Final Report
Executive Summary

HSC Public Health Agency
Research and Development

HSC R&D Division Final Progress Report

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HSC Public Health Agency
Research and Development

HSC R&D Division Award Details

HSC R&D File Reference	STL/4760/13
HSC R&D Funding Scheme	US Ireland R&D Partnership Programme
Project Title	Integrative genomic, epigenetic and functional studies in diabetic kidney disease
Award Holder Name (Employer)	Professor Peter Maxwell (Queen's University Belfast)
Host Research Organisation	Queen's University Belfast
Award Duration	5 years (with no cost extensions triggered by Covid-19 pandemic disruption to work)
Award Start Date	01.02.16
Award End Date	31.01.22
Name of Lead Supervisor: ***(only applicable to training awards)***	

Signature

Award Holder Signature:	
	Date: 2/09/2022

HSC Public Health Agency
Research and Development

Evidence Brief

(1 page: which may be used for dissemination by HSC R&D Division)

Why did we start? (The need for the research and/or Why the work was commissioned)	Diabetes is the most common global cause of chronic kidney disease (CKD). By 2040, it is predicted that CKD will be the 5th leading cause of death worldwide. Diabetic kidney disease (DKD) affects almost half of persons living with diabetes. The reasons why only some individuals with diabetes develop kidney disease are not known.
What did we do? (Methods)	We explored clinical and genetic risk factors for DKD in an international study involving partners in the USA, Finland, UK, Ireland and many other European countries. We established the largest collection of persons with type 1 diabetes (with and without kidney disease). We used genome-wide tests to establish genetic risk factors for DKD.
What answer did we get? (Findings)	Clinical risk factors for DKD include the duration of diabetes and the control of blood sugar over time. Significant genetic risk factors, associated with diabetic kidney disease, were identified in variants of genes. There are complex interactions between environmental risk factors and genetic background.
What should be done now? (Practice/Policy Implications and/or Recommendations)	Improved blood sugar control can reduce the risk of DKD in individuals at highest genetic risk of this complication. Obesity is an additional multiplying genetic risk factor. Further research is needed to identify individuals at highest clinical and genetic risk for DKD to better target preventative measures and effective existing treatments.

Final Report

(no more than 20 pages)

Please structure the report using the headings below

- **Background**

Diabetes is responsible for a large proportion of chronic kidney disease (CKD), end-stage renal disease (ESRD), blindness, amputation, heart disease and stroke [1,2]. Tight glycaemic control in type 1 diabetes (T1D) [3,4] or type 2 diabetes (T2D) [5] can delay or arrest the progression of microvascular complications. How hyperglycaemia leads to complications, and why some patients with long-standing diabetes are relatively spared, remains largely unknown, limiting the ability to target and improve preventive strategies.

Diabetes is the primary cause of ESRD, accounting for >40% of ESRD incidence in countries such as Japan, Mexico, Korea and the US [6]. Clinical features of DKD develop in up to 40% of individuals with diabetes [7]. The rising DKD incidence is predominantly driven by individuals with T2D, reflecting greater prevalence of T2D compared to T1D, plus the clustering of cardiometabolic risk factors for CKD in older adults with T2D [7,8].

CKD is predicted to become the 5th leading cause of death by 2040 and diabetes will continue to be the predominant cause of CKD (and ESRD) [9]. In 2010, the annual NHS costs of CKD in England exceeded £1.5 billion with the costs of renal replacement therapy accounting for more than half of this total [10]. Diabetes UK estimate that DKD will incur NHS costs exceeding £2 billion before 2030 [11]

Diabetes is associated with a reduced life expectancy of ~6 years, largely driven by individuals with DKD, who have a much greater reduction in life expectancy of ~16 years [12]. The presence of DKD increases the risk of not only ESRD but also cardiovascular disease, which decreases life expectancy by ~12 years [7,8,12].

DKD arises from both genetic and environmental risk factors. Modifiable risk factors for DKD include poor glycaemic control, hypertension, smoking and hyperlipidaemia [13]. Non-modifiable risk factors for DKD include genetic susceptibility, duration of diabetes, increasing age, and male sex [3,5,7,13]. Optimal glycaemic control coupled with effective blood pressure lowering can substantially reduce the risk of development and progression of DKD [3-5,14,15]. However, such interventions at best slow progression, and do not halt or reverse disease; furthermore, DKD is not clinically detectable until significant organ damage has developed. ***Thus, more effective diagnostic tools and treatments, guided by a better understanding of pathophysiology, are urgently needed*.**

Inherited variation in DNA sequence contributes to individual risk of diabetic complications [16,17,18]. Even with comparable glycaemic control there is great heterogeneity in the frequency and severity of microvascular diabetic complications [1,19, 20]. Familial aggregation of diabetic complications confirms the influence of inherited risk factors, but until recently few specific genes or variants were known [18].

The GEnetics of Nephropathy-an International Effort (GENIE) consortium, launched in 2009, is a fully integrated, multinational research partnership focused on the discovery and characterization of genetic and epigenetic determinants of DKD. Under the US-Ireland R&D Partnership initiative, we formed GENIE by bringing together investigators and resources at the Broad Institute, Children's Hospital Boston, Massachusetts General Hospital, Queen's University Belfast, University College Dublin and the University of Helsinki. More recently, and during the tenure of this grant 2016-2021, the GENIE consortium has welcomed additional US collaborators from the University of Michigan and University of Pennsylvania. This multinational funding mechanism

enabled the establishment of GENIE, a congenial, effective international collaboration. GENIE investigators have established track records of accomplishment in the clinical investigation of diabetes and its renal complications, statistical and population genetics, functional genomics, and association analyses of complex datasets. We have forged effective working arrangements to share research strategy, exchange technical expertise, equipment, bioinformatic data and material resources. We have built this capacity across all the international partners, by multiple face-to-face meetings, regular teleconferences, and frequent emails.

Over the last 10 years, genome-wide association studies (GWAS) have begun to identify the genetic factors that influence diabetic kidney disease (DKD) [21-26]. Many of these studies have been published by the GENIE consortium.

We wished to capitalize on these data, by **undertaking an ambitious programme of research aiming to integrate genomic, epigenetic and functional information to expand the current understanding of DKD biology and its relevance to the increasing clinical problem of CKD/ESRD attributed to diabetes**.

- **Aims and objectives**

Key areas in the genetic exploration of diabetic kidney disease biology remain unaddressed including:

1) the relevance of rarer coding and non-coding variation in the genome,

2) use of extreme phenotypes for DKD,

3) integration of genetic, genomic and epigenetic data, and

4) functional studies to assess the importance of genomic variation

To address these gaps in our knowledge, we proposed the following **Specific Aims:**

Specific Aim No.1:
To assemble and perform a combined analysis of available genetic data pertaining to DKD.

To jointly analyze published results and new data for association to DKD or ESRD caused by DKD.

Specific Aim No. 2:
To assemble diverse, large-scale existing and accumulating global epigenetic and expression datasets, and to generate new expression and epigenetic datasets specifically relevant to DKD.

To complement existing resources by generating data more closely related to DKD: kidney and blood methylation data from patients with or without DKD and new expression data from human renal biopsies and cell models of diabetic organ damage, to identify key biomarkers and regulatory elements.

Specific Aim No, 3:
To perform integrative analysis of the genetic, epigenetic and expression data from Aims 1 and 2 to prioritize genes and non-coding regulatory elements as most likely relevant to DKD.

To use a powerful published method we developed (DEPICT) (1) to integrate data from Aims 1 and 2, and prioritize genes and regulatory elements for further sequencing and functional analysis in Aim 4.

Specific Aim No. 4:
To sequence, in more samples, regions prioritized in Aims 1 to 3, and provide functional validation that manipulation of target genes and non-coding regions produces a phenotype in models of DKD.

To sequence ~2Mb of the most strongly prioritized coding regions and regulatory elements from Aims 1 to 3 in ~3,400 samples, including patients with ESRD secondary to DKD or long-term protection from DKD. For the most compelling known or novel associations, to characterize the functional and molecular consequences of altering these genes and regulatory elements in models of DKD

- **Methods**

Aim 1
To maximize our power to **prioritize genes for further genetic follow-up**, the first required step was to assemble and analyze the best possible set of already available genetic data in studies of DKD and ESRD. We assembled the results of our multiple ongoing collaborative efforts in this space, including genotype data (exome chip and genome-wide genotyping with imputation from the 1000Genomes reference panel), and sequencing data (exome sequencing of T1D patients with ESRD or long term non-progressors). We combined these datasets to perform single variant tests for coding and non-coding variants, gene-based analyses of coding regions that aggregate evidence from multiple variants, and also novel tests that aggregate evidence from non-coding variants, informed by epigenetic data.

Aim 2
Epigenetic data are valuable in at least three ways. First, epigenetic marks are extremely useful in extracting biological and mechanistic information from GWAS data. Second, the shared epigenetic signatures can serve as non-invasive biomarkers of underlying processes and provide complementary information to more traditional biomarkers, and may provide predictive power for prognosis. Finally, by integrating genetic and epigenetic data from the same individuals, causal regulatory mechanisms can be elucidated.

We used human kidney specific epigenome maps that we generated and also growing public repositories of epigenetic data to shed light on genetic findings.

Population-based epigenome-wide association studies (EWAS) of methylation were feasible and cost-effective and we applied these specifically to DKD to identify potential biomarkers.
To use epigenetic data for biomarker discovery, we compared the epigenomes of participants with T1D and DKD and of participants with long duration of diabetes and no evidence of DKD.

Aim 3

For complex phenotypes such as DKD, integration of multiple data sources can improve understanding of pathophysiology and identify potential therapeutic targets

Prioritization of genes. We used methods to prioritize likely causal DKD/ESRD genes for further follow-up in Aim 4, as follows:

1. We identified a subset of genes that are in loci where common variation is associated with DKD or ESRD (from meta-analysis of GWAS data from Aim 1), or have coding variants that are individually or in aggregate associated with DKD or ESRD (from meta-analysis of GWAS, exome chip and exome sequencing data from Aim 1).
2. We ranked associated genes from Step 1 based on similarity to the other associated genes in Step 1.
3. Prioritize for further follow-up (Aim 4) any genes that achieve genome-wide significance in Aim 1, plus top-ranked genes from Step 2, focusing on genes that are also differentially expressed in the kidney or in models of DKD or also differentially methylated in the DKD epigenetics datasets (Aim 2.).

Aim 4

A central goal of the GENIE consortium involves testing the functional role of associated variants and candidate genes. To date, there are few examples of successful transition from GWAS to functional impact of a gene.

We used a combination of *in silico* and *in vitro* methods to test the functional roles of candidate genes. (1) candidate gene expression was assessed with clinical correlates of renal function, and (2) we assessed the transcripts/gene expression across our transcriptomic datasets from renal biopsies from patients with DKD available to the GENIE consortium (3) co-expression analysis of the candidate gene transcripts with all other transcripts was performed by calculating the Pearson's r correlation; (4) these co-expressed, potentially co-regulated transcripts were then analyzed for enrichment of canonical pathways using Ingenuity Pathway Analysis software (www.ingenuity.com); (5) the ability of the subset of co-expressed genes to associate with disease-associated phenotype was determined by unsupervised clustering analysis; and (6) *in vitro* siRNA knockdown experiments were undertaken in murine and human cell lines.

- **Personal and Public Involvement (PPI)**

Researchers from the GENIE consortium have presented research findings (keynote lectures, oral and poster presentations) in a large number of national and international conferences including the annual meetings of the American Society of Nephrology, European Renal Association, American Diabetes Association, European Association for the Study of Diabetes, European Diabetic Nephropathy Study Group, European Alliance for Personalised Medicine and UK Kidney Association.

In Northern Ireland, researchers have made regular contributions to local patient groups including workshops with Diabetes UK, Kidney Care UK and NI Rare Disease Partnerships. Researchers have also attended and discussed the relevance of this research with patients at the annual general meetings of the Northern Ireland Kidney Patients Association and the Northern Ireland Kidney Research Fund.

- **Findings**

The GENIE consortium has established the world's largest case-control study of type 1 diabetes and diabetic kidney disease. Cases are individuals who have had type 1 diabetes for at least 10 years and have a clearly defined clinical diagnosis of diabetic kidney disease (albuminuria, hypertension and declining glomerular filtration rate). Controls are individuals with type 1 diabetes for at least 15 years with no evidence of diabetic kidney disease on repeated testing. Controls have normal blood pressure, are not receiving anti-hypertensive drug treatment and do not have microalbuminuria. Clinical co-variates such as glycaemic control (HbA1c), smoking history, lipid profiles and body mass index are available for most of the recruited individuals.

The clear distinction of the case and control phenotypes has enabled detailed clinical and genetic risk factor analyses for diabetic kidney disease. Over the last decade, the GENIE consortium has been able to publish important papers defining the genetic landscape of diabetic kidney disease [25-28]. These findings have identified multiple risk loci in the genome that predispose susceptible individuals to diabetic kidney disease especially if they have a history of prior poor glycaemic control (a **gene-environment interaction**).

We have identified 16 genome-wide genetic loci that are associated with diabetic kidney disease. [26-30]. **One of the interesting published findings is the link between genetic variants in the collagen type IV alpha 3 chain *(COL4A3)* gene and diabetic kidney disease** [29]. The *COL4A3* gene encodes a collagen protein that is a key component of the kidney's filtration barrier. **A common missense mutation in *COL4A3* associated with diabetic kidney especially in individuals with poor blood glucose control.** This is a finding that requires further investigation to understand the links between poor blood glucose control (metabolic memory) and diabetic kidney disease.

We have also broadened the scope of the research to include individuals with type 2 diabetes and kidney disease [18, 30]. Combining genome-wide association studies and meta-analyses of genomic data from both type 1 diabetes and type 2 diabetes has helped to identify some of the overlapping genetic susceptibility to kidney disease and some features that are distinct to type 1 diabetes.

Of interest, **obesity amplifies the genetic risk of developing diabetic kidney disease in both type 1 diabetes and type 2 diabetes** [31]. Obesity is a potentially modifiable influence on this risk of kidney disease and these findings have relevant public health implications.

Interactions between the background genetic susceptibility to diabetic kidney disease and clinical risk factors such as poor glycaemic control or obesity may be partly mediated by long term modification of 'risk' gene expression. Epigenetic phenomena may account for much of this altered gene expression. We have published epigenetic research derived from cross-sectional and prospective clinical studies of patients with chronic kidney disease (including a major focus on diabetic kidney disease) [32-39]. **Distinct epigenetic profiles have been identified in persons with diabetic kidney disease compared to individuals with diabetes with normal kidney function** [33,38, 39]. This GENIE consortium research has added to our understanding of how 'genetic risk' may be modified by clinical variables. This work may yield new epigenetic biomarkers to help screening of at risk populations and some of the epigenetic features could become therapeutic targets of new or repurposed therapeutics [40-42].

The GENIE consortium is exploring how best to integrate genomic and epigenetic findings and to undertake *in vitro* and *in vivo* studies to help understand the mechanisms responsible for diabetic kidney disease. Novel biomarkers may be one of the earlier clinical translations of this 'omics'-related research.

- **Conclusion**

This research has made real progress in filling many of the current gaps in our collective understanding of DKD biology and the clinical problem of ESRD caused by DKD. The novel integration of genetic, epigenetic and expression data with other biological knowledge, has improved our capacity to use 'omics' data to interrogate the clinical progression of DKD. Discoveries from this project have illuminated biological pathways that promote DKD pathogenesis, and reveal potential biomarkers and targets for prevention or treatment.

- **Practice and Policy Implications/Recommendations**

Public health measures can help to reduce many of the risk factors that contribute to diabetes (**obesity, sedentary lifestyle**) and associated cardiovascular disease (**smoking, hypertension, hyperlipidaemia**).

Clustering of these clinical risk factors contribute to diabetic kidney disease. Multiple opportunities exist to modify these risk factors at a population level e.g. increasing physical activity, weight management, smoking cessation, reduction in dietary salt intake (to help reduce the prevalence of hypertension).

These public health measures **require integrated responses** from government, local authorities, schools and workplaces to improve the built environment, provide better access to physically active travel and leisure and education on healthier lifestyle choices aided by taxation on tobacco and unhealthy foods.

Poor control of blood sugar is the most important modifiable risk factor for kidney disease in persons with diabetes. Diabetic kidney disease is attributed to prolonged (years) exposure of the kidneys to the harmful effects of high blood sugar. Improved control of diabetes through education, improvements in self-monitoring of glycaemic control combined by regular clinical follow-up and targeted interventions to limit progression of early diabetic kidney disease can change the incidence of kidney disease in susceptible individuals.

Microalbuminuria is the earliest clinical sign of diabetic kidney disease. Screening for microalbuminuria (a small concentration of albumin in urine) is recommended on an annual basis for all persons with diabetes in national and international guidelines. Drugs that inhibit sodium-glucose transporters in kidneys (**SGLT2 inhibitors**) or blockade the renin-angiotensin-aldosterone system (**ACE inhibitors or angiotensin receptor blockers**) can retard progression of diabetic

kidney disease. These drugs also modify the associated high cardiovascular risk associated with diabetic kidney disease by reducing hypertension, reducing the risk of myocardial infarction and heart failure, reducing hospitalisations and all-cause mortality.

Opportunities for screening and early intervention are missed if regular clinical follow up does not happen. Improving access for persons with diabetes to clinical teams is critical and requires continued innovation to engage those harder to reach groups (adolescents, remote and rural populations, elderly patients, patients where English is not the first language, Black and Asian communities).

Once an individual has developed diabetic kidney disease (persistent proteinuria and decreasing glomerular filtration rate) it is important that there is long-term follow up by clinicians with input from nephrologists. Diabetic kidney disease can progress to end-stage renal disease (ESRD) requiring expert and costly care (including chronic dialysis and / or renal transplantation). **Diabetic kidney disease is the commonest cause for ESRD in almost all countries including the UK, USA and Ireland.**

Research (such as the work undertaken for this report) has established that there are important **gene-environment interactions** that underpin the susceptibility to diabetic kidney disease. Certain ethnic groups have a much higher lifetime risk of developing diabetes and diabetic kidney disease. **Multiple genetic risk factors associated with diabetic kidney disease have been identified** by our research and help to explain some of the key features of the disease. For instance, genetic variation in key proteins that form the basis of the filtering capacity of the kidney make people susceptible to kidney damage, especially if their lifetime control of diabetes is poor. Epigenetic phenomena (where gene expression is altered by environmental influences) are likely to be critically important in diabetic kidney disease. **Poor blood glucose control can 'reset' gene expression in the kidney leading to activation of multiple progressive injury pathways that result in kidney damage.** These epigenetic factors may be responsible for the 'metabolic memory' of poor control of diabetes in previous years leading to future progressive kidney failure.

Future research will explore whether these genetic and epigenetic risk factors can be identified early in the life course of individuals with diabetes through novel genetic and epigenetic screening tests. This would permit more intensive efforts to improve blood sugar control, modify lifestyle risk factors, and intervene earlier with effective therapies that slow progression of diabetic kidney disease.

- **Pathway to Impact**

The GENIE consortium is an international alliance of clinicians, genetic epidemiologists, data scientists, molecular and cell biologists. The discoveries of genetic and epigenetic risk factors that explain part of the susceptibility to diabetic kidney disease are important for our understanding of why kidney injury occurs in diabetes. There are likely to be much wider applications of this new knowledge to most chronic kidney diseases (irrespective of the initial cause).

Next steps on the pathway to impact include experiments to determine the mechanisms of injury caused by the discovered gene variants (and altered gene expression) in multiple in vitro and in vivo model systems. Ultimately this research can identify better screening tools and new targets for therapies to modify risk of developing progressive diabetic kidney disease.

One important aspect of this research is the positive impact on the training and mentoring of a new cadre of scientists, clinicians and academics. Postgraduate research students and postdoctoral fellows working on GENIE-related research over the last decade are now in various posts including NHS laboratory scientists, pharma-industry scientists, clinical consultant and university academic posts.

In parallel, the GENIE consortium investigators are sharing their discoveries with public health colleagues and clinical leaders for diabetes and nephrology. Integrated policies to positively influence public health require collective engagement with patients, families, clinicians, local authorities and government to effect population changes. These are coupled with evidence-based clinical guidelines for improving the screening and treatment of diabetic kidney disease and its related complications. Regional clinical guidelines for acute injury, chronic kidney disease and hyperkalaemia have been published during the tenure of the GENIE grants (under the auspices of the PHA Guidelines and Audit Implementation Network). These GAIN guidelines help to improve patient safety https://www.rqia.org.uk/what-we-do/rqia-s-funding-programme/guidelines/

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- **Relevant Logos**

GEnetics of Nephropathy – an International Effort

Broad Institute • Queen's University Belfast • University College Dublin • University of Helsinki • Children's Hospital Boston • Massachusetts General Hospital
University of Michigan • University of Pennsylvania