



馬青雲

RONALD MA



06 DIABETES AND OBESITY

Research Progress Summary

Epidemiology of Diabetes and Diabetes complications in Asians

The research team led by Ronald Ma has continued to generate novel insights on the epidemiology of diabetes and diabetic complications in Asians, to help inform the formulation of strategies and policies to address this important public health burden. With recent support from the Theme-based Research Scheme (TRS) on Diabetes Complications and ongoing support from a Research Impact Fund (PC: Ronald), they have charted the natural history of diabetic kidney disease and the progressive decline in renal function using various novel analytic approaches, including latent trajectory analysis. This work has highlighted the heterogeneity of decline in renal function, and identified subgroups at particular risk of renal dysfunction. They have recently used proteomics, metabolomics and other omics approach to identify predisposing factors and markers associated with rapid renal function decline and the development of diabetic kidney disease. They have also conducted studies to examine sub-phenotype in diabetic kidney disease, and the long-term impact of acute kidney injury on progression of diabetic kidney disease. The team is also using big-data analytics to examine the epidemiology of diabetes complications based on population-based administrative data. Both Ronald and Andrea Luk have been invited to contribute to the recent International Diabetes Federation (IDF) Diabetes Atlas, leading subgroups on type 1 Diabetes in adults and young-onset diabetes, respectively.

Earlier work has also highlighted the burden of young-onset diabetes, and conditions that predispose to young-onset diabetes. The team has completed one of the longest follow-up studies to investigate the impact of Polycystic Ovary Syndrome (PCOS) on the development of glucose intolerance and diabetes among young women. This work has now extended to the long-

term follow-up cardiovascular complications and metabolic outcomes in women with PCOS and their offspring, as well as analyses based on population-based data.

Genetics of Diabetes and Gestational Diabetes

Work from the research team has contributed significantly to advance the understanding of the genetic basis of type 2 diabetes. Together with colleagues across Asia, they have completed one of the largest genome-wide association studies (GWAS) for type 2 diabetes, and identified 61 novel loci for type 2 diabetes. This study has considerably expanded the number of genetic loci associated with type 2 diabetes in Asians, and would form the basis of future translation towards clinical prediction and care. They are currently investigating the role of these markers in the development of glucose intolerance and other metabolic abnormalities among adolescents and children.

In a project supported by Research Grants Council – General Research Fund, Andrea is leading an analysis to identify monogenic forms of diabetes among the research team's cohort of patients with young-onset diabetes. This work will provide complementary information on rare genetic variation that contributes to the heritability of diabetes in Asians, and help to advance precision medicine in diabetes.

Gestational diabetes has become a common and major complication of pregnancy, and has long-term adverse effects for the mother and offspring. In collaboration with Xilin Yang from Tianjin Medical University, China, they have conducted a meta-analysis of genome-wide association study to identify novel genetic variants associated with gestational diabetes in the Chinese population, as well as search for metabolomic markers associated with GDM.



Principal Investigator

Ronald Ma



Team members

Andrea Luk, Risa Ozaki, Wing Yee So, Hongjiang Wu, Cadmon Lim, Heung Man Lee, Claudia Tam, Raymond Wan, Ming Wai Poon, Guozhi Jiang, Noel Ng, Fefei Cheng, Eric Lau, Aimin Yang, Baoqi Fan, Vince Chan, Chi Wai Ng, Yong Hou, Chun Hei Tam, Charmaine Lee, Kit Ying Tsoi, Qiao Jin, Chuiguo Huang, Yingnan Fan, Tsz Fung Tsoi, Xinge Zhang, Kqun Kiu Wong

Long-term Consequences of Gestational Diabetes and Related Biomarkers

In a long-term collaborative study together with Wing Hung Tam from the Department of Obstetrics and Gynaecology, the team has investigated the long-term health impact of gestational diabetes. This includes the long-term follow-up of a GDM mother-offspring cohort for more than 2 decades to follow their long-term progression to metabolic abnormalities as well as diabetes, and the multi-centre Hyperglycaemia and Adverse Pregnancy Outcome (HAPO) Follow Up Study. The latter has highlighted the long-term risk of diabetes among women with gestational diabetes, as well as the

independent association between maternal GDM and offspring adiposity. In order to unravel the link between maternal hyperglycaemia and offspring metabolic abnormalities, in work supported by the Research Grants Council, the research team is applying epigenomic profiling to identify potential methylation changes to offspring DNA following exposure to maternal hyperglycaemia. The team is also conducting a long-term follow-up offspring of mothers with GDM as they now enter adulthood, to evaluate their metabolic profile as well as skeletal health.

Genetic and Novel Biomarkers of Diabetes Complications

In work supported by the Research Grants Council Theme-based Research Scheme (TRS), Ronald's team has completed one of the largest genome-wide association studies for diabetes complications globally, and identified a number of genomic regions associated with diabetic kidney disease in Asians. In addition, through the TRS, the team has established the multi-centre Hong Kong Diabetes Biobank (HKDB), which forms a unique dataset with detailed clinical phenotyping, multi-omics profiling and long-term follow-up which would serve to advance future epidemiology research as well as biomarker

discovery. Ongoing works include investigating the biological mechanisms whereby the new genes impact the development of diabetes complications, with views to develop novel treatments to target diabetes complications. With ongoing support from the Research Grants Council Research Impact Fund, they are continuing their work on biomarkers for diabetes complications, and have expanded that effort to incorporate metabolomic profiling to integrate into their multi-omics analyses to obtain a better picture of key disease pathways. The research team has also shown the utility of leukocyte

telomere length (LTL) as a biomarker for diabetes-related complications, as well as other diabetes-related outcomes.

Precision Medicine in Diabetes

Through support from the Research Grants Council Research Impact Fund and the Croucher Foundation, the team aims to bring some of the discoveries generated from their work to translate to the bedside to impact on clinical care. This includes incorporating their biomarkers into clinical management of patients with diabetes, development of various polygenic risk scores, as well as pharmacogenomics studies to stratify patients based on treatment response for a better selection of glucose-lowering and other treatments. They are also developing genetic risk scores for stratifying risk of type 1 diabetes in Chinese. The research team has recently been invited to contribute to a major global initiative on Precision Medicine

in Diabetes, including leading a systematic review of biomarkers relevant to predicting diabetes complications.

COVID-19 and Diabetes

Since the pandemic began, COVID-19 has impacted on every aspect of daily life. People with diabetes have increased susceptibilities to COVID-19 and adverse outcomes following COVID-19 infections. The research team has been conducting epidemiological analyses relating to diabetes and COVID-19, including the impact of diabetes treatments on outcome, as well as genetic studies relating to adverse outcome in COVID-19.

Much of their research is highly multidisciplinary and collaborative, with ongoing collaborations with more than 20 research groups across the world.

Research and Scholarship

Research Awards and Recognitions

Member's Name	Details	
	Award	Organisation
Ronald Ma	Croucher Senior Research Fellow (2020-2021)	Croucher Foundation
	Member	Lancet Clinical Commission on Diabetes
	Executive Board Member	Asian Association for the Study of Diabetes (AASD)
	Section Lead	International Diabetes Federation (IDF) Diabetes Atlas 2021
	Co-chair, Workgroup on Precision Prognostics, Precision Medicine in Diabetes Initiative	American Diabetes Association (ADA) Precision Medicine in Diabetes Initiative (PMDI)
	Panel Member	RGC Biology and Medicine Panel
Andrea Luk	Co-lead	Epidemiology section, and Member, Lancet Clinical Commission on Diabetes

Member's Name	Details	
	Award	Organisation
Andrea Luk	Section Lead	International Diabetes Federation (IDF) Diabetes Atlas 2021

Fellowships

Member's Name	Details	
	Fellowship	Organisation
Ronald Ma	Croucher Senior Medical Research Fellowship (2020-2021)	Croucher Foundation
Noel Ng	RGC Postdoctoral Fellowship	Research Grants Council
Feifei Cheng	Faculty Postdoctoral Fellowship	Faculty of Medicine, The Chinese University of Hong Kong

Academic Editorship

Member's Name	Details	
	Role	Journal
Ronald Ma	Expert Editor (from 11/2020)	Journal of Diabetes Investigation
	Member of Editorial Board	PLOS Medicine Obesity Reviews
	Associate Editor	Diabetologia
Andrea Luk	Associate Editor	Diabetic Medicine



Reviewer of Journal / Conference

Member's Name	Details	
	Role	Journal / Conference
Ronald Ma	Reviewer	PLOS Medicine
		Diabetes Care
		Diabetologia
		Diabetes
		Diabetic Medicine
		Journal of Diabetes Investigation
		Diabetes/Metabolism Research and Reviews
		Diabetes Research and Clinical Practice
		Journal of Clinical Endocrinology and Metabolism
		American Journal of Clinical Nutrition
		Annals of Human Biology
		Clinical Endocrinology
		Obesity Reviews
		Obesity
		International Journal of Obesity
IETE Technical Review		
Andrea Luk	Reviewer	Diabetes Care
		Diabetologia
		Diabetic Medicine
		Diabetes
		Obesity and Metabolism
		Journal of Diabetes
		Diabetes/Metabolism Research and Reviews
		Diabetes Research and Clinical Practice
		Cardiovascular Diabetology
		Journal of Clinical Endocrinology and Metabolism
	Lancet Regional Health Western Pacific	
Programme Committee Stream Lead	Diabetes complications, World Diabetes Congress 2022, Lisbon, Portugal	

Grants and Consultancy

Name	Project Title	Funding Source	Start Date (dd/mm/yyyy)	End Date (dd/mm/yyyy)	Amount (HK\$)
Ronald Ma	A Nanotechnology Platform for Profiling Diabetes-related MiRNA for Precision Medicine	Innovation and Technology Commission – Midstream Research Programme for Universities	01/06/2021	30/11/2023	5,998,400
	Research Talent Hub - PiH/198/21	Innovation and Technology Commission	01/06/2021	30/11/2023	1,005,000
	Research Talent Hub - InP/198/21	Innovation and Technology Commission	12/07/2021	30/11/2023	541,393.54
	Research Talent Hub - PiH/242/21	Innovation and Technology Commission	12/07/2021	30/09/2022	490,677.41
	Research Talent Hub - InP/198/21	Innovation and Technology Commission	18/10/2021	30/11/2023	561,208.06
	Croucher Senior Medical Research Fellowship	Croucher Foundation	01/05/2021	30/04/2022	2,272,948
	Precision Medicine in Diabetes	Croucher Foundation	01/05/2021	30/04/2023	2,000,000
	Diabetes and Telomere Length	The Chinese University of Hong Kong – Direct Grant	30/06/2021	29/06/2022	32,000
	Translating Multi-omic Discoveries to Transform Diabetes Care and Reduce Diabetic Complications	Research Grants Council – Research Impact Fund	01/05/2019	30/04/2024	8,400,000
	Translating Multi-omic Discoveries to Transform Diabetes Care and Reduce Diabetic Complications	Research Committee – Research Impact Matching Fund	01/05/2019	30/04/2024	3,401,550
	Translating Multi-omic Discoveries to Transform Diabetes Care and Reduce Diabetic Complications	Research Committee – Funding for Research Sustainability of Major Research Grants Council Funding Schemes	27/05/2019	30/04/2024	500,000

Name	Project Title	Funding Source	Start Date (dd/mm/yyyy)	End Date (dd/mm/yyyy)	Amount (HK\$)
Ronald Ma	Unraveling the Link between Maternal Hyperglycaemia and Childhood Obesity: Genome-wide Methylation Analysis in a Prospective Cohort of Untreated Gestational Diabetes	Research Grants Council – General Research Fund	01/01/2019	31/12/2021	970,517
	Unraveling the Link between Maternal Hyperglycaemia and Childhood Obesity: Genome-wide Methylation Analysis in a Prospective Cohort of Untreated Gestational Diabetes	Research Incentive Scheme top-up for Research Grants Council – General Research Fund	01/01/2019	31/12/2021	20,000
	Progression of Glucose Intolerance and Cardiometabolic Risk Factors over a Decade in Chinese Women with Polycystic Ovary Syndrome: A Case-control Study	The Chinese University of Hong Kong – Direct Grant	05/06/2020	04/06/2021	62,000
	Genomic Medicine in Diabetic Kidney Disease	University Grants Committee – Research Matching Grant Scheme	01/06/2020	30/11/2026	2,344,848.67
	Precision Medicine in Diabetes	University Grants Committee – Research Matching Grant Scheme	01/12/2021	30/11/2026	500,000
	A Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter, Event-driven Phase III Study to Investigate the Efficacy and Safety of Finerenone on the Reduction of Cardiovascular Morbidity and Mortality in Subjects with Type 2 Diabetes Mellitus	Bayer HealthCare Limited	04/01/2016	07/07/2021	2,073,177.5

Name	Project Title	Funding Source	Start Date (dd/mm/yyyy)	End Date (dd/mm/yyyy)	Amount (HK\$)
Ronald Ma	Randomized, Double-blind, Placebo-controlled, Parallel-group Study to Assess Cardiovascular Outcomes Following Treatment with Ertugliflozin (MK-8835/PF-04971729) in Subjects with Type 2 Diabetes Mellitus and Established Vascular Disease, the Vertis CV Study	Merck Sharp & Dohme (Asia) Limited	28/02/2017	07/07/2021	958,505
	A Phase 3b, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of TRC101 in Delaying Chronic Kidney Disease Progression in Subjects with Metabolic Acidosis	Tricida, Inc.	01/04/2019	31/12/2024	1,605,460
	PIONEER 12 China Multi-regional Clinical Trial: Efficacy and Safety of Oral Semaglutide Versus Sitagliptin in Subjects with Type 2 Diabetes Mellitus Treated with Metformin	Novo Nordisk Hong Kong Limited	01/08/2019	06/04/2023	2,332,500
	Semaglutide Cardiovascular Outcomes Trial in Patients with Type 2 Diabetes (SOUL)	Novo Nordisk Hong Kong Limited	29/08/2019	29/07/2024	9,424,000
	A Multicenter, Multinational, Prospective, Interventional, Single-arm, Phase IV Study Evaluating the Clinical Efficacy and Safety of 26 Weeks of Treatment with Insulin Glargine 300U/ml (Gla-300) in Patients with Type 2 Diabetes Mellitus Uncontrolled on Basal Insulin	Sanofi-Aventis Hong Kong Limited	01/08/2019	31/12/2021	424,250
	FAME 1 EYE - The Fenofibrate and Microvascular Events in Type 1 Diabetes Eye. A Randomised Trial to Evaluate the Efficacy on Retinopathy and Safety of Fenofibrate in Adults with Type 1 Diabetes; A Multicenter Double-blind Placebo-controlled Study in Australia and Internationally	University of Sydney	01/08/2019	31/12/2024	348,160

Name	Project Title	Funding Source	Start Date (dd/mm/yyyy)	End Date (dd/mm/yyyy)	Amount (HK\$)
Ronald Ma	Effect and Safety of Semaglutide 2.4mg Once-weekly on Weight Management in Subjects with Overweight or Obesity	Novo Nordisk Hong Kong Limited	08/12/2020	31/12/2024	2,176,500
	A Non-blinded Retrospective Biomarker Add-on Study to FIGARO-DKD for Bioprofiling the Pharmacodynamic Response to Finerenone in FIGARO-DKD Subjects (FIGARO-BM)	Bayer HealthCare Limited	15/10/2021	31/12/2023	105,000
	Precision Medicine to Redefine Insulin Secretion and Monogenic Diabetes (PRISM) in Chinese Patients with Young Onset Diabetes	Food and Health Bureau - Health and Medical Research Fund Commissioned Grant	01/09/2019	31/08/2024	8,457,718
	Characterising the Hazards of Cardiac Arrhythmias and Adverse Clinical Outcomes Accompanying Hypoglycaemic Nadir in Frail Elderly Diabetics on Insulin: A Prospective, Longitudinal, Observational, Follow-up Study	Health and Medical Research Fund	01/04/2018	31/03/2021	1,197,580
	The Effect of In Utero Hyperglycaemia, Maternal Overnutrition and Interaction with Postnatal Lifestyle on Cardiometabolic Risk at Young Adulthood - Extension of HAPO Follow-up Study	Research Grants Council - General Research Fund	01/01/2020	31/12/2022	1,158,019
	To Develop A Community-based Exercise Programme to Prevent Diabetic Shoulder Problems in Hong Kong Chinese Elderly	Health and Medical Research Fund	01/10/2020	30/09/2022	775,188
	Precision Medicine to Redefine Insulin Secretion and Monogenic Diabetes (PRISM) in Chinese Patients with Young Onset Diabetes	Food and Health Bureau - Health and Medical Research Fund Commissioned Grant	01/09/2019	31/08/2024	8,457,718
Ronald Ma Andrea Luk					

Name	Project Title	Funding Source	Start Date (dd/mm/yyyy)	End Date (dd/mm/yyyy)	Amount (HK\$)
Andrea Luk	A Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter, Event-Driven Phase III Study to Investigate the Efficacy and Safety of Finerenone, In Addition To Standard of Care, on the Progression of Kidney Disease in Subjects with Type 2 Diabetes Mellitus and the Clinical Diagnosis of Diabetic Kidney Disease	Bayer Healthcare Limited	04/01/2016	31/12/2021	1,690,787.5
	A Trial Investigating the Pharmacokinetic Properties of Fast-Acting Insulin Aspart in Chinese Subjects with Type 1 Diabetes or Type 2 Diabetes	Novo Nordisk Hong Kong Limited	03/12/2020	31/12/2022	2,672,830
	Delineating the Metabolic Architecture and Response to Anti-hyperglycaemic Drug Treatment in Lean Type 2 Diabetes in Chinese	Research Grants Council - General Research Fund	01/01/2021	31/12/2023	1,178,778
	Randomised, Double-blind (within Dose Groups), Placebo-controlled and Parallel Group Trial to Investigate the Effects of Different Doses of Oral BI685509 Given over 20 Weeks	Boehringer Ingelheim Limited	15/06/2021	31/12/2023	610,000
	ReFINEDR: Observational Study of Routine Ophthalmological Examinations of Patients Included in the 2 Bayer Sponsored Phase 3 Clinical Trials FIDELIO and FIGARO to Investigate the Effect of Finerenone on Delaying the Progression of Diabetic Retinopathy	Bayer Healthcare Limited	16/02/2021	31/12/2023	80,500
	Innovative Diagnosis and Treatment for Shrimp Allergy	Research Committee - Research Impact Matching Fund	01/06/2020	31/05/2025	8,397,098

Name	Project Title	Funding Source	Start Date (dd/mm/yyyy)	End Date (dd/mm/yyyy)	Amount (HK\$)
Andrea Luk	Commissioned Programme on Early Phase Testing of Novel Pharmaceutical Products in the Phase 1 Clinical Trial Centre, the Chinese University of Hong Kong	Food and Health Bureau – Health and Medical Research Fund Commissioned Grant	02/05/2019	01/05/2024	50,000,000
Noel Ng	Evaluation of the Long-term Healthcare Impact of Polycystic Ovary Syndrome	Health and Medical Research Fund	01/10/2021	30/09/2023	1,304,136

Publications

A. Journal Papers

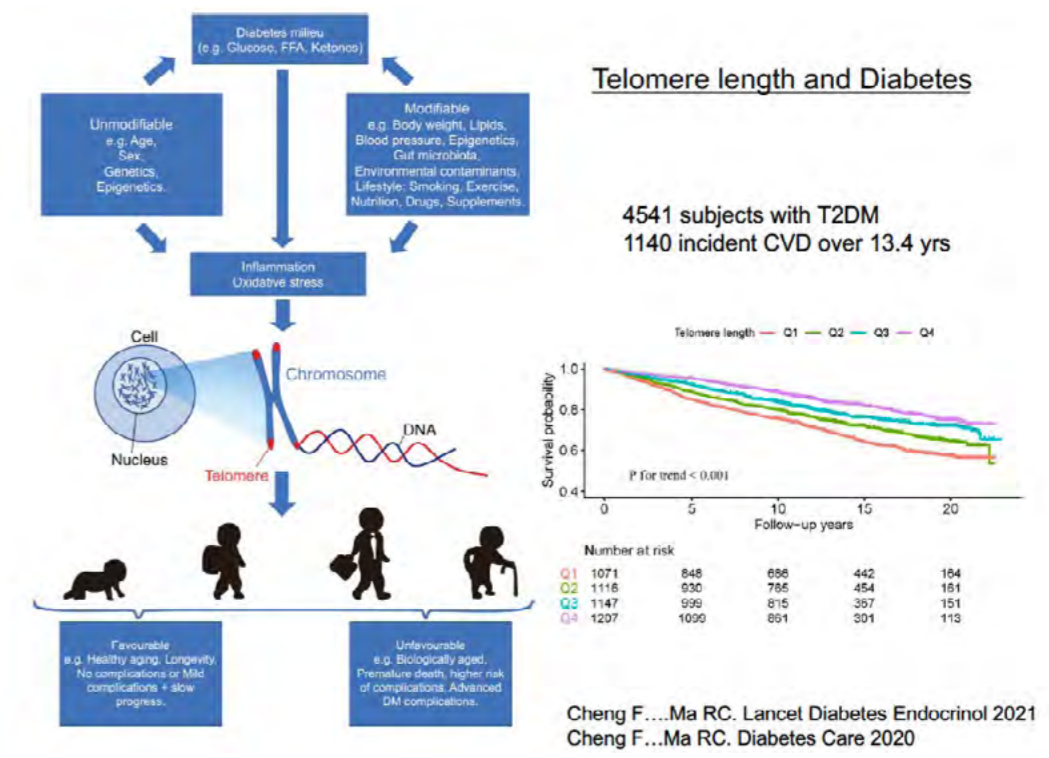
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- Jin Q, Lau ES, Luk AO, Ozaki R, Chow EY, So T, Yeung T, Loo K man, Lim CK, Kong AP, So WY, Jenkins AJ, Chan JC, Ma RC. Skin autofluorescence is associated with progression of kidney disease in type 2 diabetes: A prospective cohort study from the Hong Kong diabetes biobank. *Nutrition, Metabolism, and Cardiovascular Diseases: NMCD*. 2022;32(2). doi:10.1016/j.numecd.2021.10.007. (Epub ahead of print)

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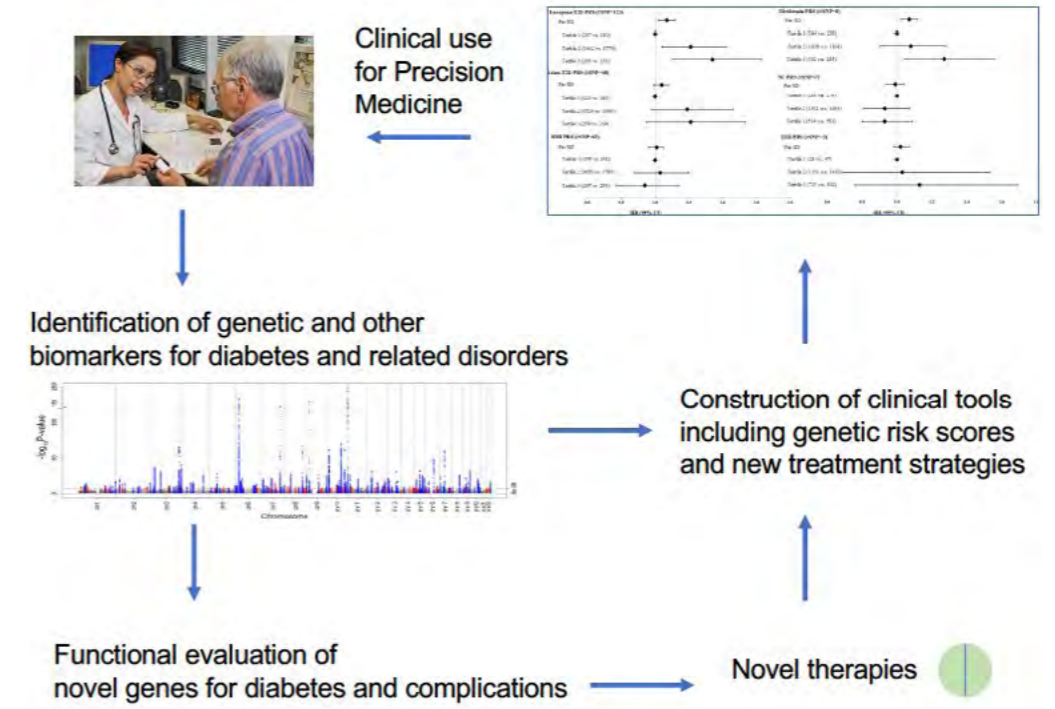
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Telomere Length in diabetes.

Source: *Diabetes, metabolic disease and telomere length (Lancet Diabetes Endocrinology 2021)*



Overall summary of research objectives of team.

Source: Ronald Ma