# Advancing Precision Diabetes Medicine

October 8–9, 2019

**Marriott Madrid Auditorium**
**Hotel & Conference Center**
Madrid, Spain

American Diabetes Association®
Research Symposium

# American Diabetes Association

## *Advancing Precision Diabetes Medicine*

October 8-9, 2019
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Madrid, Spain

## NOTES

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## NOTES

# AMERICAN DIABETES ASSOCIATION
# PRINCIPAL OFFICERS AND ELECTS
# 2019

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## NOTES

# PROGRAM INFORMATION

## Target Audience and Objectives

As part of the American Diabetes Association's new Precision Medicine in Diabetes Initiative, this scientific meeting is intended to engage diverse stakeholders in incorporating and building the evidence base for precision medicine in diabetes that achieves quantifiable, implementable, probabilistic outcomes based on etiology and risk scores. The symposium will provide excellent opportunities for information sharing, discussion and driving consensus to accelerate guidance on two priority topics: precision diagnosis and precision therapeutics.

Presentations and audience discussion will inform the development of a consensus statement regarding the advancement of precision diabetes medicine to realize a future of longer, healthier lives for people with diabetes, achieved by applying the appropriate treatment for the appropriate person at the appropriate time.

The sessions offered at the research symposium have been designed specifically for scientists, physicians, and other health care professionals with an interest in the field of diabetes and precision medicine.

## NOTES

# PROGRAM SCHEDULE

## TUESDAY, OCTOBER 8

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|---|---|---|
| 6:00 – 9:00 | **BREAKFAST BUFFET**<br>*Breakfast included with room rate* | **Madrid Buffet** |
| 8:00 – 19:00 | **REGISTRATION** | **England Gallery Foyer** |
| **Plenary Session:** | | **Oxford/Bristol Room** |

**MODERATOR**: Stephen S. Rich, PhD, University of Virginia

| | |
|---|---|
| 9:00 – 9:15 | **Welcome, Introduction and Agenda Overview**<br>Paul W. Franks, PhD and Stephen S. Rich, PhD<br>ADA Precision Diabetes Medicine Taskforce Co-Chairs |
| 9:15 – 10:00 | **Perspectives on Precision Medicine from Diabetes Organizations**<br>Louis H. Philipson, MD, PhD, FACP, University of Chicago, American Diabetes Association<br>John J. Nolan, MD, PhD, Trinity College Dublin, European Association for the Study of Diabetes<br>Christine G. Lee, MD, MS, National Institute of Diabetes and Digestive and Kidney Diseases |
| 10:00 – 10:15 | **Perspective on Precision Medicine from a Person with Diabetes**<br>João Nabais, PhD, Universidade De Évora, Portugal |
| 10:15 – 10:25 | **Setting the Stage: Precision Diagnosis and Precision Therapeutics for Diabetes**<br>Paul W. Franks, PhD, Lund University |

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|---|---|---|
| 10:25 – 10:45 | **REFRESHMENT BREAK** | **England Gallery Foyer** |

**Concurrent Roundtables: Session 1**

| | | |
|---|---|---|
| 10:45 – 12:15 | **Precision Diagnosis**<br>*Improving Diagnosis of Known Types of Diabetes*<br>Andrew Hattersley, FRCP, University of Exeter<br>Stephen S. Rich, PhD, University of Virginia | **Marsella Room** |
| | **Precision Therapeutics**<br>*Using Genotypes and Phenotypes to Direct Clinical Management*<br>Ewan Pearson, MB, BChir, MA, PhD, FRCP, University of Dundee<br>Christine G. Lee, MD, MS, National Institute of Diabetes and Digestive and Kidney Diseases | **Burdeos Room** |
| 12:15 – 13:45 | **NETWORKING LUNCH** | **Madrid Buffet** |
| 13:45 – 14.00 | **Innovative Medicines Initiatives Diabetes Projects**<br>*Partnerships for Precision Medicine in Diabetes*<br>Magda Gunn, PhD, Innovative Medicines Initiative | **Oxford/Bristol Room** |
| 14:00 – 14:15 | **Innovative Medicines Initiatives Beat-DKD**<br>*Preventing Progression of Cardiovascular/Renal Disease in Diabetes. Time for Decision Support Systems to Implement Precision Medicine*<br>Dick de Zeeuw, MD, PhD, University Medical Center Groningen | **Oxford/Bristol Room** |

| | | |
|---|---|---|
| 14:15 – 14:30 | **Precision Clustering**<br>*Time for a New Sub-Classification of Type 2 Diabetes?*<br>Leif Groop, MD, PhD, Lund University | **Oxford/Bristol Room** |

**Concurrent Roundtables: Session 2**
*(Participants Alternate from Morning Sessions)*

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|---|---|---|
| 14:30 – 16:00 | **Precision Diagnosis**<br>*Improving Diagnosis of Known Types of Diabetes*<br>Andrew Hattersley, FRCP, University of Exeter<br>Stephen S. Rich, PhD, University of Virginia | **Marsella Room** |
| | **Precision Therapeutics**<br>*Using Genotypes and Phenotypes to Direct Clinical Management*<br>Ewan Pearson, MB, BChir, MA, PhD, FRCP, University of Dundee<br>Christine G. Lee, MD, MS, National Institute of Diabetes and Digestive and Kidney Diseases | **Burdeos Room** |
| 16:00 – 16:30 | **Flash Poster Previews**<br>*Single-Slide, One-Minute Elevator Pitches on Posters* | **Oxford/Bristol Room** |
| 16:30 – 17:30 | **BREAK – Refresh Before Dinner** | |
| 17:30 – 19:00 | **Poster Reception**<br>*Hors D'oeuvres and Drinks with Poster Presentations* | **Oxford/Bristol Room** |
| 19:00 | **DINNER FOR ATTENDEES**<br>*Courtesy of Lund University Diabetes Centre* | **Oxford/Bristol Room** |

## WEDNESDAY, OCTOBER 9

| | | |
|---|---|---|
| 6:00 – 9:00 | **BREAKFAST BUFFET**<br>*Breakfast included with room rate* | **Madrid Buffet** |
| 9:00 – 13:00 | **REGISTRATION** | **England Gallery Foyer** |

**Plenary Session:** **Oxford/Bristol Room**

**MODERATOR**: Paul W. Franks, PhD, Lund University

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|---|---|
| 9:30 – 10:30 | **Stakeholder Discussion: Reclassifying Diabetes and Unmet Needs**<br>Jessica Dunne, PhD, JDRF<br>Mark McCarthy, FRCP, PhD, Genentech and University of Oxford |
| 10:30 – 11:00 | **Summary of Precision Diagnosis Roundtables and Discussion of Future Directions**<br>Andrew Hattersley, FRCP, University of Exeter<br>Stephen S. Rich, PhD, University of Virginia |
| 11:00 – 11:30 | **Summary of Precision Therapeutics Roundtables and Discussion of Future Directions**<br>Ewan Pearson, MB, BChir, MA, PhD, FRCP, University of Dundee<br>Christine G. Lee, MD, MS, National Institutes of Diabetes and Digestive and Kidney Diseases |

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|---|---|---|
| 11:30 – 12:30 | **Stakeholder Discussion: Research Gaps, Advancing Precision Diabetes Medicine**<br>Jose C. Florez, MD, PhD, Massachusetts General Hospital, Harvard Medical School<br>John J. Nolan, MD, PhD, Trinity College Dublin, European Association for the Study of Diabetes | |
| 12:30 – 13:30 | **NETWORKING LUNCH** | **Madrid Buffet** |
| 13:30 – 15:00 | **Precision Medicine Industry Forum** | **Cambridge Room** |
| 13:30 – 16:00 | **Writing Group Meeting** | **Marsella Room** |

## TASK FORCE

**Wendy Chung, MD, PhD**
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Columbia University
New York, New York

**Jose C. Florez, MD, PhD**
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*Institute Member*, Broad Institute
*Professor of Medicine*, Harvard Medical School
Chief, Endocrine Division and Diabetes Unit
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**Paul W. Franks, PhD**
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**Jill Norris, MD, PhD**
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**Stephen S. Rich, PhD**
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University of Virginia
Charlottesville, Virginia

## SPEAKERS

**Dick de Zeeuw, MD**
Professor Clinical Pharmacology
Clinical Pharmacy and Pharmacology
University Medical Center
Groningen, The Netherlands

**Jessica Dunne, PhD**
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JDRF
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**Jose C. Florez, MD, PhD**
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Institute Member, Broad Institute
Professor of Medicine, Harvard Medical School
Chief, Endocrine Division and Diabetes Unit
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**John J. Nolan, MD, PhD**
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**Stephen S. Rich, PhD**
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University of Virginia
Charlottesville, Virginia

## POSTER TITLES AND PRESENTING AUTHORS

**POSTER #1** - *GENETIC ANALYSIS OF DIETARY INTAKE IDENTIFIES NEW LOCI AND FUNCTIONAL LINKS WITH METABOLIC TRAITS*
**Merino, Dr. Jordi, PhD, Massachusetts General Hospital, Boston, MA**

**POSTER #2** - *INDIVIDUALISED SCREENING FOR DIABETIC RETINOPATHY. A RANDOMISED CONTROLLED CLINICAL TRIAL OF PRECISION MEDICINE*
**Irene Stratton, Gloucester Hospitals NHS FT, Cheltenham, Gloucestershire**

**POSTER #3** - *PARTITIONED POLYGENIC SCORES FOR TYPE 2 DIABETES CAPTURE ETIOLOGICAL AND CLINICAL HETEROGENEITY WITHIN THE DISEASE*
**Anubha Mahajan, PhD, WTCH, University of Oxford, Oxford, UK**

**POSTER #4** - *DIGITAL GENOMICS IN PRECISION DIABETES MEDICINE*
**Mirella Zulueta, MD, PhD, Patia, San Sebastián, Gipuzkoa**

**POSTER #5** - *ESTIMATING THE RISK OF GESTATIONAL DIABETES MELLITUS (GDM) BEFORE PREGNANCY AND IN EARLY PREGNANCY: A PREDICTION AND INTERVENTION MODEL BASED ON SUSCEPTIBILITY GENETIC VARIANTS*
**Mirella Zulueta, MD, PhD, Patia, San Sebastián, Gipuzkoa**

**POSTER #6** - *EARLY PREDICTION OF CARDIOVASCULAR DISEASE WITH OXIDATIVE AND ADVANCED GLYCATION END PRODUCT BIOMARKERS IN TYPE 1 DIABETES*
**Paul J. Beisswenger, MD, Precision Diabetes LLC, Geisel School of Medicine at Dartmouth, Lebanon, NH**

**POSTER #7** - *PRECISION DKD: A NOVEL TEST FOR PREDICTING LOSS OF RENAL FUNCTION IN TYPE 2 DIABETES*
**Paul J. Beisswenger, MD, Precision Diabetes LLC, Lebanon, NH**

**POSTER #8** - *METABOLOMIC MEASUREMENTS ARE ASSOCIATED WITH GLYCEMIC CONTROL AND COMPLICATIONS OF TYPE 2 DIABETES. THE BBMRI-NL DIABETES METABOLOMICS STUDY GROUP*
**Leen M. 't Hart, PhD, Leiden University Medical Center, Leiden, Z-H**

**POSTER #9** - *GLYCOMARK 1,5-ANHYDROGLUCITOL AS A BIOMARKER OF SGLT2 INHIBITOR EFFECT*
**Jeffrey Dahlen, PhD, Hikari Dx, San Diego, CA**

**POSTER #10 -** *METABOLOMIC MARKERS OF PROGRESSION TO TYPE2 DIABETES IN THE SPANISH POPULATION: THE VIVA STUDY*
**Rafael Gabriel, MD, Escuela Nacional de Sanidad. Instituto de Salud Carlos III, Madrid, Spain**

**POSTER #11 -** *THE DIABETES ASSOCIATED BIOMARKER AT 10Q25.1 IS ASSOCIATED WITH INSULIN SECRETION AND TURNOVER IN A HUMAN COHORT*
**Mads Kjolby, MD, PhD, Steno Diabetes Center Copenhagen, Aarhus, Denmark**

**POSTER #12 –** *USING ARTIFICIAL INTELLIGENCE IN TYPE 1 DIABETES FOR MANAGEMENT OF NOCTURNAL HYPOGLYCEMIA IN PEOPLE ON CONTINUOUS SUBCUTANEOUS INSULIN INFUSION*
**Morten Hasselstrøm Jensen, PhD, Aalborg Hospital, Aalborg, North Denmark**

**POSTER #13 -** *ELEVATED GLUCAGON AND GLUCAGON-LIKE PEPTIDE-1 FASTING CONCENTRATIONS IN CHILDREN WITH OVERWEIGHT AND OBESITY*
**Sara Stinson, University of Copenhagen, Copenhagen, Capital Region**

**POSTER #14 -** *BEYOND A DECADE OF EXPERIENCE WITH THE US MONOGENIC DIABETES REGISTRY- SUCCESSES, CHALLENGES AND FUTURE OPPORTUNTIES*
**Rochelle Naylor, MD, Loyola University Chicago, Maywood, IL**

**POSTER #15** - *TARGETED ASCERTAINMENT AND RECALL OF GENETIC VARIANT CARRIERS FOR EVALUATION AND TRANSLATION (TARGET-DIABETES) STUDY: PHYSIOLOGIC AND PHARMACOGENETIC TESTING THROUGH RECALL BY GENOTYPE*
**Josep M. Mercader, PhD, Broad Institute, Inc, Cambridge, MA**

**POSTER #16 -** *GENETIC PREDICTORS OF WEIGHT LOSS IN ASIANS LIVING WITH SEVERE OBESITY*
**Pronpoj Pramyothin, MD, Siriraj Hospital, Mahidol University, Bangkok, Bangkok**

**POSTER #17 -** *CHARACTERIZATION OF THE GENETIC DISCORDANCE BETWEEN BODY MASS AND TYPE 2 DIABETES MELLITUS: A PHENOME-WIDE ANALYSIS*
**Daniel Esteban Coral Candelo, MPH, Lund University, Malmö, Skåne**

**POSTER #18 -** *USING GENETICS TO TEST CAUSAL RELATIONSHIPS BETWEEN PREDIABETES AND VASCULAR COMPLICATIONS: IMPLICATIONS FOR PRECISION PREVENTION*
**Pascal Mutie, MPH, Lund University, Malmö, Skåne**

**POSTER #19 -** *A SCIENTOMETRIC ANALYSIS OF POPULATION GENETICS RESEARCH IN TYPE 2 DIABETES*
**Hugo Fitipaldi, MPH, Lund University, Malmö, Skåne**

**POSTER #20 -** *EFFECT OF G6PD VARIATION ON HEMOGLOBIN A1C IN EAST ASIANS*
**Aaron Leong, MD, MSc, Massachusetts General Hospital, Boston, MA**

**PUBLICATION #1**
*ACUTE EFFECTS OF MELATONIN ON GLUCOSE METABOLISM*
**Julie Støy, MD, PhD, Steno Diabetes Center Aarhus, Denmark**

**PUBLICATION #2**
*INCREASING KNOWLEDGE ABOUT HBA1C TESTING TO IMPROVE PATIENT OUTCOMES USING CLINICAL AUDIT AS A RESEARCH TOOL*
**Susan E. Manley, PhD, University Hospitals Birmingham NHS Foundation Trust and Univesrity of Birmingham, UK**

**PUBLICATION #3**
*THE SYNDROME OF DIABETES-A UNIFIED PATHOPHYSIOLOGIC APPROACH*
**Stanley Schwartz, MD, Univesrity of Pennsylvania, Philadelphia, PA**

**POSTER #1**

## *GENETIC ANALYSIS OF DIETARY INTAKE IDENTIFIES NEW LOCI AND FUNCTIONAL LINKS WITH METABOLIC TRAITS*

**Jordi Merino[1234],** Hassan S. Dashti[1,2], Chloé Sarnowski[5], Jacqueline M. Lane[1,2,6], Jose C. Florez[1,2,3,4], Richa Saxena[1,2,6]

1Center for Genomic Medicine, Massachusetts General Hospital, Boston, MA, USA
2Program in Medical and Population Genetics, Broad Institute, Cambridge, MA, USA
3Diabetes Unit, Massachusetts General Hospital, Boston, MA, USA
4Department of Medicine, Harvard Medical School, Boston, MA, USA
5Department of Biostatistics, Boston University School of Public Health, Boston, MA, USA
6Department of Anesthesia, Critical Care and Pain Medicine, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA

Background: Dietary intake, a major contributor to the global obesity and type 2 diabetes epidemics, is a complex phenotype partially affected by innate physiological processes. Genome-wide association studies (GWAS) for individual macronutrients have facilitated the discovery of a handful of genomic loci influencing dietary intake, however a single-nutrient approach may preclude the discovery of additional relevant loci.

Materials and methods: We conducted a multi-trait GWAS of overall variation in dietary intake to factor the significant correlation among macronutrients in 283,119 European-descent participants from the UK Biobank (n=192,005) and the CHARGE Consortium (n=91,114). In the UK Biobank, dietary data were collected using a web-based 24-hr diet recall. In the CHARGE Consortium, dietary intake was evaluated using validated cohort-specific food frequency questionnaires. Multi-trait genome-wide association analysis was conducted using the cross-phenotype association software (CPASSOC). Tissue, single-cell expression, and pathway enrichment analyses were conducted to provide insights into underlying mechanisms influencing dietary intake. Genome-wide genetic correlation across 234 traits with publically available GWAS data, and clustering of identified signals using a Bayesian non-negative matrix factorization algorithm (“soft clustering”) were used to provide potential clinical translational findings.

Results: In the multi-trait genome-wide association meta-analysis, we identified 156 lead variants in 96 distinct genomic loci reached genome-wide significance. Dietary intake signals mapped to different brain tissues and were enriched for genes expressed in specific cell-types including b1-tanycytes and serotonergic and GABAergic neurons. Further, we found enrichment of biological pathways related to neurogenesis. Genome-wide genetic correlations indicated shared biological links between dietary intake and type 2 diabetes. Clustering of identified variants catalogued three main genetic clusters with distinct associations with obesity and type 2 diabetes.

Conclusion: Overall, the present findings expand our understanding of the genetic architecture of dietary intake and may provide new avenues for the primary prevention of prevalent common complex metabolic diseases.

**POSTER #2**

*INDIVIDUALISED SCREENING FOR DIABETIC RETINOPATHY. A RANDOMISED CONTROLLED CLINICAL TRIAL OF PRECISION MEDICINE*

**Irene M Stratton[1],** Deborah M Broadbent[2], Amu Wang[3], Christopher P Cheyne[2], Marilyn James[4], James G Lathe[4], John Roberts[5], Tracy Moitt[6], Jiten P Voral[3], Mark Gabbay[2], Marta García-Fiñana[2], Simon P Harding[2]

[1]Gloucester Hospitals NHS FT
[2]University of Liverpool
[3]Royal Liverpool University Hospital
[4]University of Nottingham
[5]Mersey Diabetes Support Group, Liverpool
[6]Clinical Trials Research Centre, Liverpool

Background: Varying diabetic retinopathy (DR) screening intervals, informed by personal risk-levels, offers improved engagement of people with diabetes (PWD),and reallocation of resources to high risk groups, whilst addressing the increasing prevalence of diabetes. With design input from PWD we compared safety, efficacy and cost effectiveness of individualised risk-based variable-interval population screening to usual care.

Methods: Two- parallel arm, equivalence randomised controlled trial (minimum 2 year follow-up) in PWD aged ≥12 years in one English screening programme. Randomisation 1:1 to annual screening (control) or individualised screening (6, 12 or 24 months for high, medium and low risk) determined by a risk model using demographic, screening and clinical data. Primary outcome was attendance (safety). A secondary outcome was development of sight threatening DR (STDR). Cost effectiveness was evaluated in a 2 year time horizon from NHS and societal perspectives. Trial Registration ISRCTN 87561257

Findings: 4534 participants were randomised, 2097/2265 (individualised arm) and 2224/2269 (control arm) remained after withdrawals. Attendance rates at first follow-up were equivalent (individualised 83·6%; control 84·7%) (difference -1·0, 95% CI -3·2 to 1·2). STDR detection rates were non-inferior: individualised 1·4%, control 1·7% (-0·3, -1·1 to 0·5). Sensitivity analyses confirmed findings. Incremental QALYs were positive but not statistically significant: EQ-5D-5L 0·036 (-0·013 to 0·085), HUI3 0·008 (-0·047 to 0·066). Incremental cost savings per person were: £17·77 (16·55 to 18·88), NHS perspective; £23·68 societal perspective (CI 22·09 to 25·13). 43% fewer screening appointments were required in the individualised arm.

Interpretation: Stakeholders can be reassured by this large RCT in DR screening, using precision medicine, that individualised risk-based intervals can be safely and cost effectively introduced in established screening programmes.

Funding: This study was funded by the UK National Institute for Health Research (NIHR) (Programme Grants for Applied Research, RP-PG-1210-12016). The views expressed are those of the authors, not those of the NIHR, NHS or the Department of Health and Social Care.

**POSTER #3**

*PARTITIONED POLYGENIC SCORES FOR TYPE 2 DIABETES CAPTURE ETIOLOGICAL AND CLINICAL HETEROGENEITY WITHIN THE DISEASE*

**Anubha Mahajan[1,2],** Neil R Robertson[1,2], Mark I McCarthy[1,2,3]

1 Wellcome Centre for Human Genetics, Nuffield Department of Medicine, University of Oxford, Oxford, UK
2 Oxford Centre for Diabetes, Endocrinology and Metabolism, Radcliffe Department of Medicine, University of Oxford, Oxford, UK
3 Oxford NIHR Biomedical Research Centre, Oxford University Hospitals Trust, Oxford, UK

Genetic studies have identified >400 robust signals of T2D association to date. Whilst "global" polygenic scores using all T2D-risk variants are suitable for risk prediction, "partitioned" scores (pPS) that capture the etiological diversity of T2D may have more traction for clinical decision-making related to T2D heterogeneity.

Here, we extend previous pPS analyses to an expanded set of 337 T2D signals, using genetic clusters (GCs) defined on basis of multi-trait association patterns across 10 core traits. Fuzzy clustering defined six GCs, capturing variants with primary effects on adiposity (GC1-BMI), lipids (GC2-Lipids), insulin action (GC3-IA) and beta-cell function (GC4-BCF, GC5-BCF), plus a GC with mixed features (GC6-MIX).

First, we examined the impact of individual T2D-pPS loadings on complication risk utilizing available GWAS for CAD, atrial fibrillation (AF), hypertension (HT), CKD, renal function (eGFR, albuminuria), stroke and liver fat%, and observed multiple GC-specific associations ($p<0.0007$). AF was associated with T2D-risk mediated by GC1-BMI only (OR=1.3 per 1SD pPS increase), whereas CKD (OR 1.4) and eGFR (OR 0.95) were associated with GC2-Lipids only. HT and CAD risk were most strongly associated with GC1-BMI and GC3-IA (OR>1.3), whereas, GC2-Lipid was associated with lower CAD risk (OR 0.60) but increased liver fat (OR 2.5), counter to the broader epidemiological association between them.

Next, we sought to identify candidate biomarkers for each of these processes using metabolomics and proteomic GWAS. We detected 83 metabolite and 56 protein associations (q-value<0.05). Many of these were associated with the GC2-Lipid pPS (including AKT2, APOB, APOE). Other candidates included circulating levels of IGFBP2 and APOF as markers of insulin resistance (GC3-IA). GC4-BCF and GC5-BCF pPS showed divergent associations with proinsulin (high vs low levels, respectively) pointing to distinct mechanisms of beta-cell dysfunction. GC5-BCF was also exclusively associated with ATF6, a known marker of ER stress response.

Our findings demonstrate that pPS capture individual differences in the etiological contributions to T2D development that can be related to clinically relevant outcomes, and which provide a mechanistic framework for understanding disease heterogeneity.

**POSTER #4**

## *PARTITIONED POLYGENIC SCORES FOR TYPE 2 DIABETES CAPTURE ETIOLOGICAL AND CLINICAL HETEROGENEITY WITHIN THE DISEASE*

**Mirella Zulueta[1],** Jaime Berumen[1,2], Jaime Razkin[1], Melissa Marín[4], Lorena Orozco[4], Miguel Betancourt-Cravioto[5], Roberto Tapia-Conyer[5], Laureano Simón[1]

1 Patia, San Sebastián, Gipuzkoa
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3 Huella Génica, México City
4 Instituto Nacional de Medicina Genómica, Mexico City
5 Fundación Carlos Slim, México City

Genetic variants, parental history and obesity play key roles in Type 2 Diabetes (T2D) onset and progression. However, the contribution of each factor and their interactions in T2D variability is unclear. We have developed a system to assist in the individualized prediction, prevention and management of diabetes. The system is based on the integration of genotype, phenotype, wearable and health app data to detect risk and offer genotype-informed personal recommendations for prevention and for management of T2D.

Genotyping data utilizes information from single-nucleotide polymorphisms (SNPs) prioritized based on their predictive value and their location within genetic loci involved in a variety of cellular processes in T2D (SLC16A11, HNF1A, TCF7L2, CDKN2A/B, CDKAL1, SLC30A8, IGF2BP2, FTO, PPARG, HHEX/IDE, ADCY5, JAZF1, WFS1, INS-IGF2, KCNQ1, KCNJ11).

In the study presented here we used our system to investigate the contribution of SNPs, parental history (PH) and obesity (body mass index [BMI], waist/hip ratio) on T2D variability, comparing 1234 non-diabetic controls and 1219 diabetic patients. To replicate the data, a case-control (n = 2904) and a cross-sectional (n = 1901) study were also included. In a multivariate logistic regression model, all factors accounted for only 27.3% of T2D variability: SNPs (8.4%); PH (11.8%) and obesity (7.1%). These factors contributed more in men (33.2%) than in women (25%), specifically when the disease was diagnosed before the age of 46 (46.7% vs. 30%). Genes played a substantially more important role in men than in women (14.9% vs. 5.5%), while obesity and PH played a similar role in both genders. Genes and PH appeared to play a greater role than obesity in T2D.

Our study initiates a data-driven discussion of how a comprehensive platform of improved predictive power, prevention and management tools could contribute to precision diabetes medicine.

**POSTER #5**

*ESTIMATING THE RISK OF GESTATIONAL DIABETES MELLITUS (GDM) BEFORE PREGNANCY AND IN EARLY PREGNANCY: A PREDICTION AND INTERVENTION MODEL BASED ON SUSCEPTIBILITY GENETIC VARIANTS*

**Mirella Zulueta[1],** Leire Mendizabal[1], Teresa Tusié[2], Jaime Berumen[3], Jaime Razkin[1], Rosa Corcoy[4,5], Laureano Simón[1]

1 Patia, San Sebastián, Gipuzkoa
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5 CIBER-BBN en nombre del Consorcio DALI

Early and precise risk prediction for gestational diabetes mellitus (GDM) would facilitate early prevention strategies. Estimation of GDM risk is currently primarily based on women characteristics and medical history. More objective markers to identify women at high risk for the development of GDM are needed and would be useful for more precise and early risk estimation.

In this study we aimed to develop a clinical prediction tool that can help the clinician identify women at risk for GDM before pregnancy and early in pregnancy in order to facilitate prevention interventions. We evaluated single nucleotide polymorphisms (SNPs) predictors to develop a pre-pregnancy and first-trimester risk prediction model.

We genotyped 35 SNPs in 912 pregnant women, 399 with GDM and 513 non-GDM controls. DNA was obtained from samples in the Vitamin D and Lifestyle Intervention (DALI) Europe-wide controlled trial for GDM prevention. In the trial, glucose tolerance was measured at three time points using IADPSG criteria. The 35 SNPs were selected for analysis based on their previously shown association to: a) type 2 diabetes, or b) GDM, or c) body mass index (BMI), or d) folate and vitamin B12 metabolism. Genotyping was performed using Agena Bioscience iPLEX chemistry. A multivariable logistic regression model was developed in which SNPs genotypes were combined to predict the occurrence of GDM.

The SNPs with the highest association to GDM in our analysis reside in genetic loci associated to fasting glucose and folate metabolism. We investigated the effect of those genetic variants upon gestational age where GDM is diagnosed and developed a risk prediction model over gestational age. The performance of the model was evaluated with receiver operating characteristic (ROC) curves of the calculated cumulative hazards. The area under the curve (AUC) obtained was 0.87.

A new tool for GDM risk prediction is presented, which suggests that the utilization of genetic markers in combination with clinical characteristics may improve accuracy of GDM risk evaluation and, very importantly, reinforce the adoption of prevention interventions as early as possible and within a critical time window for prevention of GDM.

**POSTER #6**

*EARLY PREDICTION OF CARDIOVASCULAR DISEASE WITH OXIDATIVE AND ADVANCED GLYCATION END PRODUCT BIOMARKERS IN TYPE 1 DIABETES*

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Background: People with type 1 diabetes have high rates of cardiovascular disease (CVD) relative to age-matched non-diabetics, and glycemic control and traditional CVD risk factors only partly explain the increased risk. We investigated the predictive value of Oxidation (OPs) and advanced glycation end products (AGEs) as biomarkers of early detection for risk of CVD events in the Diabetes Control and Complications Trial and the follow-up Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study.

Methods: Using a case-control design, we measured plasma OPs, including methionine sulfoxide [MetSO] and the AGE carboxyethyllysine [CEL], by LC/mass spectrometry in 459 participants (93 CVD cases and 366 controls) at baseline, year 1, DCCT closeout, and EDIC year 1-2. The CVD outcome was time to 3-point MACE, confirmed angina, congestive heart failure or coronary artery revascularization. Cox models investigated the association between biomarkers as fixed (baseline and early EDIC) or time-dependent (all 4 time points) covariates and CV outcome. To assess prediction, the C-statistic was computed for biomarkers significantly associated with the outcomes in fully adjusted models.

Results: MetSO at beginning of EDIC and in the time dependent analysis was strongly inversely associated with CVD outcomes ($p < 0.001$ and HR 0.58 and 0.60 respectively) when fully adjusted for all covariates (Age, HbA1c, BMI, HDL, LDL, Sex, SBP, and DBP). The predictive power of MetSO was shown by a highly significant increase in the c-statistic from 0.712 to 0.787($p<0.001$) when added to the other covariates. Baseline CEL was also associated with CVD ($p=0.03$, HR 1.15). HbA1c was associated with CVD, but 70% of this effect was explained by MetSO levels.

Conclusion: High levels of MetSO, a product of the free oxygen radical scavenger methionine, are associated with lower incidence of composite primary CVD events, and confirm our prior type 2 studies (ACCORD and VADT). MetSO also significantly improves predictive value over traditional risk factors including HbA1c. Levels of CEL may also have value in predicting later CV events. Early identification of CVD risk in this group may allow the institution of effective therapies when prevention is still possible.

**POSTER #7**

*PRECISION DKD: A NOVEL TEST FOR PREDICTING LOSS OF RENAL FUNCTION IN TYPE 2 DIABETES*

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Diabetic kidney disease (DKD) is a common complication of type 1 and type 2 diabetes, and early assessment of DKD is difficult because current biomarkers do not identify individuals at risk with sufficient accuracy before irreversible structural changes occur. In this study, we examined the associations and predictive capabilities of advanced glycation (AGEs) and oxidative end products (OP) with renal function loss (RFL) in American Indians with type 2 diabetes. Data were from a 6-year clinical trial that assessed renoprotective efficacy of losartan. Participants remained under observation after the trial concluded. Glomerular filtration rate (GFR) was measured annually. Five AGEs were measured in serum collected at enrollment and at kidney biopsy. RFL was defined as >40% decline of measured GFR from baseline. Of 168 participants (mean baseline age 41 years, HbA1c 9.2%, GFR 164 mL/min, and albumin-to-creatinine ratio 31 mg/g), 105 reached the RFL end point during median follow-up of 8.0 years.

Multivariate logistic regression was used to evaluate the association of the AGEs with RFL with the OP methionine sulfoxide (MetSO) (odds ratio [OR] .26 [95% CI 0.11–0.65]) and the AGE methylglyoxal hydroimidazolone (MGH1) (OR 2.39 [95% CI 1.18–4.892]) having the most significant associations. Candidate panels of methionine sulfoxide and methylglyoxal hydroimidazolone with standard clinical tests and features were selected via least angle regression.

The best performing panel consisted of MetSO, MGH1, A1C, GFR, and gender (Precision DKD). For predicting RFL, ROC curve analysis of Precision DKD gave an AUC of 0.737 ($P < 0.0001$ [95% CI 0.663–0.802]). Precision DKD outperformed standard clinical variables associated with loss of renal function (age, diabetes duration, gender, mean arterial pressure, and GFR), which in combination had an AUC of 0.696 ($P < 0.0001$ [95% CI 0.620–0.764]).

Precision DKD may provide a non-invasive means to more precisely determine the risk of progressive DKD than traditional risk factors alone.

**WITHDRAWN BY AUTHOR**

**POSTER #8**

*METABOLOMIC MEASUREMENTS ARE ASSOCIATED WITH GLYCEMIC CONTROL AND COMPLICATIONS OF TYPE 2 DIABETES. THE BBMRI-NL DIABETES METABOLOMICS STUDY GROUP*

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Background: People with type 2 diabetes (T2D) show different rates of disease progression. However, who will progress rapidly is unknown. In this study group, we investigated whether blood metabolite levels are associated with glycemic control and diabetic complications (nephropathy and CVD).

Methods: We used data from up to 3089 persons with T2D from five cohorts from the Netherlands; the Hoorn DCS, Maastricht, CODAM, NEO, and Rotterdam studies. In DCS and CODAM repeated metabolomic measurements are available. We measured 158 metabolomic measurements using NMR (NightingaleHealth). We used regression models, adjusted for age, sex and lipid lowering medication use as base models. Extended models included, depending on the outcome, covariates such as BMI, fasting glucose, diabetes duration, glucose lowering, anti-hypertension, and anti-coagulant medication, blood pressure, and smoking.

Results: We show that various metabolic measures are associated with glycemic control and or diabetic complications. Overall there was little evidence for heterogeneity between cohorts. The most significantly associated metabolomic measures differ between outcomes with amino acids as the top metabolites for glycemic control and diabetic nephropathy. Lipoprotein subclasses, on the other hand, where more strongly associated with cardiovascular disease. Five metabolomic measures were associated with glycemic progression, defined as insulin initiation. In addition we show that these associations remain stable in time

Conclusions: 1) We show that metabolomic measures are associated with glycemic control and T2D progression defined as time-to-insulin initiation during follow-up. 2) We extend previous observations by showing that the associations remain largely stable in time. 3) In addition, various metabolomic measures are associated with diabetic complications. 4). Among the significantly associated measures are various metabolomic measures including the branched chain amino acids, glutamine, ApoA1 and various lipoprotein subclasses. 5) These results show that (repeated) metabolomic measurements might be promising markers for progression of type 2 diabetes independent of known risk factors.

**POSTER #9**

*GLYCOMARK 1,5-ANHYDROGLUCITOL AS A BIOMARKER OF SGLT2 INHIBITOR EFFECT*

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The GlycoMark test measures 1,5-anhydroglucitol (1,5-AG), which is an indicator of hyperglycemic excursions over the prior 1-2 weeks in patients with diabetes. Circulating serum levels of 1,5-AG decrease in response to significant hyperglycemia because glycosuria interferes with 1,5-AG reabsorption in the kidney tubules. Significant hyperglycemia and resultant glycosuria causes 1,5-AG levels to fall below the normal range (~10 ug/mL), and persistent glycosuria is associated with very low 1,5-AG levels, typically less than or equal to 2 ug/mL. SGLT2 inhibitors elicit their effect by blocking glucose reabsorption, causing persistent glycosuria. We hypothesized that the use of SGLT2 inhibitors (SGLT2i) would produce a high frequency of 1,5-AG results less than 2 µg/mL. 1,5-AG measurements performed between 2015-2018 from 902 patients were evaluated. Patients were stratified as either being prescribed SGLT2i or not. A total of 292 patients were prescribed SGLT2i and within this group, 52 patients were not taking an SGLT2i at the time of the 1,5-AG measurement. From the 240 patients taking SGLT2i, the average 1,5-AG level was 1.2 µg/mL and 92% of patients had 1,5-AG values 2 ug/mL or lower. From the 52 patients not taking SGLT2i, the average 1,5-AG level was 6.4 µg/mL and only 12% of patients had 1,5-AG values less than or equal to 2 µg/mL. The 1,5-AG results from the patients not compliant with SGLT2i were consistent with 1,5-AG results from patients that were not prescribed SGLT2i. The results of this analysis indicate that the majority of patients with diabetes that are taking SGLT2i have very low 1,5-AG results, which reflects the persistent glycosuria caused by the SGLT2i. In patients taking SGLT2i, a GlycoMark 1,5-AG result < 2 µg/mL may be useful as an indicator of the SGLT2i effect, particularly in patients with moderate to good glycemic control (HbA1C ≤ 8%). Also, GlycoMark test measurements from patients non-compliant with SGLT2i are similar to patients not prescribed SGLT2i. The results of this study suggests that the GlycoMark test may be useful as a simple biomarker test to confirm the presence and effect of SGLT2i, and in patients prescribed SGLT2i, 1,5-AG results above 2 µg/mL should be investigated for non-compliance, interference with, or reduced effectiveness of SGLT2i.

**POSTER #10**

*METABOLOMIC MARKERS OF PROGRESSION TO TYPE2 DIABETES IN THE SPANISH POPULATION: THE VIVA STUDY*

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Objectives: To characterize metabolites and metabolomic profiles associated with the progression to type 2 diabetes (T2D) in non-diabetic people identified 20-year earlier. To determine metabolomic and phenotypic profile of converters to T2D compared to non-converters.

Methods: Nested case-control study within a 20-year follow-up population-based cohort study in people 35-64 years old free of diabetes at baseline. For this analysis we selected all individuals (n=130) who developed T2D during the follow-up (OGTT criteria), and a random sample of 260 individuals who did not develop T2D during the 20-year follow-up (2 controls matched by age and sex by case). The samples were analyzed combining 3 metabolomic approaches (GC-MS; C18 reverse phase and HILIC columns). Metabolomic assays included C3, C5 acylcarnitines, glutamine / glutamate and amino acid BCAA group using both untargeted and targeted metabolomic approach in order to identify metabolites associated with T2D. All the analyses were carried out at the Metabolomic Platform of the Broad Institute (Cambridge, Mass, USA).

Results: In a first step 4,497 molecules were identified, while in the second 10,104 molecules were identified. The concentrations of metabolites were normalized to internal standard and data filtered with IQR. Univariate analysis was perform attending to fold change and t-test corrected by FDR. In total 23 features meet the criteria of more than 5-fold change and p less than 0.05 (FDR) corrected. In order to obtain meaningful data, final metabolomic analysis was focused on the 356 molecules identified by fragmentation spectrum. Thirteen out of them reached statistical significance as potential biomarkers with AUC higher than 0.55 in ROC analyses, however they exhibited little fold change between diabetes cases and controls. Converters to diabetes shown greater enrichment of lipid metabolites of the diacylglycerol and phosphatidylcholine type, and of the BCAA amino acids metabolites than non-converters. Conclusions: The dysregulation observed in these metabolic pathways is a reflection of the physiopathological alterations observed before the conversion to DT2. These results are consistent to the reported in other populations, with BCAA amino acid metabolites as independent predictors of progression to diabetes.

**POSTER #11**

*THE DIABETES ASSOCIATED BIOMARKER AT 10Q25.1 IS ASSOCIATED WITH INSULIN SECRETION AND TURNOVER IN A HUMAN COHORT*

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Background: Stratifying patients based on diabetes susceptible gene markers may soon secure more precise treatment options for patients with diabetes. In this study, plasma levels of SORCS1 protein, a product of the diabetes associated 10q25.1 SorCS1 gene variant, was investigated in a human cohort of type II diabetes patients and healthy controls. Samples obtained after an overnight fasting were available for 492 individuals. A subset of 360 participants underwent OGTT. SORCS1 was measured in 481 individuals of which 120 individuals were diabetic.

Results: BMI and leptin were positively correlated with SORCS1 (p=0.00047 and 0.0028, resp.). Further analyses were therefore adjusted for this weight correlation. Fasting insulin and C-peptide was significantly associated with SORCS1. However, insulin clearance and not insulin secretion rate was significantly associated with SORCS1.

A cut off of 10 ng/ml was used to divide individuals into two subgroups. In the group with the lowest levels of SORCS1 (< 10ng/ml) (n=218) there was a negative correlation with HOMA-IR (non-significant p=0.08), and a positive effect of SORCS1 on Matsuda and BIG-SI (measures of inulin sensitivity) (p=0.05 and p=0.03) respectively. Thus, when SORCS1 is increased insulin resistance is reduced. However, in individuals with the highest levels of SORCS1 (n=250), HOMA-IR was positively associated with SORCS1 (p= 0.002) and negatively associated with Matsuda and BIG-SI (p=0.002 and p=0.004).

Discussion: Higher levels of SORCS1 is found in patients with increased BMI. SORCS1 may prove a compensatory factor released to counteract insulin resistance accompanying increased BMI. However, this positive effect of SORCS1 does not seem to exist in the higher range of the SORCS1, where it also seems to reduce liver insulin clearance. We plan to investigate whether SORCS1 levels influence treatment strategy in diabetic patients, based on EMR data on the same cohort.

**POSTER #12**

*USING ARTIFICIAL INTELLIGENCE IN TYPE 1 DIABETES FOR MANAGEMENT OF NOCTURNAL HYPOGLYCEMIA IN PEOPLE ON CONTINUOUS SUBCUTANEOUS INSULIN INFUSION*

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Objective: Advances, such as, continuous subcutaneous insulin infusion, new insulin analogues, improved glucose monitoring devices may reduce the risk of nocturnal hypoglycemia. However, episodes during night remain a risk for people using insulin, and the related fear might reduce treatment adherence. In this study, we investigated the possibility of predicting nocturnal hypoglycemia at bedtime the evening before.

Method: 4,721 nights were included from people with type 1 diabetes (n=463) enrolled in the Onset 5® trial by Novo Nordisk using continuous subcutaneous insulin infusion of faster aspart or insulin aspart. Participants were on average 43 years old, had a diabetes duration of 24 years and experienced nocturnal hypoglycemia in 429 (9%) of the nights. Characteristics from continuous glucose monitoring (CGM), insulin dosage and meal intake were extracted and used together with demographic information in a Naïve Bayes model to make a bedtime prediction of subsequent nocturnal hypoglycemia. 80% of the subjects were used to train the model and the remaining 20% for evaluating the model. Selection of the best characteristics was performed with forward selection including 5-fold cross-validations.

Result: It was possible to make a bedtime prediction of nocturnal hypoglycemia with a sensitivity of 70% and a specificity of 80%. Area under the receiver operating characteristics curve was 0.781. Predictive information was primarily from the CGM measurements, but body mass index at baseline was also included in the model. No characteristics from insulin dosage or meal intake were selected by the algorithm.

Conclusion: The results of this study indicate that it is possible to predict nocturnal hypoglycemia, which allows for precision medicine and for empowering of the person. It would be a significant improvement for the person with diabetes to receive this information at bedtime, because it would enable him/her to react and, for example, adjust basal insulin rate to avoid the hypoglycemic episode. Intelligent safety applications like this are important to consider in diabetes, because they have the potential to improve adherence to administered treatment regimens and to improve quality of life for the individuals.

**POSTER #13**

*ELEVATED GLUCAGON AND GLUCAGON-LIKE PEPTIDE-1 FASTING CONCENTRATIONS IN CHILDREN WITH OVERWEIGHT AND OBESITY*

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Adults with obesity and type 2 diabetes have elevated fasting glucagon concentrations but it is unknown whether this also applies to children with obesity. Glucagon secretion is regulated by glucose and insulin, as well as gut incretin hormones including glucagon-like peptide-1 (GLP-1). The aim of the present study was to examine the relationship between on one hand circulating fasting concentrations of glucagon and total GLP-1 and on the other body mass index (BMI) and measures of dysglycemia, insulin resistance, dyslipidemia, inflammation, hypertension, and liver function. A total of 1,021 children and adolescents with overweight and obesity (554 females) aged 6-19 years (median 11.8) and 1,294 population-based Danish schoolchildren (763 females) aged 6-19 years (median 11.9) were included. Fasting plasma glucagon and total GLP-1 concentrations were examined by sandwich enzyme-linked immunosorbent assays (ELISA) (Mercodia, Uppsala, Sweden). Plasma glucagon and total GLP-1 concentrations were significantly higher in children and adolescents with overweight and obesity (glucagon median = 7.17 pM and GLP-1 median = 3.46 pM) compared to the population-based cohort (glucagon median = 5.30 pM, $P < 0.001$ and GLP-1 median = 2.97, $P < 0.001$). Glucagon concentrations associated with body mass index SD score (BMI SDS), insulin, the homeostasis model assessment for insulin resistance (HOMA-IR), low-density lipoprotein (LDL) cholesterol, triglycerides, high-sensitivity C-reactive protein (hs-CRP), systolic blood pressure SDS (SBP SDS), diastolic blood pressure SDS (DBP SDS), alanine aminotransferase (ALAT) and inversely correlated with HDL (high-density lipoprotein) cholesterol, but concentrations were not associated with glucose or hemoglobin A1c (HbA1c) concentrations. Similar trends were observed for total GLP-1, except for SBP SDS, DBP SDS and HDL cholesterol. Overall, elevated plasma glucagon and total GLP-1 concentrations were observed in children and adolescents with overweight and obesity. In addition, glucagon and total GLP-1 concentrations associated with markers for potential comorbidities and cardiometabolic risk factors including insulin resistance, dyslipidemia, inflammation, liver function, and hypertension in the case of glucagon.

**POSTER #14**

*BEYOND A DECADE OF EXPERIENCE WITH THE US MONOGENIC DIABETES REGISTRY- SUCCESSES, CHALLENGES AND FUTURE OPPORTUNTIES*

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The US Monogenic Diabetes Registry was established in 2008, initially to follow neonatal diabetes, and expanded in 2010 to follow all forms of monogenic diabetes. The goals of the Registry are to facilitate genetic diagnoses, contribute to the understanding of monogenic diabetes, and to follow subjects longitudinally. Since 2011, all Registry data has been housed in REDCap and processes have been increasingly automated. This includes participant registration through a secure on-line registration form and completion of annual follow-up surveys.

We examined trends in proband enrollment, referral source to the Registry, and genetic testing location for the years 2012, 2015, and 2018. We further compared completion of enrollment and completion of study surveys for the years 2017 and 2018.

Total proband enrollment was 192, 136, and 177 in 2012, 2015, and 2018, respectively. Participant referral by physician was 61%, 54%, 59%, respectively. For those years, 33%, 59%, 31% have a known causal mutation to date. 69%, 58%, and 52%, respectively, of genetic testing was performed in our research lab. In 2017, 89 people registered on our website but never completed enrollment. In 2018, 91 people did not complete enrollment. Follow-up survey response rate was 54% in 2017 and 52% in 2018.

Since inception, the number of Registry participants has grown to 3489 (1822 probands), with 925 (627 probands) people with a known genetic cause of diabetes. Over half of referrals are from physicians. The percentage of those receiving genetic testing on a research basis has declined over time, but barriers to clinical genetic testing continue to result in a large percentage needing research-based testing.

The Registry has facilitated on-going studies of monogenic diabetes within our group and through outside collaborations. Many participants are actively engaged, including participating in on-line discussion groups and family meetings held triennially in Chicago. However, while the web-based nature of the Registry has facilitated participation, we also have enrollment failures. A major goal of the Registry is longitudinal follow-up but survey completion rates are just over 50% for the last two years. As the Registry moves forward we will need to increase efforts to engage participants over time.

**POSTER #15**

## *TARGETED ASCERTAINMENT AND RECALL OF GENETIC VARIANT CARRIERS FOR EVALUATION AND TRANSLATION (TARGET-DIABETES) STUDY: PHYSIOLOGIC AND PHARMACOGENETIC TESTING THROUGH RECALL BY GENOTYPE*

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To date, hundreds of genetic loci associated with T2D and related glycemic traits have been identified, yet studies investigating their physiologic mechanisms for drug development or their impact on disease risk are limited.

Since most common variants have modest effects, large numbers of individuals genotyped for variants of interest must be recruited and undergo detailed phenotyping to achieve enough power to detect clinical or biological differences, rendering such studies impractical. In contrast, physiological and pharmacological characterization of individuals with extreme genetic risk (EGR) for T2D may be more impactful studying carriers of single variants with modest effects, as larger biological and clinical consequences are expected.

During the last years, we have identified low-frequency or ancestry-specific variants with relatively large effects, including a variant with two-fold increased risk for T2D near AGTR2 (rs146662075), and a Latino-specific protective loss-of-function in IGF2 (rs149483638). In addition to single variants of large effects, individuals at the extremes of the genome-wide polygenic score (GPS) can also have EGR for T2D.

To physiologically and pharmacologically characterize individuals of EGR, we launched TARGET–Diabetes (Targeted Assessment of genetic variant carriers through Recall by Genotype for Evaluation and Translation) a clinical study funded by the American Diabetes Association to physiologically and pharmacologically characterize individuals at the extreme of the GPSs for T2D from the Partners Healthcare Biobank.

We will study 420 Individuals with EGR and matched controls for different EGR categories, including carriers of variants in or near AGTR2 and IGF2, and individuals at the GPS extremes. Since current GPSs for T2D cannot distinguish the pathophysiologic processes through which individuals develop T2D we developed the use of multiple GPSs, including those for T2D and the homeostatic model assessment of insulin resistance and beta-cell function, to define EGR categories at the intersection of the tails of the distributions. Individuals will undergo two visits. We will evaluate their beta-cell function and insulin resistance by measuring glucose and insulin levels following perturbation by a mixed-meal tolerance test and test their response to sulfonylurea through a glipizide drug challenge.

We expect that the results of this study will provide a comprehensive physiological characterization of individuals of EGR as well as insight on whether genetic information can inform drug choices in a clinical setting.

**WITHDRAWN BY AUTHOR**

## POSTER #16

*GENETIC PREDICTORS OF WEIGHT LOSS IN ASIANS LIVING WITH SEVERE OBESITY*

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Introduction: Significant weight loss is associated with prevention and remission of type 2 diabetes. Previous studies have demonstrated significant inter-individual differences regarding response to weight loss interventions, much of which remains unexplained. The goal of this study was to describe relationships between obesity-associated genetic polymorphisms and 1-year weight loss success (defined as weight loss ≥5% of initial weight) in Asian people living with severe obesity who participated in a non-surgical weight loss program at an academic medical center in Bangkok, Thailand.

Methods: At baseline, interview, physical examination, chemistry, and DNA collection was performed. Subjects were then prospectively followed on an annual basis to document weight changes and other treatment outcomes. Thirteen obesity-associated genetic polymorphisms which have been validated in the Asian population were screened, including polymorphisms near BDNF, FTO, GNPDA2, TFAP2B, CDKAL1, GP2, PCSK1, PAX6, MC4R, SEC16B, ADCY3, GIPR, and MAP2K5 genes.

Results: Among 208 subjects enrolled, mean BMI was 38.1±7.5 kg/m2, mean age was 41.8±13.6, and 133 (63.9%) were women. Seventy (33.7%) of all subjects had diabetes, and 21 (10.1%) had impaired fasting glucose. Seventy-one participants (34.1%) received lifestyle intervention alone, while the remaining (65.9%) underwent medication-assisted weight loss. Overall mean weight loss at 1 year was -2.9±7.2%, with 60 subjects (28.8%) losing >5% and 30 (14.4%) losing >10% of their initial weight at 1 year. Genotyping revealed that carriers of AT genotype at rs4776970 near MAP2K5 were more likely to achieve 5% weight loss at 1 year compared with carriers of TT genotype (39/110, 35.5% vs. 18/66, 21.4%, p=0.024). A multivariate logistic regression model showed that after adjustment for initial BMI, age, and sex, genotype at rs4776970 was predictive of ability to lose 5% of body weight at 1 year, with odds ratio of 2.07 (95% confidence interval 1.08-4.00, p=0.029) for carriers of the AT relative to the TT genotype.

Conclusion: rs4776970 near MAP2K5 was an independent predictor of successful 1-year weight loss in Asian adults living with severe obesity who participated in a non-surgical weight loss program.

**WITHDRAWN BY AUTHOR**

## POSTER #17

*CHARACTERIZATION OF THE GENETIC DISCORDANCE BETWEEN BODY MASS AND TYPE 2 DIABETES MELLITUS: A PHENOME-WIDE ANALYSIS*

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Background: Globally, a steep and parallel rise has been observed in T2D and obesity, both being more than tripled in only 3 decades. The interaction between them is highly complex, with genetic variation playing an important role in their development, as well as in other related traits, through pleiotropic effects.

Aim: To assess the difference in phenome-wide association patterns between genetic variants found within the significant T2D – BMI genetic intersection, having either concordant or discordant direction of effects for those two conditions.

Design: Phenome-wide association study.

Methods: The latest and largest-to-date T2D and BMI GWAS meta-analyses conducted in European populations were used to find the significant genetic intersection and classify genetic variants as concordant or discordant. Phenoscanner was used to retrieve their effects or those from their proxies at LD r2=0.8 across multiple traits. Standardized effect sizes aligned to the BMI increasing allele were compared within each trait using a bootstrap approach, as well as in a multivariate analysis using PCA and the COVVSURF algorithm. The predictive models constructed were trained with the aid of the ROSE algorithm designed for unbalanced data analysis. Accuracy was measured using the Matthews Correlation Coefficient.

Results: 127 SNPs were found significantly associated with both T2D and BMI (15% discordant, 85% concordant; mean standardized effect difference for BMI: 3.68 [95% CI, 2.63 – 4.79, pbootstrap = 0.046]; mean standardized effect difference for T2D: 4.19 [95% CI, 0.94 – 9.09, pbootstrap = 0.047]). The query in Phenoscanner returned 1827 traits, after filtering for missing values and redundancy. Concordant and discordant SNPs showed nominal significant difference in 223 traits (12.2%) while reaching a 5% FDR correction in 66 (3.17%). PCA showed that fat distribution variables explained ~ 60% of the variation in the dataset. COVVSURF models were constructed and tested using all variables, the nominally significant or those reaching the FDR correction, with a resulting MCC of 0.35, 0.82 and 0.73, respectively. The best predictive model used 2 clusters mainly composed by glucose measures, diabetic microvascular complications, hypertension and heart disease.

Conclusion: Concordant and discordant SNPs show their main differences in glucose measures, diabetic complications, hypertension and heart disease. Fat distribution also shows distinct patterns. Carriers of discordant SNPs (mean allele frequency ~50%) may present clinically relevant differences that are important to recognize to improve outcomes.

**POSTER #18**

*USING GENETICS TO TEST CAUSAL RELATIONSHIPS BETWEEN PREDIABETES AND VASCULAR COMPLICATIONS: IMPLICATIONS FOR PRECISION PREVENTION*

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Background: Prediabetes is a state of glycaemic dysregulation below a level indicative of type 2 diabetes (T2D) that affects about 352 million people globally, of which about 35-50% will progress to T2D within five years. T2D and its complications are costly to treat, causing great suffering and early death. Observational studies have shown associations between prediabetes and cardiovascular complications, though these cannot be interpreted as causal. We reviewed and summarized observational data on prediabetes and major T2D complications and assessed the causal basis of these associations via a Mendelian randomization analysis.

Methods and results: We performed a systematic review and meta-analysis of 37 observational studies and thereafter a Mendelian randomization analysis, using genetic instrumental variables to define an exposure of prediabetes (non-diabetic variation in fasting glucose), to assess the causal association of these exposures with coronary artery disease (CAD), stroke, and chronic kidney disease (CKD).

In observational data, prediabetes was associated with higher risk of CAD (RR=1.13; 95% CI 1.07, 1.2; Q= 67.1, p=0.008; I2= 37.5%) and stroke (RR = 1.10; 95% CI 1.03, 1.18; Q=28.5, p=0.23; I2=16%), but not CKD (RR=1.04; 95%CI 0.98, 1.11; Q= 27.2, p=0.002; I2= 63.3%). In the causal inference analysis, each 1 mmol/L fasting glucose conveyed an OR of 1.22 (95% CI 1.10, 1.35) for CAD. No causal effects of glucose in stroke or CKD were detected.

Conclusions: Prediabetes is likely causally associated with CAD but not stroke or CKD; therefore, it may be appropriate to begin the prevention of T2D-associated CAD before diabetes diagnosis. It is also feasible, based on these findings, to identify unique sub-populations at a high risk of impaired glucose regulation and subsequent CAD early and institute appropriate interventions to mitigate adverse outcomes.

**POSTER #19**

*A SCIENTOMETRIC ANALYSIS OF POPULATION GENETICS RESEARCH IN TYPE 2 DIABETES*

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Background: Genomic association studies have identified loci that help to elucidate the inherited basis of T2D, providing insights into the genetic and pathophysiological architecture of this complex disease and shedding light on previously unknown molecular mechanisms. The knowledge gained through these studies may one day help improve the specificity of interventions focused on the prevention and treatment of diabetes, a concept broadly termed precision medicine.

Aims: i) to undertake a scientometric analysis of the published literature on the major T2D genetic discovery studies; ii) to evaluate the geographic, ethnic, socioeconomic and sex characteristics of the populations from which these data emanate, iii) to determine the locations and socioeconomic characteristics of research centers that were primarily responsible for analyzing and reporting these data, and iv) to quantify the extent to which male and female investigators conducted and led the research.

Methods: NHGRI-EBI GWAS Catalog of published genome-wide association studies was used as the source to identify target studies. We've assembled R programming tools to collect and process the following information from each study: authors' affiliations sex and income (based on location of institutional affiliation); participants' sex, income (based on origins of cohorts) and ethnicity, and geographic location of the cohorts.

Results: Most authors of the included studies were male (70%), from high-income countries (84%), and with affiliations in the US (30%). The researched cohorts were comprised in equal parts on average of male and female participants. Most participants were of European ancestry (63%) and from high-income countries (88%). The largest single contributing region was the Nordics, from which almost 1/3 of participants from the researched cohorts emanated.

Conclusion: Our findings illustrate that the understanding of the genetic basis of T2D is heavily predicated on the genetic architecture of European ancestry populations, despite the burden of disease being greatest in non-European populations. Our study also found that this has been managed predominantly by male senior investigators from the UK and US, whereas the junior leaders of the published papers are largely female researchers from these same countries.

**POSTER #20**

*EFFECT OF G6PD VARIATION ON HEMOGLOBIN A1C IN EAST ASIANS*

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Objective: Hemoglobin A1c (A1C) accuracy is important for diabetes diagnosis and estimation of glycemia. The G6PD-Asahi variant which causes Glucose-6-phosphate dehydrogenase (G6PD) deficiency has been shown to lower A1C independently of glycemia in African ancestry. As G6PD variants in Asian ancestry tend to cause more severe forms of G6PD deficiency, we sought to identify Asian-specific G6PD variants associated with A1C.

Methods: In eight Asian studies, we performed imputation on the chromosome X using the 1000 Genomes reference panel and tested for association with A1C. Sex-stratified analyses were conducted in 10,005 East Asians and 2,051 South Asians. Results were then meta-analyzed. To assess the impact of A1C-related variants on diabetes/prediabetes classification, we compared the proportion of individuals classified as having FG-defined prediabetes/diabetes (FG ≥ 100 mg/dL) or A1C-defined prediabetes/diabetes (A1C ≥ 5.7%-units) by genotype categories.

Results: In East Asian men, 36 variants were associated with A1C at G6PD (genome-wide significance, $P < 5x10-8$). The strongest association was a low-frequency missense variant, G6PD-Canton (rs72554665, n = 2,844, MAF = 2.2%, effect in men= -0.76%, $P = 1.25x10-27$). Conditional analyses identified a secondary distinct signal driven by another low-frequency missense variant, G6PD-Kaiping (rs72554664, MAF=1.6%, effectmen= -1.12%, $P=3.12x10-15$, P conditional for Canton = 7.57x10-11). Adjusting for glucose levels did not attenuate their effects. The proportion of individuals with FG-defined prediabetes/diabetes did not differ by carrier status of G6PD-Canton (P=0.21); whereas the proportion of individuals with A1C-defined prediabetes/diabetes was lower in carriers (5%) compared to non-carriers of G6PD-Canton (30%, P = 0.03). Larger samples were needed to perform a similar analysis for G6PD-Kaiping.

Conclusions: We identified and replicated associations of two G6PD variants that lowered A1C in East Asian men, highlighting the importance of well-powered genetic studies focused on uncovering ancestry-specific variants with direct implications on routinely performed diagnostic tests. Carriers of these variants are more likely to be underdiagnosed than noncarriers if screened by A1C for diabetes/prediabetes and not direct glucose measurements.

## PUBLICATION #1

*ACUTE EFFECTS OF MELATONIN ON GLUCOSE METABOLISM*

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Background and Aim: Sleep disturbances are strong risk factors of type 2 diabetes (T2DM). Melatonin is implicated in the regulation of circadian rhythm and sleep, but it is also ascribed anti-oxidative properties and effects on glucose homeostasis. In addition, a specific single nucleotide polymorphism in the melatonin receptor gene, MTNR1B rs10830963, is associated with an increased risk of T2DM. The aim of the present study was to examine the acute effects of high dose melatonin on glucose metabolism, primarily insulin sensitivity and insulin secretion.

Material and Methods: Twenty healthy young men were examined on two occasions after 10 hours of fasting on two nonconsecutive days; one day with four doses of 10 mg oral melatonin administered with 60 minutes intervals during the study day and the other day placebo capsules with the same time intervals. Insulin sensitivity and insulin secretion were assessed by a hyperinsulinemic euglycemic clamp, using 1.0 mU/kg/min and by an intravenous glucose tolerance test (IVGTT) respectively. Blood-samples were drawn to determine the MTNR1B rs10830963 genotype, and to determine melatonin concentrations and other hormonal, metabolic and inflammatory parameters. To estimate potential effects of melatonin on substrate utilization and energy metabolism indirect calorimetry was performed twice on each study day. Bedside blood pressure was measured as previous studies have suggested a blood pressure lowering effect of melatonin.

Results: Study participants were 24.6 ± 4.15 years old and had a BMI of 23.9 ± 2.5. Insulin sensitivity expressed as the insulin sensitivity index during the hyperinsulinemic euglycemic clamp under steady state conditions was significantly reduced on the melatonin day (0.024 ± 0.014 (P) vs 0.021 ± 0.010 (M); p = 0.04) whereas insulin secretion based on IVGTT calculations was unchanged on the two study days. Systolic blood pressure decreased significantly on the melatonin day (125.6 ± 7.9 (M) vs. 130.4 ± 7.8 (P); p = 0.01), whereas diastolic blood pressure remained unchanged (70.6 ± 7.0 mmHg (M) vs. 69.9 ± 6.8 mmHg (P); p = 0.60). Indirect calorimetry showed no significant changes in energy expenditure, respiratory quotient (RQ), glucose-, lipid- or protein-oxidation.

Conclusion and Perspectives: Our results indicate that melatonin might have a negative effect on insulin sensitivity in healthy young men. On the other hand, we confirm that melatonin may have blood pressure lowering effects. Our data suggest an unfavorable effect of melatonin on glucose metabolism and underscore the importance of gaining more insights into the glucosemetabolic effects of melatonin as its use as a ‘safe’ sleep-aid is rapidly increasing.

**PUBLICATION #2**

*INCREASING KNOWLEDGE ABOUT HBA1C TESTING TO IMPROVE PATIENT OUTCOMES USING CLINICAL AUDIT AS A RESEARCH TOOL*

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Introduction: Research using routine measurements of HbA1c is ongoing at the Diabetes Centre, Queen Elizabeth Hospital Birmingham (QEHB), a large UK hospital that is the major trauma unit for the West Midlands. The Diabetes Translational Research Group founded within the UK National Health Service consists of clinicians, scientists, statisticians, and bioinformaticians. The group has recently relocated to the new Birmingham Institute of Translational Medicine based on the hospital site.

Aim: To identify and investigate questions/issues concerning the diagnosis and monitoring of diabetes raised during routine clinical care.

Methods: Data was obtained from the electronic patient record for registered clinical audits and also from clinical research studies performed in the Diabetes Centre. Procedures initiated by the UKPDS for long term, randomised clinical trials were followed with regard to data handling from a biochemical and statistical perspective (Cull, Clinical Chemistry 1997). The R programming language was used for data analysis and visualisation, including correlation grids and 3-way diagrams of prevalence highlighting ‘at risk’ groups.

Results: Comparison of different methods for measurement of HbA1c showed negligible differences between the method used in the QEHB pathology laboratory and elsewhere but not so for insulin. In people pre-liver transplant or treated with ribavirin or dapsone, HbA1c was markedly depressed across the range by 20 mmol/mol or more. On investigation of complex pathology relationships, this depression was shown to be associated with abnormal red blood cell morphology. An audit of 100,000 admissions (40,000 were emergencies) showed that 5% of people admitted as an emergency had admission plasma glucose in the ‘diabetes’ range (8% for South Asians and 7% for Afro-Caribbeans) and 16% in the ‘at risk’ range. Differences were observed in the relationships of admission plasma glucose and HbA1c in South Asians and Afro-Caribbeans when compared to White Europeans admitted as an emergency. The glucose workload decreased appreciably after introduction of HbA1c for diagnosis with a corresponding increase in the HbA1c workload.

Conclusion: Real world evidence can provide answers to important issues raised during care for people in hospital and complements established research practice. Appropriate training for such researchers and adequate funding from research bodies is required to further this approach to medical science.

## PUBLICATION #3

*THE SYNDROME OF DIABETES-A UNIFIED PATHOPHYSIOLOGIC APPROACH*

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We have previously presented a proposal for a new, beta-cell centric classification of diabetes based on a consilience of genetic, metabolic, and clinical research that have accrued since the current classification was instituted . It recognizes that the beta-cell is THE core defect in all patients with diabetes. Differences in the genetics (and epigenetics), insulin resistance, environment and inflammation/immune characteristics resulting in the damage to the beta-cell in each individual will determine the phenotypic presentation of hyperglycemia and allow for a patient-centric, precision-medicine therapeutic approach , part of which we labeled 'the Egregious Eleven'.

We now recognize the same pathophysiologic mechanisms that account for damage to the beta-cells govern the susceptibility of the cells involved in the complications and other conditions 'tied to' diabetes to damage by the abnormal metabolic environment that typifies beta-cell dysfunction and 'fuel excess'. This abnormal metabolic environment is typified by oxidative stress which alters metabolic pathways (a la Brownlee's Hypothesis model), alterations in gene expression, epigenetics, and inflammation. This Unifying Pathophysiological Approach to Diabetes, its Complications and Conditions with Overlapping Pathophysiologic Mechanisms in the context of the Beta-Cell Classification of Diabetes allows us to understand the varied risk of developing complications of diabetes, including malignancies, dementia, NASH, psoriasis with similar levels of glycemic control, how non-glycemic effects of some medications for diabetes result in marked complication risk modification and the value treating co-morbidities of diabetes in modifying complication risk.

Principles we outlined in using 'the Egregious Eleven' model- use agents that preserve beta-cell function, treat with least number of agents that treat most number of mechanisms of hyperglycemia- can be extended to use those agents, in combination, that also engender weight loss, and decrease CV outcomes. This approach allows for a more accurate assessment of each patient's disease and effecting true precision medicine

Schwartz, S, et al,Diabetes Care 2016, 39:179-186.
Schwartz SS, et al Trends Endocrinol Metab. 2017;28(9):645-655.

## NOTES

## NOTES

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