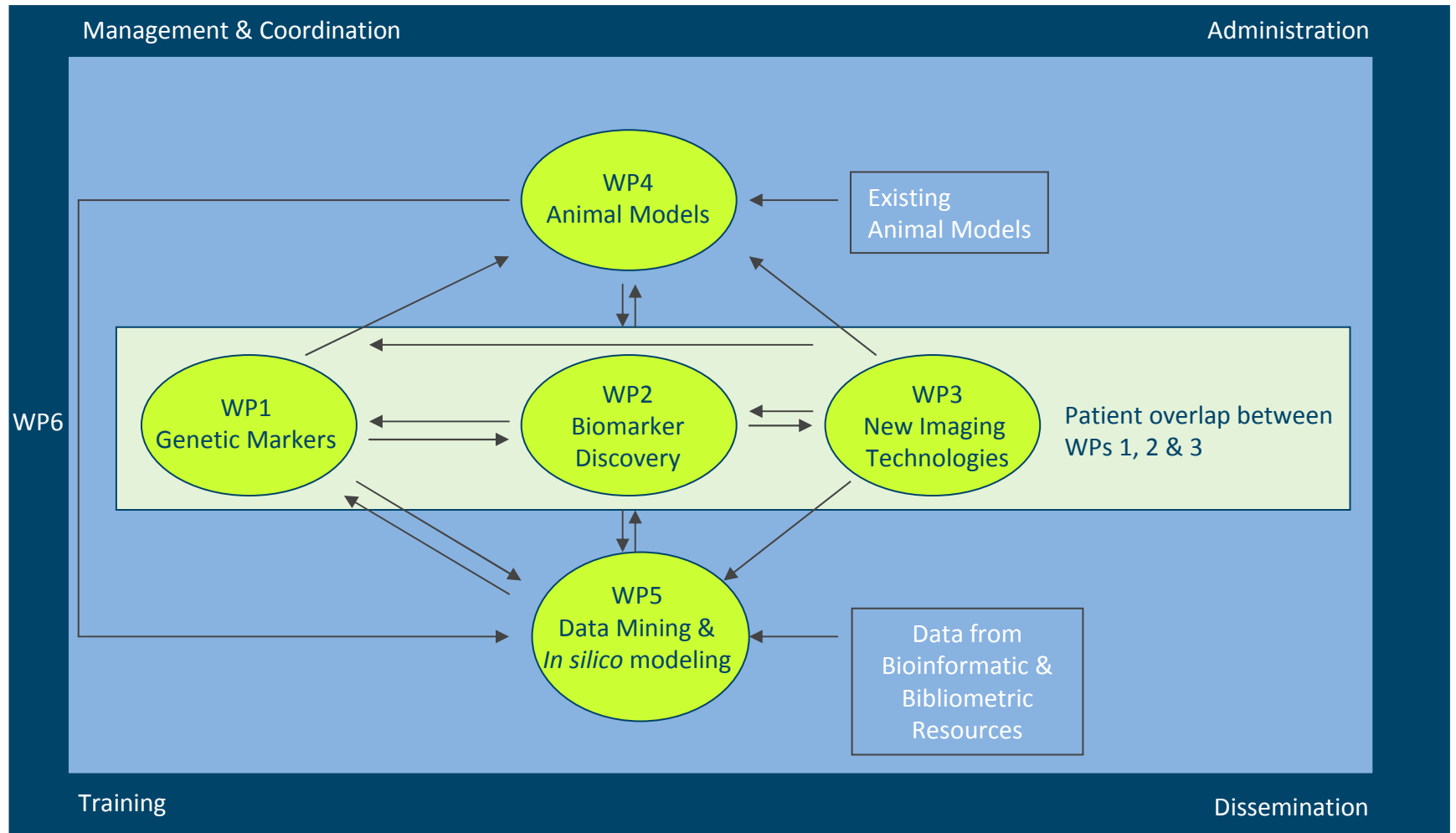
Will focus on DN, DR and CVD complications in T1D and T2D patients.

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

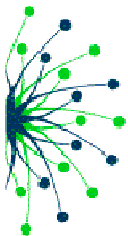


# Expected benefit to patients

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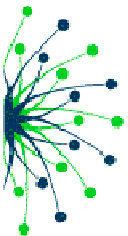
- Early identification of patients at risk of developing diabetic complications allows implementation of aggressive treatment and preventive measures
- Faster development of drugs targeted on prevention and treatment of diabetic complications



# 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

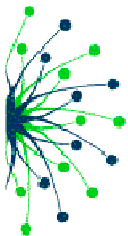


# Added value of the consortium

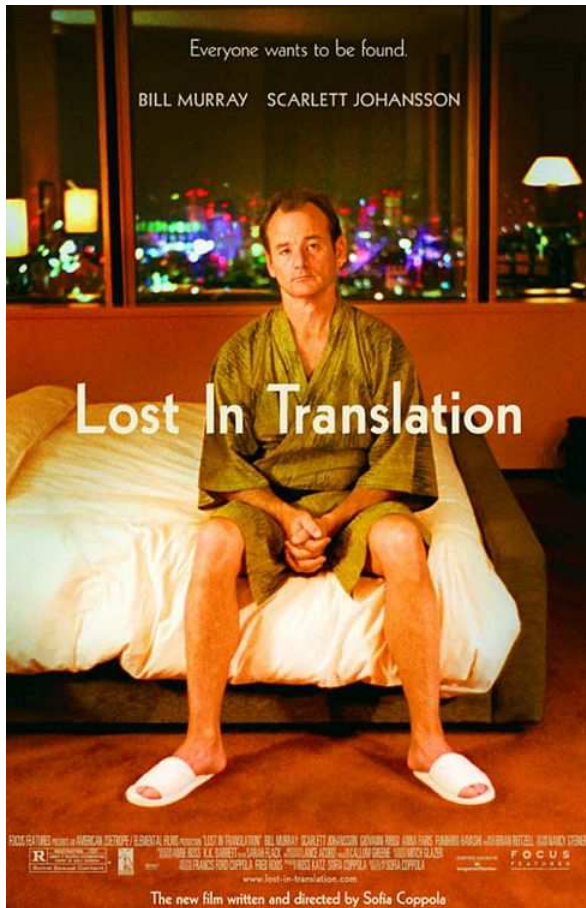
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- Academic Partners:
  - Intensified networking through new collaborations
  - Aligned research efforts and new funding schemes enable projects with high impact on patients needs
- EFPIA partners:
  - Intensified exchange with the scientific community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



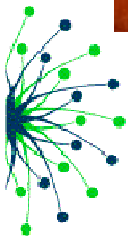
**New biological insights relevant to T2D in general**

**Better measures of individual aetiology**



**Clinical advances for "everyone"**  
 New therapeutic targets  
 New biomarkers  
 New preventative measures

**Personalized medicine**  
 Prognostics  
 Diagnostics  
 Therapeutic optimisation

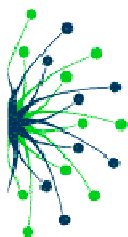


# Results/achievements so far



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

Partner	Project name		
ULUND	Botnia	UNEXE	EXTRA
	Diabetes Registry		DARE
	Malmö Preventive Project		Y2T2D
	Malmö Diet & Cancer		Warren 2
	Nordil		EUGENE2
	KHD		FinnDiane
	MES		FINRISK-92
KI	Procardis	UGOT	FINRISK-97
	Improve	FH	FINRISK-2002
	Greater Stockholm Area	THL	FINRISK-2007
	DIGAMI		Health 2000
HMGU	MONICA/KORA Augsburg		UKU
	KORA DM	UOXF.H7	ENGAGE
MN	BENEDICT	UNIPI	RISC
	DEMAND		DAI
UCAM	Nephropathy Family Study	UCSC	ASCEND
	UK GRID		PERFORM
	Oxford Regional Prospective Study		
	Adolescent statins intervention		
UNIVDU N	EuroDiab		
	Coronary artery calcification study		
	The Wellcome Trust Functional Genomics UK Collection for T2D		



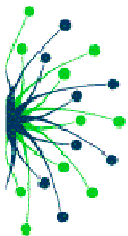


# Results/achievements so far

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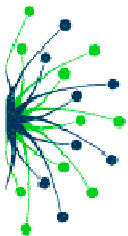
- Access to further cohorts through other consortia
- Relevant numbers of patients with and without DN, DR and CVD
- Samples for DNA, plasma, serum and urine as well as RNA from lymphocytes and tissue (kidney, vascular wall)
- GWAS data for several cohorts existing
- Phenotype definitions
- Patients/samples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



# Results/achievements so far



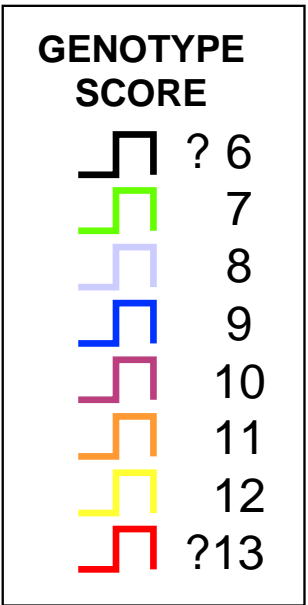
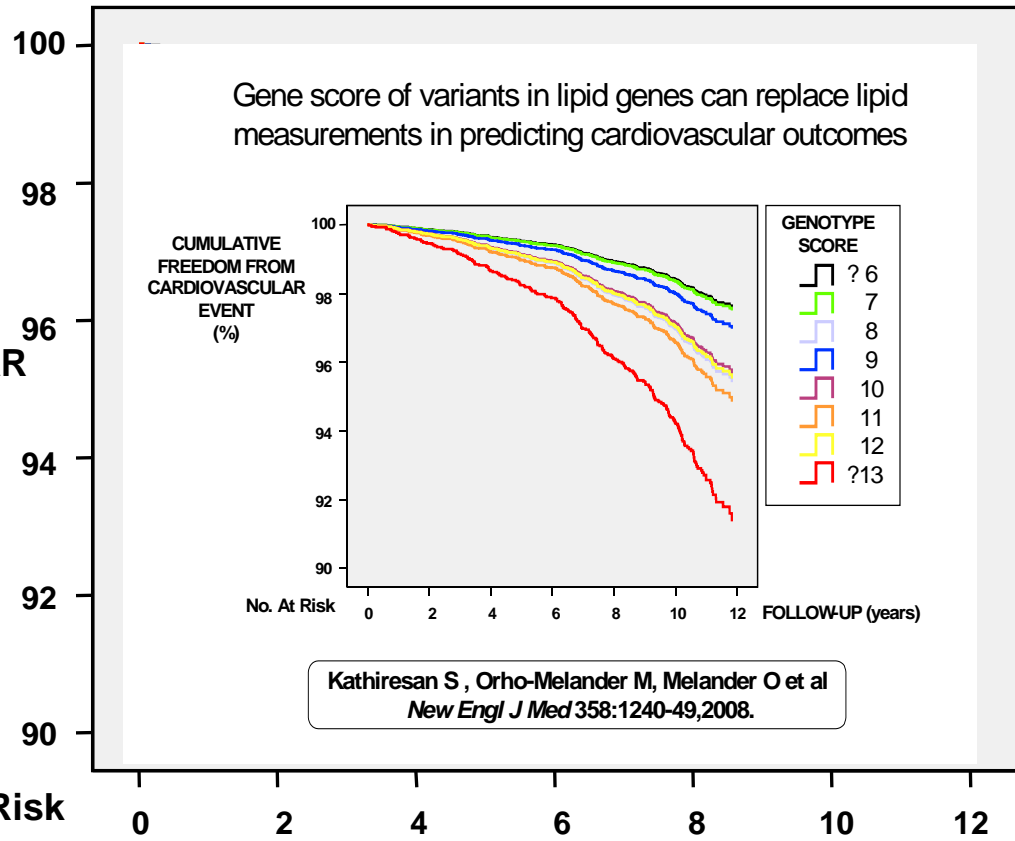
- **WP 1:** First studies to identify genetic markers which can predict diabetic nephropathy
- **WP 2:** First panel of biomarkers to be tested for their ability to predict diabetic complications
- **WP 3:** Development of novel imaging techniques to detect early atherosclerosis (virtual histology) and 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



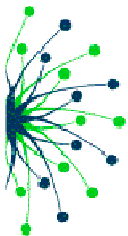
# Gene score of variants in lipid genes can replace lipid measurements in predicting cardiovascular outcomes



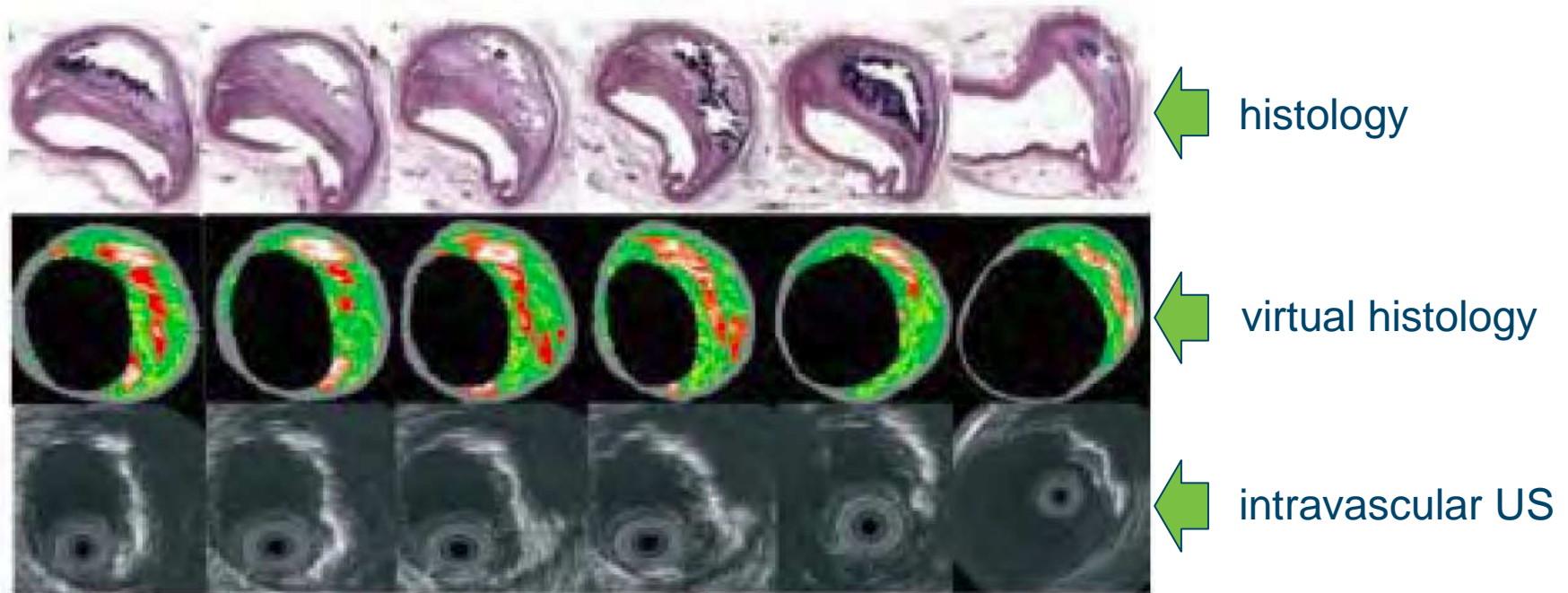
**CUMULATIVE  
 FREEDOM FROM  
 CARDIOVASCULAR  
 EVENT  
 (%)**



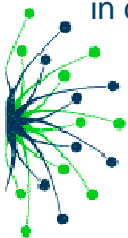
**Kathiresan S , Orho-Melander M, Melander O et al  
*New Engl J Med* 358:1240-49,2008.**



# Virtual histology



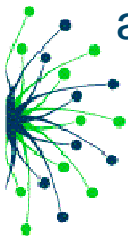
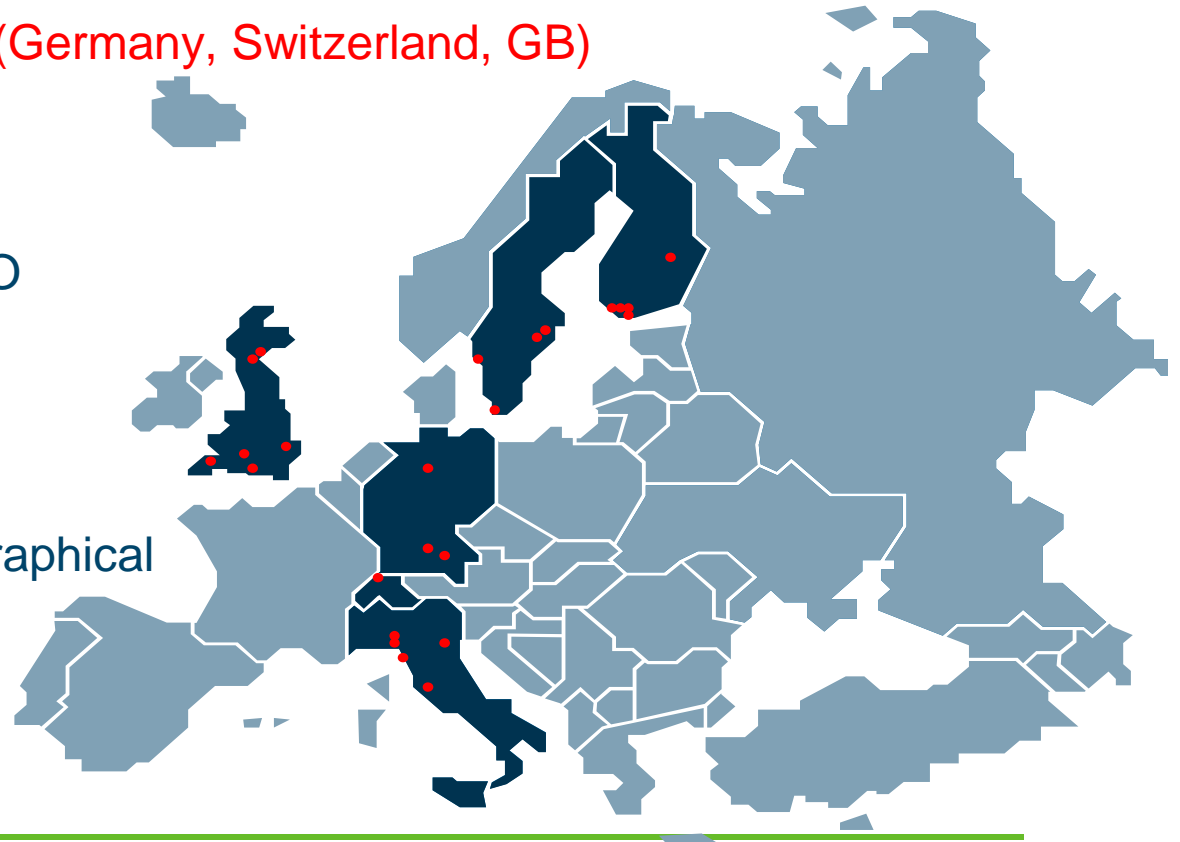
Consecutive series of the same coronary plaque. In the histology images black is calcium, strong magenta is fibrous tissue and light pink is the core. In the Virtual Histology® 4 different categories of tissues are seen: fibrous tissue (green), fibro-fatty (greenish yellow), necrotic core (red) and calcium 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)
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- EFPIA: ~10 million EURO
  - IMI JU: ~14 million EURO
  - Total costs: 28.5 million EURO
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- Start: November 1, 2010
  - Duration: 5 years
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- Excellent scientific and geographical coverage
  - High challenge to coordinate and manage SUMMIT



# Participants



## Academia/public sector:

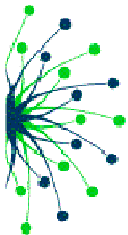
- Lund University
- Karolinska Institute
- Helmholtz Zentrum Munich,
- Istituto di Recerche Farmacologiche  
“Mario Negri”
- The University of Cambridge
- University of Dundee
- The University of Exeter
- Goeteborgs Universitet
- Folkhälsan, Helsinki
- The National Institute for Health and  
Welfare, 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



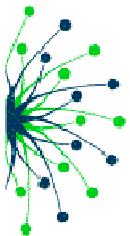
# SUMMIT-Contact

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