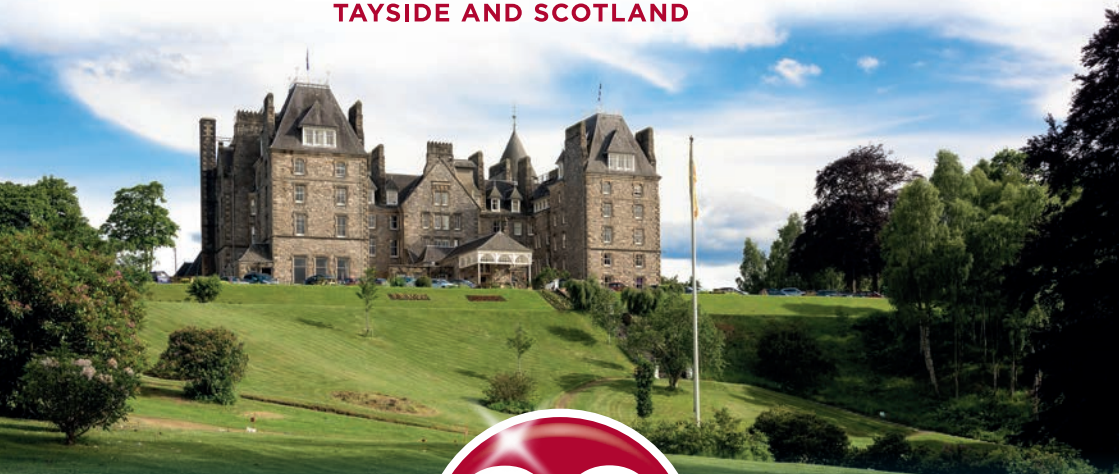


ATHOLL PALACE HOTEL, PITLOCHRY • 26-28 SEPTEMBER 2018

GoDARTS

GENETICS OF DIABETES AUDIT AND RESEARCH
TAYSIDE AND SCOTLAND



CELEBRATING



OF GoDARTS

PRECISION MEDICINE IN DIABETES

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DIABETES SPECIALITIES CENTRE

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CELEBRATING

20
YEARS

OF GoDARTS



OUR HISTORY

DARTS (Diabetes Audit and Research in Tayside Scotland) was started in 1996 as a joint collaboration between the University of Dundee's Department of Medicine and Medicines Monitoring Unit (MEMO), three Tayside Health Care Trusts and a group of Tayside general practitioners (GPs) with a special interest in diabetes care.

Initially supported by the Scottish Home and Health Department, the Wellcome Trust, the Robertson Trust and Tenovus Tayside, the aim of the study was to identify all patients with diabetes within the wider Tayside region, through electronic record linkage, in order to improve health care over and above that which was practical through existing general practice lists alone.

In 1998, consenting patients within this electronic database were recruited to the Genetics of DARTS (**GoDARTS**) study and invited to provide a blood sample for DNA extraction, for research purposes. At the same time, they were invited to provide phenotypic data (clinical and lifestyle factors), through questionnaires and clinical examination.

This valuable resource is intended to help identify the relative contribution of specific genetic and environmental factors that are associated with disease onset, progression and response to treatment.

GoDARTS is currently partnered with Dr Mohan's Madras Diabetes Research Foundation and the **SHARE** initiative to investigate how genes influence susceptibility to type 2 diabetes (The **INSPIRED** Project – NIHR Global Health Research).

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THE TEAM



Professor Helen Colhoun holds the AXA Research Fund endowed Chair in Medical Informatics and Life Course Epidemiology at the University of Edinburgh within the Institute of Genetics and Molecular Medicine (IGMM) where she leads the Diabetes Medical Informatics and Epidemiology programme. Helen joined the University of Edinburgh in 2016 having previously held tenured professorial posts in epidemiology at the University of Dundee, University College London and University College Dublin. She also holds an honorary Consultant post in Public Health in the National Health Service. Professor

Colhoun's epidemiological and clinical trials research have impacted on and been cited in clinical guidelines internationally and in national policy for diabetes. Professor Colhoun's current research programme uses large scale population based approaches to further understanding of the pathogenesis and means of prevention of diabetes complications. In particular it uses electronic health data to model the risk of diabetes complications and avails of linkage to biobanks to generate and examine the utility of other high dimensional data including molecular and 'omics data for prediction. Professor Colhoun leads the large Scottish Diabetes Research Network Type 1 Bioresource research collaboration. She is a member of the Diabetes UK Research Committee, co-Chairs the Wellcome Trust Science Interview Panel and is a member of the Wellcome Trust Science Strategy Advisory.



Professor Chim Lang is Professor of Cardiology, a consultant cardiologist and clinical pharmacologist at Ninewells Hospital & Medical School, Dundee. He trained in cardiology and clinical pharmacology in the UK and USA where he was a

- Merck International Fellow in Clinical Pharmacology at Vanderbilt University, Nashville
- Fulbright Scholar at Columbia University, New York.

He is a Fellow of the Royal Colleges of Physicians of London and Edinburgh and the American College of Cardiology.

His research takes a multi-disciplinary approach to the understanding of pathophysiology and pharmacogenetics of cardiovascular diseases and the development of treatment strategies in patients with cardiovascular diseases. He leads an integrated cardiovascular research laboratory dedicated to the study of cardiac/vasomotor regulation. These techniques are applied towards translational research and the development of biomarkers/ novel treatment strategies in patients with cardiovascular diseases.

A wide range of funding bodies including the British Heart Foundation, MRC, Chief Scientist Office, Chest Heart and Stroke Scotland, European Federation for the Study of Diabetes and the European commission funds his research.

Prof Lang has published 237 peer reviewed papers and his h-index is 47.



Rory McCrimmon trained at the University of Edinburgh and completed his clinical and speciality training in the South-East of Scotland before becoming an NHS Consultant Physician in Diabetes and Endocrinology at University Hospital Aintree, Liverpool, in 2000. In 2002, he joined the faculty at Yale University, Connecticut, to investigate why people with type 1 and 2 diabetes are very prone to developing low glucose (Hypoglycaemia). He returned to Scotland in 2009 to establish his laboratory at the University of Dundee, where he is currently Dean of Medicine, Professor of Experimental Diabetes and Metabolism and

Honorary Consultant He was recently awarded the 2015 RD Lawrence Lecture by Diabetes UK for his research in Hypoglycaemia.

Prof McCrimmon is currently also Lead Clinician for the **Scottish Diabetes Research Network (SDRN)**, which provides the necessary infrastructure to co-ordinate and enable academic and commercial research throughout Scotland. The SDRN hosts a National Research Register of over 11,000 subjects with diabetes pre-consented to be contacted about clinical trials. The register is directly linked to SCI-diabetes, which contains secure clinical and biochemical data on over 350,000 people with diabetes in Scotland.

Prof McCrimmon serves on Editorial Boards of *Diabetologia* and *Diabetes*. He is a panel member for: Medical Research Council Population and Systems Medicine Board, Diabetes UK, Clinical Studies Group Management Committee; Diabetes UK, Intermediate Clinical Fellowships Panel; Juvenile Diabetes Research Foundation PEAK Programme; Panel member, International Hypoglycaemia Study.



Since August 2017 **Professor Andrew Morris** has been the inaugural Director of Health Data Research UK, the multi-funder UK Institute for health and biomedical informatics research that will capitalise on the UK's renowned data resources and research strengths to transform lives through health data science. He is seconded from his position as Professor of Medicine, and Vice Principal of Data Science at the University of Edinburgh, having taken up position in August 2014. Prior to this Andrew was Dean of Medicine at the University of Dundee.

Andrew was Chief Scientist at the Scottish Government Health Directorate (2012-2017) and has served and chaired numerous national and international grant committees and Governmental bodies.

Andrew was awarded a CBE (Commander of the Most Excellent Order of the British Empire) in the 2018 New Year's Honour's List.

His research interests span informatics and chronic diseases. He has published over 300 original papers and has attracted over £50million in grant funding.



Professor Colin Palmer was appointed Interim Associate Dean of Research on 1st August 2018. Colin has a major international reputation in relation to his research on identification of the genetic basis of human traits, complex diseases and pharmacogenetics. He has published >250 papers in major journals, including Science, Nature, Nature Genetics and the NEJM. He has an H factor of 77; his papers have been cited over 30,000 times.

He pioneered population pharmacogenetic research, with establishment of the GoDARTS cohort in Tayside 1997, now a major resource for the study of diabetes with >40,000 patients and controls; he has been able to use this to create linkage to the electronic medical records, especially national prescribing datasets. Development of these unique resources allowed him to play a key role in GWAS discovery of genes for T2D, height and obesity, including discovery of the role FTO gene in regulating eating behaviours. The pharmacogenetic value of this approach is demonstrated by a major study that identified a locus accounting for a proportion of the hypoglycaemic actions of metformin. Other studies on asthma in children have provided novel pharmacogenetic discoveries, including collaboration with Professor Irwin Mclean and identification of the Fillaggrin gene as a determinant of eczema and asthma.

His recent research focusses on the discovery of genes that modulate drug response and adverse drug reactions for commonly used drugs such as Statins and ACE inhibitors.

He is Director of The Scottish Health Research Register (SHARE) which aims to involve the entire Scottish population in health research. Nearly 200,000 people have currently registered as volunteers with SHARE. In addition, he leads the NIHR Unit for Global Diabetes Outcomes Research, a partnership between India and Scotland which studies over 600,000 people in order to provide precision medicine in type 2 diabetes.



Professor Graham Leese is an NHS consultant in Endocrinology and Diabetes. He has diverse research interest, but they are especially focussed on the diabetic foot, diabetic eye disease and Endocrine epidemiology. He has linked his work in these three areas with GoDARTS, and has collaborated in a number of other areas. He is also part of the SDRN epidemiology group.

He has published about 240 peer reviewed papers.



Ewan Pearson is Professor of Diabetic Medicine at the University of Dundee, Visiting Professor at the University of Edinburgh, and Honorary Consultant in Diabetes and Endocrinology at Ninewells Hospital and Medical School in Dundee. In the School of Medicine, he is the Lead for Clinical Translational Research and the Director of the Dundee Clinical Academic Track.

Professor Pearson obtained his medical degree from the University of Cambridge School of Clinical Medicine, UK. He undertook a Wellcome Trust Clinical Training fellowship with Prof Andrew Hattersley at the University of Exeter Medical School, UK and completed his PhD in the physiology and treatment of monogenic diabetes. He then moved to Dundee where he was supported by a Chief Scientist Office Clinician Scientist fellowship and, more recently, by a Wellcome Trust Investigator Award. Over the last ten years in Dundee his research interests have been in the phenotypic and genotypic determinants of drug response in diabetes, and in stratified approaches to the management of diabetes. He leads the IMI-DIRECT project on stratification in type 2 diabetes and is strand 2 lead on the ABPI-MRC funded MASTERMIND project. Ewan has been awarded the Royal College of Physicians of Edinburgh Croom Lecture, an EASD Rising Star award, the Diabetes UK RD Lawrence Lecture and the EASD Minkowski Award for his work in these areas.

GoDARTS underpins the majority of the research of the Pearson group, which focuses on stratification of treatment in diabetes and understanding and predicting glycaemic deterioration in Diabetes. Using the extensive prescribing and health record data linked to the GoDARTS bioresource we have identified novel variants associated with glycaemic response to metformin at the ATM locus and at a variant altering expression of GLUT2 (PMID 27500523). We have also established that PK variants alter glycaemic response to sulphonylureas and thiazolidinediones, and loss of function variants in the metformin transporter OCT1 are associated with increased risk of gastrointestinal side effects of metformin treatment. We are undertaking recruit by genotype and physiological tracer studies to investigate the mechanisms for these response and intolerance phenotypes. Ewan Pearson is the PI for the GoDARTS Scotland study, which is now recruiting across Scotland and aims to create a national bioresource of up to 6000 individuals recruited close to diagnosis of diabetes.

KEYNOTE SPEAKERS BIOGRAPHIES

**Mark McCarthy**

Mark McCarthy is the Robert Turner Professor of Diabetes Medicine at the University of Oxford based at both Oxford Centre for Diabetes, Endocrinology and Metabolism and the Wellcome Centre for Human Genetics. His research group is focused on the identification and characterisation of genetic variants influencing risk of type 2 diabetes and related traits, and on using those discoveries to drive biological inference and translational opportunities. He has played a leading role

in many of the major international efforts to identify the genetic variants that influence predisposition to type 2 diabetes including DIAGRAM, T2DGENES and GoT2D. These consortia have used genome wide association and sequencing approaches to identify over 400 genetic signals for type 2 diabetes. Equivalent efforts focused on diabetes-related traits, including obesity, fat distribution and birthweight have been similarly productive.

With collaborators, his group's activities are now increasingly focused on the exploitation of these discoveries to gain insights into the biological mechanisms underlying disease development. Integration of genetic association signals with genomic annotations derived from pancreatic islets and other diabetes-relevant tissues is providing robust insights into the molecular and pathophysiological mechanisms through which many of these signals operate. This also makes it possible to use this information to open new translational opportunities through target validation, risk stratification and biomarker discovery.

**Andrew Hattersley**

Professor Andrew Hattersley is a consultant diabetologist at the Royal Devon and Exeter hospital and the Professor of Molecular Medicine at the University of Exeter. His clinical training in diabetes and endocrinology was at the Hammersmith and Birmingham and his research training with Prof. Robert Turner in Oxford. With Professor Sian Ellard he has taken Exeter from a centre without a genetics lab in 1995 to being the top international lab for monogenic diabetes that has had over 16,000 referrals from over 95 countries worldwide. His work

combines clinical observations, cutting edge molecular genetics and in depth clinical and physiological studies. With the Exeter team he has described 14 new subtypes of monogenic diabetes and developed diagnostic and treatment approaches for monogenic diabetes that are adopted throughout the world. Recent work has focused on "Precision Diabetes" identifying subgroups in Type 1 and Type 2 diabetes with different treatment responses. He has published over 550 papers with over 47,000 citations, given over 300 national and international lectures and received many awards for his work including being appointed as a fellow of The Royal Society in 2010 and awarded a CBE in 2017.



Kathy Giacomini

Dr. Giacomini is a Professor in the Department of Bioengineering and Therapeutic Sciences at the University of California, San Francisco. She is currently Co-Principal Investigator of the NIH Pharmacogenomics Research Network Hub, and Co-Principal Investigator of the UCSF Stanford Center of Excellence in Regulatory Sciences and Innovation (CERSI), a major center funded by the FDA with the goal of advancing scientific issues related to the safe and effective use of medical

products. Dr. Giacomini is considered a leader in the field of membrane transporters, and in particular, she is widely recognized for her work on transporter genomics and pharmacogenomics. Dr. Giacomini has been recognized by many awards and is an elected member of the National Academy of Medicine. She is a recipient of an honorary doctoral degree from Uppsala University, and was awarded the North American Scientific Achievement Award from the International Society for the Study of Xenobiotics in 2017. Most recently in 2018, Dr. Giacomini was awarded the Volwiler Research Achievement Award and was recognized by her peers as one of the leading researchers in Pharmaceutical Sciences.



Dr V Mohan

Prof. VISWANATHAN MOHAN, M.D., Ph.D., D.Sc., FRCP, FNA, FACE, FTWAS, MACP President & Chief of Diabetes Research, Madras Diabetes Research Foundation

Chairman & Chief Diabetologist, Dr. Mohan's Diabetes Specialities Centre, Chennai – 600 086, India

* Dr. V. Mohan is an internationally acclaimed Diabetologist and Scientist who has been working for over 40 years in the fields of Diabetes Research, Health Care, Education and Charity.

* Dr. Mohan has 1,140 research publications, which includes 743 original articles, 151 chapters in textbooks and 246 review articles/editorials.

* His work has received 55,552 citations with an h-index of 106.

* Dr. Mohan's field of interest include Epidemiology of Diabetes, Genomics of Diabetes and Precision Diabetes.

* Dr. Mohan's Diabetes Specialities Centre (DMDSC) established by Dr. Mohan has 45 branches in 10 states of India and treats 430,000 diabetic patients.

* Dr. Mohan has trained over 3000 Community Medicine Specialists in 96 medical colleges and over 12,500 Physicians in 170 towns and cities in India on diabetes management.

* Dr. Mohan was conferred the Harold Rifkin Distinguished International Service in the Cause of Diabetes Award by American Diabetes Association for the year 2018. He is the first Indian to be conferred this award.

* In 2012, Dr. Mohan was awarded the Padma Shri, one of the highest civilian award of the Govt. of India.



Jose Florez

Jose C. Florez, M.D., Ph.D. is the Chief of the Diabetes Unit at the Massachusetts General Hospital, Professor of Medicine at Harvard Medical School, and an Institute Member at the Broad Institute, where he leads the Diabetes Research Group, co-leads the Program in Metabolism, and is active in the Program in Medical and Population Genetics.

He and his group have contributed to the performance and analysis of high-throughput genome-wide association and sequencing studies in type 2 diabetes and related traits, in the Diabetes Genetics Initiative, the Framingham Heart Study, and other international consortia such as MAGIC, GENIE, DIAGRAM, T2D-GENES, AMP-T2D and SIGMA, where he plays management roles. He leads the genetic research efforts of the Diabetes Prevention Program, where the effects of genetic variants on the development of diabetes can be examined prospectively, and their impact on specific behavioral and pharmacological preventive interventions can be assessed. He is the Principal Investigator of the Study to Understand the Genetics of the Acute Response to Metformin and Glipizide in Humans (SUGAR-MGH), and also conducts other pharmacogenetic studies at MGH. He is an author on 180+ original publications and 50+ reviews/book chapters.

In addition to his research and teaching duties, he is clinically active in the MGH Diabetes Center, the Endocrine inpatient consult service, and the Down Syndrome Program. He serves on the Editorial Board for Human Genetics, and has been on Editorial Boards for *Diabetes*, *Diabetologia* and the *Journal of Clinical Endocrinology and Metabolism*; he is also the Editor-in-Chief for *Current Diabetes Reports*. He is the recipient of the MGH Physician Scientist Development Award, a Doris Duke Charitable Foundation Clinical Scientist Development Award, the MGH Department of Medicine Stephen Krane Award, the MGH Research Scholars Award, and the 2010 Presidential Early Career Award for Scientists and Engineers, the highest honor bestowed by the United States government on science and engineering professionals in the early stages of their independent research careers.

Lab website: http://chgr.org/index-faculty_florez.html

TIMETABLE

Wednesday 26th September

Arrival of Delegates

Registration

Dinner in the Tay Room (Sittings between 7 - 9.30pm)**Meet in Stag Bar after Dinner****Thursday 27th September, Bow Lounge, Atholl Palace Hotel**

09.00 – 10.15	GoDARTS – A History Establishing the GoDARTS cohort (30 mins) Recruiting challenges (15 mins) What has GoDARTS contributed? (30 mins)	Chair: Ewan Pearson Andrew Morris Bridget Shepherd Colin Palmer
10.15 – 10.45	Refreshments/View Posters	
10.45 – 11.15	Insights into Diabetes from Genetics Keynote Type 2 diabetes: will human genetics get us where we need to go?	Chair: Colin Palmer Mark McCarthy
11.15 – 12.35	Favourable adiposity Sleep phenotypes and genotypes and what they can tell us about the links between sleep patterns and diabetes? Large scale genetic discovery and translation in T2DM 20 years since the foetal insulin hypothesis	Hanieh Yaghootkar Mike Weedon Anubha Mahajan Rachel Freathy
12.35 – 14.00	Lunch will be served in the Verandah Restaurant	
14.00 – 14.30	Precision medicine 1: Monogenics and clinical stratification Keynote Learning from monogenic diabetes – lessons for Precision Medicine in Type 2 diabetes	Chair: Graham Leese Andrew Hattersley
14.30 – 15.30	Using simple clinical measures to differentiate Type 1 from Type 2 diabetes Using simple clinical measures to define likely glycaemic response to oral agents in Type 2 diabetes Using simple clinical measures in decision support tools to improve diagnosis and management of diabetes	Angus Jones John Dennis Bev Shields

15.30 – 16.15	Refreshments/View Posters	
16.15 – 17.15	Precision Medicine 2: Pharmacogenomics of Diabetes and Cardiovascular Therapies	Chair: Tim Frayling
	Keynote:	
16.15 – 16.45	Metformin, transporters and diabetes	Kathy Giacomini
16.45 – 17.15	Pharmacogenomics of statins. Pharmacogenomics of diabetes treatments	Moneeza Siddiqui Adem Dawed
18.15	Drinks and Entertainment in the Piano Bar	
18.45	Tay Room, Dinner and Entertainment	

Friday 28th September, Bow Lounge, Atholl Palace Hotel

Attendees must have checked out by 11am

	Diabetes in India and the NIHR Unit	Chair: Colin Palmer
09.00 – 09.30	Keynote	
	Diabetes in India: Challenges and Opportunities	Dr V Mohan
09.30 – 10.30	Epidemiology of diabetes in India Interventions in rural and urban populations Genetics of type 2 diabetes and monogenic diabetes in India	Dr Anjana Dr Pradeepa Dr Radha
10.30 – 11.00	Refreshments	
11.00 – 12.00	Genetics and Non-Genetic Biomarkers of Complications	Chair: Helen Colhoun
	Genetic and non-genetic biomarkers of retinopathy Genetics of macrovascular disease Genetics of neuropathic pain	Yvonne Huang Natalie Van Zuydam Abirami Veluchamy
12.00 – 12.10	<i>Leg stretch!</i>	
12.10 – 12.50	The Future and Big Data	Chair: Andrew Hattersley
	AI, imaging and diabetes GoDarts and beyond - the strengths and utility of Scottish bioresources	Manuel Trucco Ewan Pearson
12.50 – 13.20	Keynote	
	Precision medicine in diabetes	Jose Florez
13.20	Lunch in the Verandah Restaurant	
14.15	Meeting Close	

GODARTS PRIZE POSTER PRESENTATIONS

Phenotypic and genetic variants associated with the variation in HDL-c levels to statin treatment and polygenic risk score.

Mehul Chourasia, University of Dundee

Background: Statins mainly act on the reduction of low-density lipoprotein-cholesterol (LDL-C) levels. Statin therapy also helps in improving high-density lipoprotein-cholesterol (HDL-C) levels up to 10-15%. However, Inter-individual variation in HDL-c response to statins therapy could be partially explained by genetic variation.

The main Objective of this study was to investigate phenotypic and genetic variants associated with the variation in HDL-c levels to statin treatment in GoDARTS cohorts and construct a polygenic risk score (PRS).

Methods: 10,633 statin users were included in the study. For each individual, multiple clinical measurements were available over a period of time. Change in HDL-c levels was the main study outcome and BMI, age, sex, baseline HDL-c, statin dose and time difference along with reported SNPs were included as the predictor variables. Paired t-test to assess the difference between before and after HDL-c levels. Multivariate linear regression was done to assess the association between study outcome and predictor variables. PRS was calculated from previously reported SNPs by Genome-wide association studies (GWAS) and GLGC study.

Results: A modest elevation in HDL-c levels were (0.27 ± 0.32 ; t-test p-value < 0.001) observed. Among all reported SNPs, rs3764261 (CETP), rs1532085 (LIPC) and rs12678919 (LPL) were among few which significantly associated with raise in HDL-c levels (adjusted for age, sex, BMI, baseline HDL-c, and statin dose). GRS had slightly improved the predictor model (to be modified).

Way forward: GWAS all the three platforms (Affymetrix, Illumina, and Broad) and meta-analysis of GWAS will be carried out to find the novel loci. Based on GWAS results, a polygenic risk score will be validated and constructed in the study population

Deep Learning in Gemonics

Jyothsna Divyananda, University of Dundee

Artificial Intelligence is an area of Computer science, which focuses on developing machines which behave like human beings. Machine Learning is an application of Artificial Intelligence, which gives the systems the ability to learn and improve on the experience without being directly programmed. Deep learning is a subfield of machine learning, which deals with algorithms inspired by the functions of the brain.

Deep learning is a pedigree of techniques which constitute main part of extant artificial

intelligence (AI). Deep learning programs take inspiration from neurons of the brain, deep learning programs are neural networks which are also known as deep neural networks (DNN). These neural networks consist many layers, which enable a machine to learn data and represent it at several levels of detail

Deep learning has greatly improved the state-of-the-art in speech recognition, object detection and in biomedical applications like drug discovery and genomics. Various methods of deep learning have been applied in the field of genomics for example to predict protein structures, regulatory genomics, DNA & RNA sequence prediction, Design and generation of DNA sequence etc.

Deep learning methods have been applied successfully to predict protein structure, Splicing, Specificities of DNA and RNA binding proteins. This document is groundwork of the literature review of deep learning and its applications mainly in the field of genomics.

This document is a concise, preliminary review of the literature of deep learning and its applications in genomics. It was prepared as one of the initial exercises within the author's PhD, started in March 2018. A set of initial exercises were carried out to acquire familiarity with the literature and techniques of DL, their applications to fields closely related to research in the NIHR project, and DL programming environments and tools.

The PhD theme has recently been identified as the use of DL in precision therapeutics for diabetes, in collaboration with Prof Pearson's group. Familiarity with the DL techniques identified in this review will be useful for the project as defined currently.

Clinical Determinants of Dipeptidyl Peptidase-4(DPP-4) inhibitors

Sushrima Gan, University of Dundee

Background: There is considerable heterogeneity in glycaemic response to medications in type 2 diabetes (T2D). Dipeptidyl peptidase-4(DPP-4) inhibitors are one of the newer oral antihyperglycemic agents which have recently emerged as suitable options to treat T2D. Glycaemic response to DPP-4Is has been shown to vary within and between study subjects of different ethnicities. However, there are limited studies investigating determinants of response to DPP-4Is.

Methods: This study focuses on the anthropometric and clinical determinants of glycaemic response to treatment with DPP-4Is in T2D individuals (n=4996) from Tayside and Fife who are on stable treatment with DPP-4Is. Association of baseline clinical and anthropometric variables with the change in HbA1c after 6-months of therapy was studied in non-insulin treated patients who started DPP-4 inhibitor as monotherapy or add on to other antihyperglycaemic drugs using step wise backward linear regression model.

Results: In a model consisting of age at diagnosis, gender, BMI, HDL, cholesterol and BMI change, Age at diagnosis was found to be significant ($\beta=0.007$, $P < 0.001$) where older people at diagnosis respond better. Baseline BMI and BMI change are also associated with glycaemic response to DPP-4Is independently. BMI at baseline ($\beta= -0.008$, $P=0.004$)

and the change in BMI ($\beta=0.058, P=0.002$) were also associated with glycaemic response to DPP-4Is. Obese people at baseline had poor response and weight loss is positively correlated with greater response to treatment.

Conclusion: While Age at diagnosis and weight loss are associated with greater response, Baseline BMI is correlated with reduced response. This is in line with previous reports showing association of markers of insulin resistance with glycaemic response to DPP-4Is.

Convolutional neural network architectures for image classification and detection

Syed Mohammad Ghouse, University of Dundee

Convolutional neural networks (CNNs) and related deep learning architectures have demonstrated to be very well suitable for image classification and detection in several domains. Many CNN architectures have been developed since the late 90s and applied, among others, to open computer vision challenges like ILSVRC, COCO, Kaggle and CIFAR. As an initial exercise for my PhD on deep-learning discovery of features in retinal images specifically associating to clinical outcomes, I am studying some notable CNN architectures which have demonstrated the applicability of deep learning to image classification and detection tasks. Examples include LeNet-5, introduced in 1998 to classify hand written digits, AlexNet (2012), ZFNet (2013), GoogLeNet/Inception (2014), VGGNet (2014), and ResNet (2015). Over time, the error rate in classifying and detecting objects in large collections of unconstrained images have reduced from 25.8% to 3.57%. The above mentioned CNN architectures are summarized along with some key properties, such as number of layers and number of network parameters trained.

Evaluating Big data technologies for storage and querying of large-scale phenotype and genotype data in Clinical genetic research

George Gittu, University of Dundee

In recent years there has been tremendous growth in medical data. Advancement in Next-generation sequencing (NGS) has brought down the cost of sequencing to a great extent, and hence genomic data as a whole is growing faster than Moore's law. Genomic data will exceed any big-data domains like YouTube, Facebook, Twitter or astronomical data by 2025, due to the velocity and volume at which data is generated. It is also worth to mention that the amount of patient data being digitally collected and stored are expanding rapidly. Both the phenotype and genotype data could be combined to deliver personalized medicine, which will be the next generation of medicine. So there need to be enough preparations to tackle this data tsunami in medical research. As the medical data (clinical and genetic data) scale to a great extent, the possibility of handling and processing the data in traditional data warehousing systems are not efficient and the unstructured nature of the data makes it even impossible.

The main initiatives here are in evaluating big data frameworks and advanced file formats, to look at the various options in tackling the large genomic data. A proposal in implementing Hadoop framework to effectively store and process the phenotype and genomic data in one place for the effectiveness in Clinical genetic research. This approach would make it easier to carry out any research that requires dealing with both the clinical and genotype data like when performing a GWAS or PheWAS. Investigation is not only restricting to storage and processing of the medical data but also to analyze and bridge the gap between the medical researchers and growing big data, which is mainly caused because of the high-tech skills required in using these big data technologies.

Development, evaluation and external validation of clinical prediction models to identify adult patients (aged 18 – 50) with type 1 diabetes requiring early insulin therapy

Anita Grubb, University of Exeter

Objective: Correctly distinguishing type 1 diabetes subtype at diagnosis is important for appropriate treatment, but is often difficult in young adults and misclassification is common. We aimed to develop and validate a clinical prediction model to provide estimates of a patient's risk of having type 1 diabetes requiring early insulin therapy.

Research Design and Methods: We developed prediction models to identify type 1 diabetes robustly defined by severe endogenous insulin deficiency (C-peptide < 200 pmol/L) and early insulin requirement (<= 3 years) in a cohort of 1,352 participants diagnosed with diabetes age 18-50. Predictor variables were clinical features (age at diagnosis, BMI), GAD65 islet autoantibodies (GADA), Islet Antigen 2 (IA-2) and Type 1 Diabetes Genetic Risk Score. We assessed model performance using internal validation and in an external validation cohort of 582 participants (clinical features and GADA only).

Results: Type 1 diabetes was present in 13% of participants in the development sample. All five predictor variables were discriminative and independent predictors of type 1 diabetes ($p < 0.001$ for all). Internal validation model performance was high, ROC AUC ranged from 0.90 (clinical features only) to 0.97 (all predictors). Results were consistent in the external validation (clinical features and GADA ROC AUC 0.93).

Conclusions: This is the first study to develop a clinical prediction model combining clinical features and biomarkers to identify patients with type 1 diabetes in an age group where misclassification is common. Our model has excellent discrimination. Routine use of this model in clinical practice is likely to reduce misclassification.

Deep learning on rapid chronic kidney disease progression in type 2 diabetes

Ryan Shun-Yuen Kwan, University of Dundee

Background: Diabetes is a global public health problem and it is associated with Chronic Kidney Disease (CKD). In addition, people with both diabetes and CKD have an increased risk of cardiovascular disease and all-cause mortality. The study aimed at identifying the serum biomarkers for the progression of CKD in type 2 diabetes.

Methods: We revisited a study of Looker et al. which contains 7 clinical variables and 207 protein and metabolite biomarkers of 307 diabetic patients from Go-DARTS cohort. 153 rapid progressors had more than 30% eGFR decline and 154 non-progressing controls had less than 30% eGFR decline over a period of 3.5 years. Machine learning models including artificial neural network (NN) and random forest were applied to impute the missing serum biomarkers and for feature selection. Both generalized linear regression and random forest models were applied for prediction of kidney progression.

Results: The imputed data by NN had lower mean squared error (0.55) and higher correlation to the observed data (0.67) comparing to bPCA and MICE methods. When the baseline linear model with only clinical variables were used for prediction, urine albumin, age and BMI were selected. However, none of the clinical variables were selected by random forest with the introduction of informative serum biomarkers. The top five biomarkers selected by the later model were CST3, NT-proBNP, TNNT2, CP 2, and GDF15.

Conclusions: Machine learning models not only showed great potential in both imputation and prediction on medical data, but also provided a different perspective from linear models.

Exome sequencing reveals variants in F5 are associated with ACE inhibitor and ARB induced angioedema

Cyrielle Maroteau, University of Dundee

Aims: Angioedema occurring in the head and neck region is a rare extreme life-threatening reaction to angiotensin converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB). The European consortium PREDICTION-ADR was launched in 2013 to investigate the genetic variation responsible for extreme adverse drug reactions (ADRs) induced by ACEI or ARB and statins, using ascertained cases.

Methods and results: Adjudicated cases of extreme ACEI or ARB-induced angioedema (ACEI-AE, ARB-AE) and controls had been recruited in 4 different centres: Uppsala (Sweden), Dundee (Scotland), Utrecht (The Netherlands), Liverpool (England). Sequencing of 1066 samples (408 ACEI and ARB cases, 658 controls) was performed using exome-enriched sequence data (SureSelect QXT, XT and XT2 reagents, Agilent Technologies,

Wokingham, UK). After QC control, 1033 individuals (387 cases, 646 controls) with 128,157 SNPs (MAF<1%) and 50,838 SNPs (MAF>1%) were analysed.

Common and rare F5 variants seemed to be associated with ACEI-AE and ARB-AE phenotype. Common variant rs6025 (MAF=0.05) was found significantly associated with both ACEI and ARB angioedema [OR: 2.85, 95% confidence interval (CI): 1.89-4.25] where those homozygous for Arg534 had increased odds of developing ACEI-AE or ARB-AE. A group of 5 rare variants (MAF=5x10⁻⁴) in the F5 gene (rs140530655, CHR1:169529903, rs200157005, rs149389480, rs143509841), was found close to significance, p-value=2.09x10⁻³ (corrected threshold 10⁻⁵). A combined genetic risk score (GRS) of these variants and rs6020 showed individuals carrying at least one of these variants had 2.21 (95% CI: 1.49-3.27) times the odds of having ACEI-AE or ARB-AE.

Conclusion: This study suggests a role of the anticoagulation system in angioedema. Carrying an alternative variant of F5 (rs6025, rs6020, rs200157005, rs149389480, rs143509841, CHR1:169529903 and CHR1:169529903) increases the odds of developing angioedema when treated with ACEI or ARB.

Quantifying the effect of image centring towards standardization of retinal vascular measurements

Muthu Mookiah, University of Dundee

VAMPIRE (Vascular Assessment and Measurement Platform for Images of the REtina) is a suite of software tools for retinal image analysis, part of an international research initiative coordinated by the Universities of Dundee and Edinburgh. VAMPIRE tools have been used for years on retinal fundus images of individuals in GoDARTS (7,000+ retinal images currently measured) to investigate associations between the morphology of the retinal vasculature, and its changes, and a variety of conditions and related variables (e.g., complications of diabetes, dementia, CVD). VAMPIRE is being used in the NIHR Chennai-Dundee project on precision medicine for diabetes.

Within the general framework of consistent and reproducible morphometric measurements of the retinal vasculature in fundus images, we present a quantitative pilot study of the changes in measurements commonly used in retinal biomarker studies (e.g. caliber-related, tortuosity and fractal dimension of the vascular network) induced by centring fundus image acquisition on either the optic disc or on the macula. To our best knowledge, no such study has been reported so far. Analyzing 149 parameters computed from 80 retinal images (20 subjects, right and left eye, optic-disc and macula centred), we find strong variations and limited concordance in images of the two types. Although analysis of larger cohorts is obviously necessary, our results strengthen the need for a structured investigation into the uncertainty of retinal vasculature measurements, ideally in the framework of an international debate on standardization.

Genetic Architecture of Type 2 Diabetes in South Asians

Charvi Nangia, University of Dundee

Background: Diabetes is a complex disease that exhibits considerable heterogeneity across populations. South Asians (SAS) have a 4- fold higher risk of developing diabetes relative to the Caucasians. This is due to a greater genetic predisposition. A study using Whole Exome Sequencing technology on 56 Bangladeshi individuals has identified genetic variants in the genes HNF1B (rs139107479) and WFS1 (rs71530907). They are known to be associated with Type 2 Diabetes (T2D) in South Asians. The aim of the study is to identify specific causal genetic risk factors associated with T2D within a South Asian Population.

Method: The Minor Allele Frequencies of South Asian specific variants from the sequencing study will be validated on a larger population. Whole exome sequencing will be done on 1700 Bangladeshi individuals living in East London (East London Genes and Health study). Variants will also be studied using GWAS on 30,000 individuals from South India. Our first objective will be to look at the Age of Onset of type 2 diabetes in SAS. For data analysis, in-house pipelines will be used for both sequencing and genotyping. For sequencing, the core algorithm uses BWA for alignment and GATK for variant calling and for GWAS PLINK and BOLT-LMM will be used for quality control and analysis. The frequencies of these variants will also be compared to those in European populations on gNOM AD.

Conclusion: This will be the first such study looking at South Asian specific genetic determinants using both sequencing and genotyping. We are looking to validate specific MODY mutations to study their age of onset as compared to Caucasians. This will help us in understanding the genetic risk associated with T2D in SAS and also the heterogeneity between populations.

Data driven cluster analysis of type 2 diabetes data from Tayside and Fife, Scotland

Anand Nair, University of Dundee

Background: Type 2 Diabetes is a complex heterogenous disease condition. Sub-classification of diabetes based on the variables at diagnosis may aid in developing early intensification of treatment for specific groups of individuals.

Methods: We analysed recently diagnosed type 2 diabetes data (n=29172) from the Scottish Clinical Care Information-Diabetes Care (SCI-Diabetes) to identify unique clusters. This analysis used five diabetes related variables Age at diagnosis, BMI, HbA1c value and HDL levels at diagnosis. We determined the appropriate number of clusters for the data and applied a K-Means cluster algorithm. Longitudinal cluster stability and time to first and second antidiabetic prescription were assessed.

Results: The optimum cluster number for the data was identified as four and cluster analysis identified four replicable clusters. Each cluster showed different characteristics in relation to the five variables included in the analysis. The cluster 1 (Low-Age High-BMI) was 28.0%, cluster 2 (High-Age Low-HDL) was 36.9%, cluster 3 (High-HbA1c) 17.6% and cluster 4 (High-Age High-HDL) was 17.4% of the total study population. Four clusters showed stability of their features over the time. Time to first and second antidiabetic prescription was shortest in cluster 3 compared to other clusters.

Conclusion: Our analysis identifies four unique type 2 diabetes clusters based on the five variables at the time of diagnosis. Type 2 diabetes cases requiring early intervention can be recognized based on these findings potentially improving the glycaemic control in this high-risk population.

Exploring Causal Relationship between changes in retinal vasculopathy, phenotypic risk factors

Aditya Nar, University of Dundee

Diabetic population is vulnerable for microvascular and macrovascular disorders like nephropathy, neuropathy etc. Literature suggests that vascular changes are evident before the disease is diagnosed. Since diabetic patients also undertake retinal screening due to high risk of diabetic retinopathy (DR), fundus cameras are widely used due to portability and ease of use to capture the retinal images during the screening. Human Retina offers inexpensive, in-vivo and non-invasive clinical assessment of microvasculature and advancement in imaging technology, fundus imaging generates a two-dimensional (2D) image of the interior three-dimensional (3D) surface of the eye and translates into quantitative values. The use of retinal digital image allows us to analyse aspects of retinal vascular topography, including retinal vascular widths, geometrical attributes at vessel bifurcations and vessel tracking. These automated images allow us to identify retinal vasculature as biomarker to understand disease etiology among diabetic population. Previously published observational studies have mentioned that retinal vasculature among diabetics show early signs of stroke, dementia, hypertension (termed as phenotype).

However, the true casual relationship between changes in retinal vasculopathy, phenotypic risk factors is still unknown. This is an observational study between two ethnic groups i.e. Scotland and India; and will to explore causal inference using retinal images as biomarkers and gene risk score as confirmatory variable.

Association of VEGF Gene polymorphisms with Diabetic Retinopathy in GoDARTS Cohort

Aravind Lathika Rajendrakumar, University of Dundee

Background: Retinopathy is a frequent microvascular complication in diabetic individuals in the productive age group.

Development and progression of retinopathy varies between individuals. The reason for this variability is not clear and requires further research. Vascular endothelial growth factor (VEGF) is a mitogen that causes increased vascular permeability and neovascularization in the diabetic retina. In studies, VEGF was shown to have a significant association with circulating levels of vascular endothelial growth factor.

Methods: We analysed GoDARTS diabetes eye data (n=5099) in combination with the novel and traditional VEGF SNPs identified from studies. Secular trends in retinopathy such as prevalence and cumulative incidence were explored. Time to incidence of any retinopathy in relation to the SNPs in this cohort was analysed using an extended Cox model due to the absence of proportional hazards.

Results: The data showed that prevalence of higher retinopathy grades have decreased over time. Risk of retinopathy seemed to rise with increase in duration of diabetes. More than half, (57.7%) of the participants developed retinopathy at the end of 10 years. In survival analyses only rs10761741 (hazard ratio 1.08 [95% CI 1.02- 1.14], p=0.007) and rs7043199 (hazard ratio 1.086 [1.01-1.16], p=0.019) showed significant association with incidence of any retinopathy at 10 years.

Conclusion: Multiple VEGF polymorphisms are associated with incidence of diabetic retinopathy in this cohort. The effect size was not large for each SNP. However, the effect can be significant when different polymorphisms are considered together.

Genetic variants modify susceptibility to AF in patients on thyroid hormone replacement therapy

Enrique Soto, University of Dundee

Purpose: Hypothyroidism has been associated with atrial fibrillation (AF) in some studies. This study aimed to characterize thyroid related genetic variants that may change susceptibility to AF in patients on levothyroxine.

Methods: A case-control study was done among patients of European Caucasian ethnicity from the Genetics of Diabetes Audit and Research Tayside (GoDARTS) recruited in Tayside (Scotland, UK). Electronic medical records (biochemistry, prescribing, hospital admissions and demographics) were used to ascertain patients with atrial fibrillation and their controls as well as patients with hypothyroidism, and linked to genetic biobank data. Genetic tests of association were performed by means of logistic regression models adjusted for age, gender and average thyroid-stimulating hormone.

Results: We analysed 1,031 cases of AF and 10,757 controls. Loci on chromosomes 3 (Thyroid Hormone Receptor Beta -THRB), 6 (human leukocyte antigen- HLA), and 14 (Thyroid Stimulating Hormone Receptor- TSHR) were associated to AF in patients on levothyroxine. A significant interaction between HLA-rs2517532 and levothyroxine use was found (OR=1.32, 95%CI: 1.03- 1.67, P=2.6e-02). A significant interaction was also found between TSHR-2234919 and levothyroxine use (OR=0.48, 95%CI: 0.24- 0.97, P=4.2e-02). Fifteen unlinked single-nucleotide polymorphisms (SNPs) located on chromosome 3 at THRB showed interactions with similar size effect estimates (OR= 1.3- 1.5, P<5e-02), and two SNPs at THRB (rs7652234 and rs826219) showed larger size estimates (OR=1.9-2.0, P<2e-02).

Conclusions: This study provides evidence that genetic factors, such as polymorphisms in the THRB, HLA, and TSHR genes, might contribute to inter-individual variations in susceptibility to AF in patients on levothyroxine.

Glucagon Genes and Non-Alcoholic Liver Disease

Ally Taylor, University of Dundee

Non-Alcoholic Fatty Liver Disease (NAFLD) is a common cause of chronic liver illness, and is increasing in prevalence globally due to levels of obesity rising. NAFLD is associated with a wide range of endpoints, including cirrhosis and liver cancer. Genetics have been found to play a key role in the development of these endpoints.

In this study, it was hypothesised that genes related to glucagon would have an effect on incidence of NAFLD and NAFLD endpoints. Glucagon inhibits glycolysis and stimulates the liver to convert stored glycogen to glucose which can be released into the bloodstream. Previous research showed that patients with NAFLD have impaired GLP-1 secretion, and higher fasting glucagon secretion.

Genetic variants which are related to glucagon were analysed with NAFLD outcomes. This was done in the GoDARTS cohort, which is composed of medical records and genomic data for ~18,000 individuals. 9,493 of these individuals had NAFLD.

It was found that heterozygosity for GCG rs5384 was protective against NAFLD. ($p = 0.0209$) Associations for other glucagon genes including GCG, GCGR, GLPIR, GIP, GIPR and TCF7L2 were found. ($p = 1.97 \times 10^{-7} - 0.0492$) Many of these were interactions with other known NAFLD genes such as PNPLA3, CPN1 and MBOAT7. GIPR rs10403723 and GCGR rs5384 had significant effects on NASH ($p = 0.014915$ and 0.0430 respectively).

Knowledge of these associations may be applied to aid prediction of NAFLD and make a step towards personalised medicine for NAFLD. It may aid drug discovery as drugs which act on glucagon pathways may be developed.

NOTES

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GO DARTS

GENETICS OF DIABETES AUDIT AND RESEARCH
TAYSIDE AND SCOTLAND



PRECISION MEDICINE IN DIABETES