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Multiomic approaches to chronic disease risk

Dr Gareth McKay
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16th June 2023

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Acknowledgements

Broad/MGH/BCH
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Rachel O'Neill
Michael Corr
David Simpson
Jinnan Zang

University of Dundee
Manuel Trucco
Alex Doney

University of Hong Kong
Carol Cheung

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Outline of my talk

- A bit about me
- Northern Ireland
- Queen's University Belfast
- My career track
- Chronic Kidney Disease (CKD)
- Diabetic Kidney Disease (DKD) Genetics
- DKD Epigenetics
- DKD miRNA analysis
- Oculomics
- Kidney Transplantation

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EST 1845


ATLANTIC OCEAN
IRISH SEA
CELTIC SEA
North Channel
Isle of Man
Northern Ireland (U.K)
Creeslough
Gweedore
Letterkenny
Derry
Coleraine
Stranraer
Ballymena
Larne
Lifford
Leifear
Strabane
Ardara
Donegal
Antrim
Carrickfergus
Bangor
Newtownards
Omagh
Cookstown
Belfast
Ballyshannon
Lisburn
Lurgan
Portadown
Enniskillen
Armagh
Downpatrick
Sligo
Sligeach
Bangor Erris
Ballina
Monaghan
Muineachán
Newry
Kilkeel
Carrick on Shannon
Cora Droma Rúisc
Cavan
Dundalk
Dun Dealgan
Castlebar
Caisleán an Bharraigh
Kingscourt
Ardee
Westport
Longford
An Longfort
Navan
An Uaimh
Drogheda
Droichead Átha
Clairemorris
Roscommon
Ros Comáin
Trim
Baile Átha Troim
Clifden
Tuam
Mullingar
An Muileann gCearr
Athlone
Baile Átha Luain
Swords
Dublin
Dun Laoghaire
Bray
Naas
Nás na Riogh
Galway
Loughrea
Tullamore
Tulach Mhór
Holyhead
Aran Islands
Portlaoise
Wicklow
Cill Mhantáin
Roscrea
Enistimon
Ennis
Inis
Durrow
Carlow
Ceatharlach
Arklow
Kilkee
Limerick
Luimneach
Kilkenny
Cill Chainnigh
Enniscorthy
Tipperary
Tiobraid Árann
Clonmel
Cluain Meala
New Ross
Wexford
Loch Garman
Tralee
Trá Lí
Waterford
Rosslare Harbour
Dingle
Fermoy
Mallow
Dungarvan
Killarney
Youghal
Macroom
Cork
Corcaigh
Kenmare
Waterville
Bantry
IRELAND
ÉIRE
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County seat
City; town
Airport
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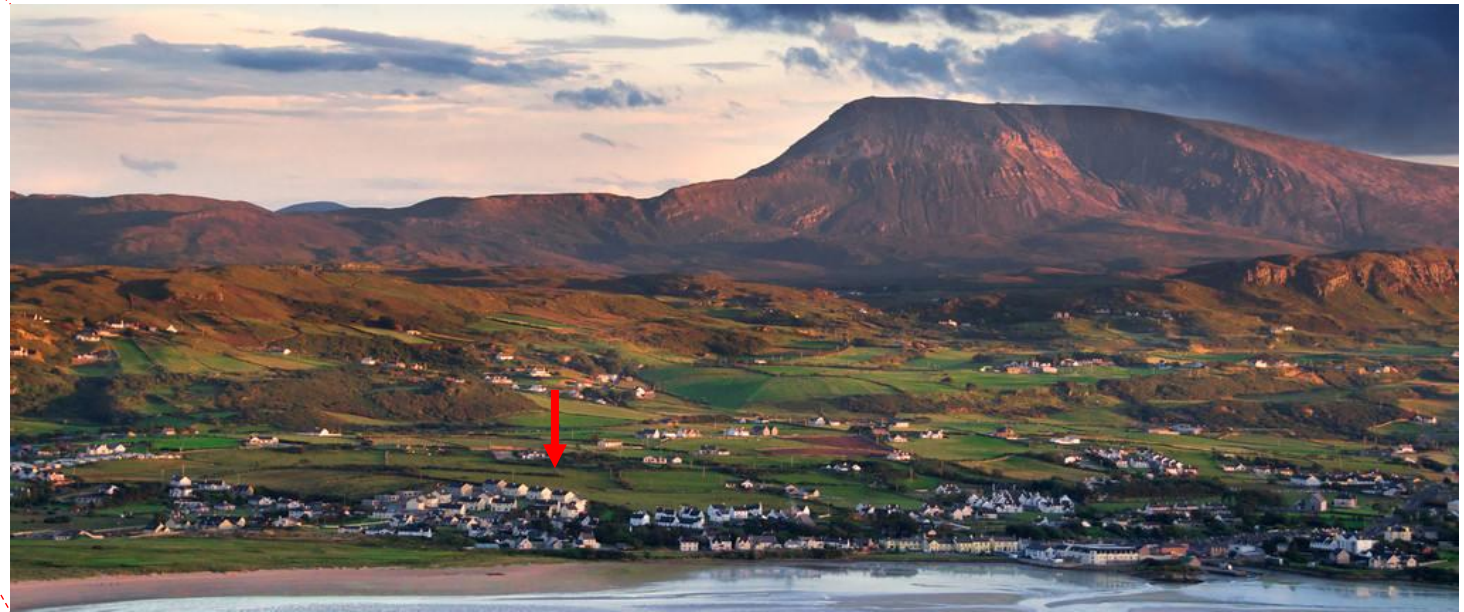
Expressway
Main road
Secondary road
Railroad
0 25 50 75 100 km
0 30 60 mi

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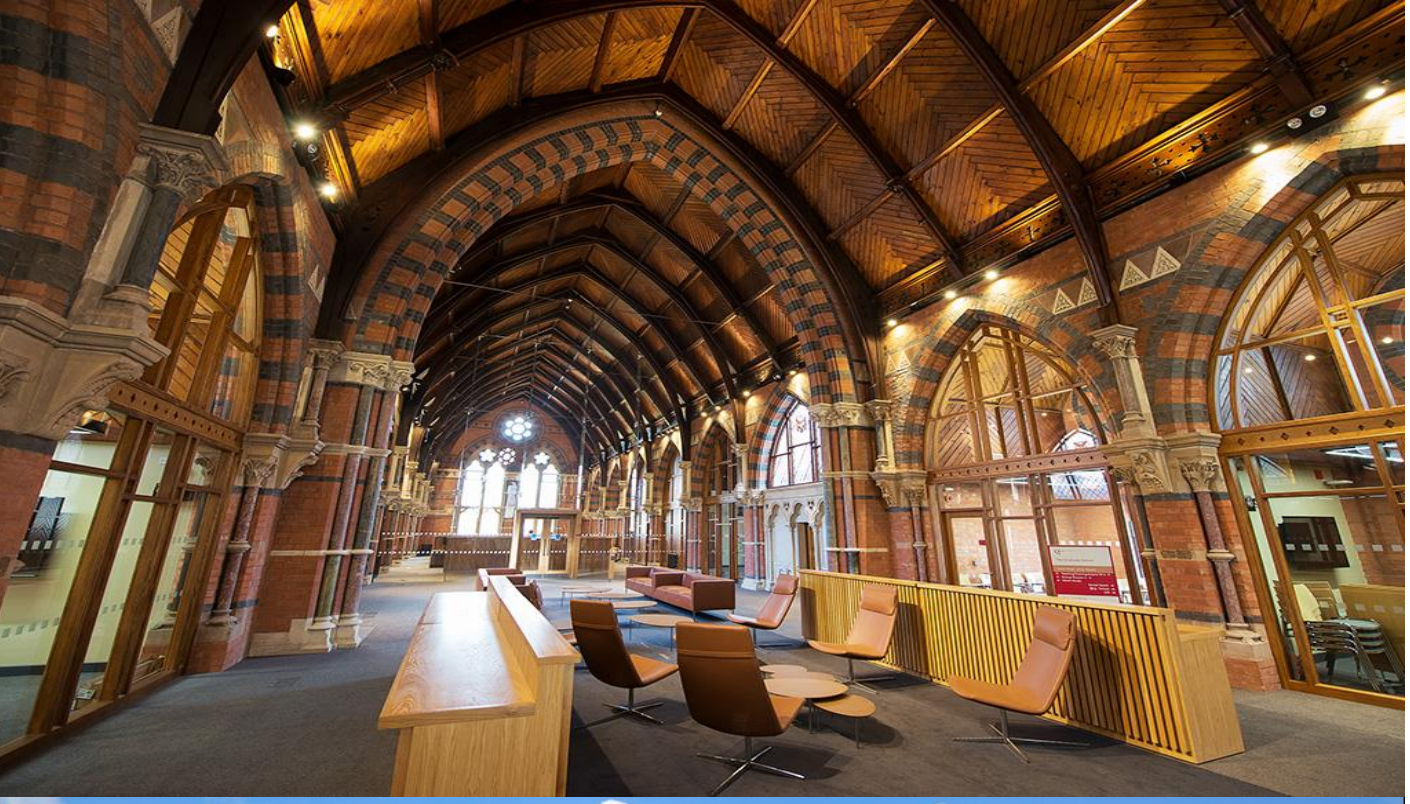

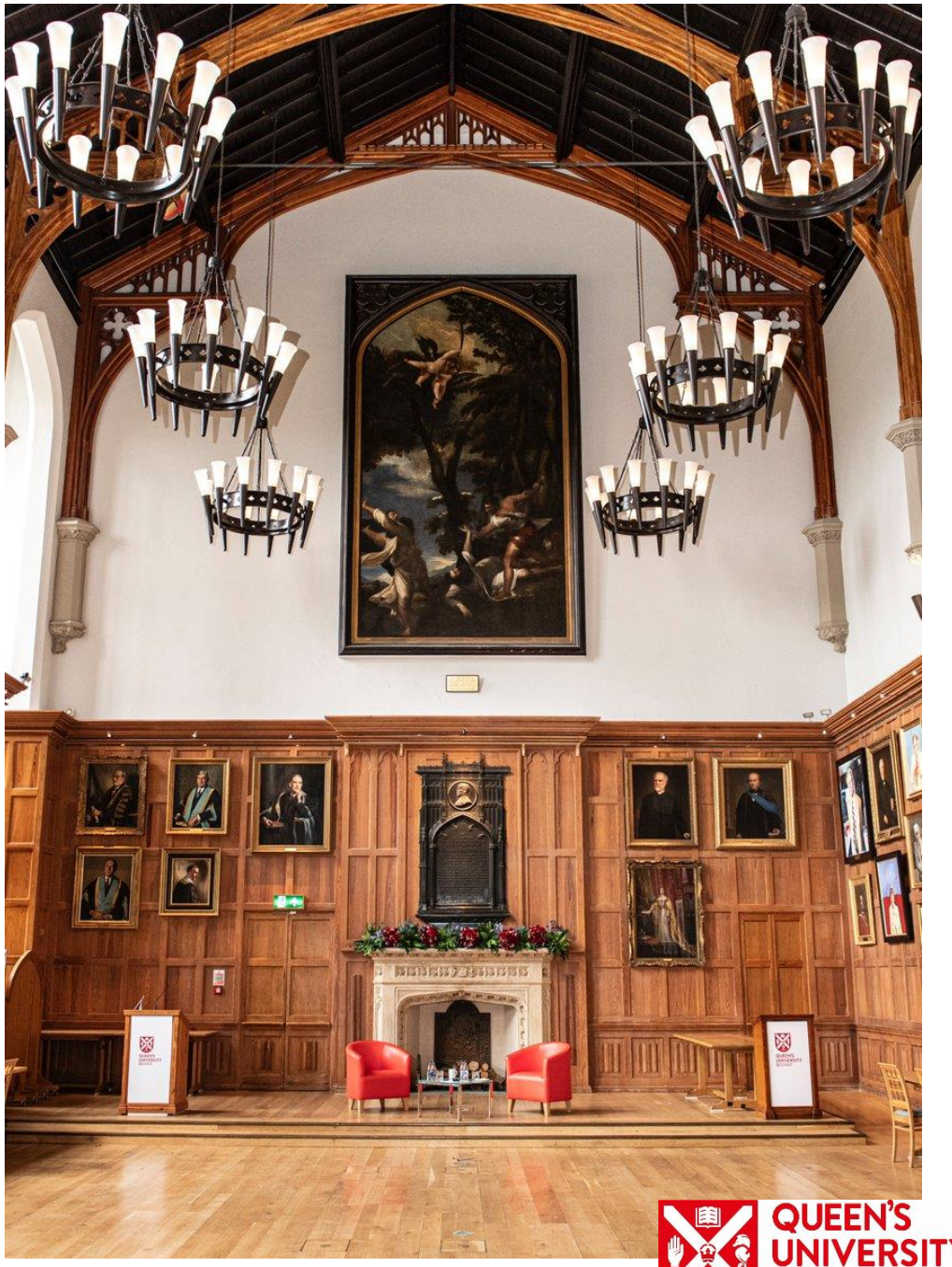

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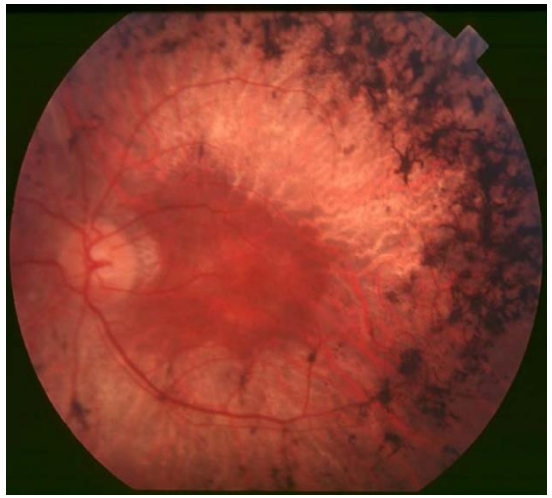
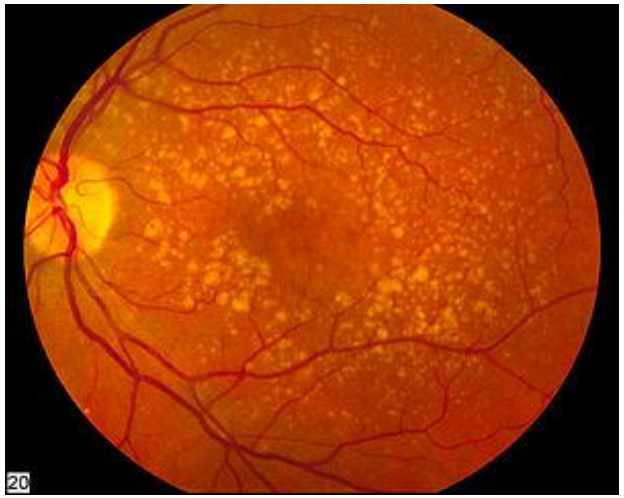

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https://ec.europa.eu/info/funding-tenders/opportunities/portal/screen/work-as-an-expert

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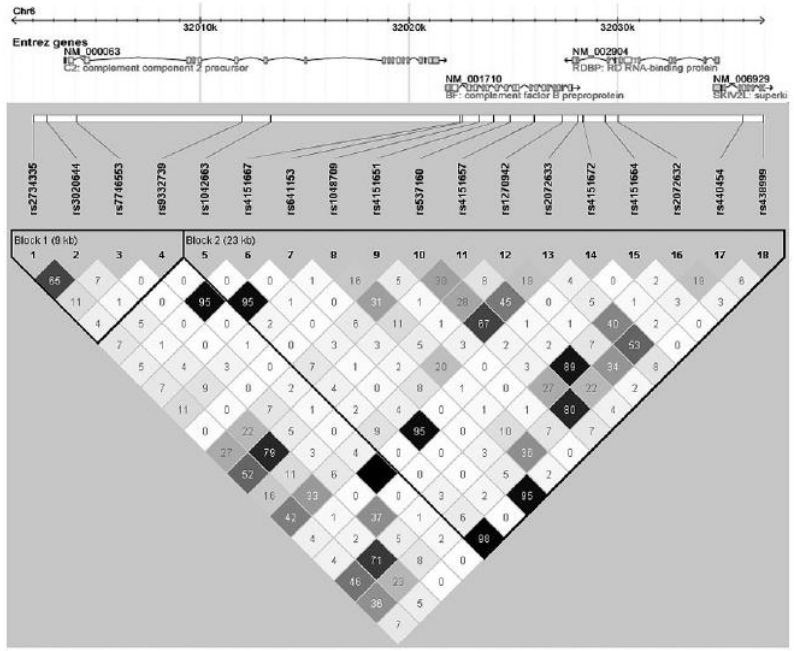


Further Assessment of the Complement Component 2 and Factor B Region Associated with Age-Related Macular Degeneration

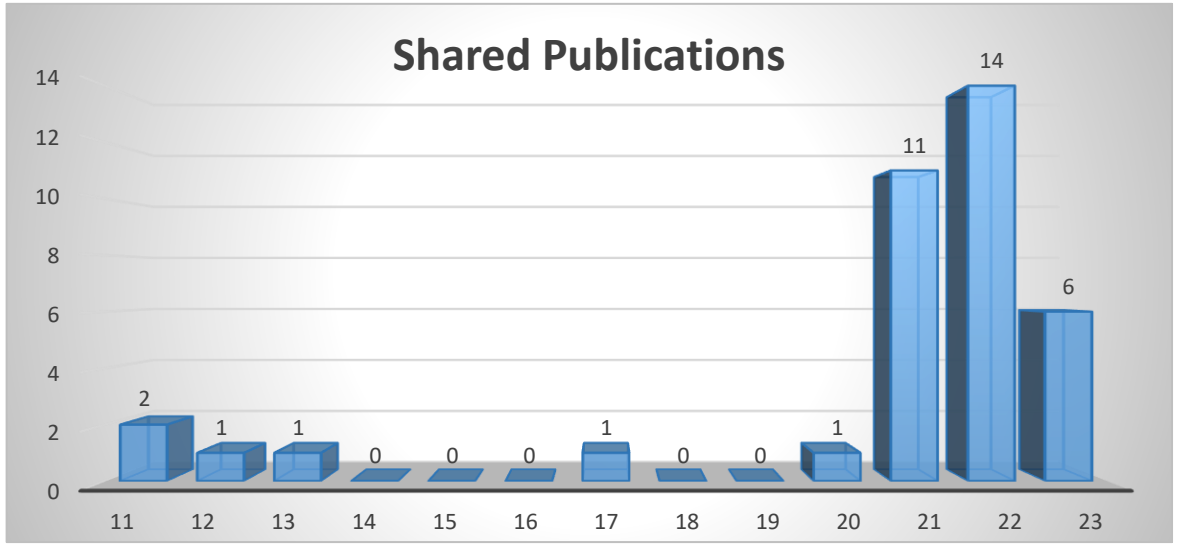
Gareth J. McKay,[1] Giuliana Silvestri,[1] Christopher C. Patterson,[2] Ruth E. Hogg,[1] Usha Chakravarthy,[1] and Anne E. Hughes[2]

Investigative Ophthalmology & Visual Science, February 2009, Vol. 50, No. 2

From: Ammarin Thakkinstian <raatk@mahidol.ac.th>
Sent: 08 June 2010 01:57
To: Gareth McKay <g.j.mckay@qub.ac.uk>
Subject: C2-C3 & AMD

Tuesday, June 08, 2010

Dear Prof McKay,



We are currently performing a meta-analysis of C2-C3 polymorphisms and age-related macular degeneration. We have identified your study that published in

McKay GJ, Silvestri G, Patterson CC, Hogg RE, Chakravarthy U, Hughes AE: **Further assessment of the complement component 2 and factor B region associated with age-related macular degeneration.** *Invest Ophthalmol Vis Sci* 2009, **50**:533-539.

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Diabetes and it’s complications

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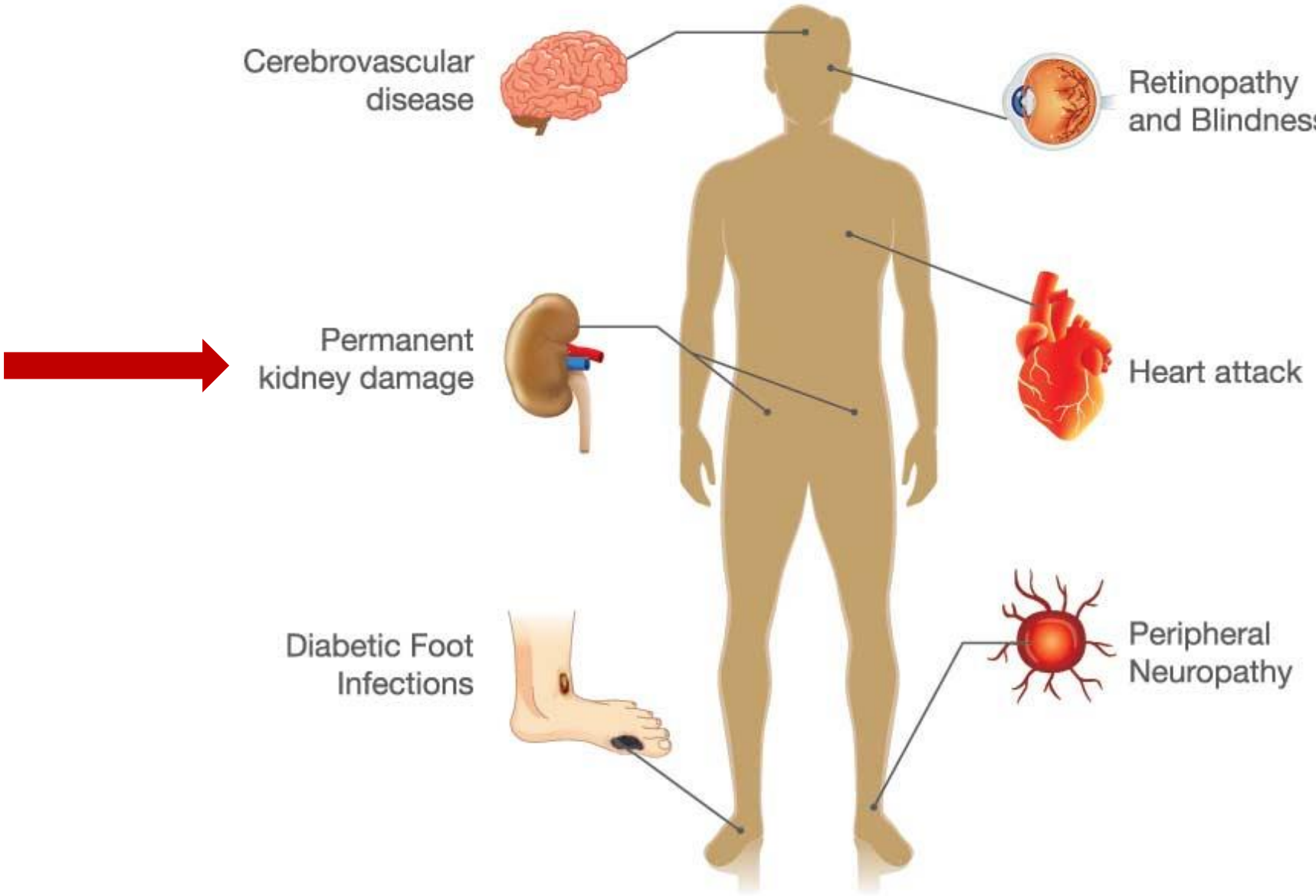
Diabetes around the world in 2021

	Europe	Western Pacific
537 million adults are living with diabetes	**61 million** adults living with diabetes.	**206 million** adults living with diabetes.
3 in 4 adults with diabetes live in low- and middle-income countries	**1 in 3 adults** with diabetes are undiagnosed.	**1 in 2 adults** with diabetes are undiagnosed.
6.7 million deaths due to diabetes in 2021	**1.1 million** deaths caused by diabetes in 2021.	**2.3 million** deaths caused by diabetes in 2021.

Complications of diabetes mellitus



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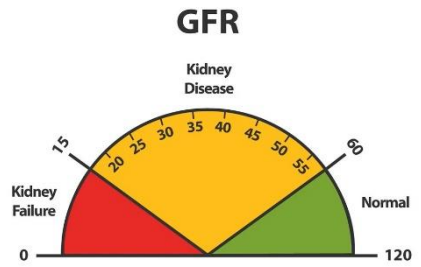
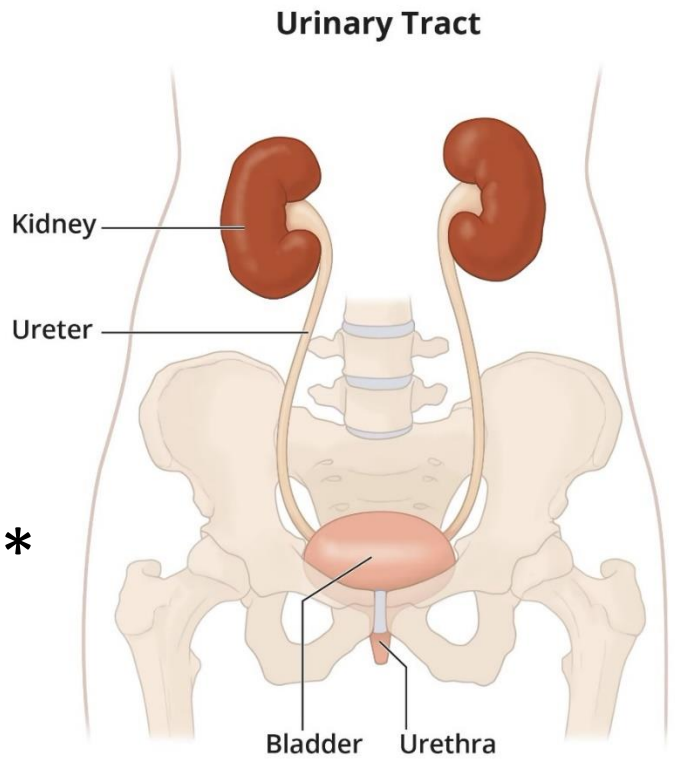
Chronic Kidney Disease (CKD)



- CKD means your kidneys are damaged and can't filter blood the way they should.
- The disease is called "chronic" because the damage to your kidneys happens slowly over a long period of time.
- This damage can cause waste to build up in your body.
- CKD can also cause other health problems.
- Estimated to be the 5th leading cause of death by 2040.*



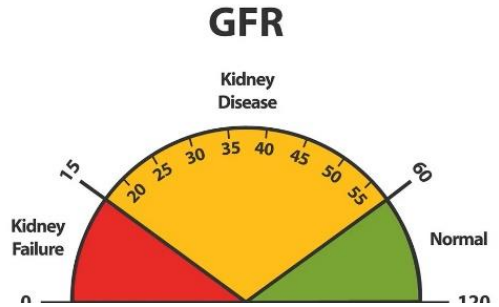
*NCD Alliance

Criteria for CKD

- Abnormalities of kidney structure or function, present for >3 months, with implications for health

- Either of the following must be present for >3 months:
  - GFR <60 mL/min/1.73 m^2
  - ACR >30 mg/g
  - Markers of kidney damage (one or more*)

*Markers of kidney damage can include nephrotic syndrome, nephritic syndrome, tubular syndromes, urinary tract symptoms, asymptomatic urinalysis abnormalities, asymptomatic radiologic abnormalities, hypertension due to kidney disease.



Prognosis of CKD by GFR and Albuminuria Categories

GFR categories (ml/min/1.73 m^2) Description and range				Albuminuria categories Description and range		
				A1	**A2**	**A3**
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30-299 mg/g 3-29 mg/mmol	≥300 mg/g ≥30 mg/mmol
	G1	Normal or high	≥90			
	G2	Mildly decreased	60-90			
	G3a	Mildly to moderately decreased	45-59			
	G3b	Moderately to severely decreased	30-44			
	G4	Severely decreased	15-29			
	G5	Kidney failure	<15			

Green: low risk (if no other markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; Red, very high risk.
KDIGO 2012

Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. *Kidney Int Suppls*. 2013;3:1-150.

Main CKD Risk Factors

Non-Modifiable

- Family history of kidney disease, diabetes, or hypertension
- Age 60 or older (GFR declines normally with age)
- Belong to a population group with a high rate of diabetes or hypertension, such as African Americans, Hispanic Americans, Asian, Pacific Islanders, and American Indians

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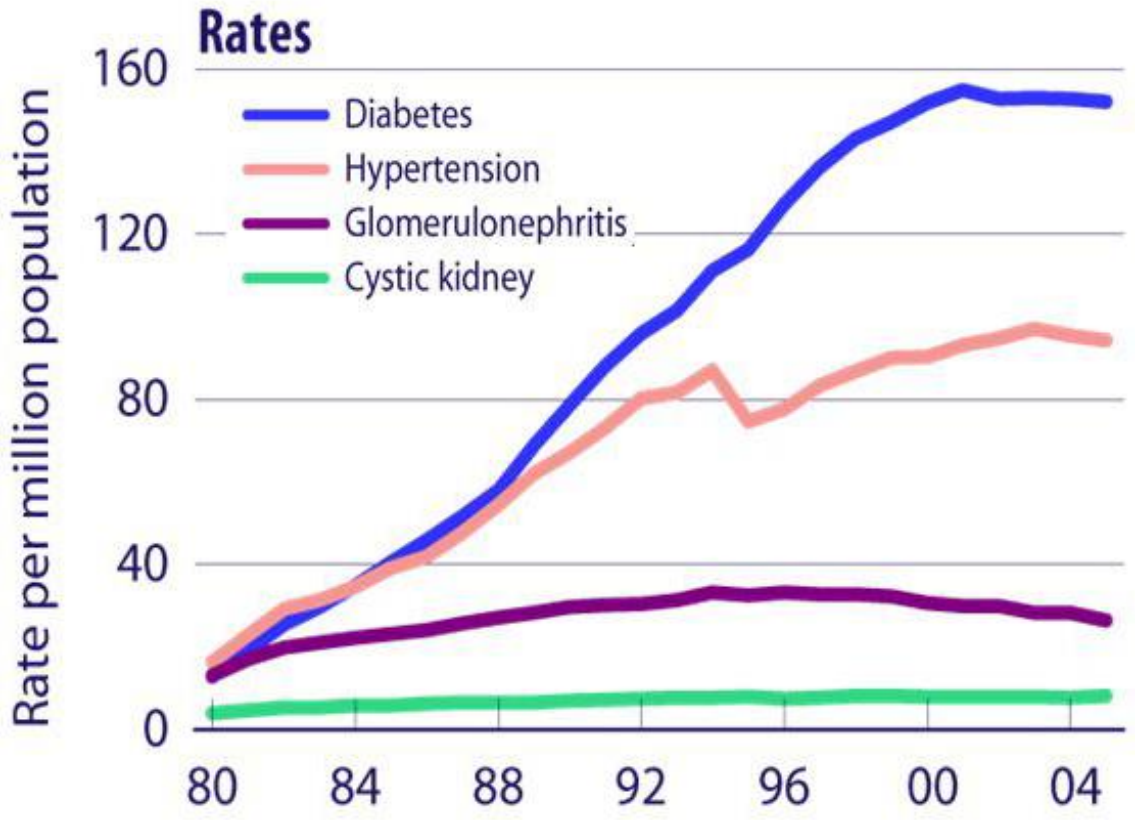
Main CKD Risk Factors

Modifiable

- Diabetes
- Hypertension
- History of AKI
- Frequent NSAID use



Incident ESRD rates, by primary diagnosis, adjusted for age, sex, & race.

Diabetes and hypertension are leading causes of kidney failure

ESRD, end stage renal disease. USRDS ADR, 2007

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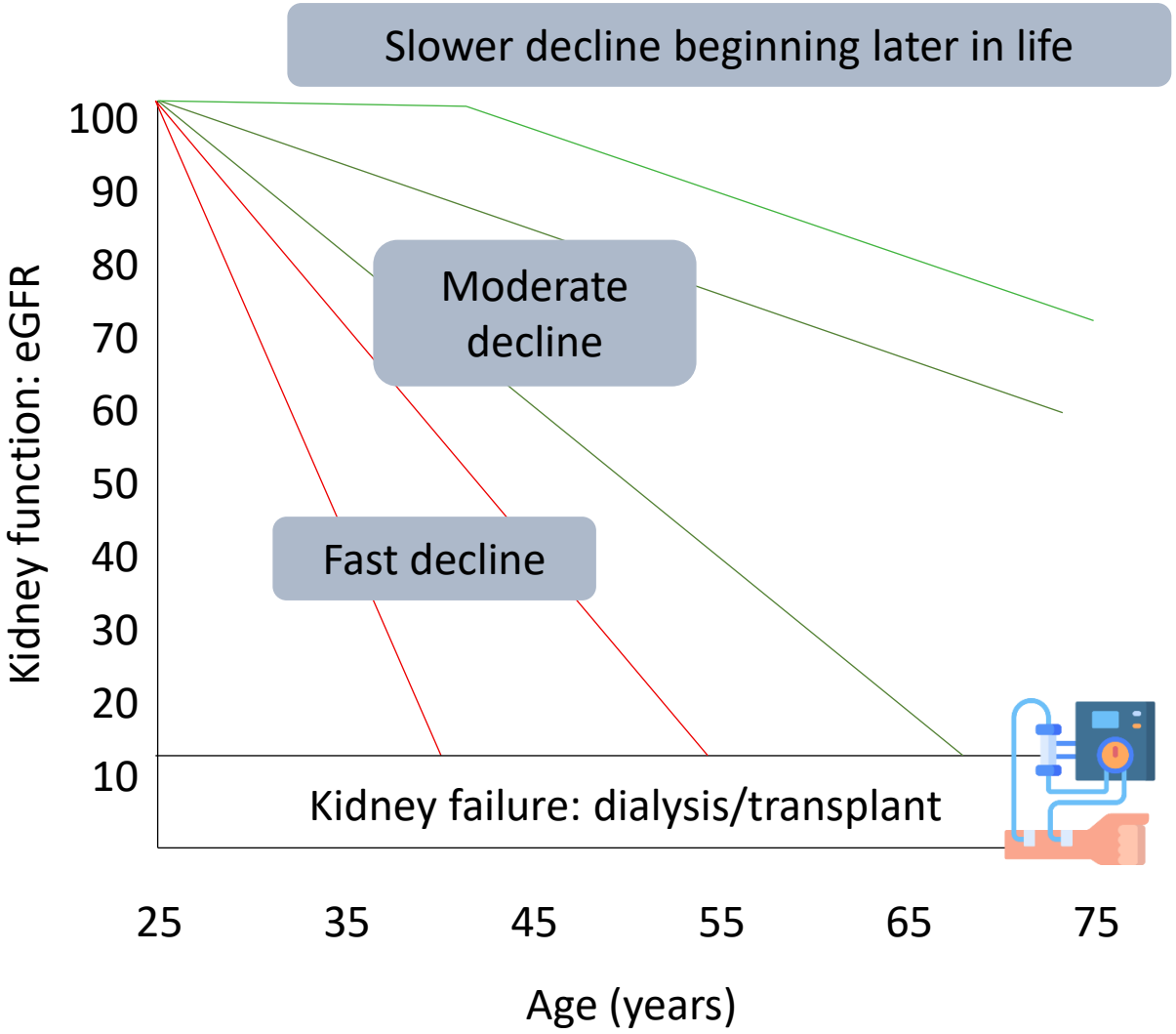
CKD Treatment Rationale



- Renal function declines over time
- Eventual outcome: dialysis or kidney transplant
- Rate of decline varies by person
- Aim: slow the rate of decline = delay dialysis/transplant

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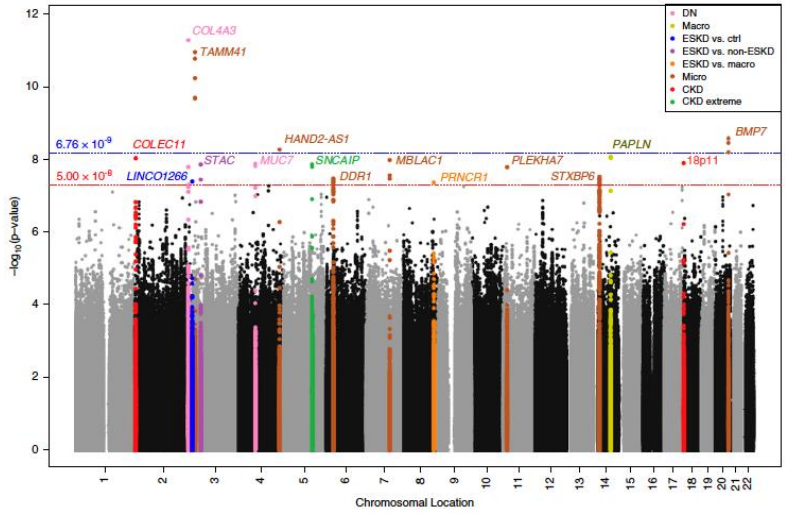
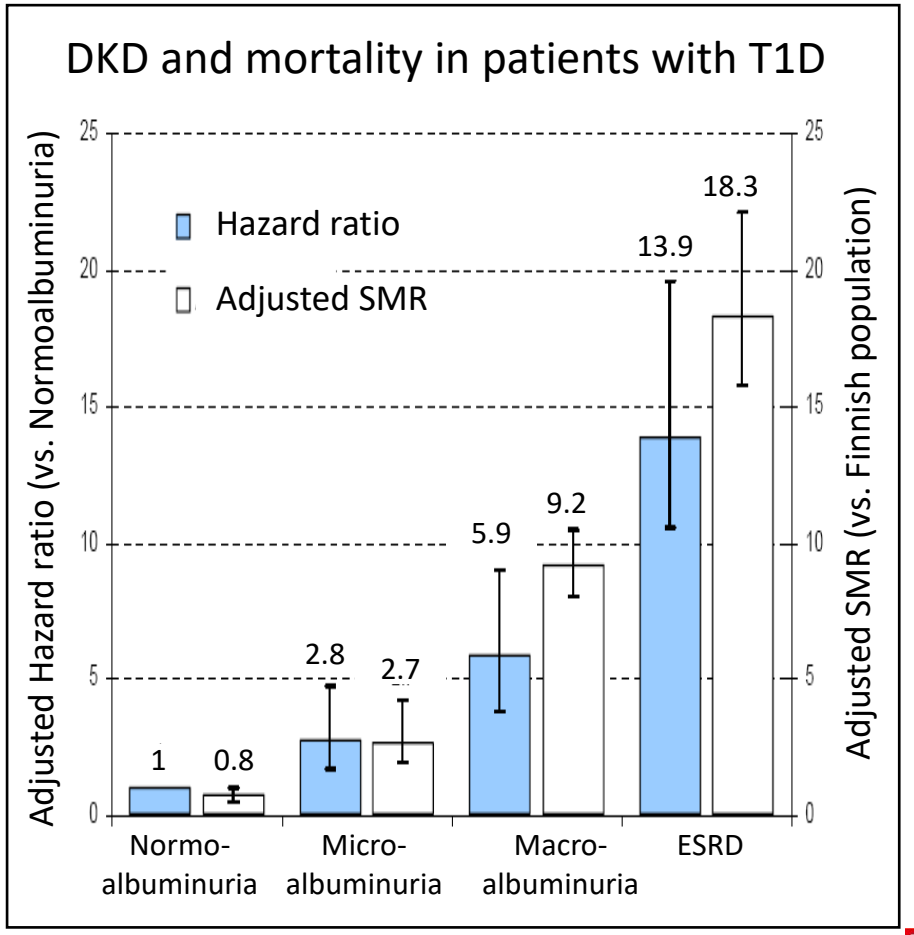
Genetics and Diabetic Kidney Disease



Genetic Risk in Diabetic Kidney Disease (DKD)

- Diabetes is the leading risk factor for kidney disease
- Type 1 diabetes affects >9M people globally, with approximately 40% developing diabetic kidney disease.
- All excess mortality in type 1 diabetes (T1D) associated with DKD[1]
- DKD is inherited in T1D[2,3,4]
  - Sibling risk $\lambda_S = 2.1$ [3]



[1] Groop et al. Diabetes 2009
[2] Seaquist et al. NEJM 1989; [3] Quinn et al. Diabetologia 1996; [4] Harjutsalo et al Diabetes 2004

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Familial aggregation of DKD

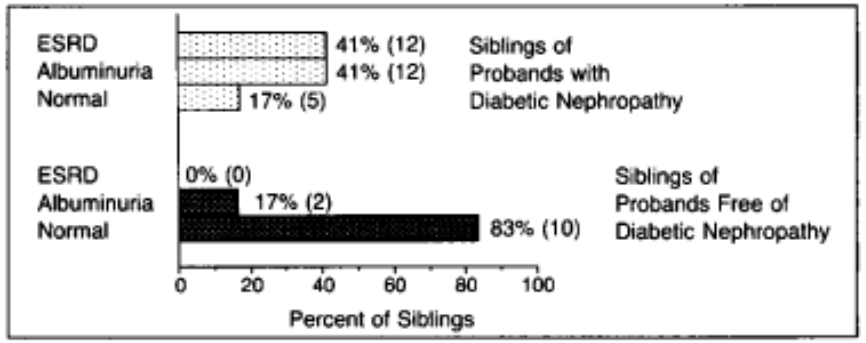
The New England
Journal of Medicine

Volume 320 MAY 4, 1989 Number 18

FAMILIAL CLUSTERING OF DIABETIC KIDNEY DISEASE

Evidence for Genetic Susceptibility to Diabetic Nephropathy

ELIZABETH R. SEAQUIST, M.D., FREDERICK C. GOETZ, M.D., STEPHEN RICH, PH.D., AND JOSÉ BARBOSA, M.D.



2.1-2.3X increased risk of DKD

in T1D siblings of probands with DKD

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GWAS in DKD

ORIGINAL ARTICLE

Genome-Wide Association Scan for Diabetic Nephropathy Susceptibility Genes in Type 1 Diabetes

Marcus G. Pezzolesi,[1] G. David Poznik,[1] Josyf C. Mychaleckyj,[2] Andrew D. Paterson,[3,4] Michelle T. Barati,[5] Jon B. Klein,[5] Daniel P.K. Ng,[1,6] Grzegorz Placha,[1,7] Luis H. Canani,[1,8] Jacek Bochenski,[1] Daryl Waggott,[9] Michael L. Merchant,[5] Bozena Krolewski,[1] Lucia Mirea,[4,9] Krzysztof Wanic,[1] Pisut Katavetin,[1] Masahiko Kure,[1] Pawel Wolkow,[1,10] Jonathon S. Dunn,[1] Adam Smiles,[1] William H. Walker,[1] Andrew P. Boright,[11] Shelley B. Bull,[4,9] the DCCT/EDIC Research Group,* Alessandro Doria,[1] John J. Rogus,[1] Stephen S. Rich,[2] James H. Warram,[1] and Andrzej S. Krolewski[1]

- *Diabetes* 2009
- US GoKinD
- Discovery 1.7K
- No GWS findings

OPEN ACCESS Freely available online

PLOS | GENETICS

New Susceptibility Loci Associated with Kidney Disease in Type 1 Diabetes

Niina Sandholm[1,2,3☯], Rany M. Salem[4,5,6☯], Amy Jayne McKnight[7☯], Eoin P. Brennan[8,9☯], Carol Forsblom[1,2], Tamara Isakova[10], Gareth J. McKay[7], Winfred W. Williams[6,11], Denise M. Sadlier[8,9],

- 2012
- GENIE
- Discovery 6K
- 2 GWS findings for ESRD, none for DN

Chromosome 2q31.1 Associates with ESRD in Women with Type 1 Diabetes

Niina Sandholm,*†‡ Amy Jayne McKnight,§ Rany M. Salem,‖¶** Eoin P. Brennan,†† ‡‡ Carol Forsblom,*† Valma Harjutsalo,*†§§ Ville-Petteri Mäkinen,*† ‖‖ Gareth J. McKay,§ Denise M. Sadlier,†‡‡‡ Winfred W. Williams,**¶¶ Finian Martin,†‡‡‡ Nicolae Mircea Panduru,*** Lise Tarnow,†††‡‡‡ Jaakko Tuomilehto,§§ §§§‖‖¶¶¶ Karl Tryggvason,**** Gianpaolo Zerbini,†††† Mary E. Comeau, ‡‡‡‡ Carl D. Langefeld,‡‡‡‡ for the FIND Consortium; Catherine Godson,†‡‡‡ Joel N. Hirschhorn, ‖¶** Alexander P. Maxwell,§ §§§§ Jose C. Florez,‖**¶¶ and Per-Henrik Groop,*† ‖‖‖‖ on behalf of the FinnDiane Study Group and the GENIE Consortium.

- *JASN* 2013
- FinnDiane
- Discovery 3.6K
- 1 GWS finding for ESRD in women

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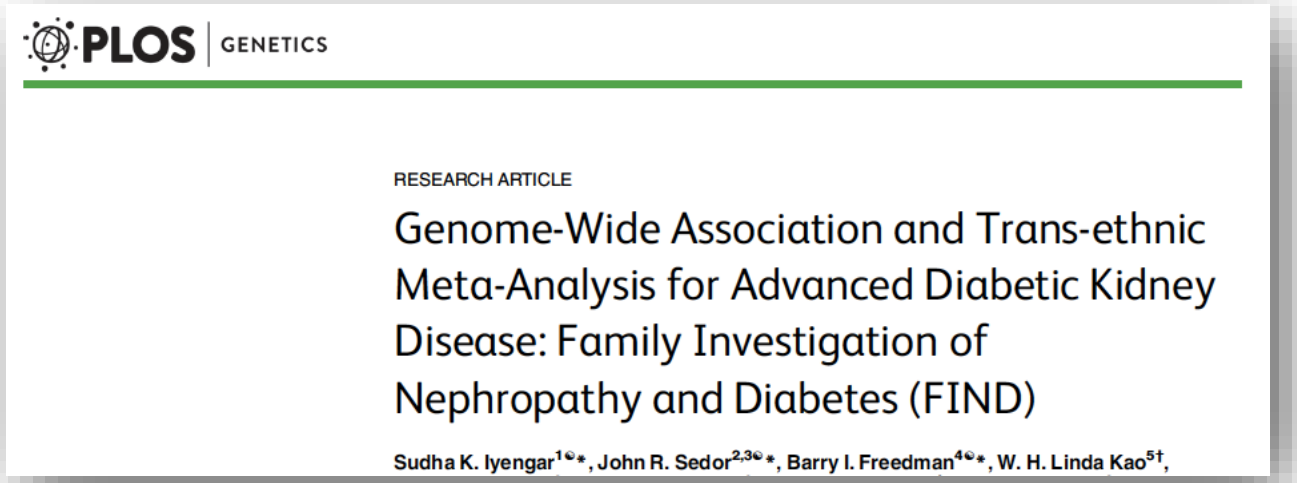
T2D DKD GWAS



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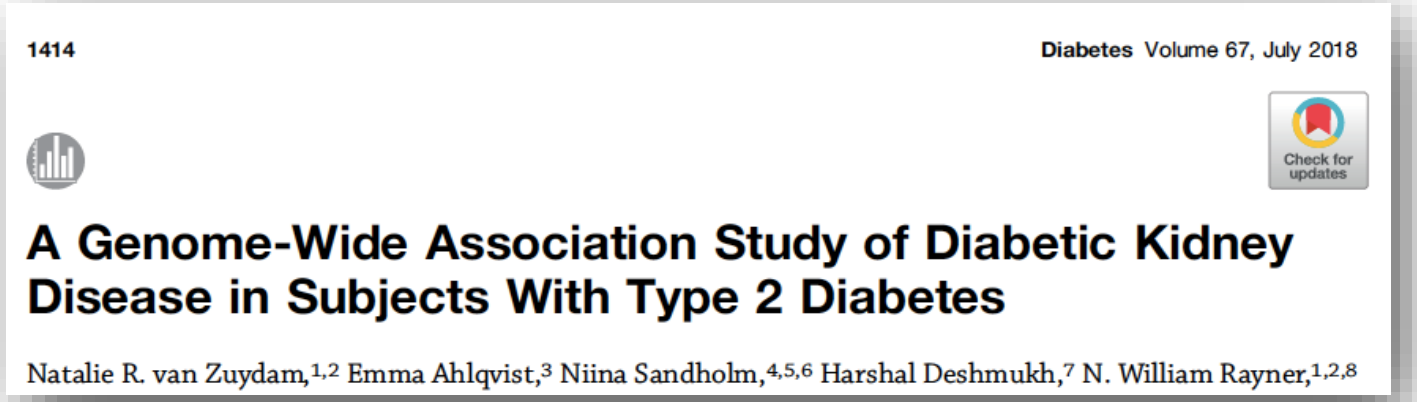
RESEARCH ARTICLE

Genome-Wide Association and Trans-ethnic Meta-Analysis for Advanced Diabetic Kidney Disease: Family Investigation of Nephropathy and Diabetes (FIND)

Sudha K. Iyengar[1☯*], John R. Sedor[2,3☯*], Barry I. Freedman[4☯*], W. H. Linda Kao[5†],

- *PLoS Genet* 2015
- FIND
- Discovery 6.2K
- Multiethnic
- One GWS finding at *SCAF8-CNKSR3*



1414 Diabetes Volume 67, July 2018

Check for updates

A Genome-Wide Association Study of Diabetic Kidney Disease in Subjects With Type 2 Diabetes

Natalie R. van Zuydam,[1,2] Emma Ahlqvist,[3] Niina Sandholm,[4,5,6] Harshal Deshmukh,[7] N. William Rayner,[1,2,8]

- *Diabetes* 2018
- SUMMIT
- Discovery 5.7K
- No reproducible findings
- Combined T2D+T1D

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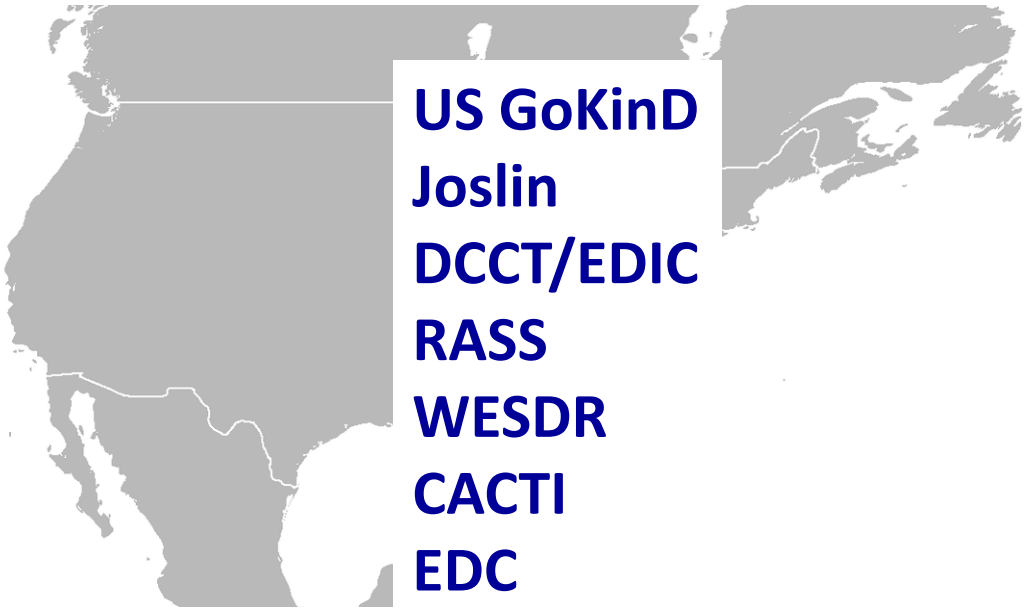
Diabetic Nephropathy Collaborative Research Initiative



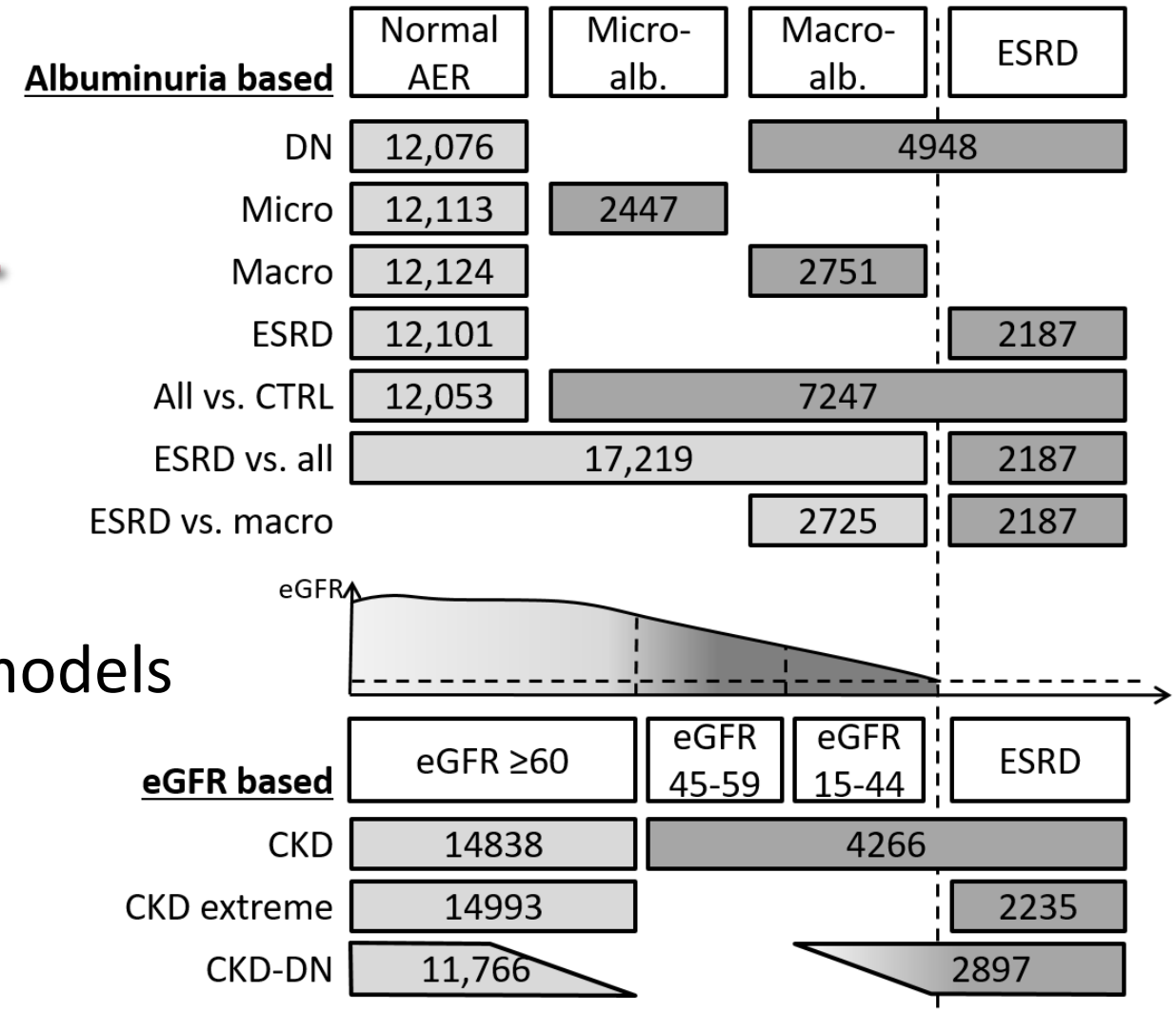
US GoKinD
Joslin
DCCT/EDIC
RASS
WESDR
CACTI
EDC

FinnDiane
InterDiane
UK-ROI
Scotland
France-Belgium
Steno (Denmark)
Sweden
Italy

17 cohorts
19,406 participants

Phenotype definitions and contrasts

- Genome-wide significance:
  - $P<5\times10^{-8}$
- 10 phenotypes + 2 covariate models
- 7.4 effective tests
- Experiment-wide significance:
  - $P<6.76\times10^{-9}$



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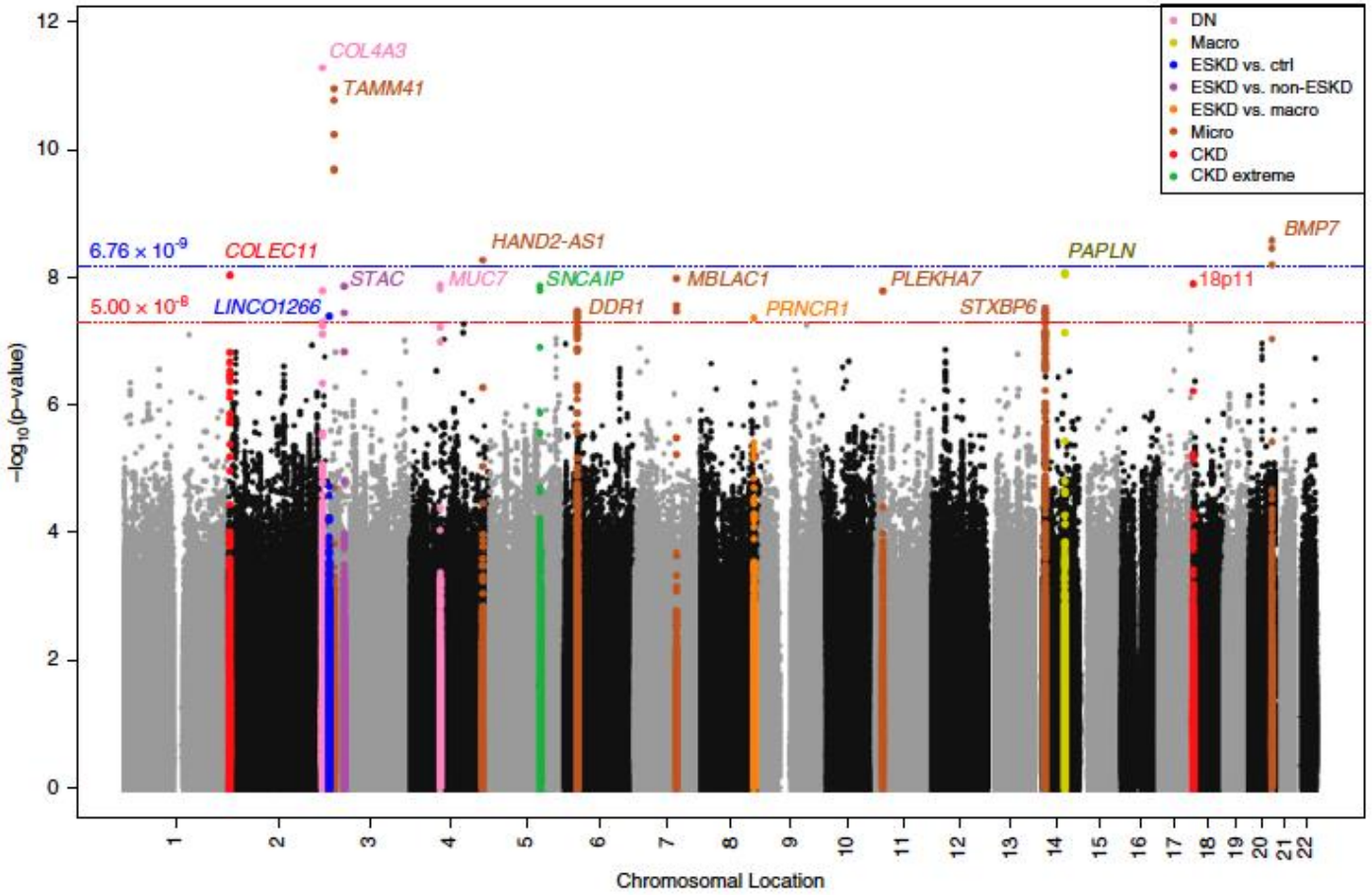
CLINICAL RESEARCH www.jasn.org

Genome-Wide Association Study of Diabetic Kidney Disease Highlights Biology Involved in Glomerular Basement Membrane Collagen

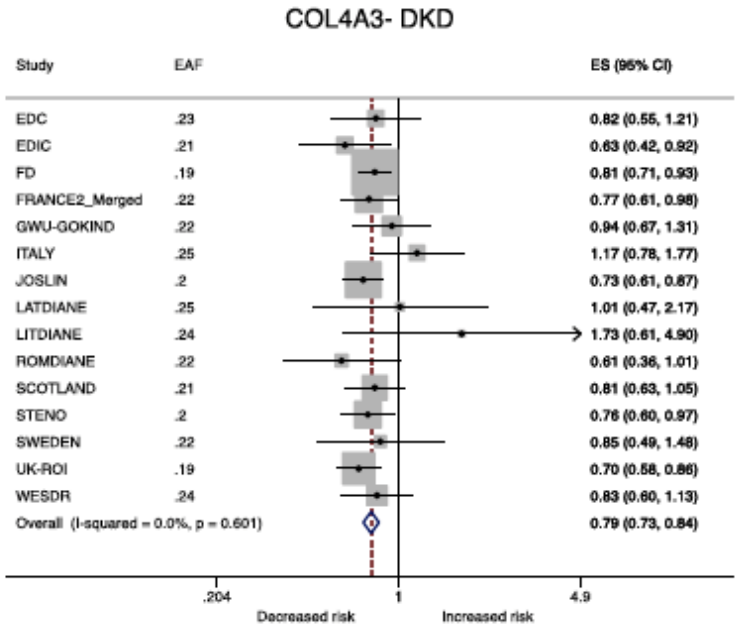
Rany M. Salem,[1] Jennifer N. Todd,[2,3,4] Niina Sandholm,[5,6,7] Joanne B. Cole,[2,3,4] Wei-Min Chen,[8] Darrell Andrews,[9] Marcus G. Pezzolesi,[10] Paul M. McKeigue,[11] Linda T. Hiraki,[12] Chengxiang Qiu,[13] Viji Nair,[14] Chen Di Liao,[12] Jing Jing Cao,[12] Erkka Valo,[5,6,7] Suna Onengut-Gumuscu,[8] Adam M. Smiles,[15] Stuart J. McGurnaghan,[16] Jani K. Haukka,[5,6,7] Valma Harjutsalo,[5,6,7,17] Eoin P. Brennan,[9] Natalie van Zuydam,[18,19] Emma Ahlqvist,[20] Ross Doyle,[9] Tarunveer S. Ahluwalia,[21] Maria Lajer,[21] Maria F. Hughes,[9] Jihwan Park,[13] Jan Skupien,[15] Athina Spiliopoulou,[11] Andrew Liu,[22] Rajasree Menon,[14,23] Carine M. Boustany-Kari,[24] Hyun M. Kang,[23,25] Robert G. Nelson,[26] Ronald Klein,[27] Barbara E. Klein,[27] Kristine E. Lee,[27] Xiaoyu Gao,[28] Michael Mauer,[29] Silvia Maestroni,[30] Maria Luiza Caramori,[29] Ian H. de Boer,[31] Rachel G. Miller,[32] Jingchuan Guo,[32] Andrew P. Boright,[12] David Tregouet,[33,34] Beata Gyorgy,[33,34] Janet K. Snell-Bergeon,[35] David M. Maahs,[36] Shelley B. Bull,[37] Angelo J. Canty,[38] Colin N.A. Palmer,[39] Lars Stechemesser,[40] Bernhard Paulweber,[40] Raimund Weitgasser,[40,41] Jelizaveta Sokolovska,[42] Vita Rovite,[43] Valdis Pīrāgs,[42,44] Edita Prakapiene,[45] Lina Radzeviciene,[46] Rasa Verkauskiene,[46] Nicolae Mircea Panduru,[6,47] Leif C. Groop,[20,48] Mark I. McCarthy,[18,19,49,50] Harvest F. Gu,[51,52] Anna Möllsten,[53] Henrik Falhammar,[54,55] Kerstin Brismar,[54,55] Finian Martin,[9] Peter Rossing,[21,56] Tina Costacou,[32] Gianpaolo Zerbini,[30] Michel Marre,[57,58,59,60] Samy Hadjadj,[61,62,63] Amy J. McKnight,[64] Carol Forsblom,[5,6,7] Gareth McKay,[64] Catherine Godson,[9] A. Peter Maxwell,[64] Matthias Kretzler,[14,23] Katalin Susztak,[13] Helen M. Colhoun,[16] Andrzej Krolewski,[15] Andrew D. Paterson,[12] Per-Henrik Groop,[5,6,7,65] Stephen S. Rich,[8] Joel N. Hirschhorn,[2,3] Jose C. Florez,[3,4,66,67] and SUMMIT Consortium, DCCT/EDIC Research Group, GENIE Consortium

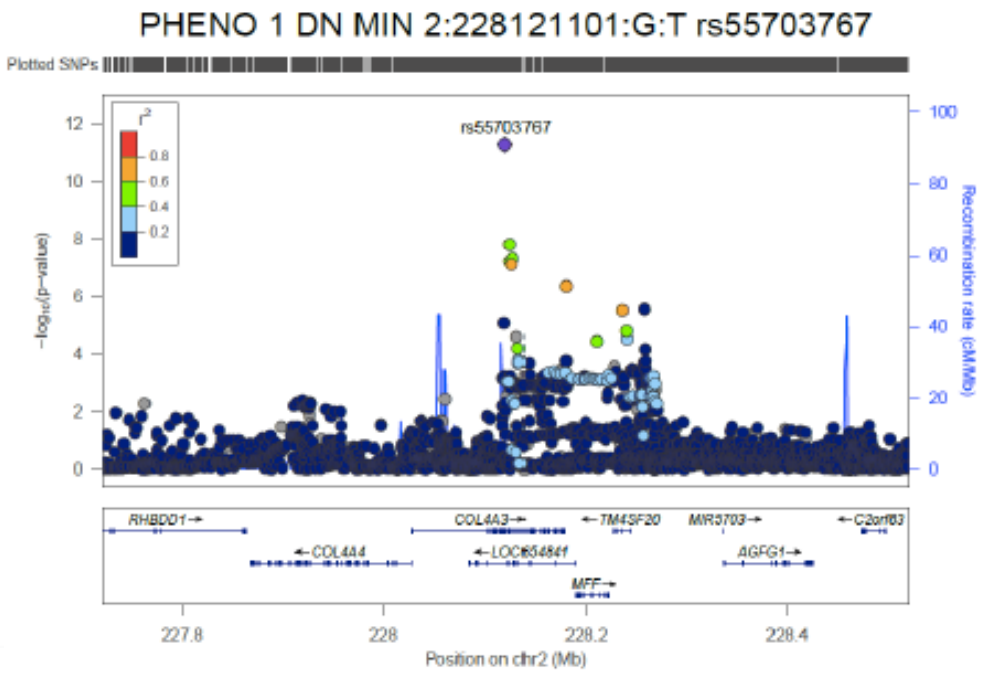
JASN **30:** 2000–2016, 2019

Results



Associations point to causal genes: Asp326Tyr in *COL4A3* protects against DKD



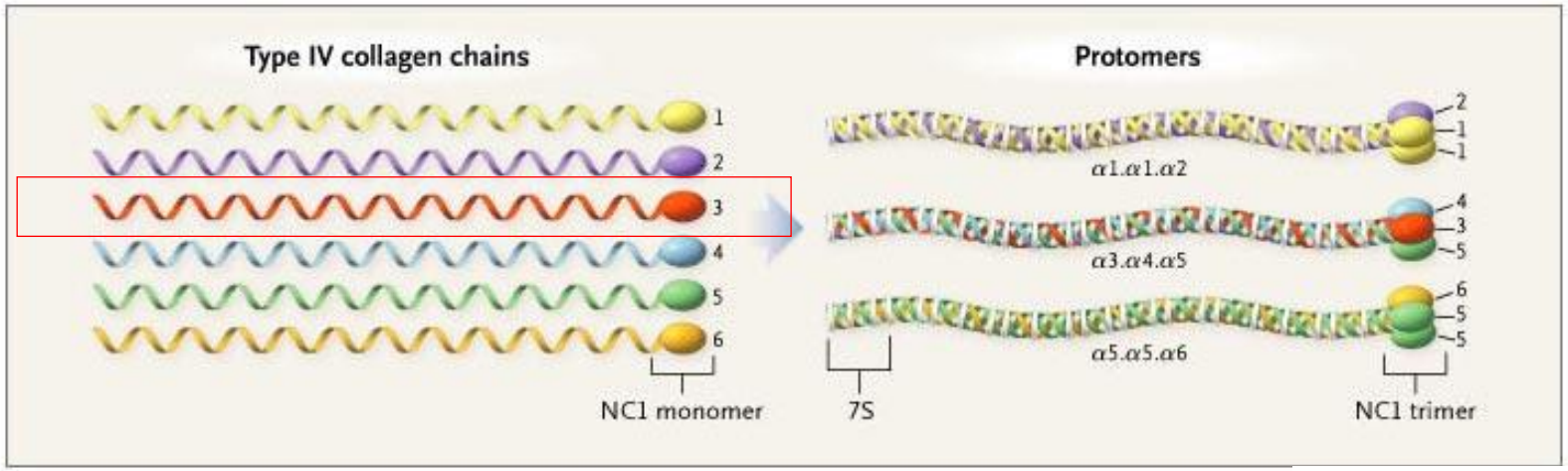


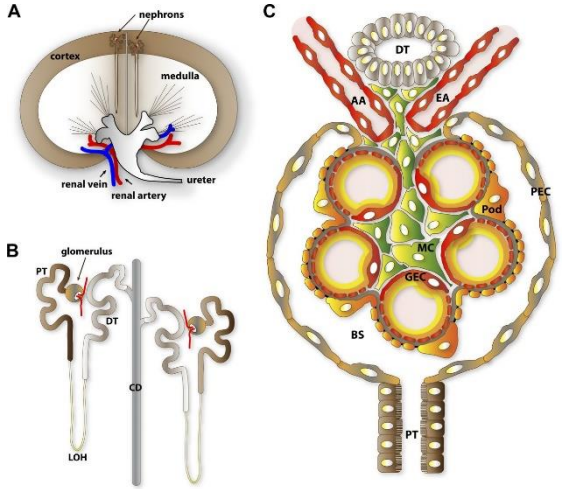
OR 0.79, *P* = 5×10^{-12}

EAF 20.6% in Europeans

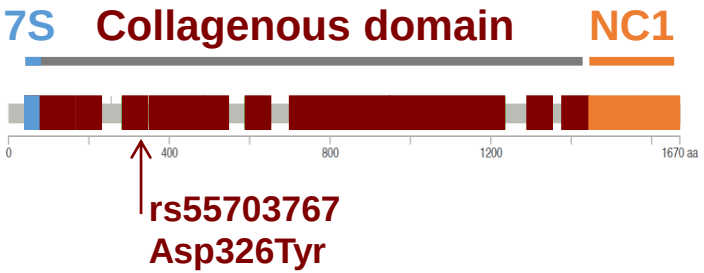
(5% in Africa, 11% in Asia)

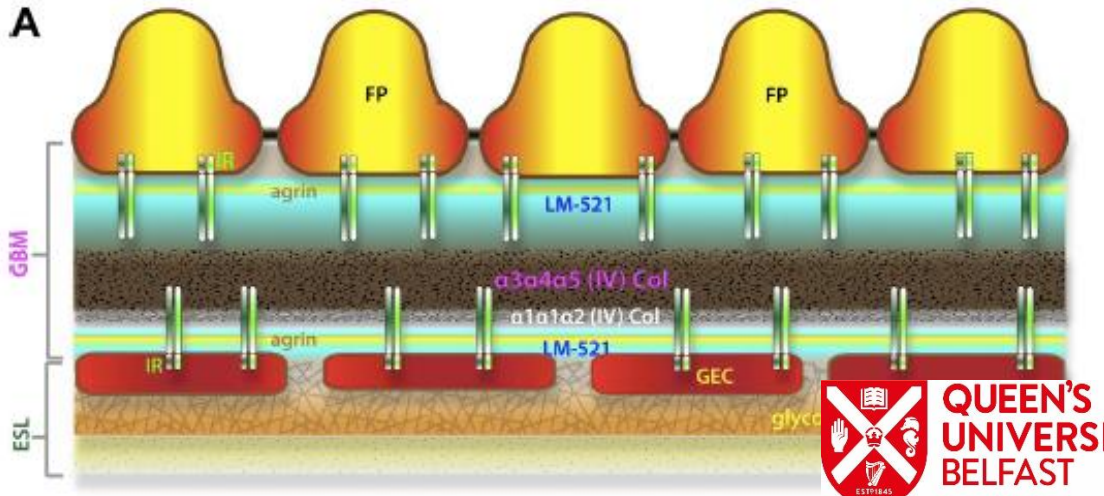
COL4A3 encodes the a-3 subunit of type IV collagen, a major structural component of the GBM





Hudson BG et al. *N Engl J Med* 2003;348:2543-2556





Rizaldy Scott & Susan Quaggin
J Cell Biol 2015;209:199-210

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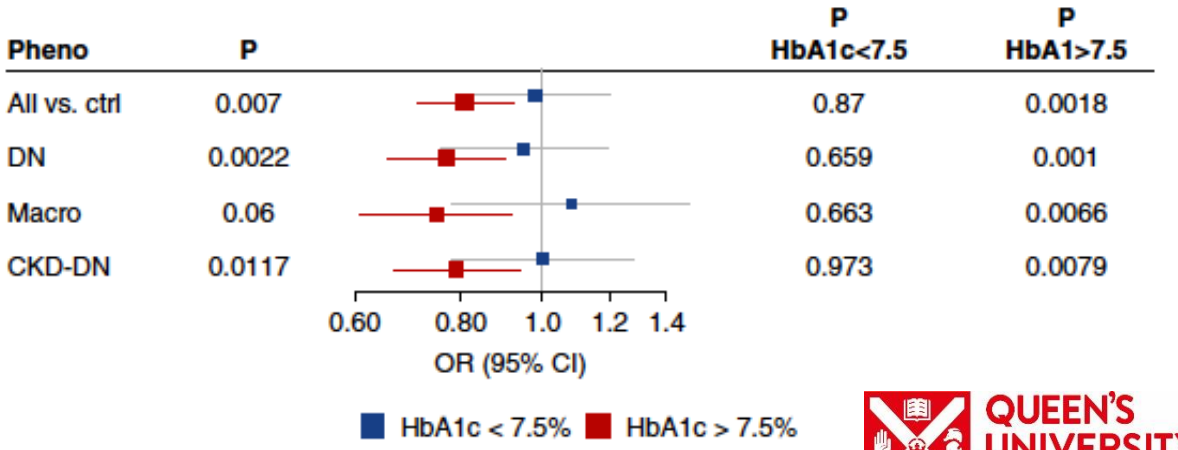
Interaction with hyperglycemia

- Stratification by HbA_{1c} in FinnDiane
- **Time-weighted mean HbA_{1c}**: 1-129 measurements (mean 19, IQR 9-32)
- Stratification at HbA_{1c} ≥7.5% or <7.5% (58 mmol/mol)
- ***COL4A3:*** Association when HbA_{1c} ≥7.5%, no association when HbA1c <7.5% (protection in hyperglycemia)
- Protection stronger in conventional arm of DCCT/EDIC (higher HbA_{1c})
- → ***Diabetic*** nephropathy



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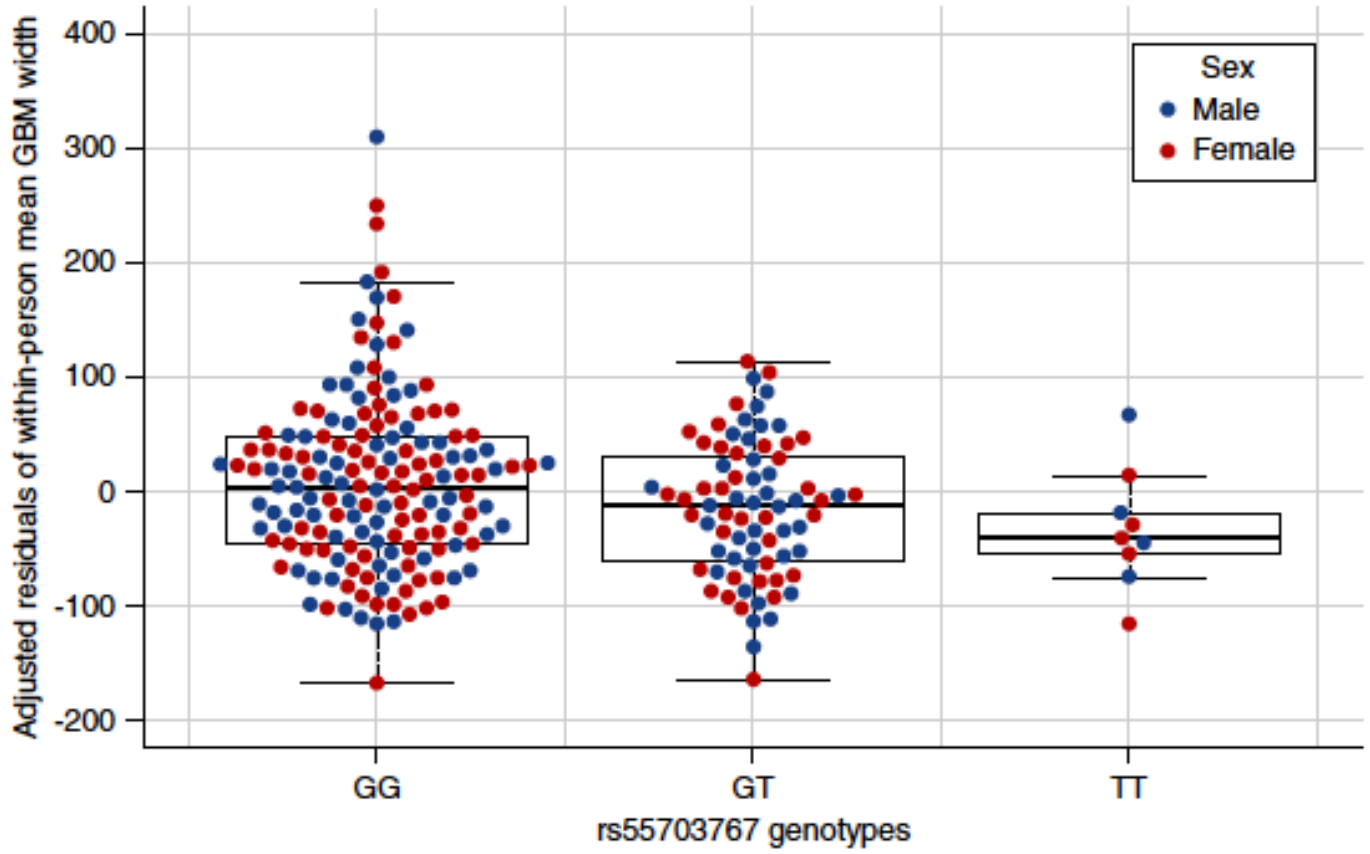
Ultrastructural phenotype



- RASS study
- *N*=253
- Thicker GBM seen in DKD
- Protective T allele associated with thinner GBM (22.8 nm per allele, *P*=0.006)

With SUMMIT T2D: *COL4A3* remains the top association signal

Table 1: GWAS meta-analysis result summary: loci with $p<5\times10^{-8}$

Phenotype	CHR:POS	SNP	EA	NEA	EAF	OR (95% CI)	*P*-value	Dir	N (studies)	Genes
Novel locus										
CKD+DKD	5:166978230	rs72831309	A	G	0.039	2.08 (1.62 - 2.67)	9.8×10^{-9}	+++	8,570 (7)	*TENM2**
Previous loci										
CKD	2:3745215	rs12615970	A	G	0.867	1.31 (1.20 - 1.44)	9.4×10^{-9}	+??	18,488 (13)	*ALLC, COLEC11*
All vs. Ctrl	2:228121101	rs55703767	T	G	0.207	0.86 (0.82 - 0.90)	1.9×10^{-9}	-+-	26,898 (24)	*COL4A3**
CKD+DKD	2:228121101	rs55703767	T	G	0.210	0.81 (0.75 - 0.88)	4.7×10^{-8}	-+-	17,611 (17)	*COL4A3**
Severe DKD	2:228121101	rs55703767	T	G	0.208	0.82 (0.77 - 0.87)	3.6×10^{-11}	---	21,898 (23)	*COL4A3**
ESRD	3:926345	rs115061173	A	T	0.014	9.40 (4.22 - 20.93)	4.1×10^{-8}	+??	4,827 (3)	*LINC01266, CNTN6**
Micro	3:11910635	rs142823282	A	G	0.983	0.15 (0.08 - 0.27)	8.3×10^{-10}	-??	6,076 (2)	*TAMM41*
ESRD vs. All	3:36566312	rs116216059	A	C	0.016	8.73 (4.13 - 18.45)	1.4×10^{-8}	+??	3,667 (2)	*STAC – DCLK3*
Severe DKD	4:71358776	rs191449639	A	T	0.005	32.42 (9.77 - 107.59)	1.3×10^{-8}	+??	7,768 (2)	*MUC7, AMTN*
Micro	7:99728546	rs77273076	T	C	0.008	9.16 (4.29 - 19.56)	1.1×10^{-8}	+??	7,500 (2)	*MBLAC1 - ZNF3*
ESRD vs. macro	8:128100029	rs551191707	CA	C	0.122	1.69 (1.40 - 2.04)	4.4×10^{-8}	+??	3,634 (7)	*PRNCR1*
Micro	11:16937846	rs183937294	T	G	0.993	0.06 (0.02 - 0.16)	1.7×10^{-8}	-??	6,076 (2)	*PLEKHA7**
CKD	18:1811108	rs185299109	T	C	0.007	20.75 (7.30 – 59.00)	1.3×10^{-8}	+??	7,223 (2)	*LINC00470*

EA: Effect allele. NEA: Non-effect allele. EAF: Effect allele frequency. Dir: Direction of association in DNCRI (T1D), SUMMIT T2D, and in SUMMIT T1D, respectively. N (studies): Number of contributing individuals and (studies). Genes: closest gene(s). * indicates gene prioritized by PoPS. Genes underlying the lead SNP are underlined.

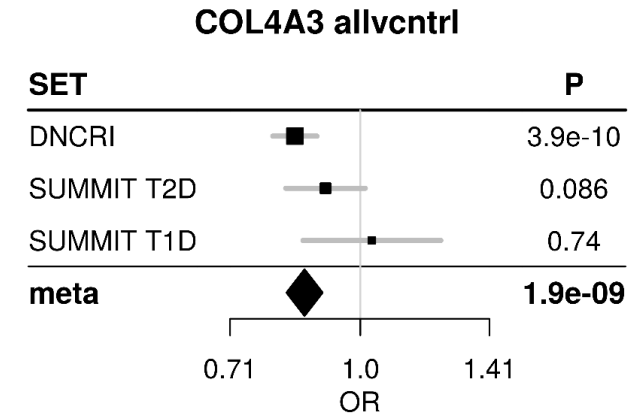
n=26,785

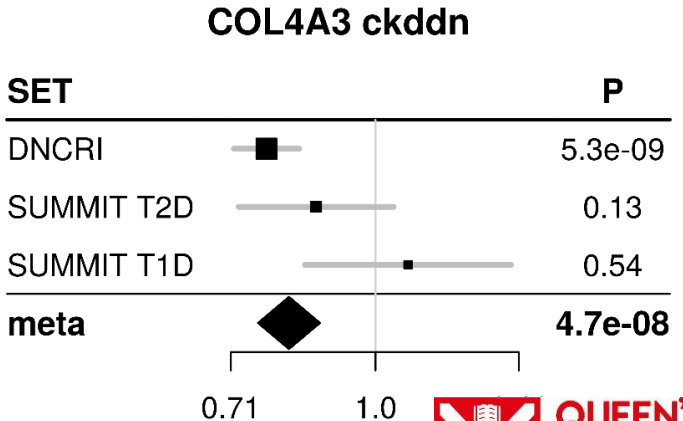
Diabetologia
https://doi.org/10.1007/s00125-022-05735-0

ARTICLE

Genome-wide meta-analysis and omics integration identifies novel genes associated with diabetic kidney disease

Niina Sandholm[1,2,3] · Joanne B. Cole[4,5,6] · Viji Nair[7] · Xin Sheng[8,9,10] · Hongbo Liu[8,9,10] · Emma Ahlqvist[11] · Natalie van Zuydam[12,13,14] · Emma H. Dahlström[1,2,3] · Damian Fermin[7] · Laura J. Smyth[15] · Rany M. Salem[16] · Carol Forsblom[1,2,3] · Erkka Valo[1,2,3] · Valma Harjutsalo[1,2,3,17] · Eoin P. Brennan[18] · Gareth J. McKay[15] · Darrell Andrews[18] · Ross Doyle[18] · Helen C. Looker[19] · Robert G. Nelson[19] · Colin Palmer[12] · Amy Jayne McKnight[15] · Catherine Godson[18] · Alexander P. Maxwell[15,20] · Leif Groop[11,21] · Mark I. McCarthy[13,14] · Matthias Kretzler[7] · Katalin Susztak[8,9,10] · Joel N. Hirschhorn[4,5,22] · Jose C. Florez[4,6,23] ·





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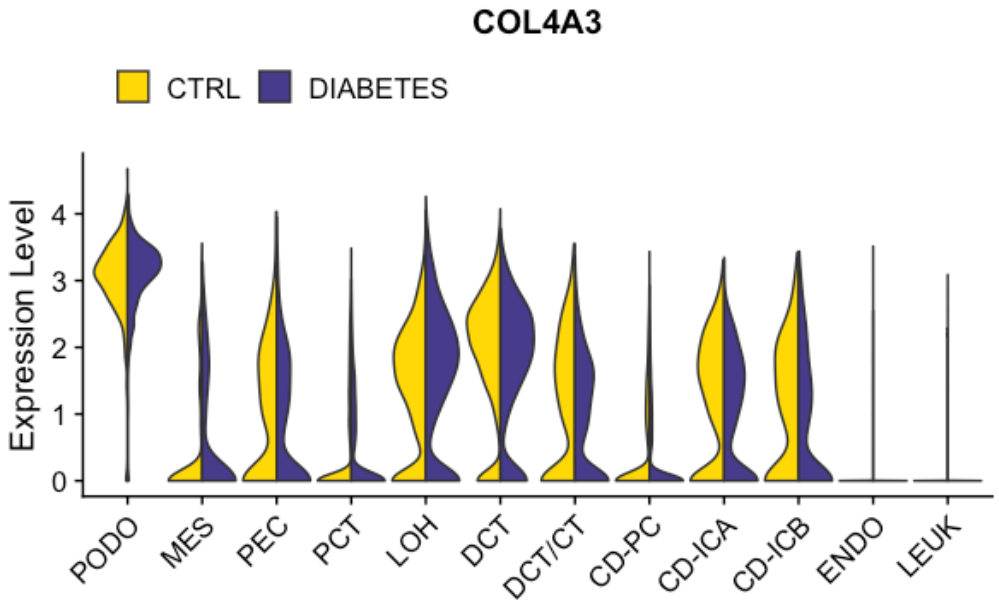
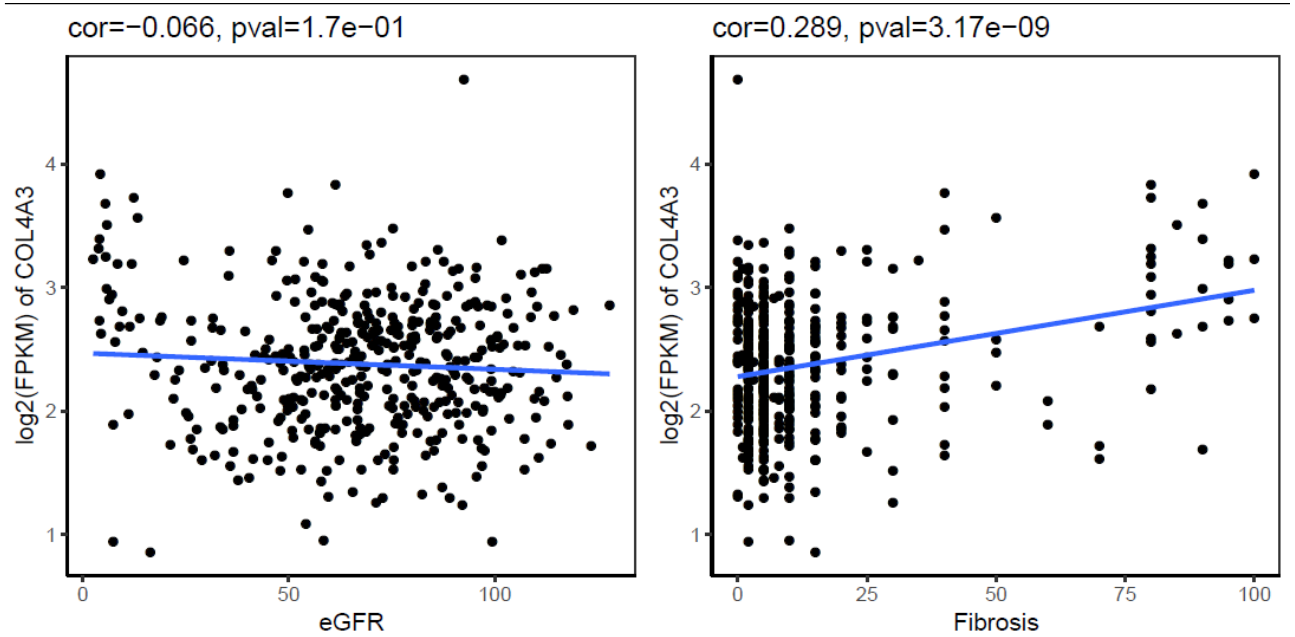
COL4A3 is preferentially expressed in podocytes, and correlates with fibrosis





Human Diabetic Kidney data set (23,980 nuclei)
Wilson *et al. PNAS* 2019
http://humphreyslab.com/SingleCell/displaycharts.php

433 tubular and 335 glomerular nephrectomy samples with DKD and hypertensive CKD
Sandholm, Cole *et al.* (*Diabetologia* 2022)

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GWAS Summary for DKD

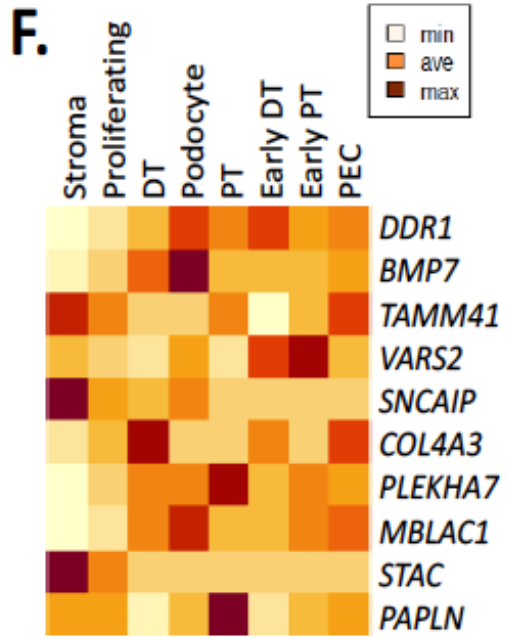
- In the largest genetic study of T1DKD to date, we discovered 16 novel associations with DKD
- We found a **protective** missense variant in *COL4A3*
  - The effect was **consistent** across cohorts
  - The association appeared to be driven by **proteinuria**
  - The association was dependent on **glycemia**
  - The variant was associated with a **structural phenotype**
- Expression of *COL4A3* is correlated with fibrosis in human tubular samples
- There is no association of the index variant with levels of *COL4A3* expression
- Other signals lie in genes with biological plausibility (*COLLEC11*, *DDR1*)

Current directions for DKD genetics studies – GENIE 3

- Combine T1DKD and **T2DKD** (>150K)

Cohort	Ethnicity	Investigator	*N* cases	*N* controls	*N* total
FIND	Multiethnic	Sudha Iyengar	4,295	2,189	6,484
ANDIS	European	Leif Groop	5,250	15,750	21,000
DIREVA	European	Leif Groop	1,375	4,125	5,500
SDR	European	Leif Groop	1,500	4,500	6,000
Singapore	Asian	Xueling Sim	1,665	1,778	3,443
BioVU	Multiethnic	Adriana Hung	2,264	8,199	10,463
MVP	Multiethnic	Adriana Hung	24,960	27,408	52,368
GoDARTS	European	Colin Palmer	1,728	2,576	4,304
Chennai	South Asia	V. Mohan	1,703	3,423	5,126
ARIC	Multiethnic	Rany Salem	406	1,584	1,990
CHS	Multiethnic	Rany Salem	181	533	714
MESA	Multiethnic	Rany Salem	614	891	1,505
FHS	European	Rany Salem	177	189	366
UKBiobank	Multiethnic	Rany Salem	5,507	28,939	34,346
HCHS-SOL	Latino	Rany Salem	653	1,890	2,543
JHS	African	Rany Salem	142	339	481
Total:			52,420	104,213	156,633

- **Functional** follow-up of findings
  - Humanized mouse – J. Miner
  - Collagen biomechanics – R. Lennon
  - Organoids – M. Kretzler, J. Harder, P.-H. Groop
  - scRNAseq – K. Susztak



V. Nair,
M. Kretzler,
J. Harder
(unpublished)

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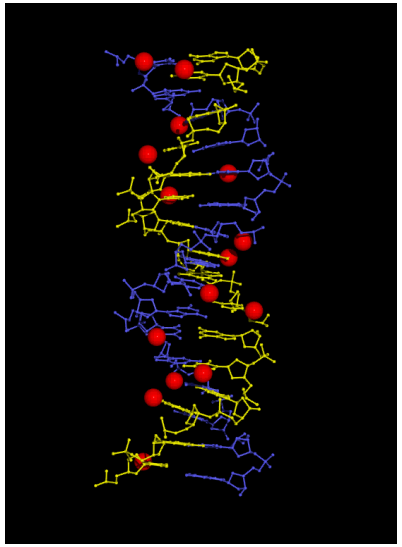
Epigenetics and Diabetic Kidney Disease



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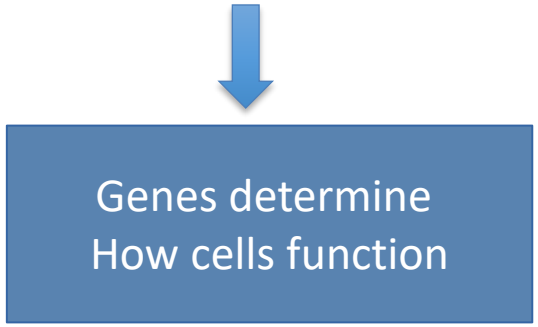
What is ‘Epi’ genetics?

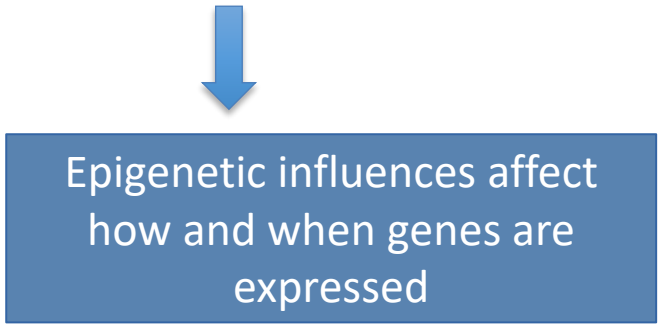
- ‘Epi’: On top of

- Definition:
  - changes in organisms caused by modification of gene expression rather than alteration of the genetic code itself.

Genes are inherited - they only influence individual development if they are expressed.

Gene *expression* depends on a range of factors including those in the environment





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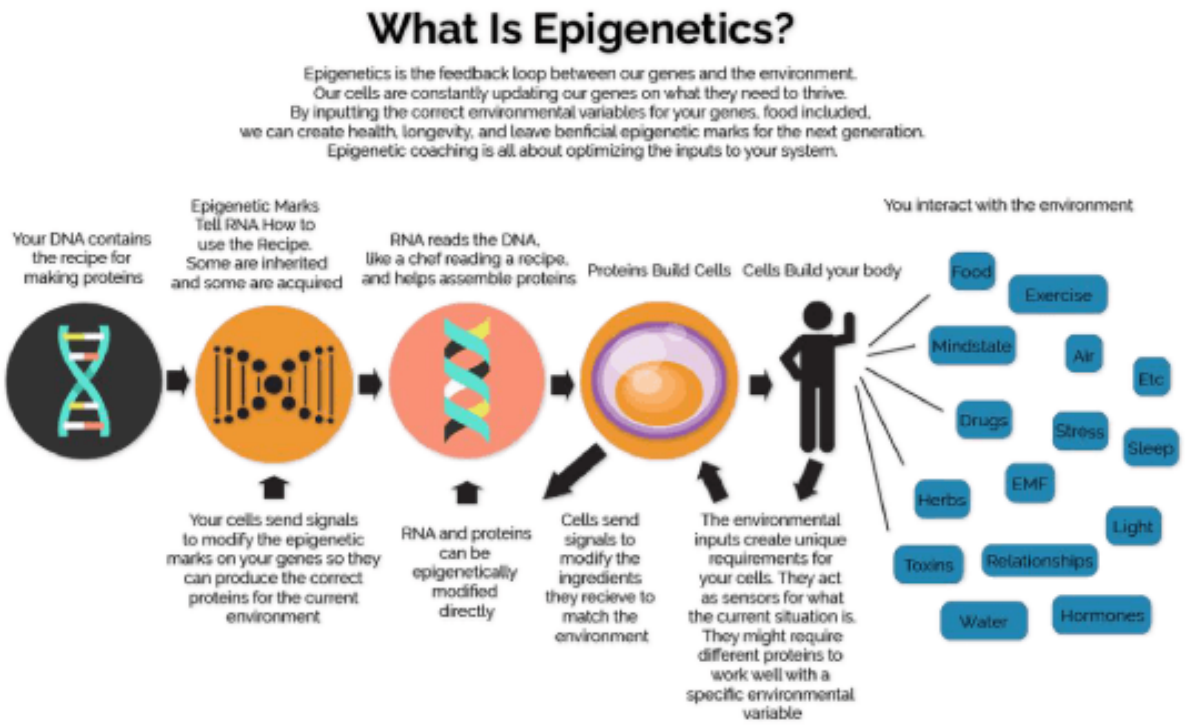
Epigenetics

The nature-nurture debate

The historical debate over the relative influence of genes and environment on characteristics

Nature = genetic influence

Nurture = environmental influence



Epigenetics is the science of how genes and environment interact within an individual

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Epigenetic mechanisms

Expression of a DNA depends on two main factors acting on the DNA tail:

Methylation

- Adding a methyl group prevents the genes being read and effectively ‘turns off’ the genes.

Acetylation

- Adding an acetyl group makes a DNA strand accessible and effectively turns it on.

Diet, exercise, pollution, sun exposure, smoking/toxins and age are the main factors effecting epigenetics






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Epigenome-wide meta-analysis identifies DNA methylation biomarkers associated with diabetic kidney disease

nature communications

Article

https://doi.org/10.1038/s41467-022-34963-6

Epigenome-wide meta-analysis identifies DNA methylation biomarkers associated with diabetic kidney disease

Received: 27 April 2022

Accepted: 14 November 2022

Published online: 22 December 2022

Check for updates

Laura J. Smyth[1,20], Emma H. Dahlström[2,3,4,20], Anna Syreeni[2,3,4], Katie Kerr[1], Jill Kilner[1], Ross Doyle[5], Eoin Brennan[5], Viji Nair[6], Damian Fermin[7], Robert G. Nelson[8], Helen C. Looker[8], Christopher Wooster[1], Darrell Andrews[5], Kerry Anderson[1], Gareth J. McKay[1], Joanne B. Cole[9,10], Rany M. Salem[11], Peter J. Conlon[12], Matthias Kretzler[13], Joel N. Hirschhorn[9,14,15], Denise Sadlier[16], Catherine Godson[5], Jose C. Florez[9,10,17], GENIE consortium*, Carol Forsblom[2,3,4], Alexander P. Maxwell[1,18], Per-Henrik Groop[2,3,4,19], Niina Sandholm[2,3,4] ✉ & Amy Jayne McKnight[1] ✉

- Evidence suggests epigenetic alterations, such as DNA methylation, in DKD.
- Blood-derived genome-wide DNA methylation assessed for association with DKD in 1304 well characterised individuals from T1D cohorts from United Kingdom/Ireland & Finland.
- DKD cases had persistent macroalbuminuria (AER > 300mg/ml) in urine; controls had normal range AER despite a long duration of T1D (≥15 yrs).

DNA bisulphite treated (Zymo EZ DNA methylation kit) → Sample analyses Illumina MethylationEPIC Array and iScan

→ Illumina's BeadArray Controls Reporter to ensure output .idat files passed quality thresholds

↓

RnBeads was used for additional QC ← RnBeads and Bioconductor R packages used to adjust for covariates ← β values generated, M values derived, and p values computed for all CpG sites ← Comparisons of differentially methylated CpGs (dmCpGs) between cases and controls

↘

Analyses were performed for each cohort in turn before meta-analysing the results using METAL

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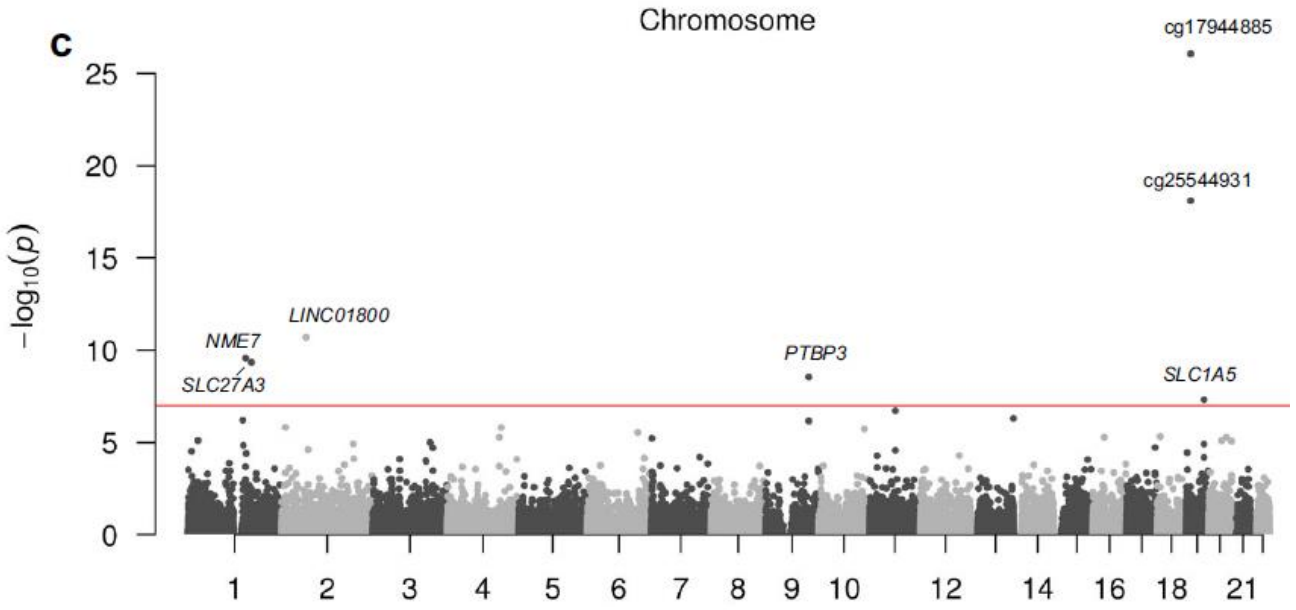
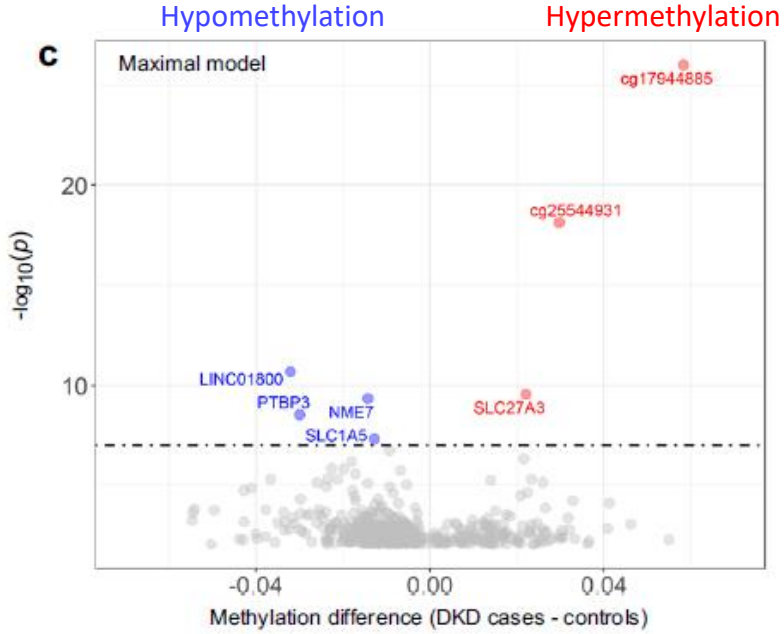
Epigenetic associations with diabetic kidney disease





- Meta-analysis identified 32 differentially methylated CpGs with DKD in T1D, 18 of which were located within genes differentially expressed in kidneys or correlated with pathological traits in DKD.
- Follow-up data was available for 397 DKD cases to evaluate progression to kidney failure.
- Methylation at 21 of the 32 CpGs were shown to predict development of kidney failure, potentially identifying individuals at greater risk for DKD in T1D.

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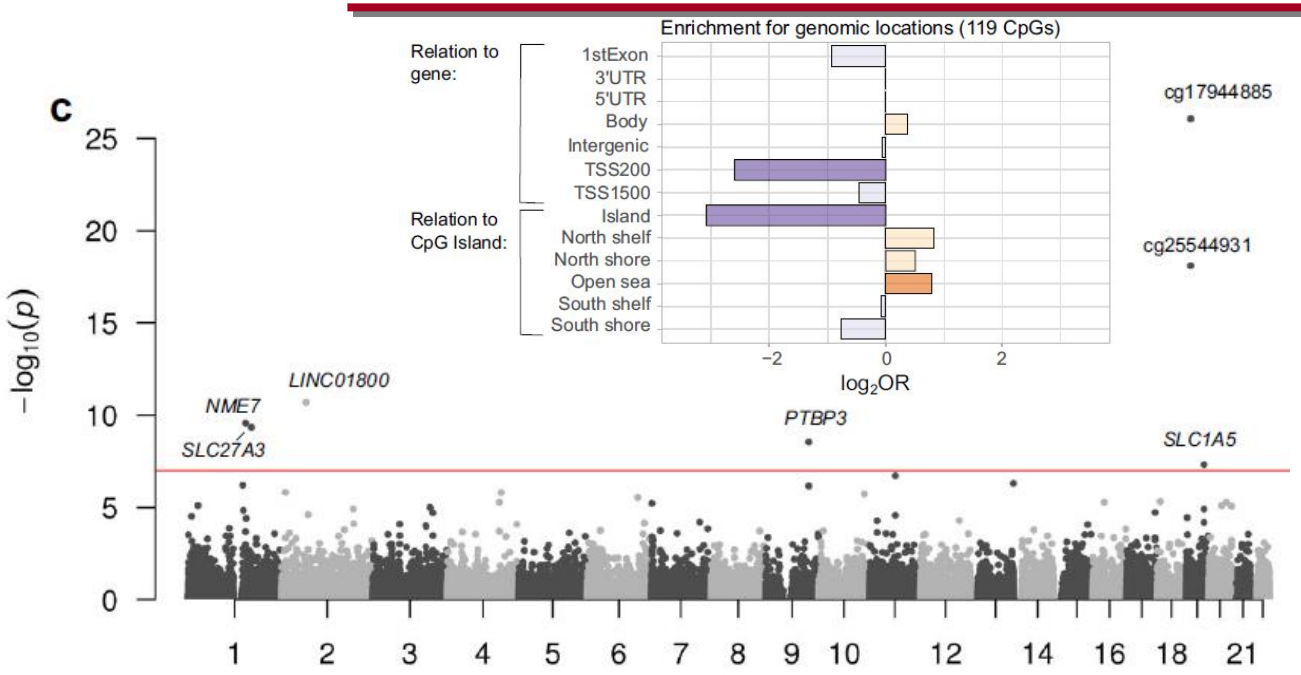
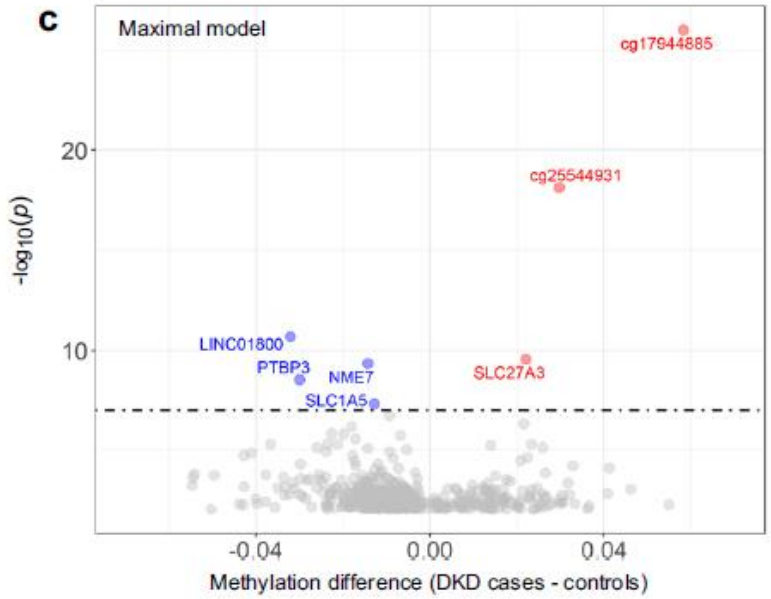
Epigenetic associations with diabetic kidney disease





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- Follow-up data was available for 397 DKD cases to evaluate progression to kidney failure.
- Methylation at 21 of the 32 CpGs were shown to predict development of kidney failure, potentially identifying individuals at greater risk for DKD in T1D.
- Enrichment of DKD-associated CpGs in TSS.

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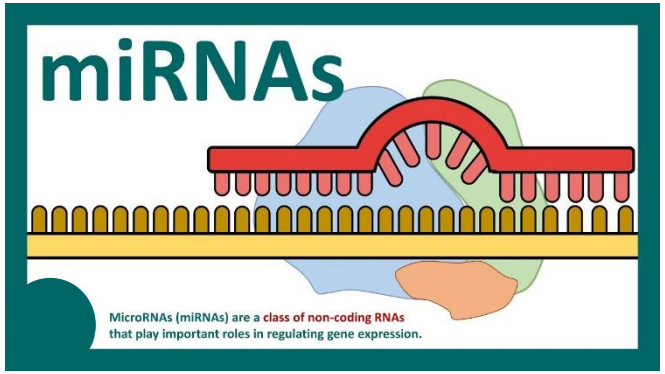
miRNA’s and Diabetic Kidney Disease



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Differential urinary exosomal microRNA expression in DKD

Differential Expression of Urinary Exosomal MicroRNAs miR-21-5p and miR-30b-5p in Individuals with Diabetic Kidney Disease

Jinnan Zang[1], Alexander P. Maxwell[1], David A. Simpson[2] & Gareth J. McKay[1]

SCIENTIFIC REPORTS | (2019) 9:10900 | https://doi.org/10.1038/s41598-019-47504-x

SCIENTIFIC REPORTS
nature research

- Current biomarkers to identify DKD lack sensitivity to detect early kidney damage.
- miRNAs - short, non-coding, regulatory RNA molecules commonly found in urinary exosomes and differentially expressed as renal function declines.
- **Study 1 -** We evaluated 87 urinary exosomal miRNA expression using **miRCURY PCR panel** (Qiagen) in a discovery cohort with T2DKD (n = 14) and age & sex-matched controls with T2D & normal renal function (T2DNRF; n = 15).

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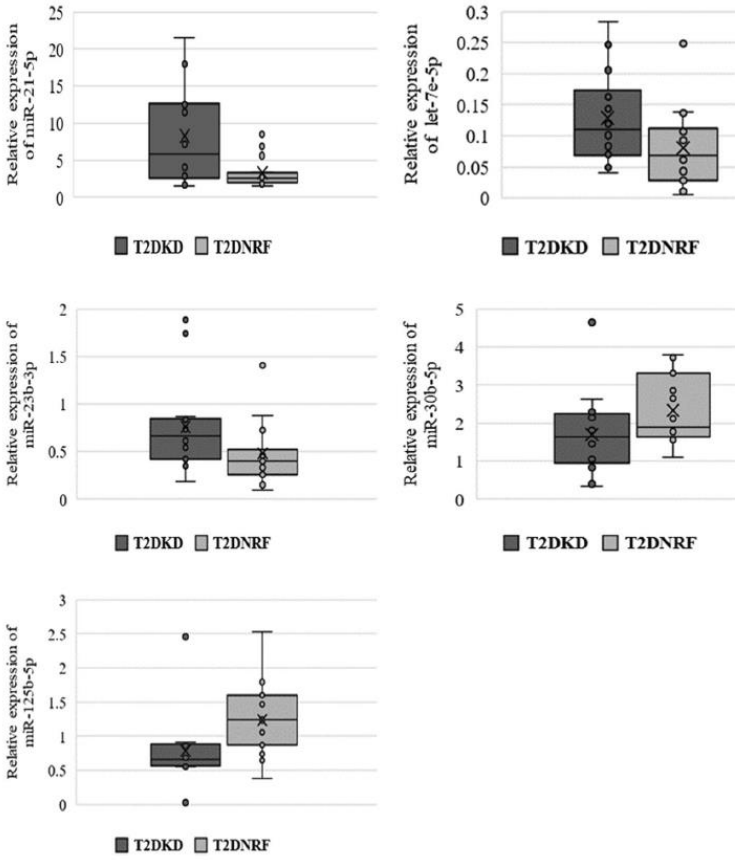
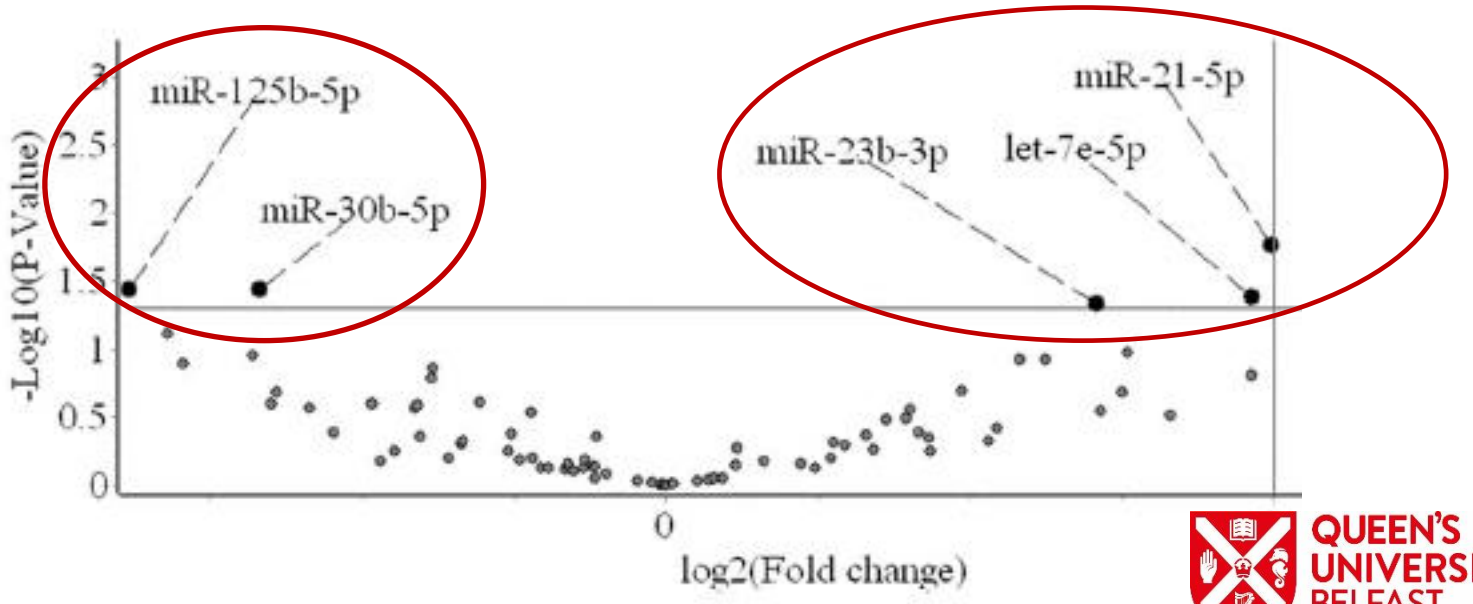
Differential urinary exosomal microRNA expression in DKD

- In discovery cohort, miR-21-5p, let-7e-5p & miR-23b-3p significantly upregulated in T2DKD.
- Conversely, miR-30b-5p & miR-125b-5p significantly lower in T2DKD.





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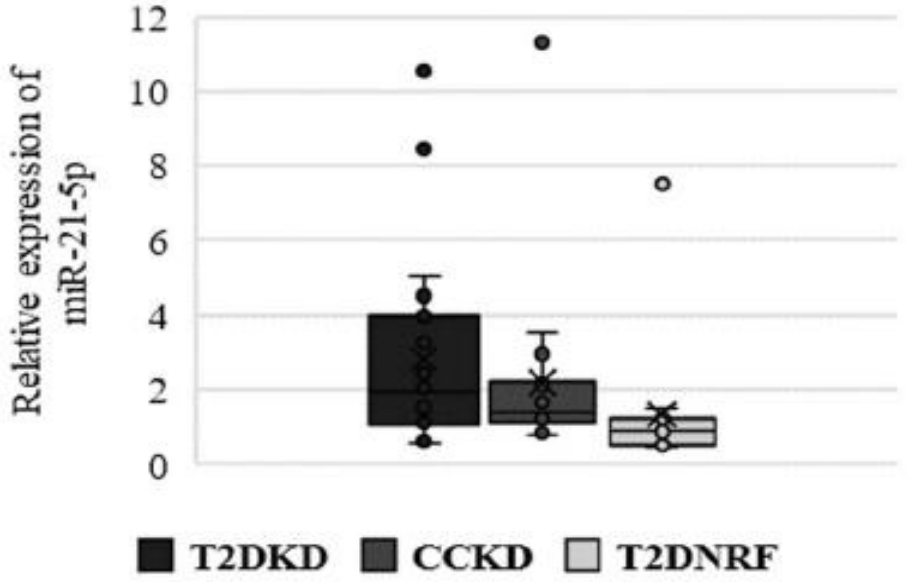
Differential urinary exosomal microRNA expression in DKD

- Independent miRNA validation performed in 2nd cohort with T2DKD (n = 22) & 2 control groups: T2DNRF (n = 15) & CKD controls without diabetes (CCKD; n = 18).
- Independent validation confirmed 2 miRs - up-regulation of miR-21-5p in T2DKD (2.13-fold, p = 0.006) & CCKD (1.73-fold, p = 0.024).



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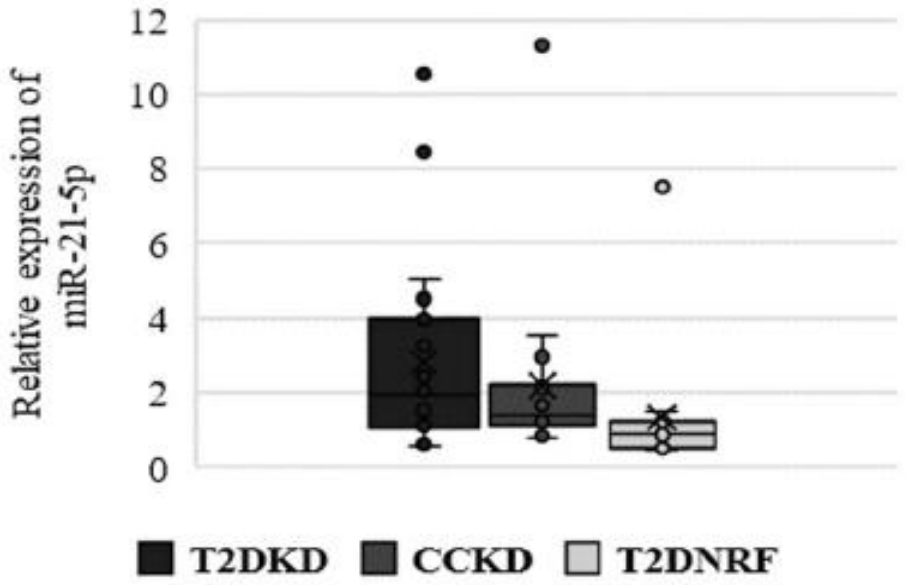
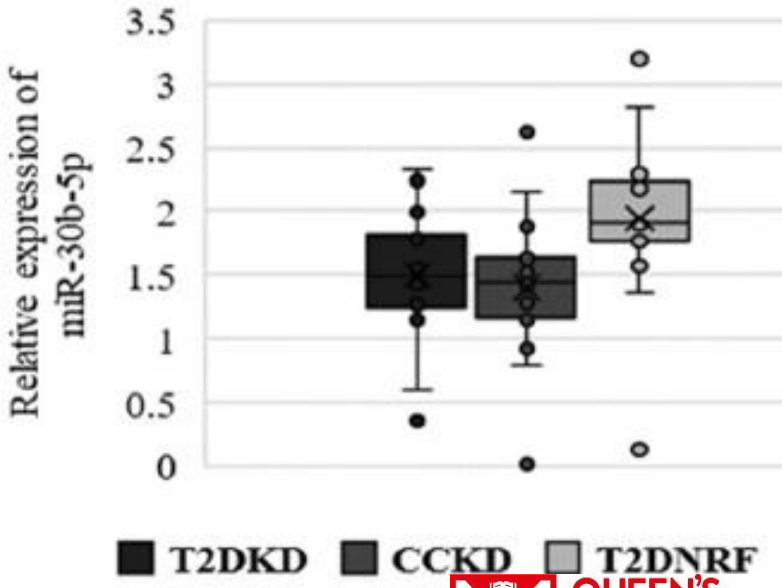
- In contrast, miR-30b-5p was downregulated in T2DKD (0.82-fold, p = 0.006) & CCKD (0.66-fold, p < 0.002).





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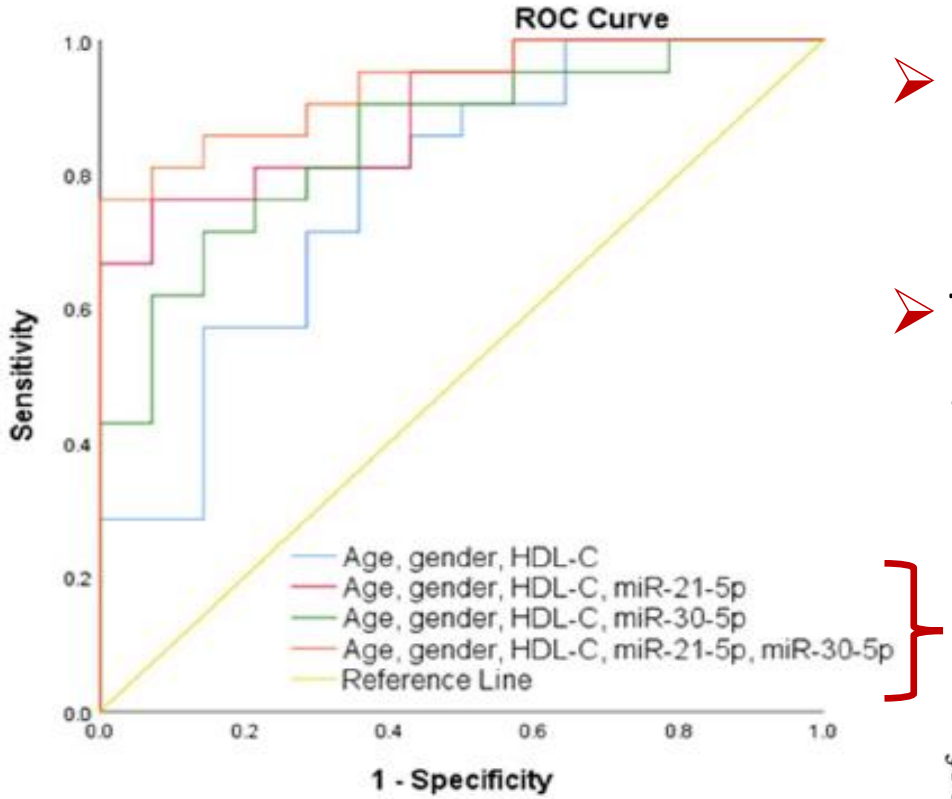
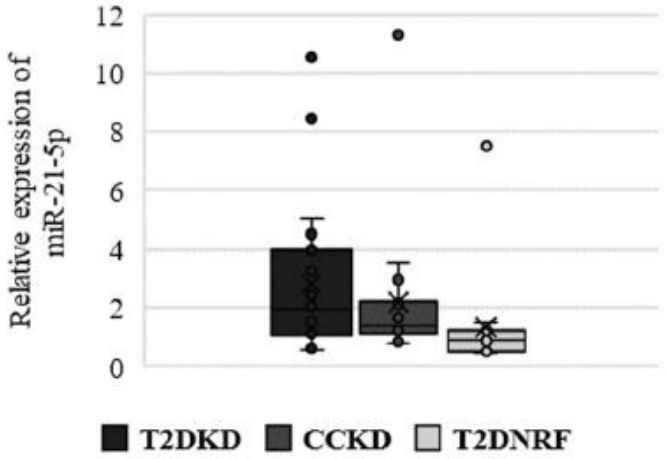
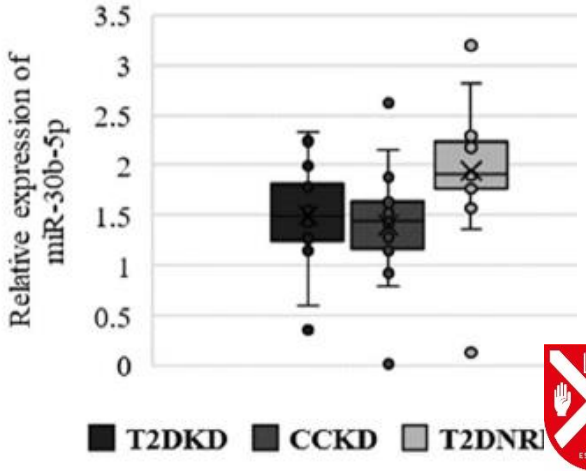
Differential urinary exosomal microRNA expression in DKD



Covariates	AUC	95% CI	p value
Discovery Cohort			
Age, gender, HDL	0.560	0.338-0.782	0.593
Age, gender, HDL, miR-21-5p	0.830	0.673-0.986	0.004
Age, gender, HDL, miR-30b-5p	0.714	0.517-0.911	0.058
Age, gender, HDL, miR-21-5p, miR-30b-5p	0.813	0.652-0.974	0.006
Validation Cohort			
Age, gender, HDL	0.779	0.620-0.938	0.006
Age, gender, HDL, miR-21-5p	0.895	0.793-0.996	< 0.001
Age, gender, HDL, miR-30b-5p	0.850	0.724-0.977	0.001
Age, gender, HDL, miR-21-5p, miR-30b-5p	0.932	0.853-1.000	< 0.001

- Identified differential expression of miR-21-5p & miR-30b-5p in individuals with either DKD or poor renal function.
- These miRNAs may represent potential biomarkers associated with the pathogenesis of renal dysfunction.





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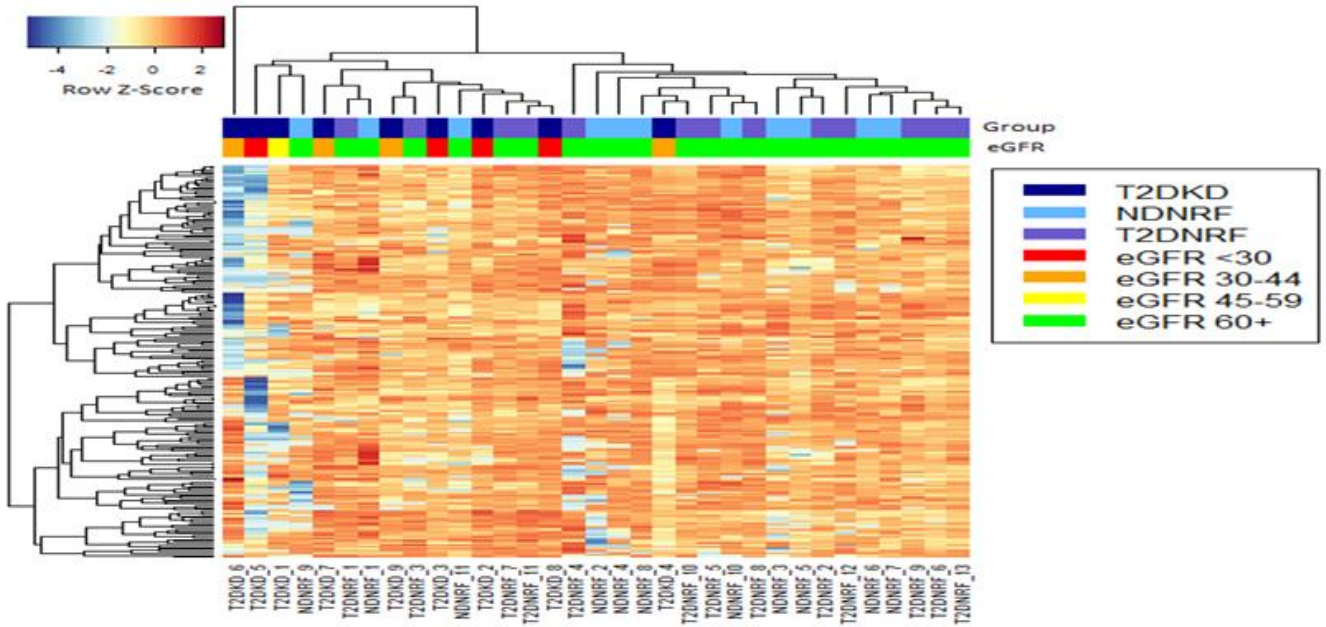
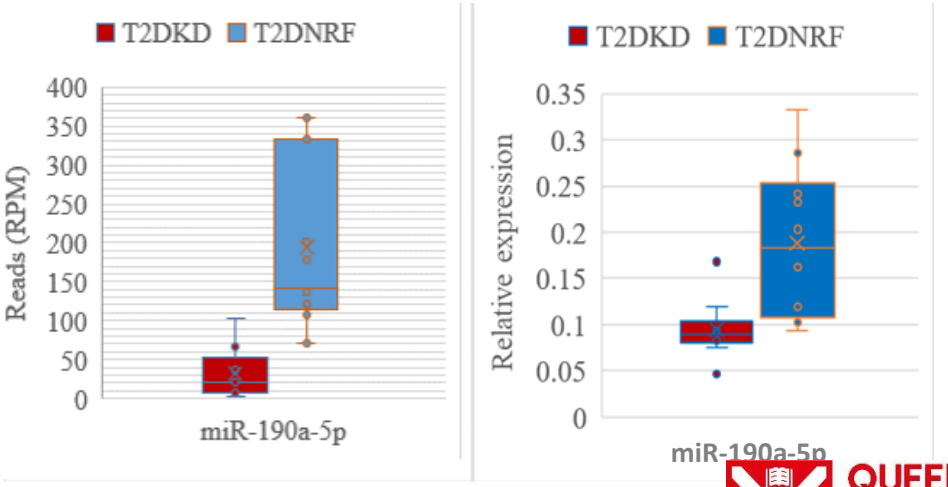
Reduced tubular miR-190a-5p a novel biomarker for stratification of patients with DKD

Study 2

- Used miRNA NGS RNA - Seq to measure differential expression of plasma miRNAs in T2D patients with (n=9) or without (n=13) kidney disease and non-diabetic normal renal function (n=11) to identify novel miR biomarkers of kidney dysfunction.
- miR-190a-3p significant lower expression in T2DKD in discovery and validation cohorts





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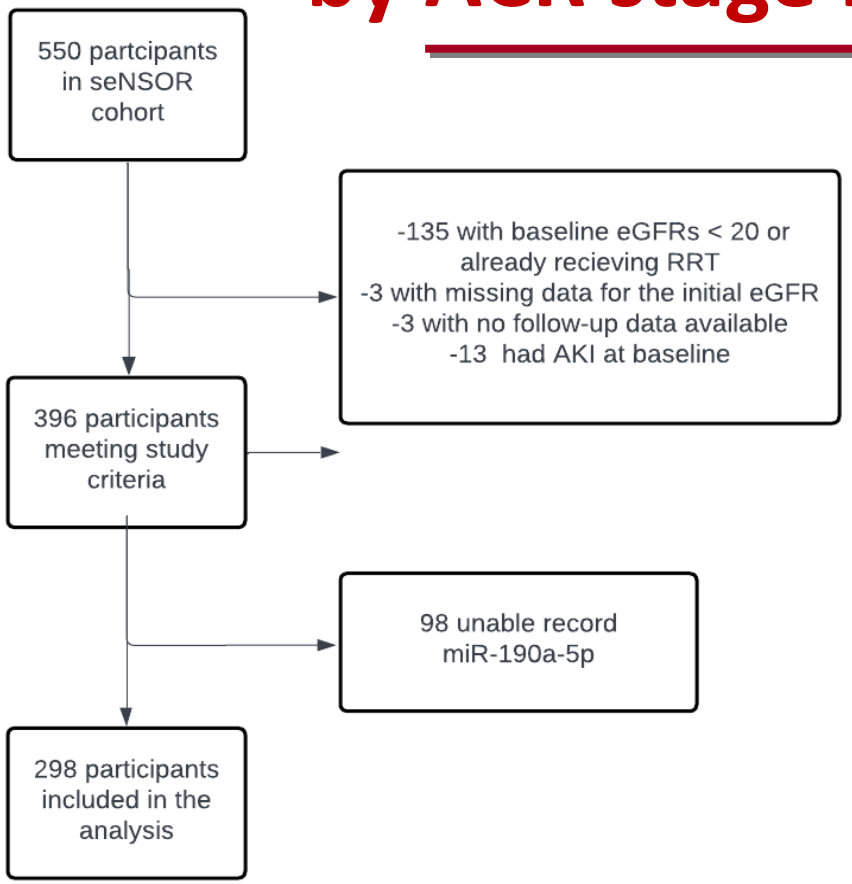
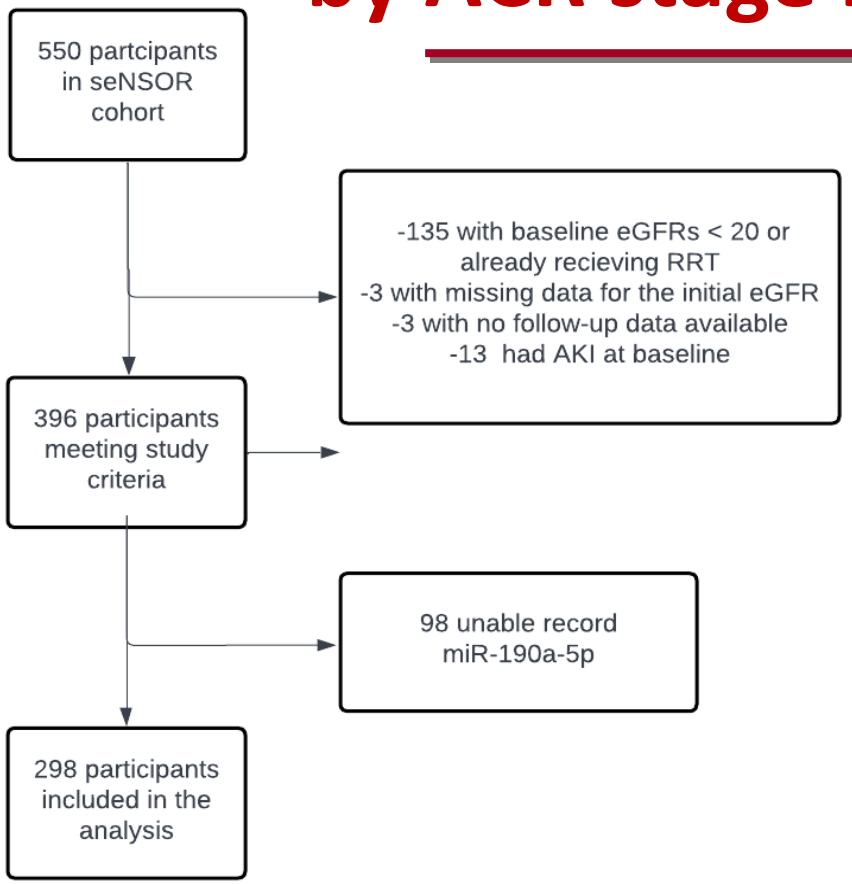
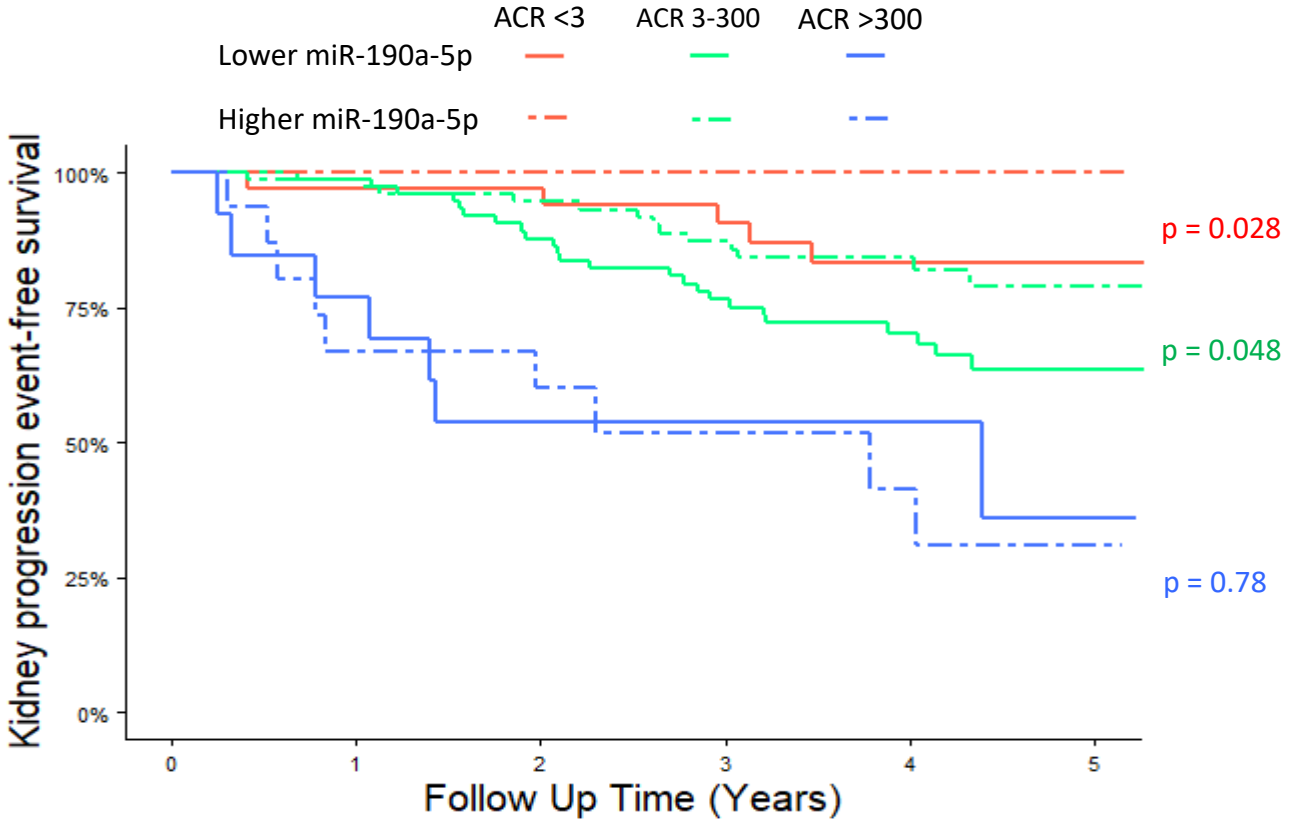
Validation of differential expression of mir-190a-5p in DKD by ACR stage in the prospective seNSOR cohort



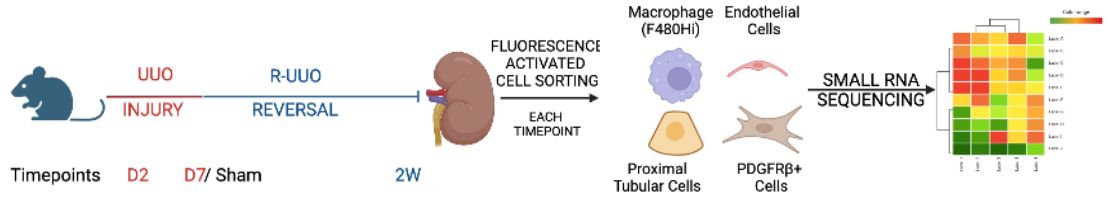
Validation of differential expression of mir-190a-5p in DKD by ACR stage in the prospective seNSOR cohort

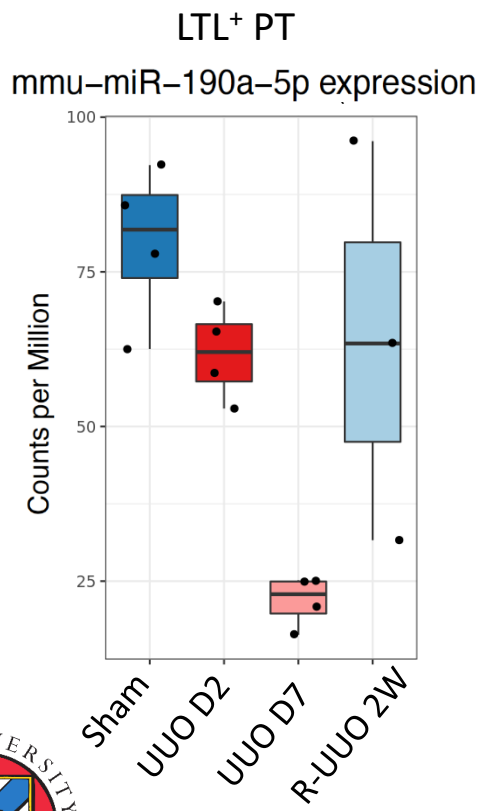


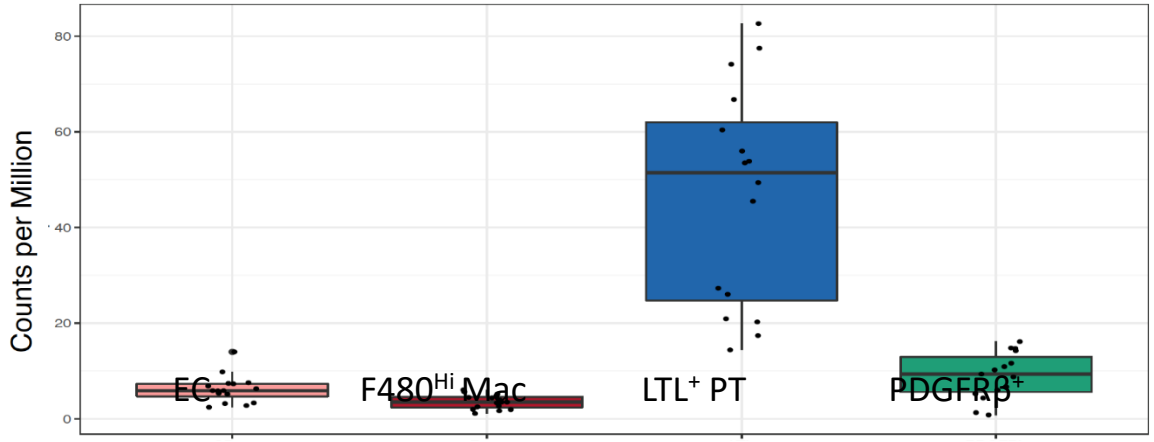


- Positive correlation between miR-190a-5p and eGFR (rho = 0.12, p=0.04) & inversely with age (rho = -0.12, p=0.04).
- MiR-190a-5p levels below the median predict CKD progression in those with minimal and moderate albuminuria (ACR < 300mg/mmol respectively) but not in those with severe albuminuria (ACR > 300mg/mmol).

Murine model miR-190a-5p expression



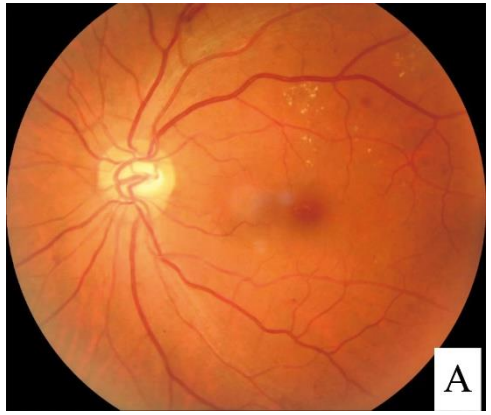




- miR-190a expression in renal cell types in the reversible unilateral ureter obstruction mouse model shows enrichment in proximal tubule cells
- miR-190a expression falls significantly following injury before increasing again during the repair phase.

- Low serum miR-190a may predict declining renal function in patients with low or moderate proteinuria, independent of existing risk factors.

Oculomics in Diabetic Kidney Disease



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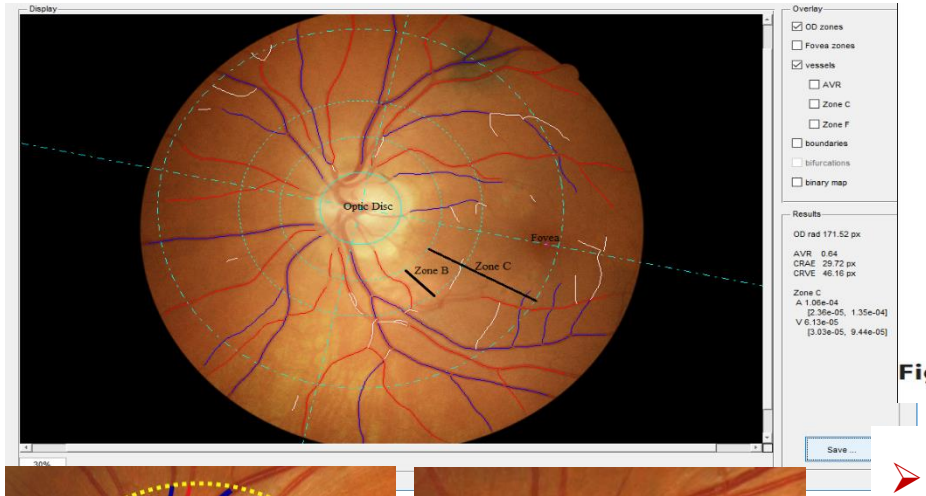
What and why measure the eye?



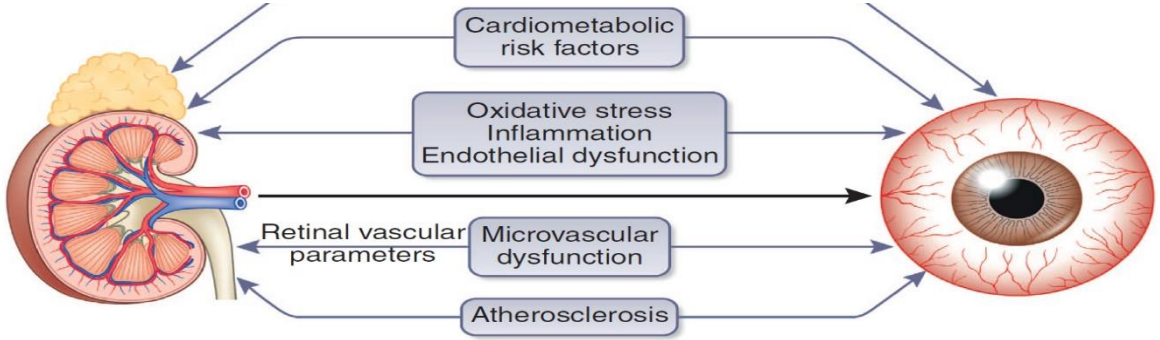
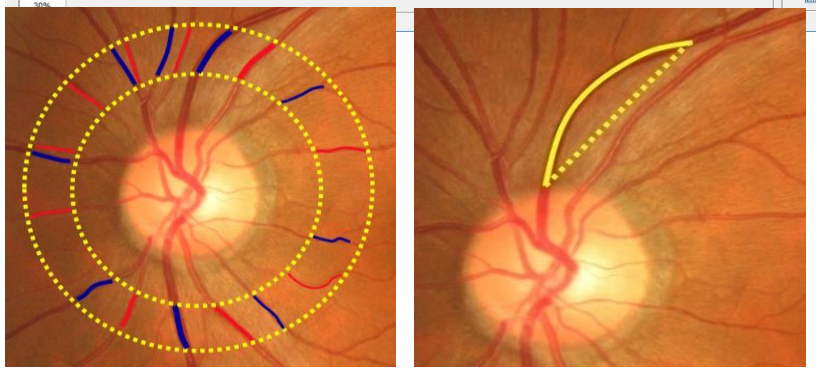
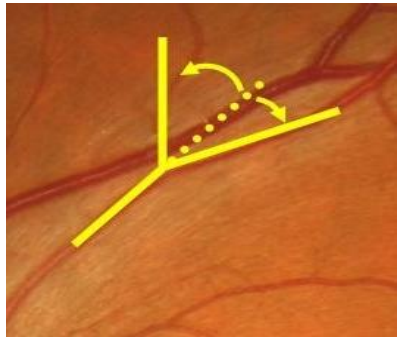
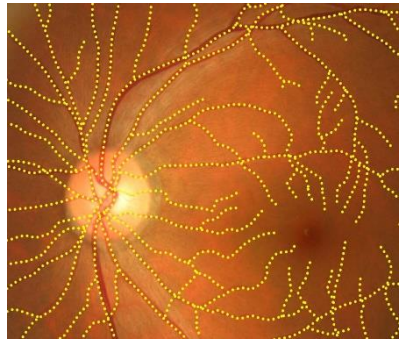


Figure 1 | Common pathogenetic mechanisms underlying renal and retinal diseases.

Wong et al., Kidney International, 2013







- Leading causes of visual impairment associated with CKD (Zhu et. al. 2020) - Cataract, AMD, Glaucoma and any retinopathy
- Previous reported associations between renal function & retinal parameters.
- Associations may reflect systemic vascular effects and /or renovascular damage.
- Retina - a non-invasive, opportunistic microvascular imaging.
- Significant advances in retinal imaging technology and analysis applications.
- Renal biopsy and vascular imaging procedures are invasive

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Northern Ireland Cohort of Longitudinal Ageing (NICOLA)

- Stratified random sample of ~8500 men/women aged 50+ in Northern Ireland
- Computer Assisted Personal Interview (CAPI) plus self-completed questionnaires- social, behavioural, economic and environmental aspects of ageing including diet, mental health, physical activity
- Longitudinal : Repeated measures every 2-4 years
- Health Assessment –
  - Cardiovascular, cognitive and respiratory health
  - Visual function including retinal imaging
  - Anthropometry
  - Physical function
  - Biological samples

O'Neill *et al. BMC Nephrology* (2020) 21:382
https://doi.org/10.1186/s12882-020-02031-0

BMC Nephrology

RESEARCH ARTICLE Open Access

Association of retinal venular tortuosity with impaired renal function in the Northern Ireland Cohort for the Longitudinal Study of Ageing

R. A. O'Neill, A. P. Maxwell, F. Kee, I. Young, B. McGuinness, R. E. Hogg and McKay GJ*

CKD status SeCr		Adjusted (Min)			Adjusted (Full)	
Retinal parameter	**OR**	**95% CI**	**P Value**	**OR**	**95% CI**	**P Value**
Arteriolar Calibre (PX)	1.23	0.25,5.96	0.80	1.85	0.30, 11.50	0.51
Venular Calibre (PX)	0.97	0.18, 5.43	0.98	0.59	0.08, 4.24	0.60
Arteriolar Fractal dimension	1.11	0.92, 1.34	0.28	1.16	0.94, 1.42	0.16
Venular Fractal dimension	0.84	0.70, 1.00	0.05	0.86	0.70, 1.06	0.17
Arteriolar Tortuosity	1.05	0.88, 1.25	0.60	1.03	0.85, 1.24	0.77
Venular Tortuosity	1.34	1.13, 1.58	<0.01	1.29	1.08, 1.54	<0.01

Min adj: age, sex; Full: age, sex, diabetes, smoking, education, BMI, antihypertensive medication, MABP, triglycerides, HDL & LDL.

Associations of retinal thinning and poorer renal function

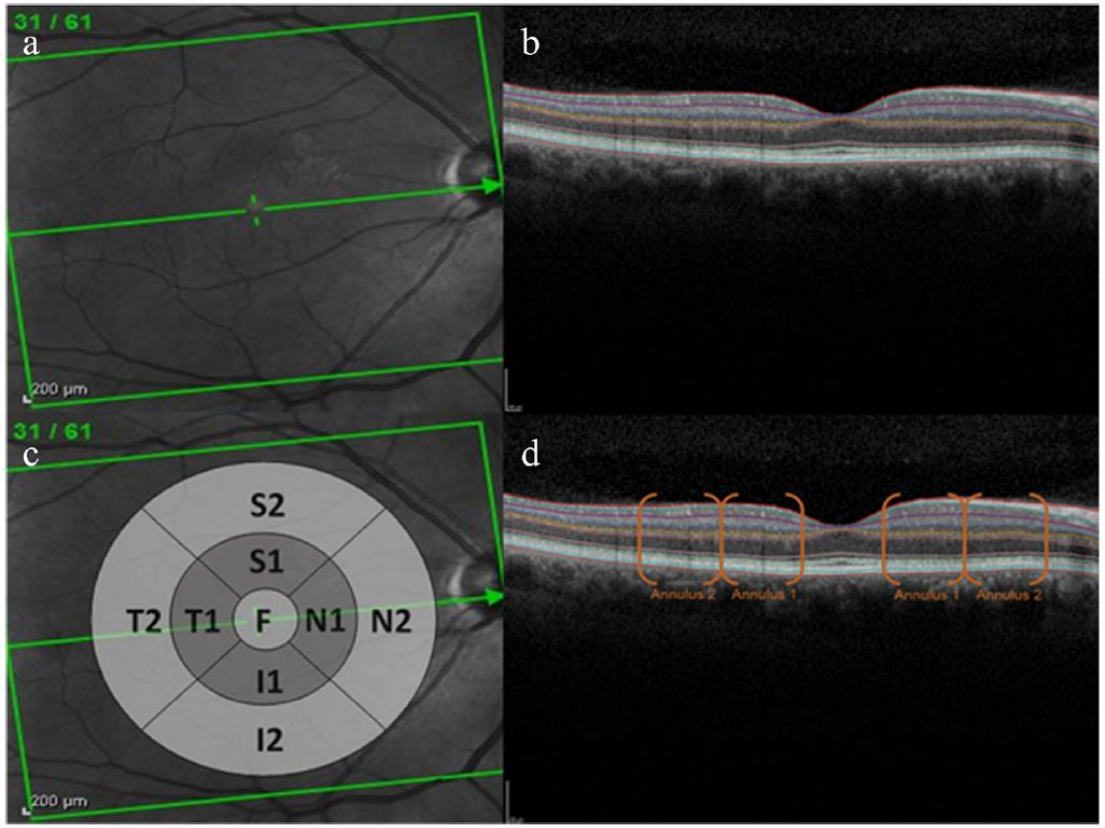
Paterson *et al. BMC Nephrology* (2020) 21:37
https://doi.org/10.1186/s12882-019-1679-1

BMC Nephrology

RESEARCH ARTICLE Open Access

Association of reduced inner retinal thicknesses with chronic kidney disease

Euan N. Paterson[1], Meera L. Ravindran[1], Kayleigh Griffiths[1], Claire A. Le Velly[1], Chris C. Cardwell[1], Rachel V. McCarter[1], Patrick Nicol[1], Jay K. Chhablani[2], Mohammed Abdul Rasheed[3], Kiran Kumar Vupparaboina[3], Thomas J. MacGillivray[4], Mark Harbinson[5], Alexander P. Maxwell[1], Ruth E. Hogg[1] and Gareth J. McKay[1*]



- Participants (n = 241) - mean age: 65 yrs; mean eGFR: 67 ml/min/1.73m^2. 39% had diabetes.
- Reduced retinal thickness, in particular a thinner inner retinal layer and microvascular complexity associated with CKD stage 4–5 independent of other important risk factors (age, MABP, diabetes, LDL, BMI & sex).
- Associations were limited to layers of the retina supplied by the retinal microvasculature.
- No associations with early stage CKD, but distinct association with CKD st 4–5.

QUEEN'S UNIVERSITY BELFAST

Sparser retinal microvascular network and reduced renal function

Paterson *et al. BMC Nephrology* (2021) 22:72
https://doi.org/10.1186/s12882-021-02273-6

BMC Nephrology

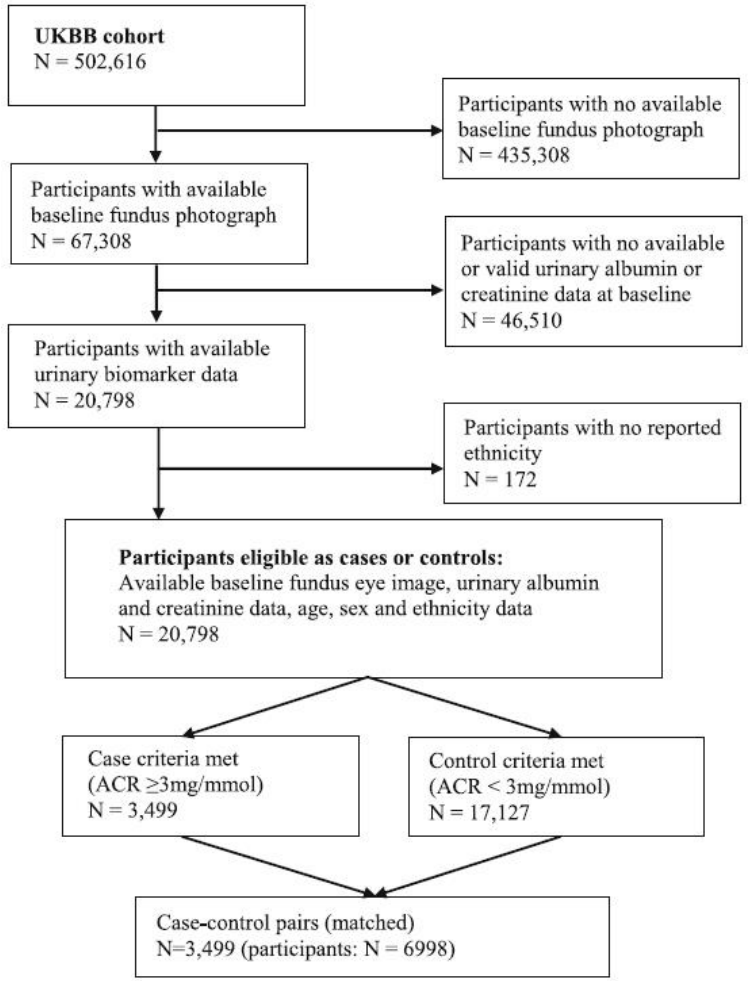
RESEARCH ARTICLE Open Access

Investigation of associations between retinal microvascular parameters and albuminuria in UK Biobank: a cross-sectional case-control study

Euan N. Paterson[1], Chris Cardwell[1], Thomas J. MacGillivray[2], Emanuele Trucco[3], Alexander S. Doney[4], Paul Foster[5], Alexander P. Maxwell[1], Gareth J. McKay[1*] and on behalf of The UK Biobank Eye and Vision Consortium

Table 5 Associations between retinal microvascular parameters (Z scores) vs CKD status based on ACR > 3 mg/mmol and/or eGFR < 60 ml/min/1.73m^2 (SCr & SCys)

	Model 1 OR (95% CI)	*p*	Model 2 OR (95% CI)	*p*	Model 3 OR (95% CI)	*p*
CRAE	1.01 (0.90, 1.13)	0.88	0.97 (0.86, 1.09)	0.59	0.98 (0.87, 1.11)	0.79
CRVE	1.03 (0.93, 1.14)	0.59	0.99 (0.89, 1.10)	0.90	1.01 (0.90, 1.12)	0.92
AVR	0.92 (0.81, 1.05)	0.21	0.93 (0.80, 1.06)	0.27	0.93 (0.80, 1.07)	0.29
FDa	1.22 (1.07, 1.39)	0.003	1.20 (1.05, 1.37)	0.01	1.22 (1.06, 1.39)	0.01
FDv	1.27 (1.08, 1.49)	0.004	1.28 (1.08, 1.52)	0.01	1.26 (1.06, 1.50)	0.01
Torta	0.99 (0.90, 1.09)	0.85	1.00 (0.90, 1.10)	0.92	0.98 (0.89, 1.08)	0.69
Tortv	0.97 (0.88, 1.07)	0.52	0.98 (0.88, 1.08)	0.65	0.98 (0.88, 1.08)	0.63



- Case-control study of healthy versus unhealthy ACR suggests reduced retinal microvascular FD, i.e. sparser retinal microvascular networks, associate with albuminuria & lower eGFR.

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Not all associations are positive!

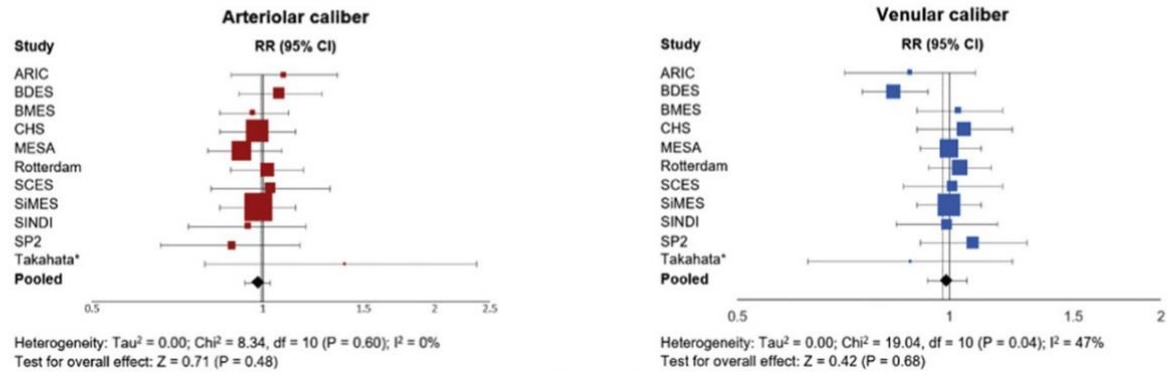
www.kidney-international.org clinical investigation

A systematic review and participant-level meta-analysis found little association of retinal microvascular caliber with reduced kidney function

Weng Kit Lye[1,12], Euan Paterson[2,12], Christopher C. Patterson[2], Alexander P. Maxwell[2], Riswana Banu Binte Mohammed Abdul[1], E. Shyong Tai[1], Ching Yu Cheng[1], Takamasa Kayama[3], Hidetoshi Yamashita[4], Mark Sarnak[5], Michael Shlipak[6], Kunihiro Matsushita[7], Unal Mutlu[8,9], Mohammad A. Ikram[8], Caroline Klaver[8,9], Annette Kifley[10], Paul Mitchell[10], Chelsea Myers[11], Barbara E. Klein[11], Ronald Klein[11], Tien Y. Wong[1], Charumathi Sabanayagam[1,13] and Gareth J. McKay[2,13]

A systematic review and participant-level meta-analysis found little association of retinal microvascular caliber with reduced kidney function.

Relative Risk (RR) for estimated glomerular filtration rate <60ml/min/1.73m² per 20 µm increase in caliber. 44,803 individuals across 11 cohorts



Pooled analyses adjusted for age, center, gender, ethnicity (if multi-ethnic cohort), education, current smoking, diabetes, hypertension, BMI, total cholesterol, and fellow vessel central retinal arteriolar equivalent.

CONCLUSION:
No evidence of association between retinal microvascular caliber and CKD stages 3-5 was found in pooled analyses of 11 population-based cohorts.

ISN kidney INTERNATIONAL
OFFICIAL JOURNAL OF THE INTERNATIONAL SOCIETY OF NEPHROLOGY

Lye et al, 2020

SCIENTIFIC REPORTS

OPEN

Retinal microvascular parameters are not associated with reduced renal function in a study of individuals with type 2 diabetes

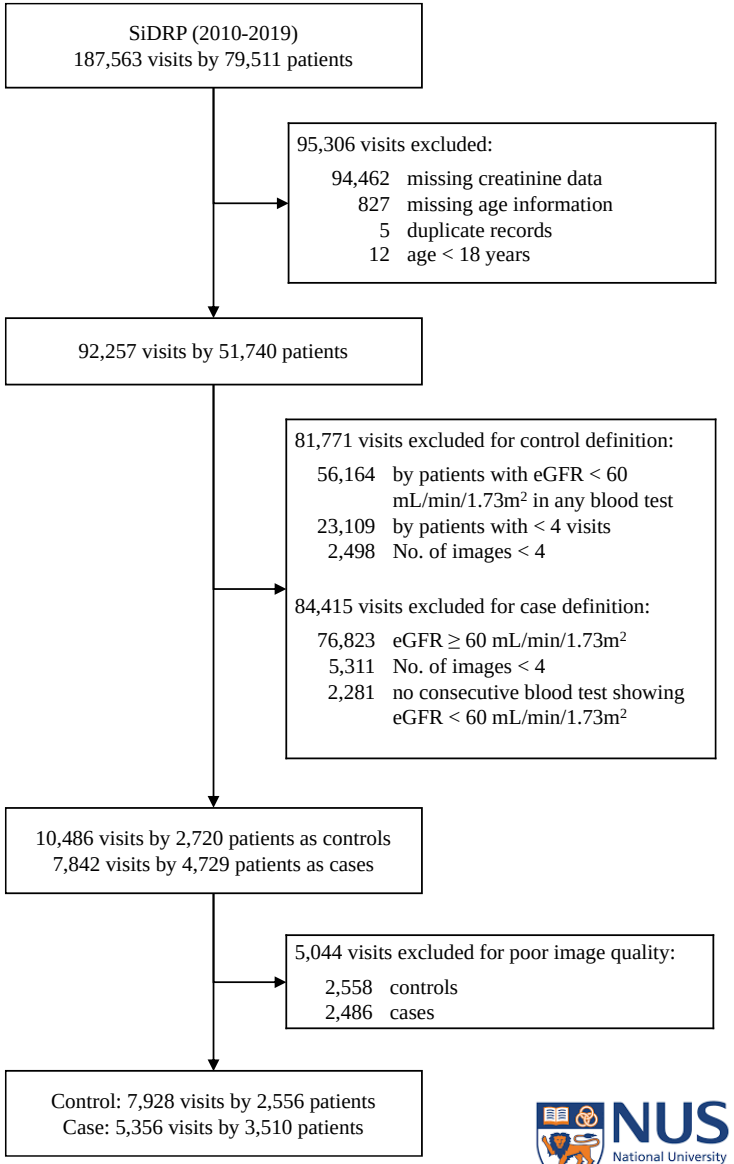
Received: 21 November 2017
Accepted: 22 February 2018
Published online: 02 March 2018

Gareth J. McKay[1], Euan N. Paterson[1], Alexander P. Maxwell[1], Christopher C. Cardwell[1], Ruixuan Wang[2], Stephen Hogg[2], Thomas J. MacGillivray[3], Emanuele Trucco[2] & Alexander S. Doney[4]

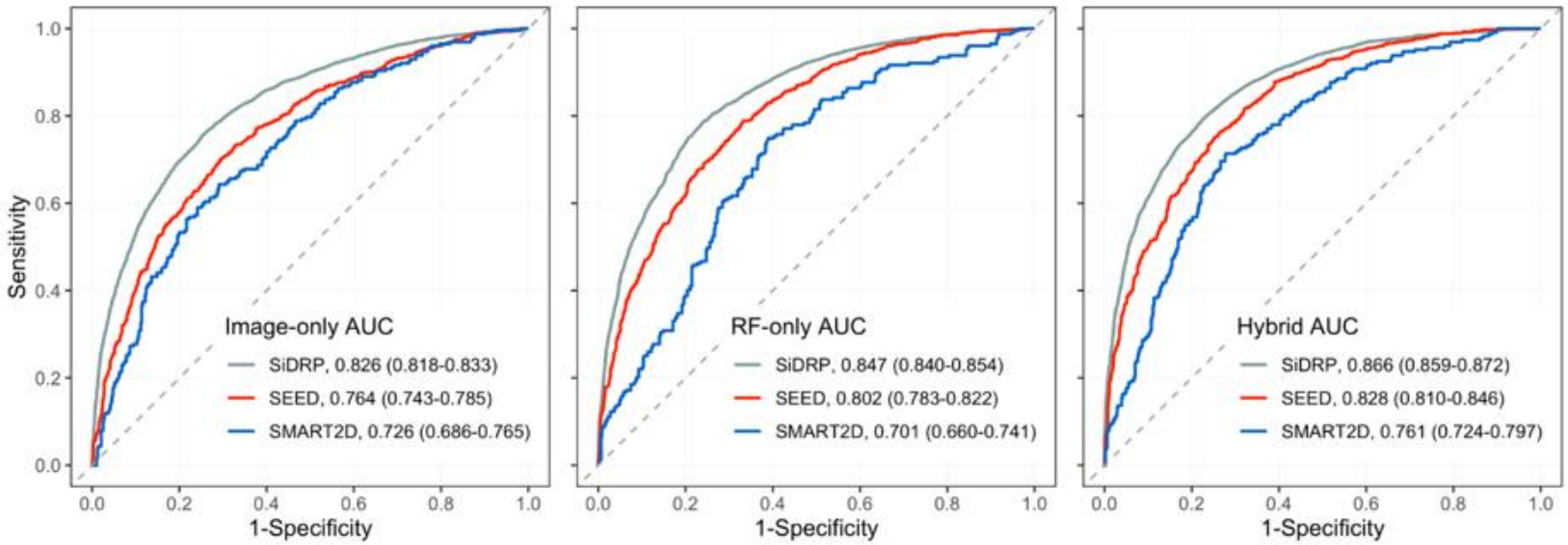
Baseline Variables	Sample n = 1068	Progressors n = 335	Non-progressors n = 570	p
Age, yrs (SD)	63.0 (7.6)	62.5 (7.7)	63.1 (7.8)	0.21
Gender, female (%)	521 (49)	168 (50)	281 (49)	0.81
eGFR, ml/min/1.73 m² (SD)	94.0 (17.2)	98.6 (21.3)	91.3 (14.3)	<0.001
SBP, mmHg (SD)	138 (13)	139 (14)	137 (13)	0.08
DBP, mmHg (SD)	77 (8)	76 (9)	77(8)	0.63
HbA_{1C}, % (SD); mmol/mol	7.41 (1.38); 57.5	7.51 (1.36); 58.6	7.40 (1.41); 57.4	0.25
Diabetic retinopathy present, n (%)	244 (23)	82 (25)	118 (21)	0.19
Mean follow-up period, yrs (SD)	3.01 (0.35)	3.02 (0.35)	3.02 (0.34)	0.98

Retinal microvascular parameter (per unit increase)	Unadjusted β eGFR (95% CI)	p	Adjusted β eGFR (95% CI)	p
Calibre				
Central retinal arteriolar equivalent	−0.47 (−0.87, −0.07)	0.02	−0.38 (−0.80, 0.05)	0.08
Central retinal venular equivalent	−0.30 (−0.60, 0.00)	0.05	−0.27 (−0.58, 0.05)	0.10
Arteriovenous ratio	−3.32 (−21.81, 15.16)	0.72	−0.52 (−19.64, 18.60)	0.96
Fractal dimension				
Arteriolar	−18.41 (−36.92, 0.10)	0.05	−17.64 (−36.71, 1.44)	0.07
Venular	−3.74 (−22.79, 15.31)	0.70	−3.46 (−23.36, 16.43)	0.73
No. of First branches in zone C				
Arteriolar	−0.67 (−1.63, 0.30)	0.17	−0.50 (−1.50, 0.49)	0.32
Venular	0.66 (−0.43, 1.75)	0.24	0.82 (−0.31, 1.95)	0.15
Tortuosity				
[a]Arteriolar	−0.01 (−2.66, 2.65)	1.00	−0.01 (−2.75, 2.73)	0.99
[a]Venular	−3.20 (−6.73, 0.32)	0.08	−2.22 (−5.86, 1.43)	0.23

Deep learning algorithms to detect DKD from retinal photographs in multi-ethnic populations with diabetes



- The CNN DLA was trained on 26568 retinal images from 6066 SiDRP participants.
- The DLA models were based on ResNet18 architecture with pre-training using a large-scale diabetic retinopathy dataset (Kaggle) to improve generalizability.
- Prediction compared with the ground truth label and revised via back-propagation.
- 5-fold cross-validation to evaluate model performance.



Models showed reasonable performance, fairing well in internal validation (AUC image-only = 0.826), with moderate performance in external validation (AUC image-only = 0.764 in SEED; 0.726 in SMART2D). In particular, the image-only model performed comparably well in all datasets compared to the RF-only model.

NUS National University of Singapore

Greater retinal microvascular complexity & dementia risk in diabetes

Retinal vascular measures from diabetes retinal screening photographs and risk of incident dementia in type 2 diabetes: A GoDARTS study

Alexander S. F. Doney[1*], Aditya Nar[1], Yu Huang[1], Emanuele Trucco[2], Tom MacGillivray[3], Peter Connelly[4], Graham P. Leese[1], Gareth J. McKay[5] and on behalf of the INSPIRED consortium

frontiers | Frontiers in Digital Health

TYPE Original Research
PUBLISHED 31 August 2022
DOI 10.3389/fdgth.2022.945276

- Cox's proportional hazards with entry time as date of image acquisition and exit time as first available evidence of dementia diagnosis in EMR.
- Censoring was end of available follow-up EMR data or death without EMR evidence of dementia.
- In addition to ACD, AD and VD also considered separately.

TABLE 3 AUC changes with inclusion of RVMs.

	Model with RMVs		Model without RMVs		
	AUC	95% CI	AUC	95%CI	*p*
ACD	0.7896	0.7731–0.8060	0.7855	0.7689–0.8022	**0.022**
VD	0.7831	0.7566–0.8095	0.7769	0.7498–0.8041	0.090
AD	0.7759	0.7532–0.7986	0.7685	0.7459–0.7910	0.094

- Increased retinal FDa associated with greater risk of ACD (HR 1.17; 1.08–1.26) & AD (HR 1.33; 1.16–1.52).
- RVMs help predict future dementia incidence independent of other risk factors.
- Differences in retinal microvascular parameters are easily measured and help predict dementia susceptibility in patients with diabetes which may inform dementia prevention strategies.

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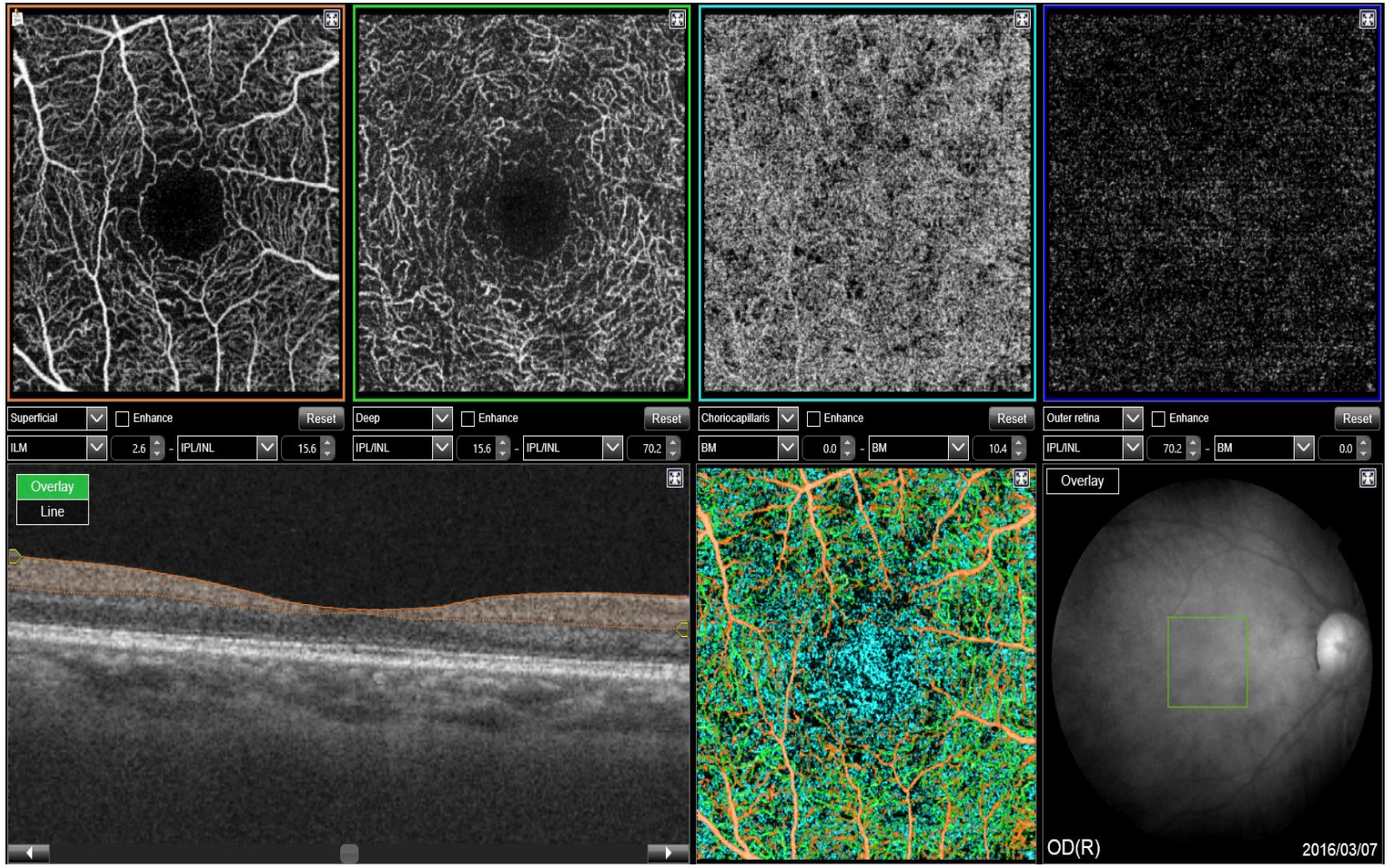
Optical coherence tomography angiography



Courtesy of Dr Carol Cheung, The Chinese University of Hong Kong

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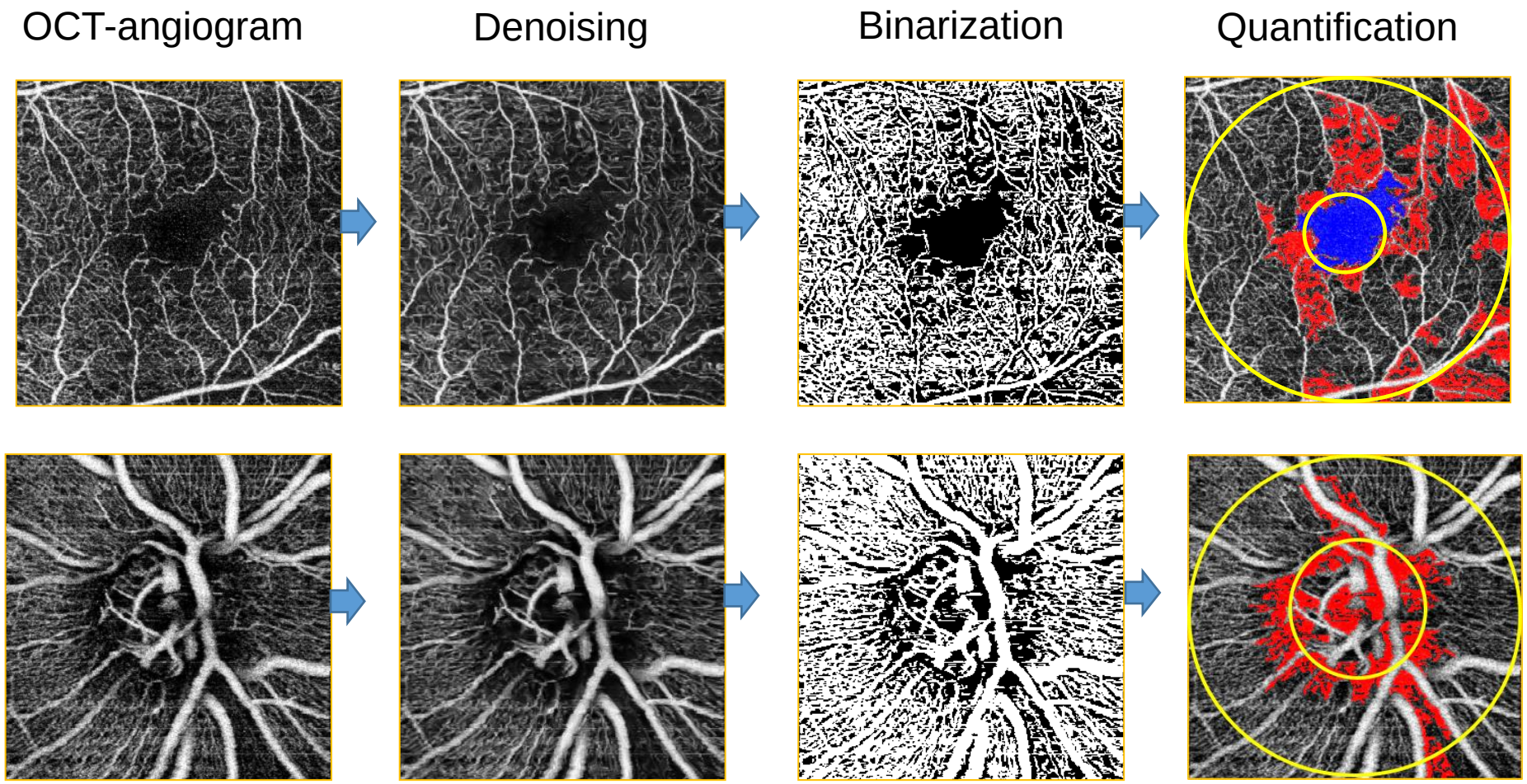
Automated image processing



Courtesy of Dr Carol Cheung, The Chinese University of Hong Kong

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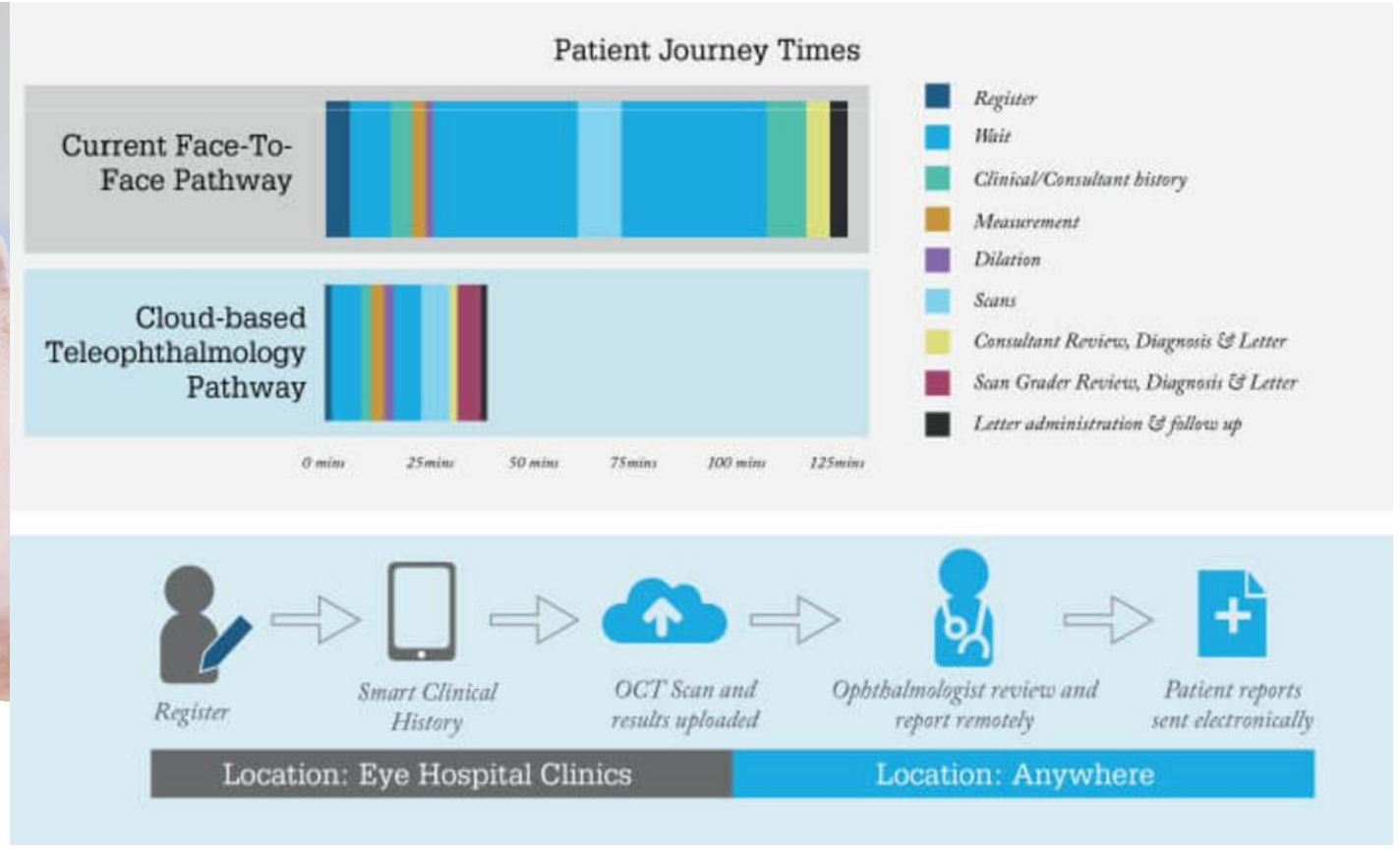
Impact – Cloud-based technology



Optomed

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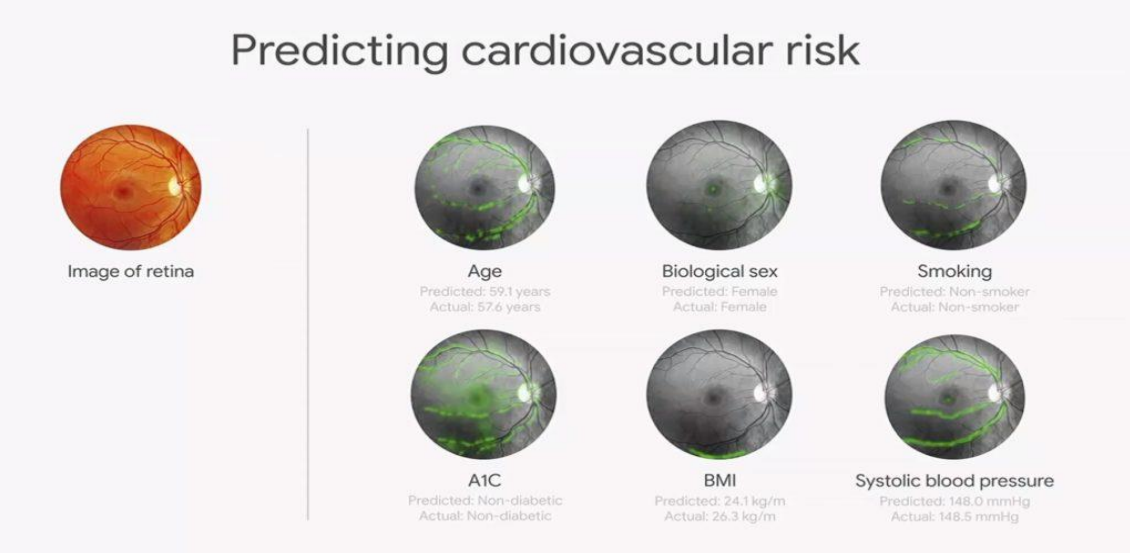
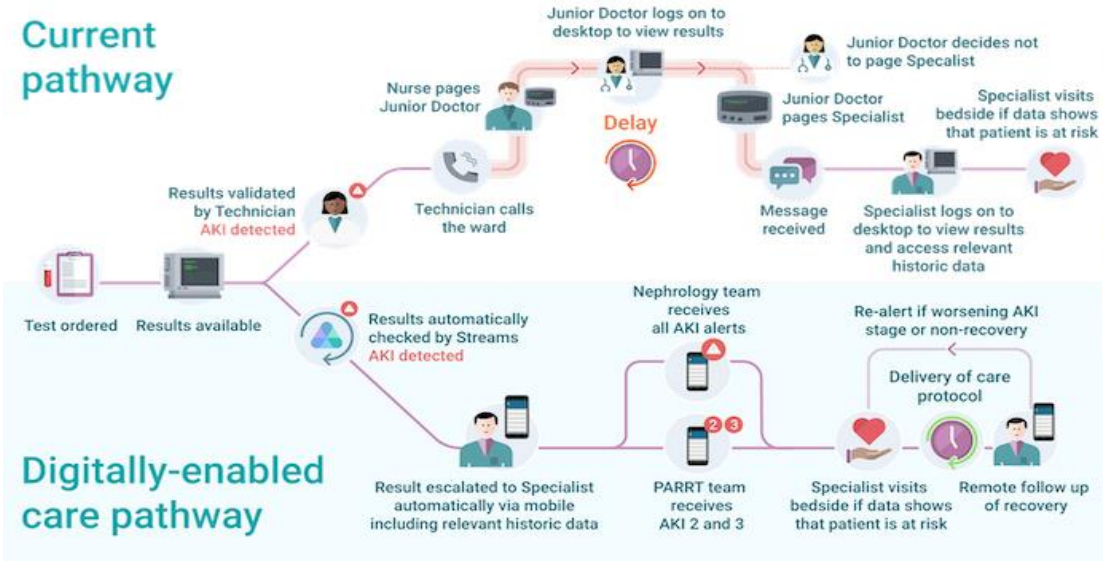
Impact - The future is AI?





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ARTICLES
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Prediction of cardiovascular risk factors from retinal fundus photographs via deep learning

Ryan Poplin[1,4], Avinash V. Varadarajan[1,4], Katy Blumer[1], Yun Liu[1], Michael V. McConnell[2,3], Greg S. Corrado[1], Lily Peng[1,4*] and Dale R. Webster[1,4]

Traditionally, medical discoveries are made by observing associations, making hypotheses from them and then designing and running experiments to test the hypotheses. However, with medical images, observing and quantifying associations can often be difficult because of the wide variety of features, patterns, colours, values and shapes that are present in real data. Here, we show that deep learning can extract new knowledge from retinal fundus images. Using deep-learning models trained on data from 284,335 patients and validated on two independent datasets of 12,026 and 999 patients, we predicted cardiovascular risk factors not previously thought to be present or quantifiable in retinal images, such as age (mean absolute error within 3.26 years), gender (area under the receiver operating characteristic curve (AUC) = 0.97), smoking status (AUC = 0.71), systolic blood pressure (mean absolute error within 11.23 mmHg) and major adverse cardiac events (AUC = 0.70). We also show that the trained deep-learning models used anatomical features, such as the optic disc or blood vessels, to generate each prediction.

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Direction of travel

- Oculomics
- DKD – MultiOmics Health

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Expanding multiomics approaches –

Why do kidney transplants fail so early in young people?

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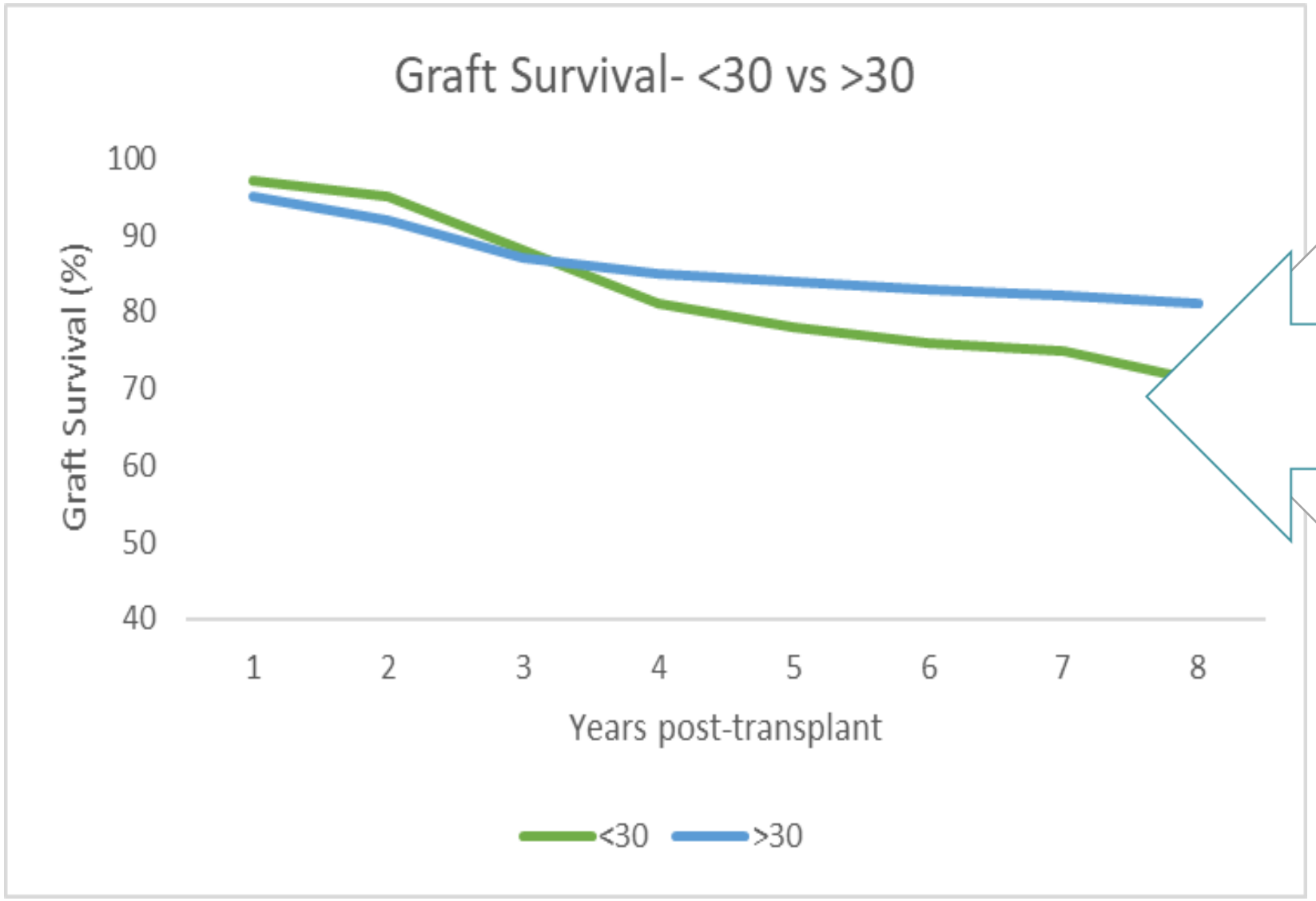

Why does this matter?

Individual

Cost

Societal

3200 renal transplants anually in the UK & Ireland

25% of our local transplants in individuals <30

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The science and the art of post transplant care

In clinical practice determination of ‘optimal’ immunosupression is limited by little objective parameters to guide decision making

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Monitoring transplant function

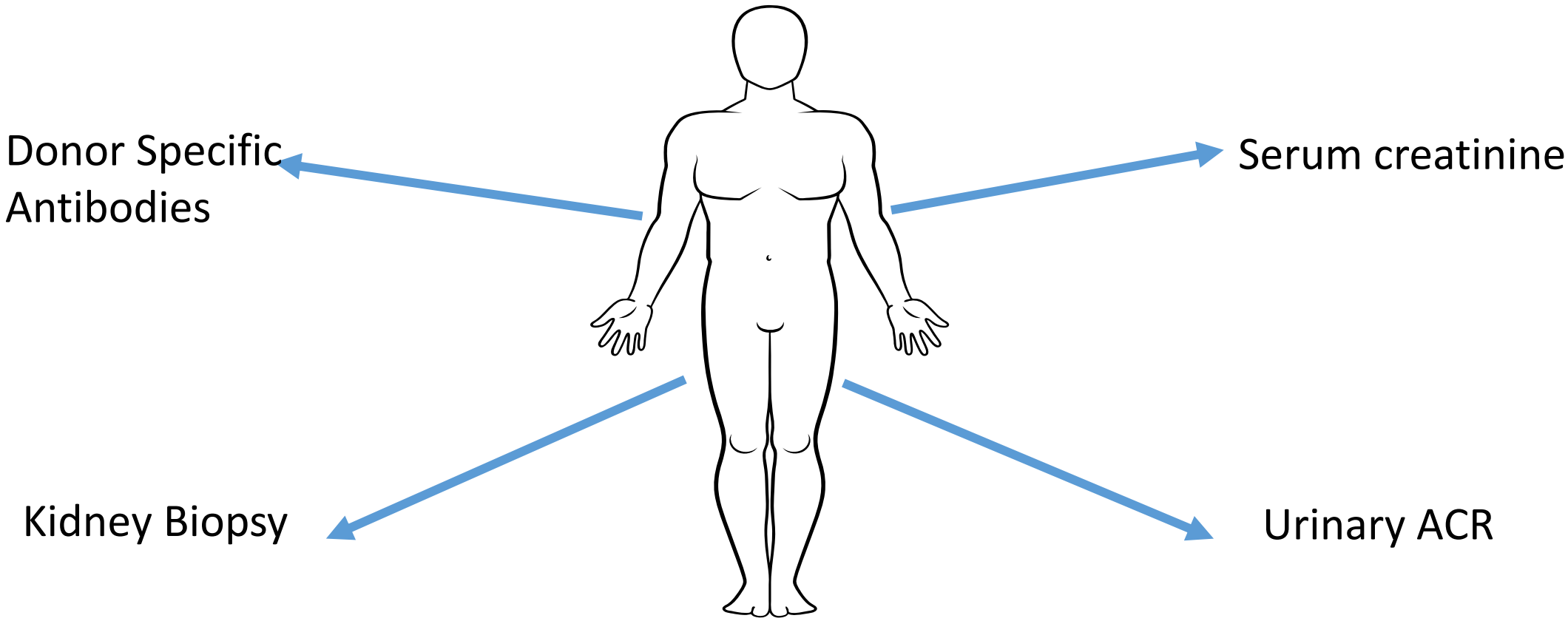

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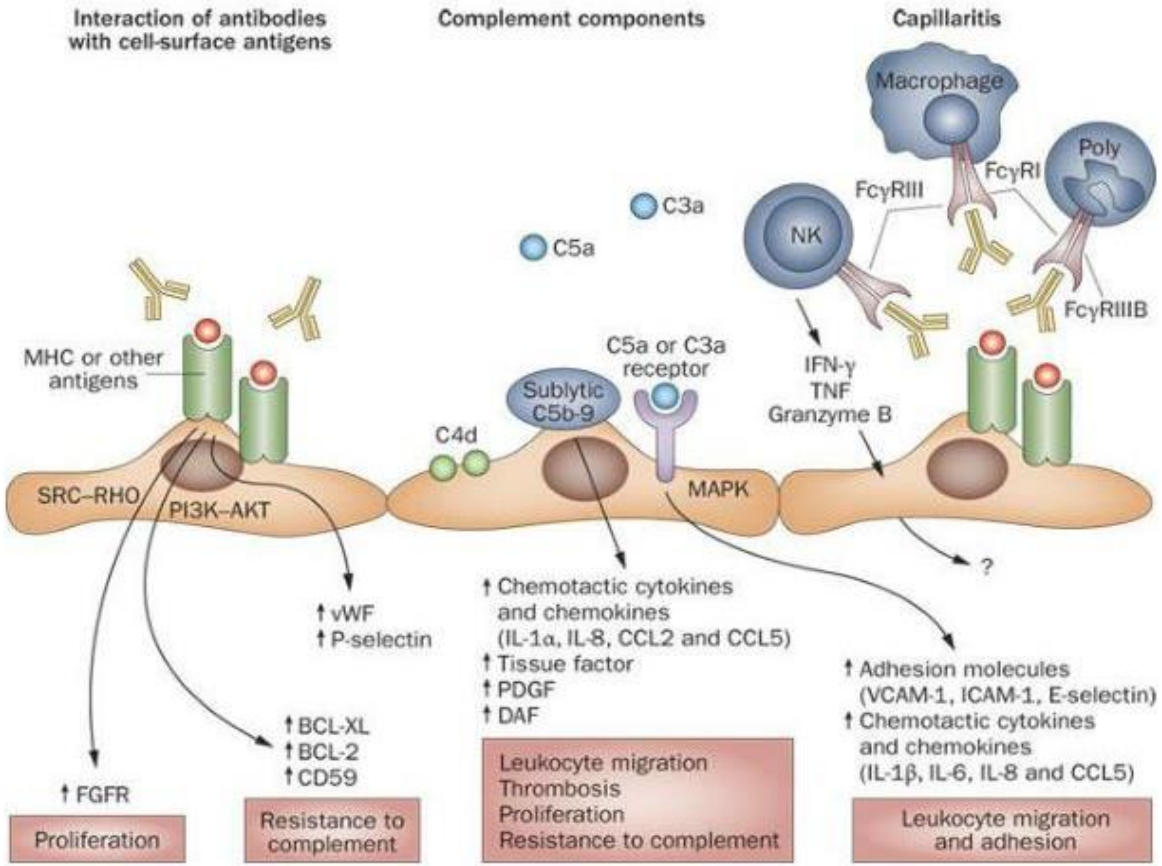
Figure 1 Mechanisms of donor-specific antibody-mediated endothelial injury in renal allografts



Farkash, E. A. & Colvin, R. B. (2012) Diagnostic challenges in chronic antibody-mediated rejection *Nat. Rev. Nephrol.* doi:10.1038/nrneph.2012.61

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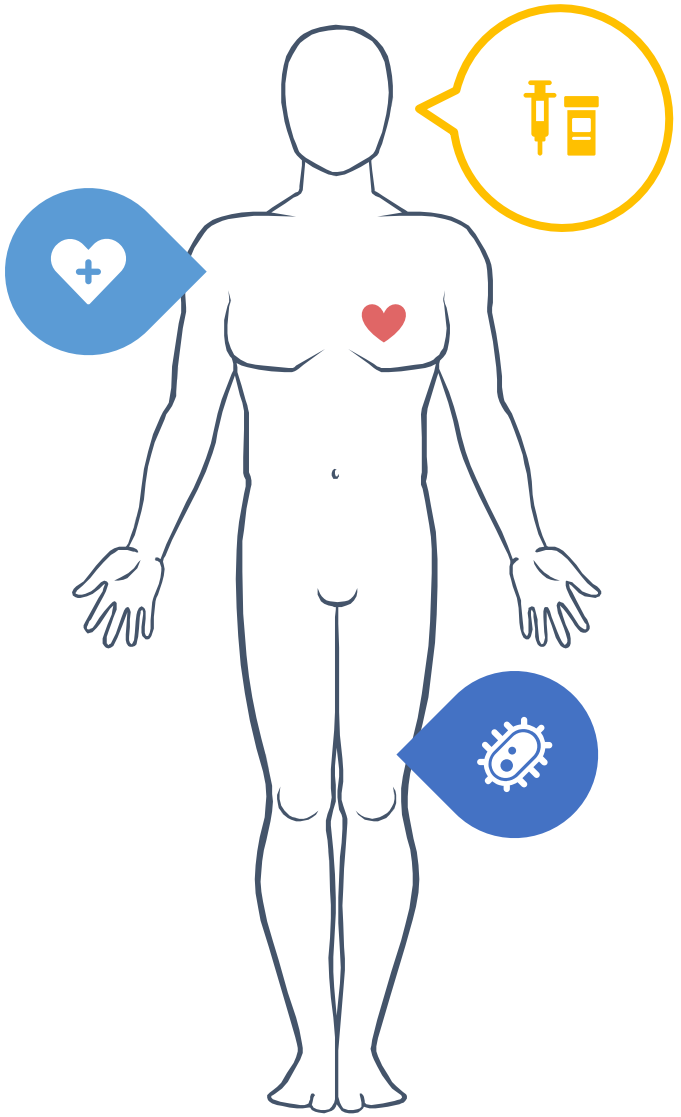
Why do kidney transplants fail so early in young people?

-better understanding of underlying pathophysiology

-identify early molecular markers of immunological mediated graft injury



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Relatively large homogenous renal transplant population

Database- excellent phenotypical knowledge of our patients

Access to historical samples stored as part of H&I testing

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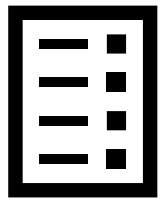
Aim

To explore long-term kidney transplant outcomes between younger recipients (< 30 yrs) vs older recipients (≥ 30 yrs) for association with:

- Differences in epidemiological risk factors.



Northern Ireland Renal Transplant Database n=2800

Identify epidemiological risk factors associated with graft outcome

Assess for variations between these risk factors in <30 yrs vs ≥30 yrs

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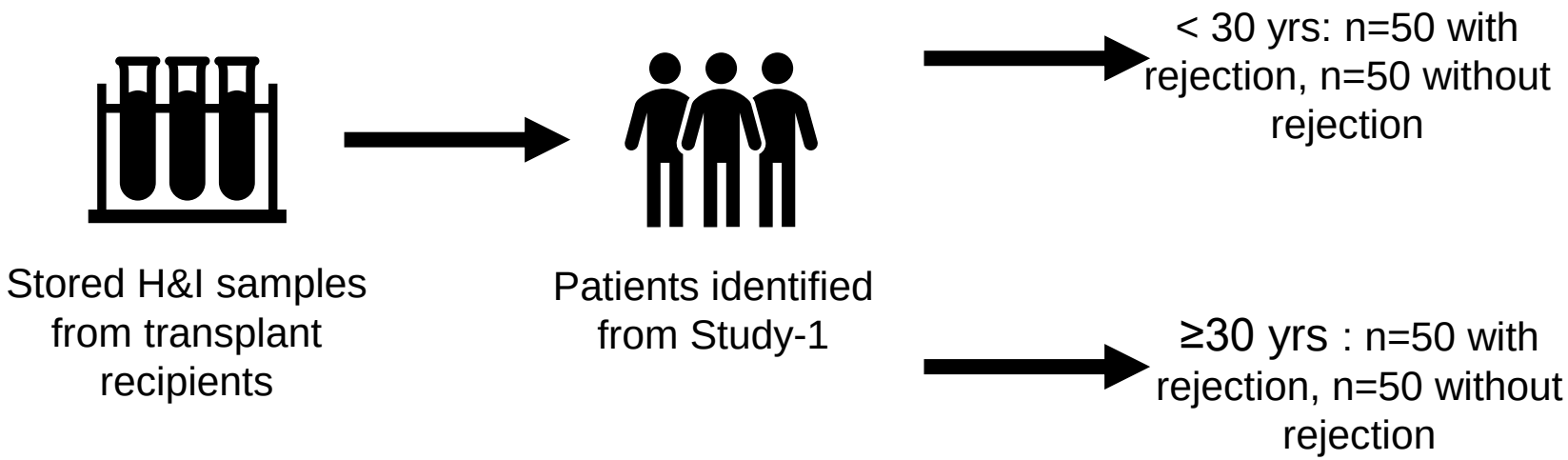
Aim

To explore whether variable long-term kidney transplant outcomes between younger recipients (< 30 yrs) vs older recipients (≥ 30 yrs) is associated with:

- Proteomic/ Metabolomic/ WGS profiles.



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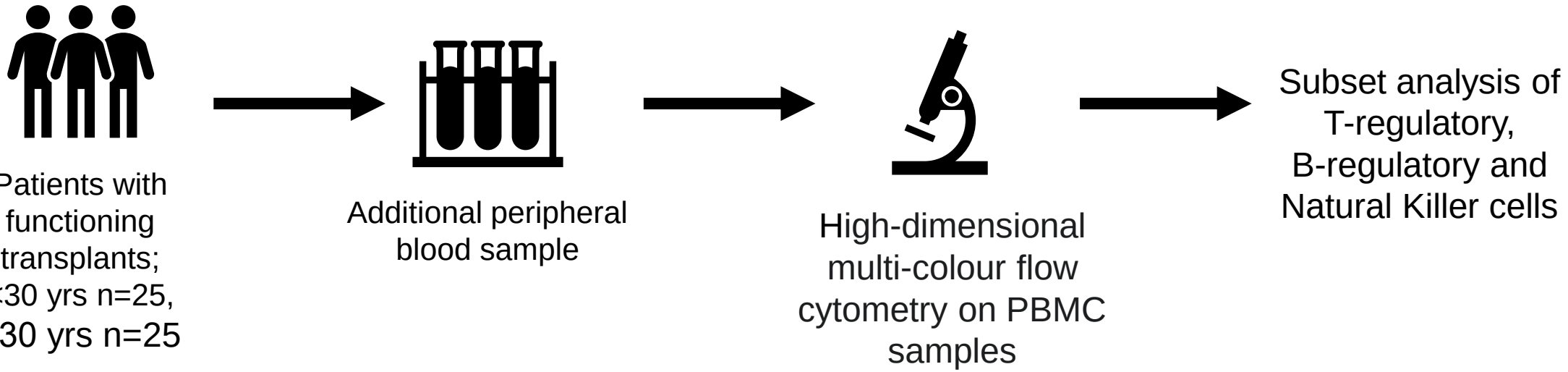
Aim

To explore whether variable long-term kidney transplant outcomes between younger recipients (< 30 yrs) vs older recipients (≥30 yrs) is associated with:

- Cellular modelling.



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Concluding Thoughts

- Comorbid chronic disease prevalence for many conditions continue to increase with improved healthcare provision and ageing populations
- Genetics studies facilitate identification of risk variants & disease pathways
- Epigenetic studies help determine the influence of environmental & lifestyle factors on disease outcomes
- miRNA's influence gene expression and may help predict disease outcomes
- Oculomics enables non-invasive evaluation of microvascular health
- Proteomic & metabolomic approaches can identify potential drug targets.
- Multiomic approaches & data integration represent novel opportunities to elucidate disease risks, mechanisms, progression and therapeutic targets.

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Thank you for your attention