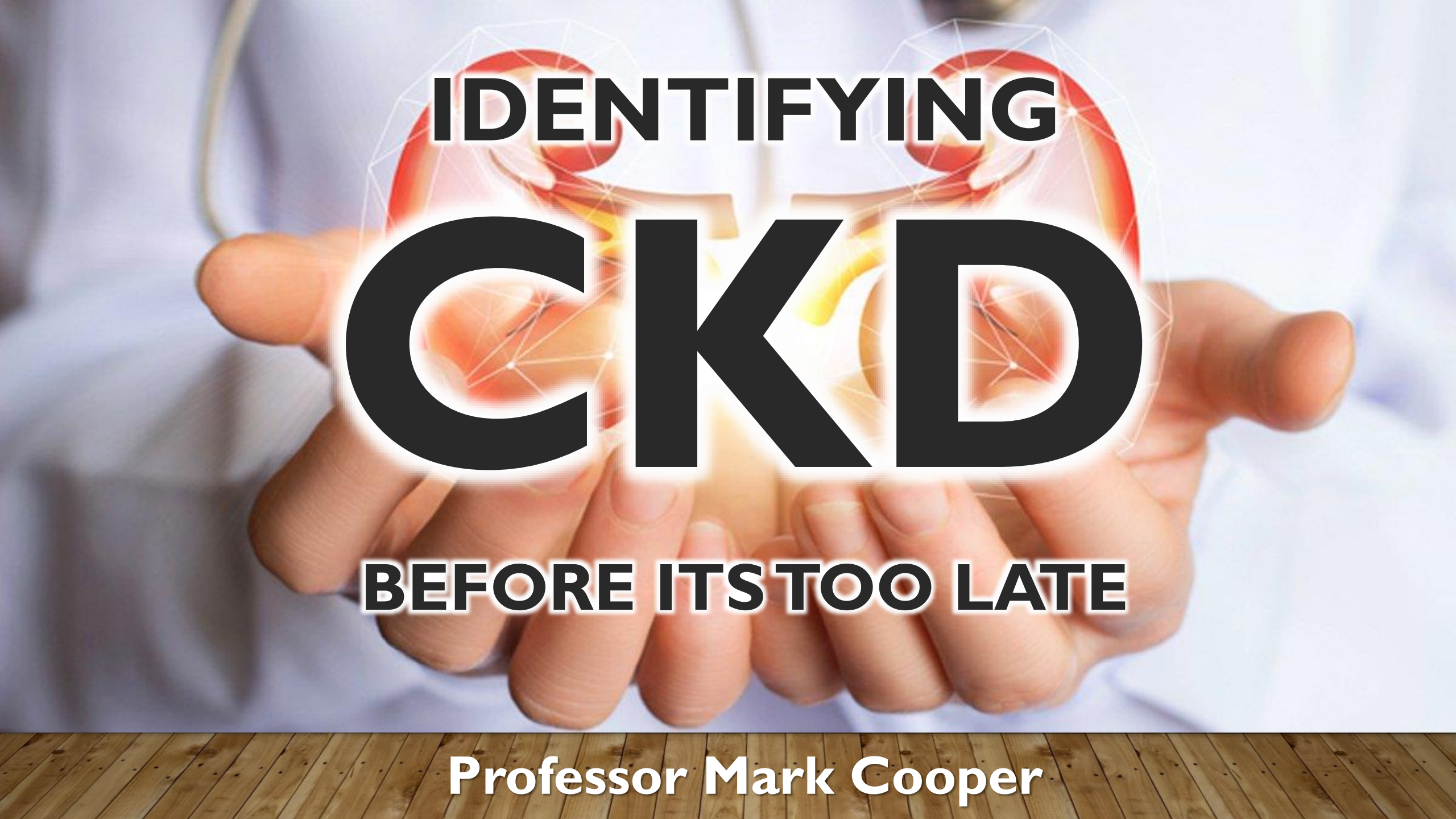
DISCLOSURES AND CONFLICT OF INTEREST

MC has received support from Boehringer Ingelheim

Honoraria for educational meetings performed on behalf of Boehringer Ingelheim, Lilly, Novartis, AstraZeneca and Sanofi

Advisory Board member for AstraZeneca & MSD


IDENTIFYING
CKD
BEFORE ITS TOO LATE
Professor Mark Cooper

THERE IS NO REVERSE!

36 WEEKS

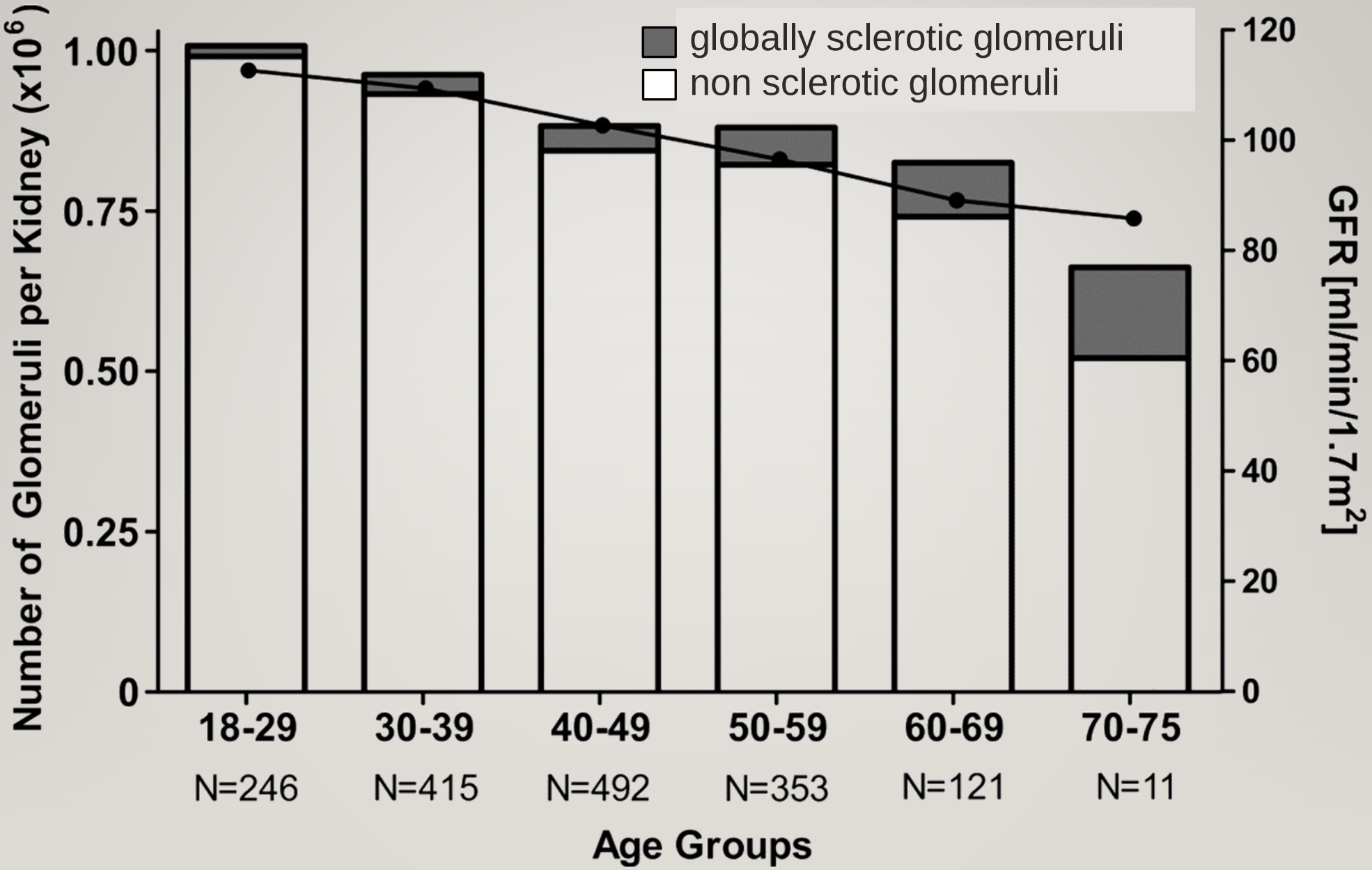
ONLY SLOWER

OR FASTER

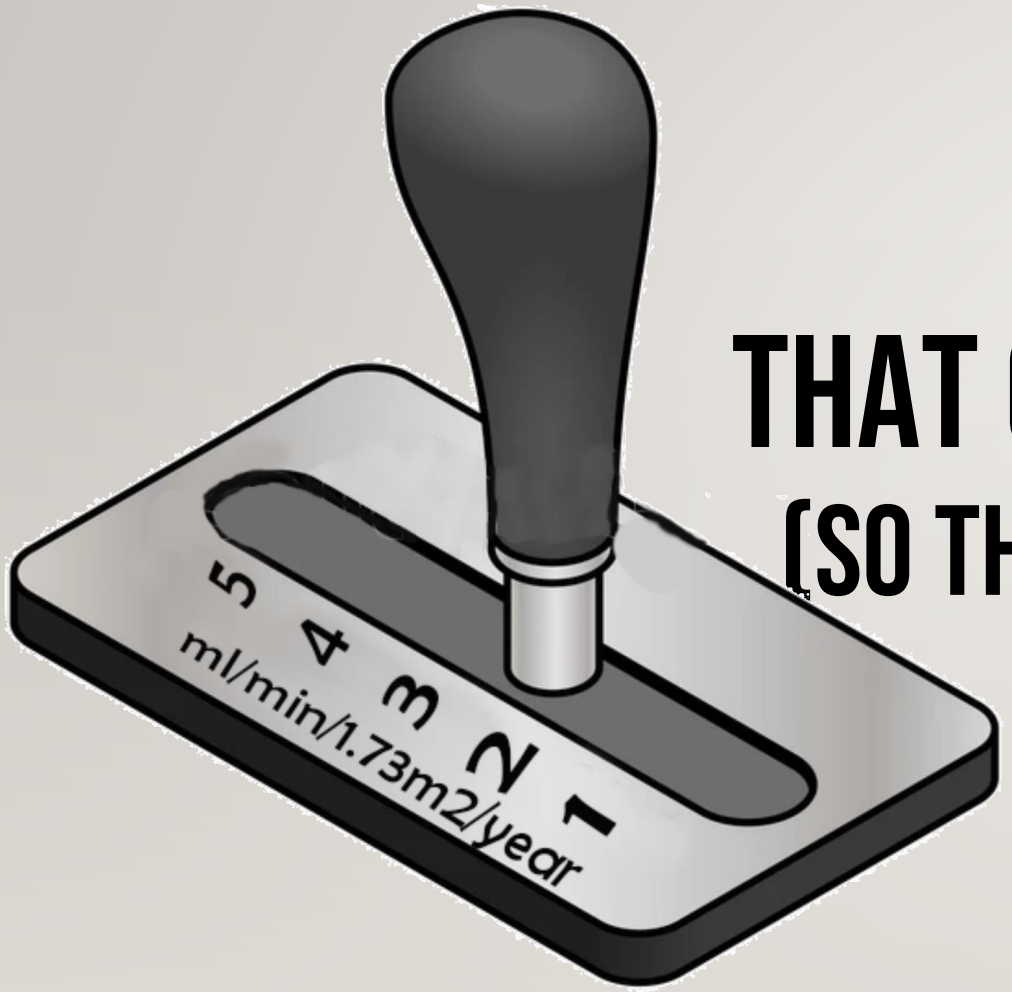
NEPHRON NUMBERS

By the time you discover that the eGFR is abnormal (< 60)

Subjects have irreversibly lost half of their functioning nephrons



Aleksandar Denic et al. JASN 2017;28:313-320

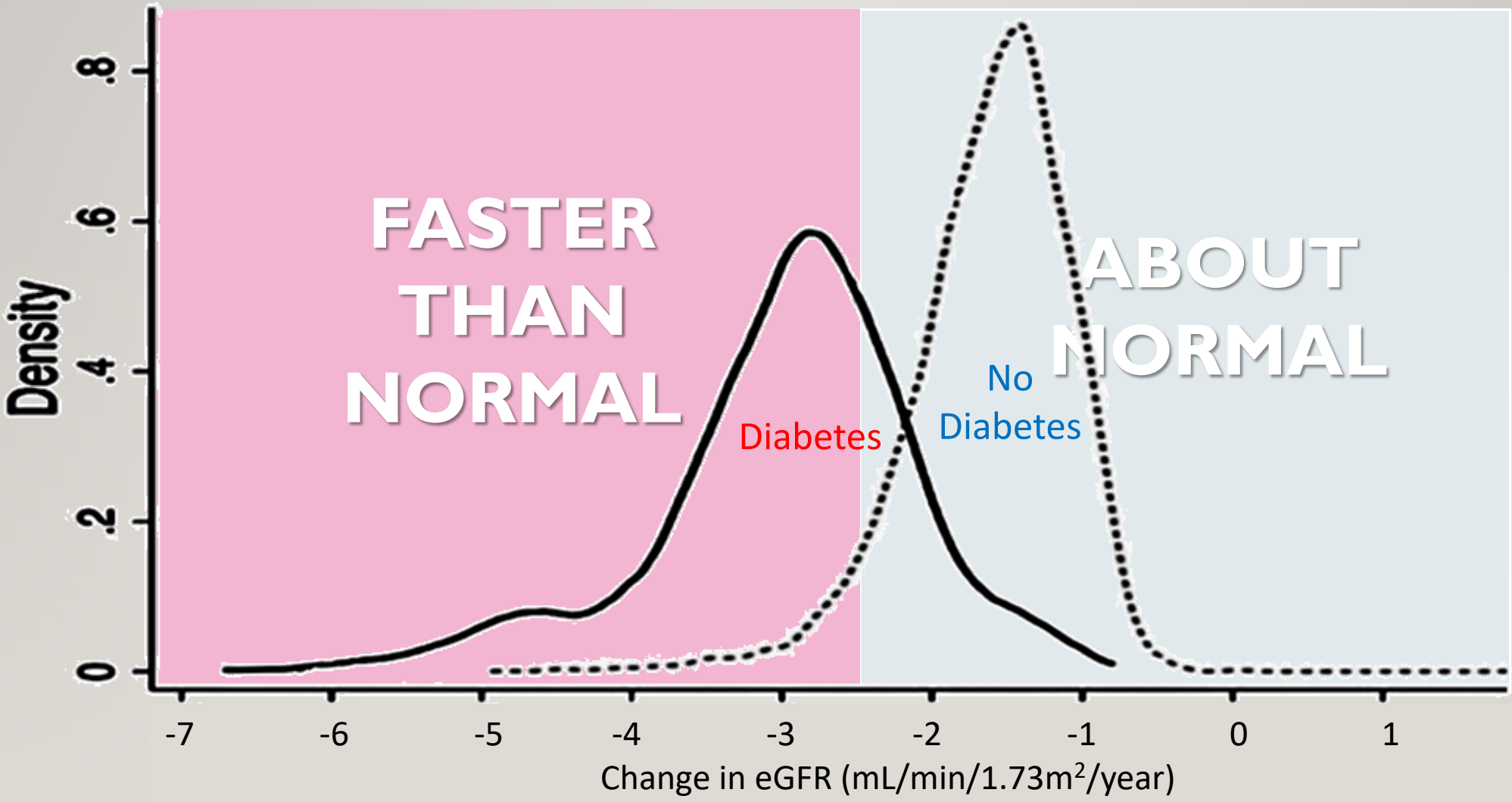


HOW CAN WE KNOW THAT GFR DECLINE IS GOING TOO FAST

(SO THAT WE MIGHT SLOW THIS GFR DECLINE BEFORE IT'S TOO LATE)

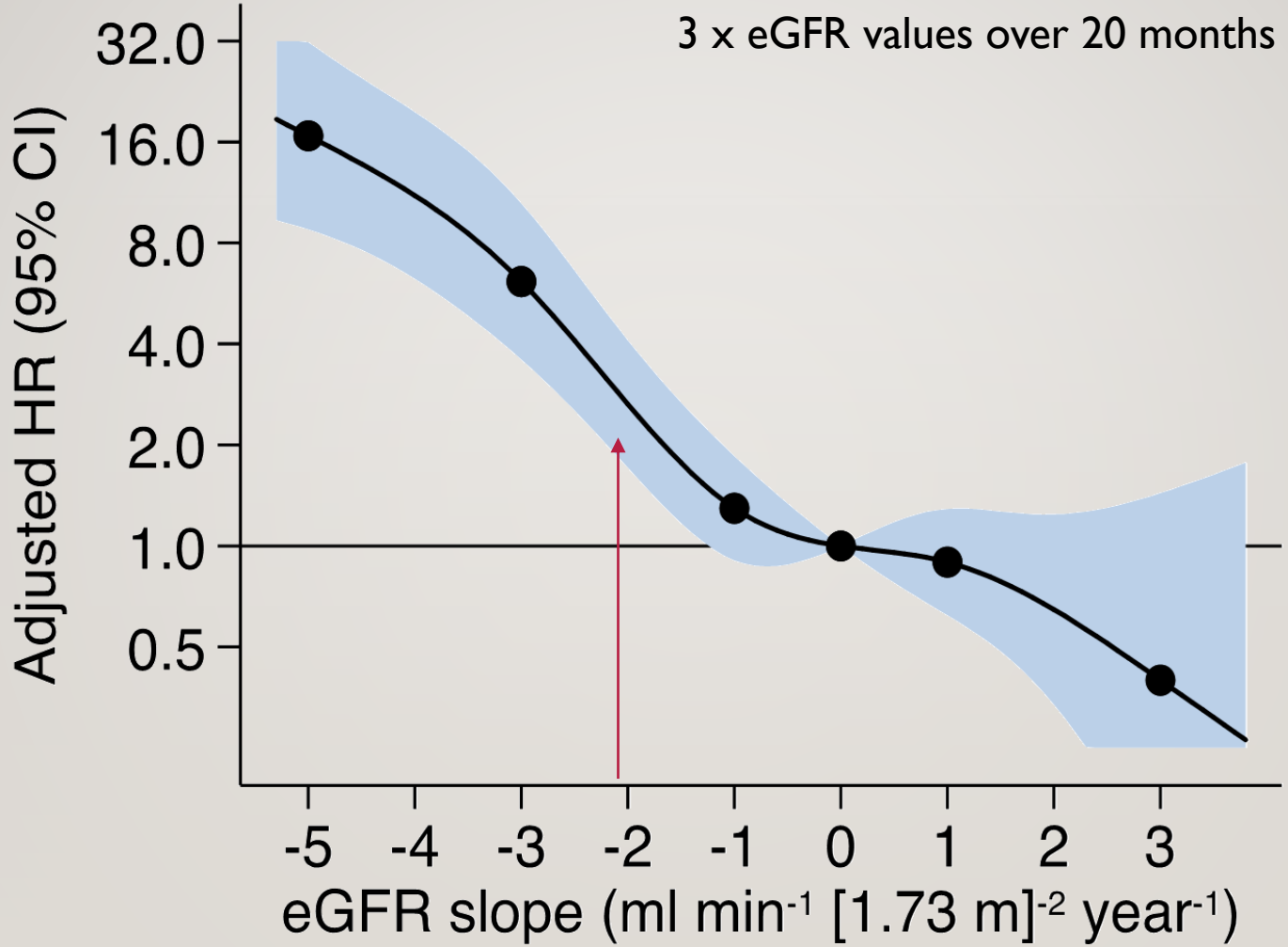
Some patients are more likely to develop CKD

- they are already "speeding" (rapid decline in GFR)
- elevated albuminuria
- other co-morbidity (e.g. CVD, PVD, NAFLD, retinopathy)
- poorly controlled BP
- other risk factors (e.g. Indigenous, FHx, etc)



Warren *et al. Diabetes Care* 2018; 41:1646

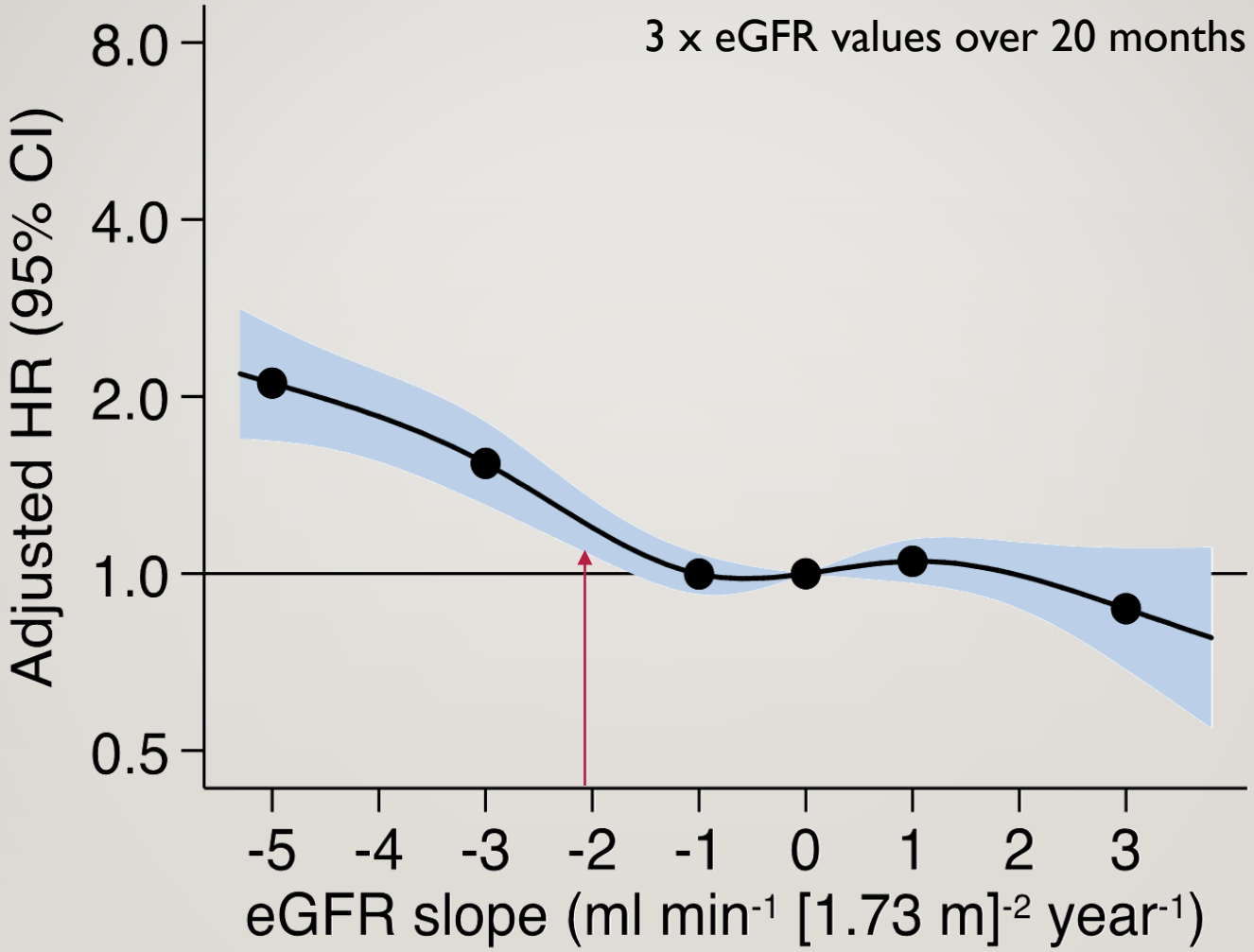
Change in eGFR and combined major renal events



Oshima et al. Diabetologia (2019)

ADVANCE Study. eGFR slope estimated using three measurements of eGFR at 4, 12 and 24 months after randomisation over 20 months.
Values were trimmed at a slope of <-5.4 and >3.8 ml min^{-1} (1.73 m)$^{-2}$ year^{-1} (each included 1.0% of participants). Knots were placed at -5, -3, -1, 1 and 3 ml min^{-1} (1.73 m)$^{-2}$ year^{-1}, using 0 ml min^{-1} (1.73 m)$^{-2}$ year^{-1} as the reference point. Covariates: Registration values of age, sex, region of residence, duration of diabetes, log-transformed UACR, systolic BP, diastolic BP, a history of macrovascular disease, smoking, drinking, treated hypertension, HbA_{1c}, HDL-cholesterol, LDL-cholesterol, log-transformed triacylglycerol and BMI, 4-month eGFR and randomised treatment allocation (BP and glucose treatment)

Change in eGFR and all cause mortality



Oshima et al. Diabetologia (2019)

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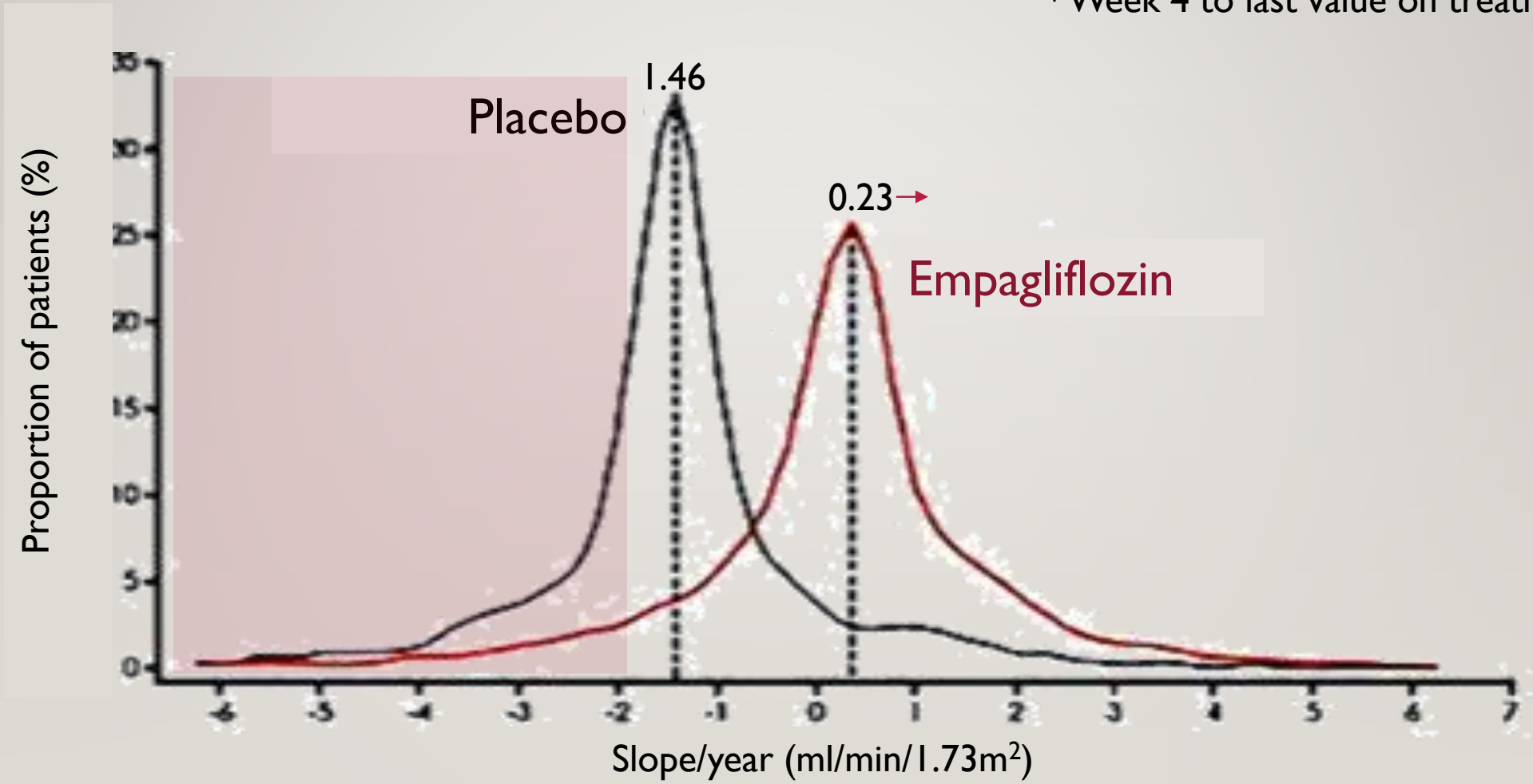
Slower decline in eGFR when treated with empagliflozin

EMPA-REG OUTCOME

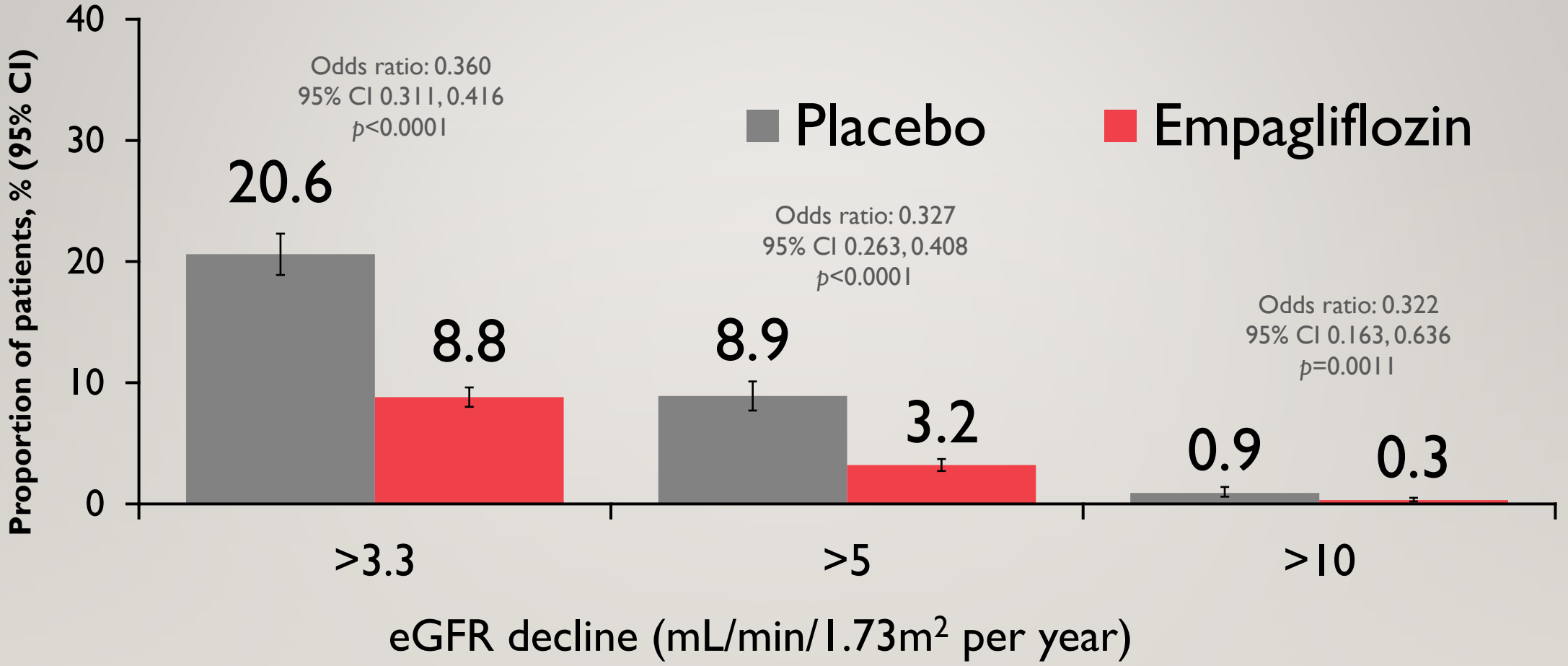
*Week 4 to last value on treatment



Wanner et al. JASN 2018, 29 (11) 2755-2769;

Fewer fast progressors when treated with empagliflozin

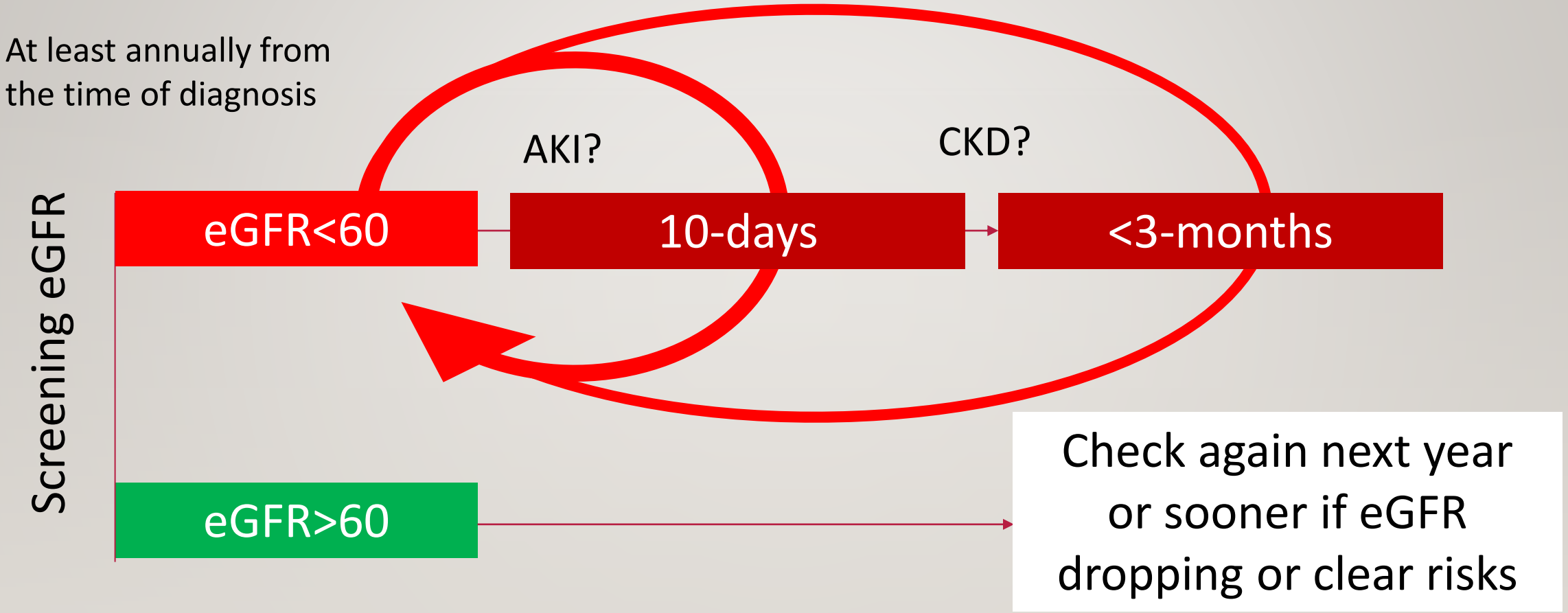
EMPA-REG OUTCOME



Logistic regression analysis included treatment, sex, baseline BMI category, baseline HbA1c category, baseline eGFR category, geographical region and age, in patients treated with ≥1 dose of study drug. eGFR assessed by MDRD formula. Baseline eGFR values were available for 6967 participants. Median treatment duration was 2.6 years. Median observation time was 3.1 years.

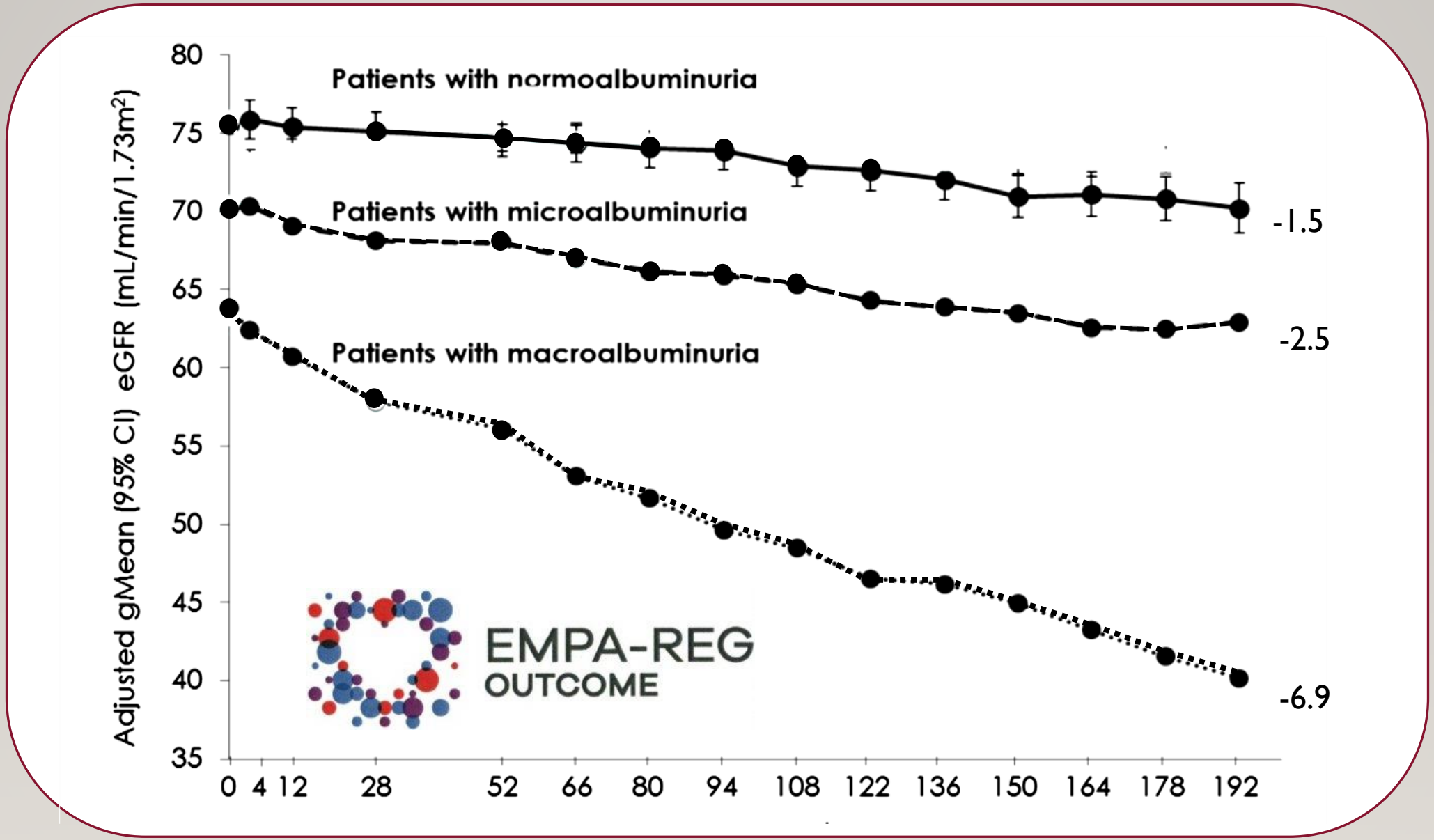
BMI, body mass index; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; MDRD, Modification of Diet in Renal Disease.

Annual eGFR screening



But some patients are more likely to get CKD sooner

- fast declining GFR
- elevated albuminuria
- other co-morbidity (e.g. CVD, PVD, NAFLD, retinopathy)
- poorly controlled BP
- other risk factors (e.g. Indigenous, FHx, etc)



Cherney D et al. Lancet Diabetes Endocrinol 2017;5:610

Identifying CKD in Type 2 Diabetes[1]

Test AER in all patients with T2D (without CKD)

From the time of diagnosis & annually thereafter

It can be most easily quantified by measuring the **urine albumin-to-creatinine ratio (UACR)**[1,2]

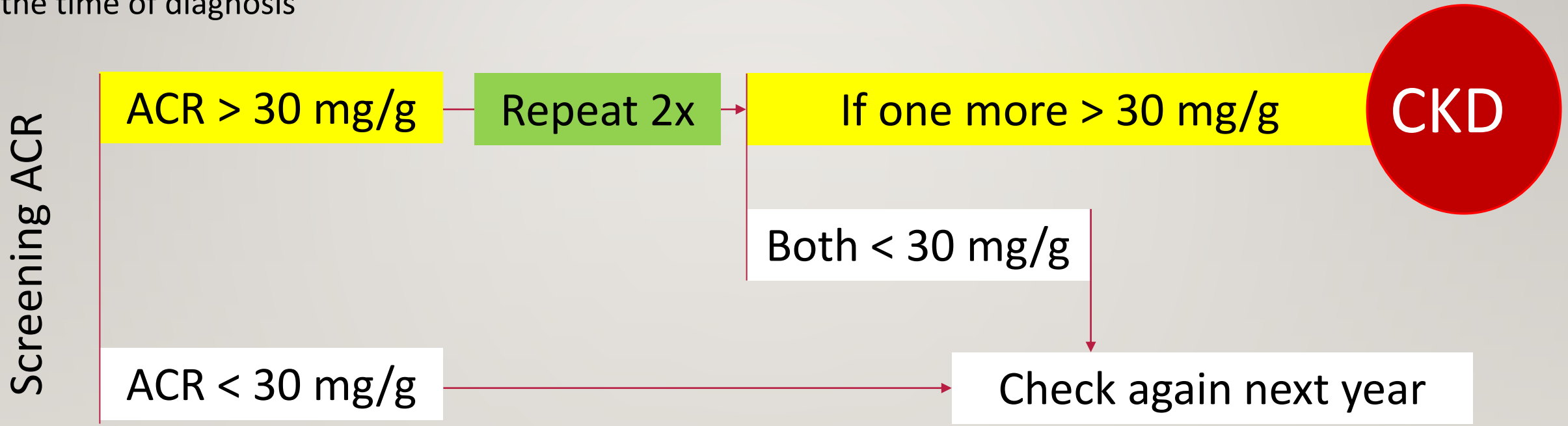
UACR = albumin concentration (mg) / creatinine concentration (g)

- Measured using a single spot urine test (morning sample preferred).
- Albuminuria can also be quantified by collecting 24-h urine[1,3,4]

1. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. *Kidney Int Suppl* 2013;3; 2. Polkinghorne KR *et al. Clin Biochem Rev* 2014;35:67;
3. National Kidney Foundation 2019. https://www.kidney.org/kidneydisease/siemens_hcp_acr (accessed Mar 2020); 4. Tuttle KR *et al. Am J Kidney Dis* 2014;64:510

SCREENING FOR AN ELEVATED AER

At least annually from the time of diagnosis



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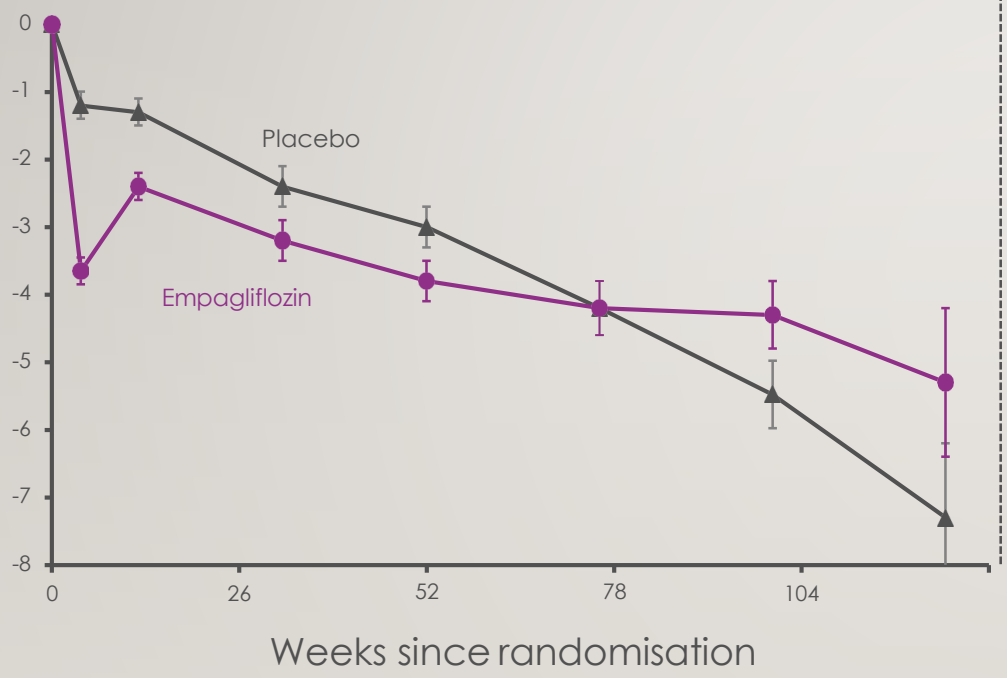
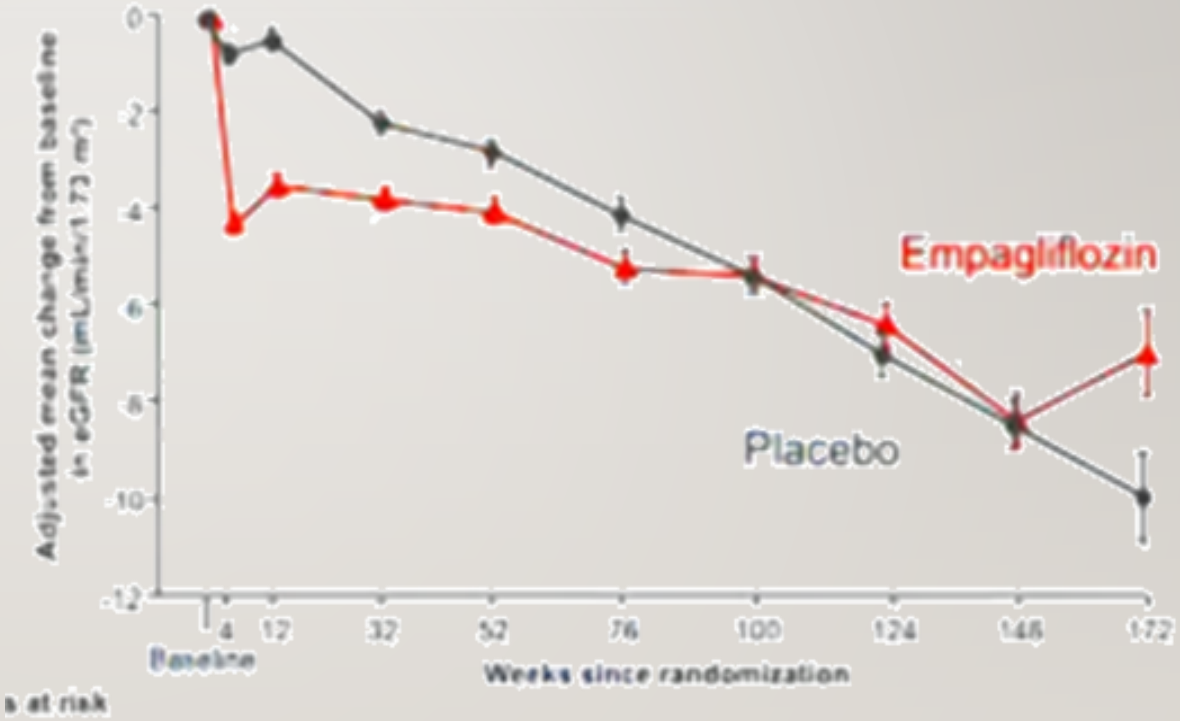
- elevated albuminuria
- other co-morbidity (e.g. CVD, CHF, NAFLD, OSA)
- poorly controlled BP
- other risk factors (e.g. Indigenous, FHx, etc)

In patients with Heart Failure SGLT2 inhibition slows their decline in eGFR

EMPEROR-Reduced



EMPEROR-Preserved



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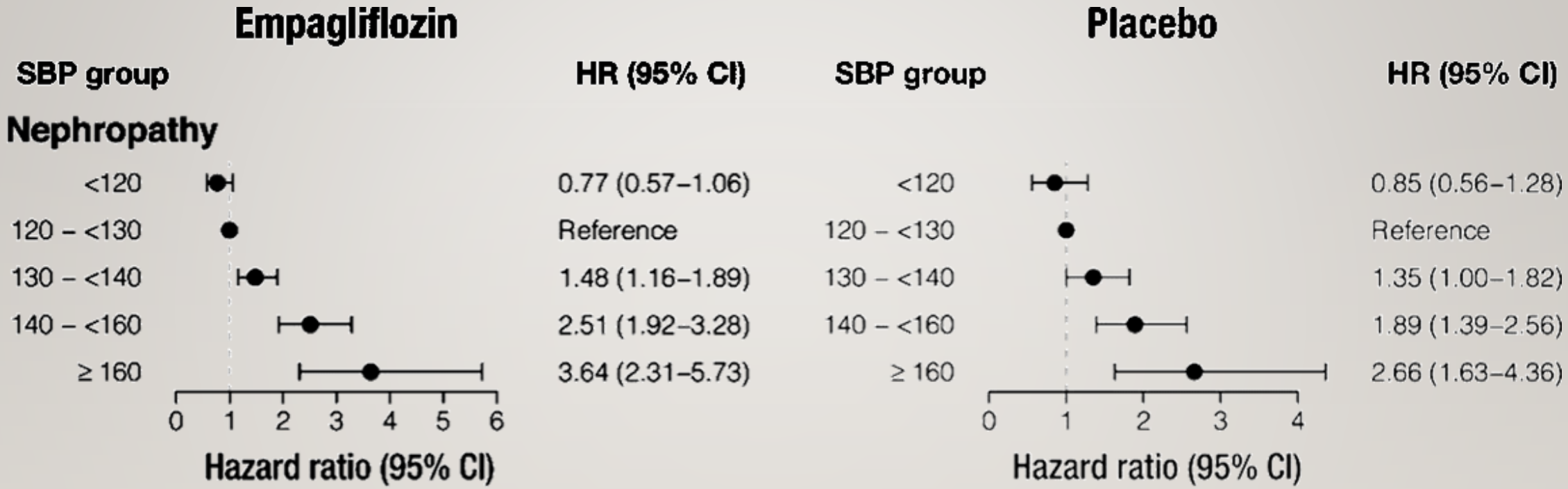
- other risk factors (e.g. Indigenous, FHx, etc)

EMPA-REG OUTCOME



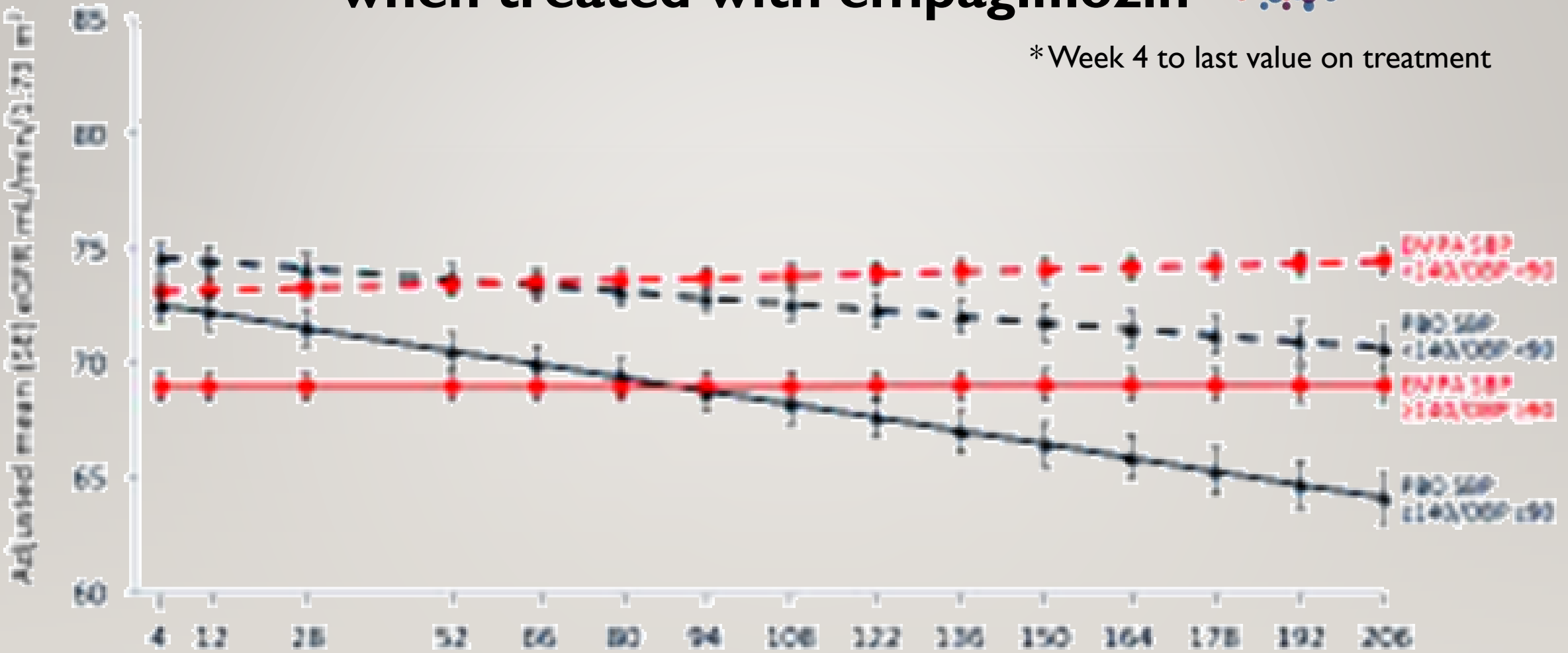
Blood pressure control is associated with incident CKD in patients with T2D + CVD

Böhm M, et al. .J Hypertens. 2020 Sep;38(9):1829-1840.

Slower decline in eGFR when treated with empagliflozin

EMPA-REG OUTCOME

*Week 4 to last value on treatment



Christoph Wanner, et al. JASN November 2018, 29 (11) 2755-2769;

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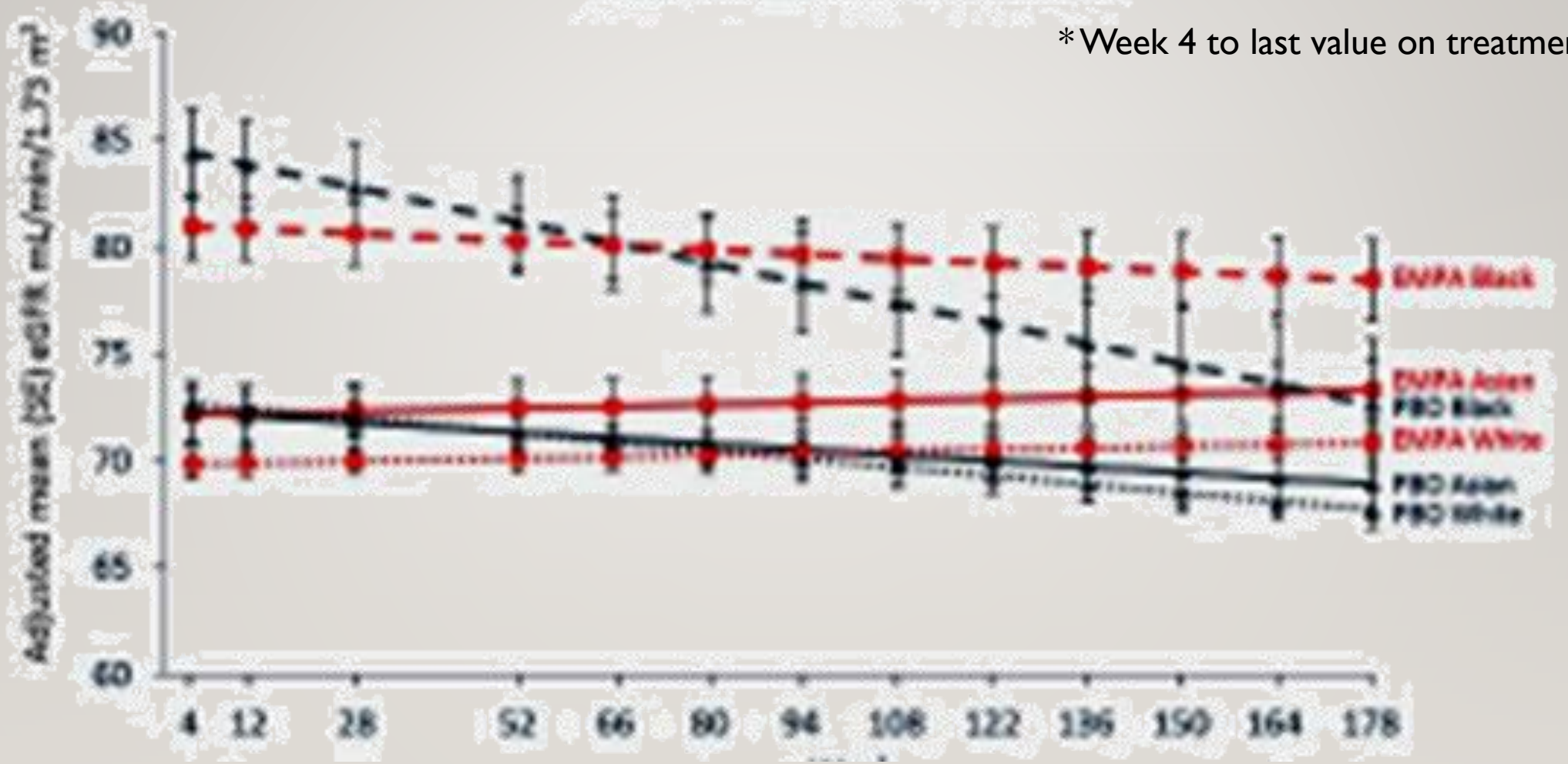
Slower decline in eGFR when treated with empagliflozin

EMPA-REG OUTCOME

*Week 4 to last value on treatment

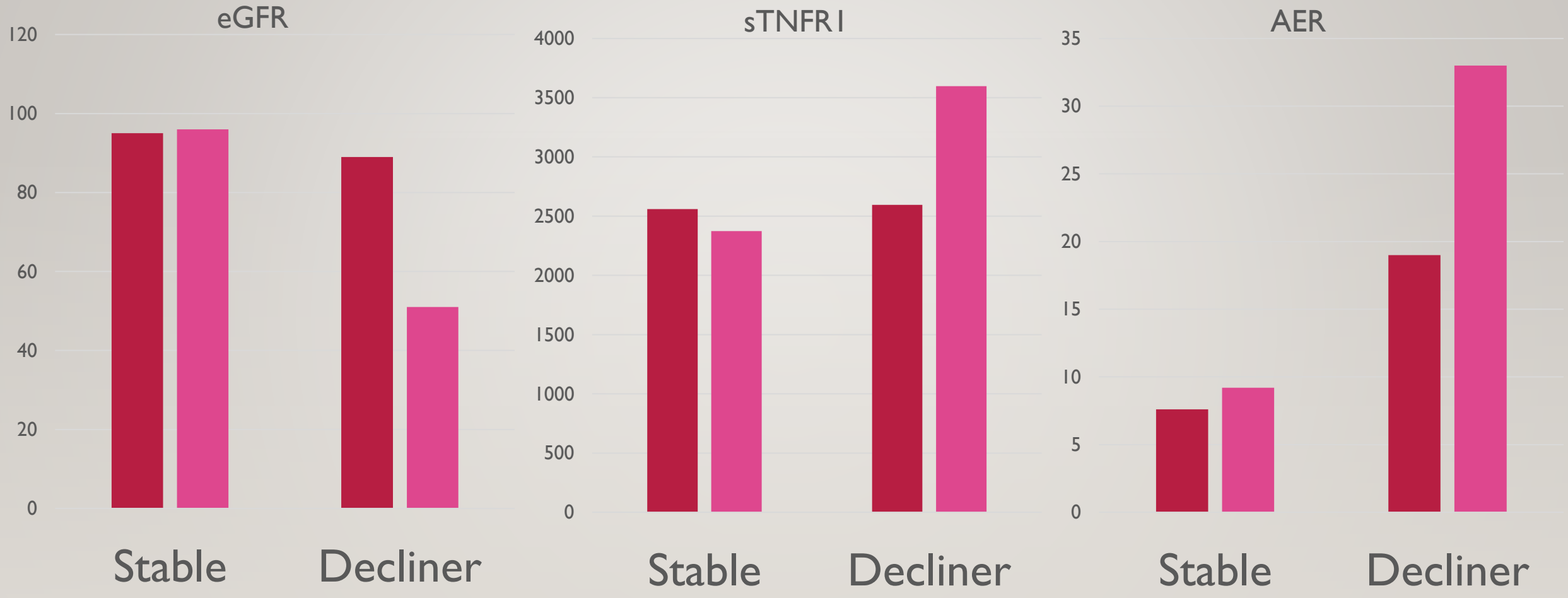


Wanner et al. JASN 2018, 29 (11) 2755-2769;

NOVEL BIOMARKERS FOR PRE-CKD?

- Soluble TNFR?
- Promarker D
- Urine biomarkers?
- Epigenetic markers?
- Artificial Intelligence?

SOLUBLE TUMOR NECROSIS FACTOR RECEPTOR TYPE 1 (TNFR1) PREDICTS EARLY DECLINE IN PATIENTS WITH T2



* from baseline in patients with an early decline in renal function (*n* = 30) after 8 years of follow up

MacIsaac et al. J Diab Complications (2019)

Multi-Ethnic Study of Atherosclerosis (MESA) and Reasons for Geographic and Racial Differences in Stroke (REGARDS) cohorts.

Case Cohort & Methods

MESA (n = 497 in the random subcohort and 163 incident CKD cases)

REGARDS (n = 497 in the random subcohort and 497 incident CKD cases)

Patients without Diabetes

eGFR > 60ml/min/1.73m²

Outcome

Incident chronic kidney disease
(eGFR< 60ml/min AND ≥ 40% decline from baseline)

	For each 2-fold increase	HR
MESA 9.2-year median follow-up	▪ KIM-1	1.38 (1.05- 1.81)
	▪ SuPAR	1.96 (1.10- 3.49)
	▪ TNFR-1	1.65 (1.04 -2.62)
	▪ TNFR-2	2.02 (1.21- 3.38)
	▪ YKL-40	1.38 (1.09- 1.75)
REGARDS 9.4-year median follow-up	▪ TNFR-1	1.99 (1.43- 2.76)
	▪ TNFR-2	1.76 (1.22- 2.54)

KI REPORTS
Kidney International Reports

Sarnak MJ, 2022

Visual abstract by:
Dilushi Wijayaratne, MD MRCP
@Dilushwijay

Conclusion Plasma concentrations of soluble TNFR-1 and TNFR-2 are consistently associated with incident CKD in non-diabetic community-living individuals in MESA and REGARDS.

PromarkerD

- Panel of three novel protein biomarkers (ApoA4, CD5L and IGFBP3)
- Combined with three clinical risk factors (HDL, age, eGFR)

LOW RISK	MODERATE RISK	HIGH RISK
0% to <10% **Low four-year risk of developing DKD.**	**10% to <20%** **Moderate four-year risk of developing DKD.**	**20% to 100%** **High four-year risk of developing DKD.**
Standard diabetes monitoring. Retest annually.‡	Consider more frequent monitoring. Retest every 3-6 months.‡	Consider very close monitoring. Retest every 3 months.‡

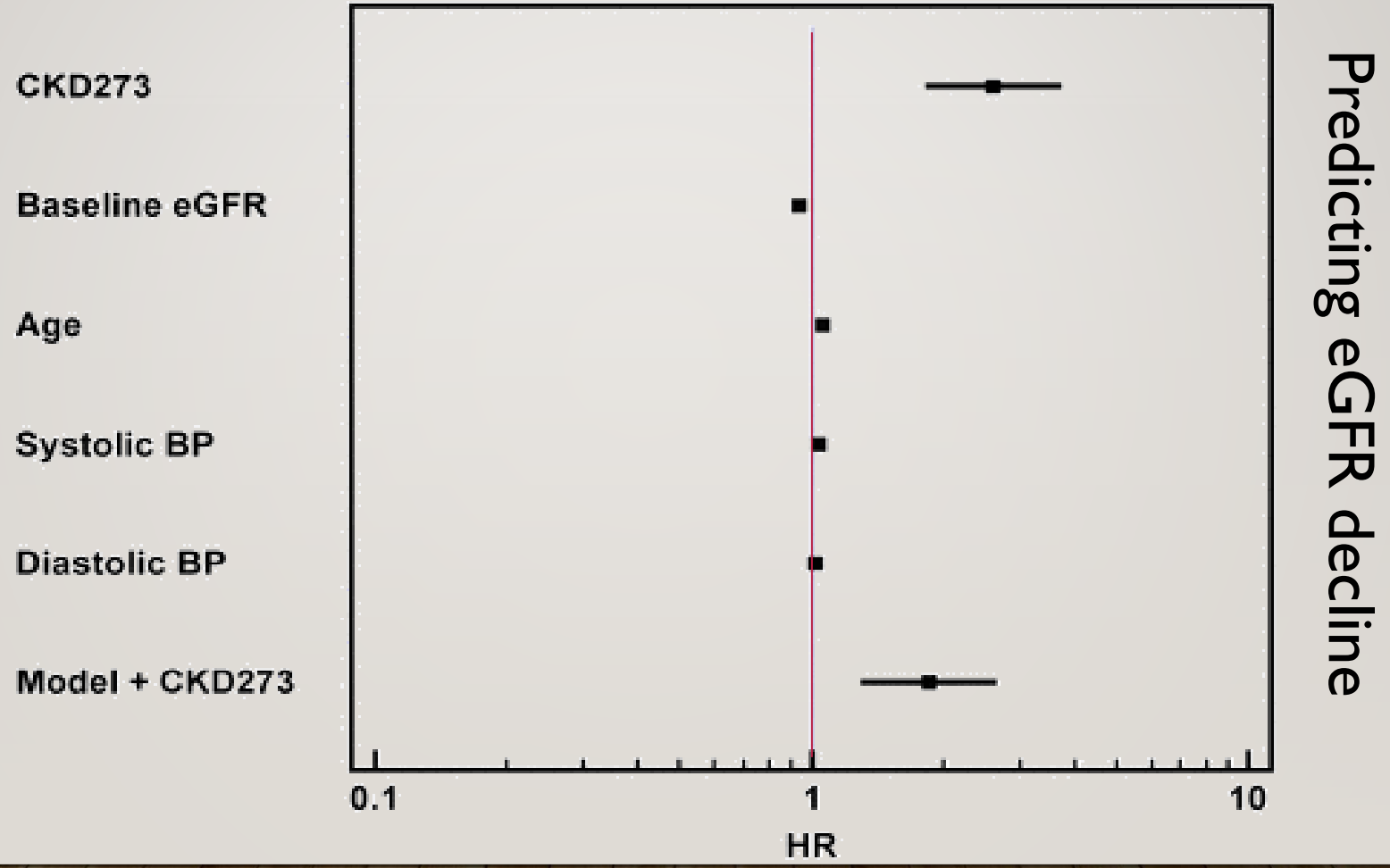
Promarker D – predicting loss of kidney function in the Fremantle Diabetes Study

Rapid eGFR decline:	≥30% decline	Incident CKD	eGFR trajectory	≥5mL/yr decline
Development Cohort				
AUC (95%CI)	0.81 (0.75-0.87)	**0.89 (0.85-0.94)**	0.86 (0.80-0.93)	0.70 (0.61-0.80)
Sn/Sp (%)	97/62	**95/68**	84/82	61/73
Calibration *P*	0.06	**0.39**	0.41	0.07
Validation Cohort				
AUC (95%CI)	0.72 (0.63-0.82)	**0.88 (0.84-0.93)**	NI	0.62 (0.53-0.72)
Sn/Sp (%)	65/71	**86/78**	NI	69/57
Calibration *P*	0.68	**0.77**	NI	0.61

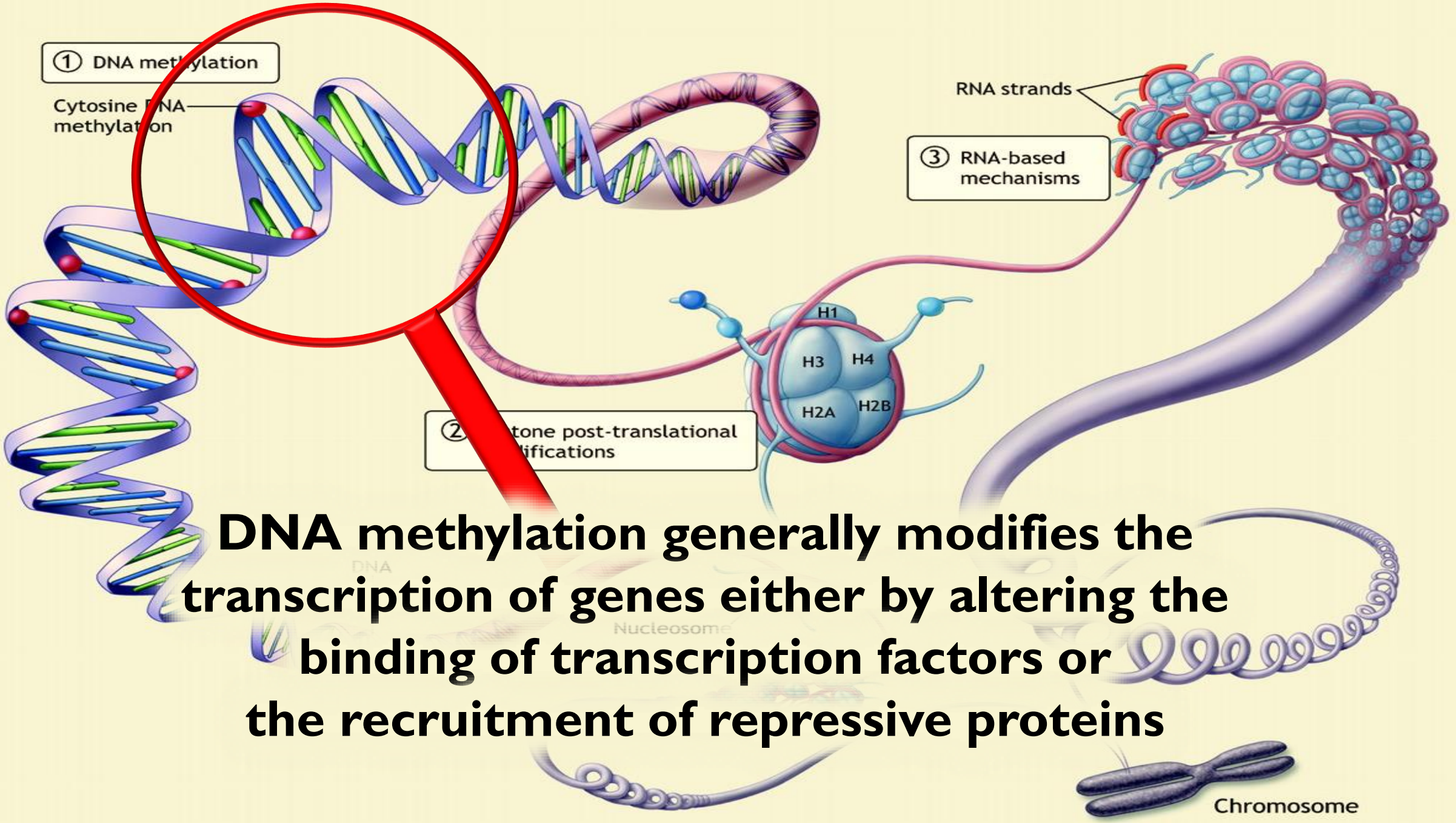
Peters ….Davis. J Diab Compl 2019

CKD273 – urine proteomic profile

based on 273 protein fragments (mostly collagen peptides)



Zurbig et al Diabetologia (2019)

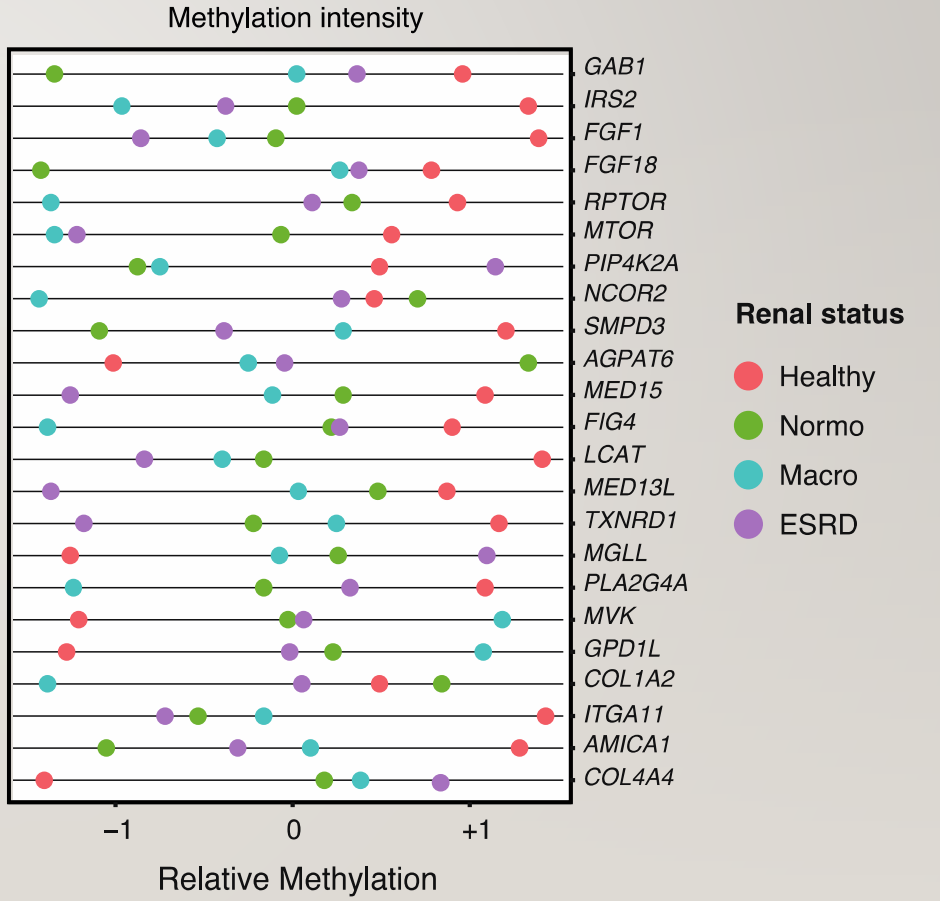


DNA methylation generally modifies the transcription of genes either by altering the binding of transcription factors or the recruitment of repressive proteins

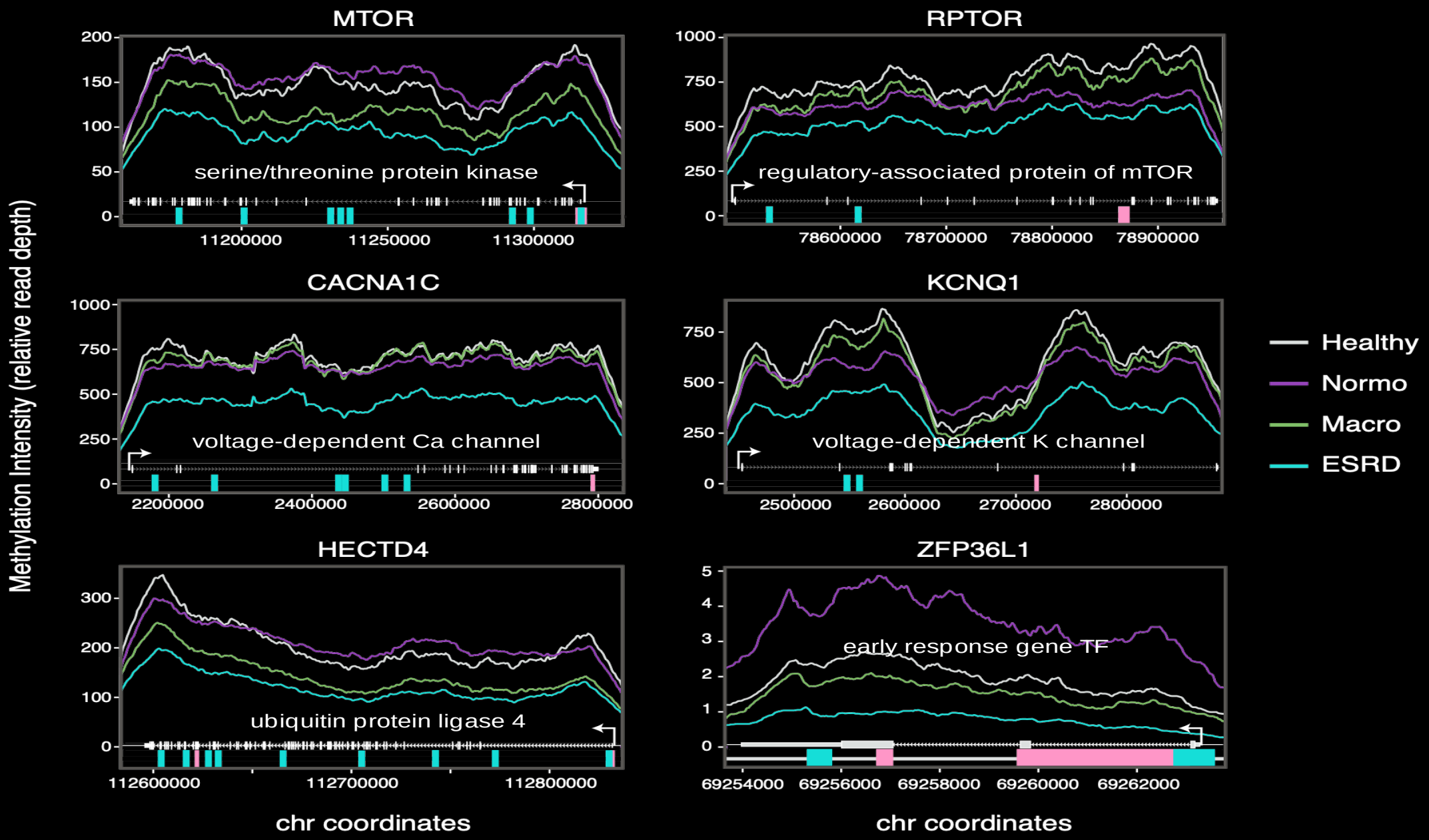
Convergence of DNA methylation and Diabetes-Associated pathways

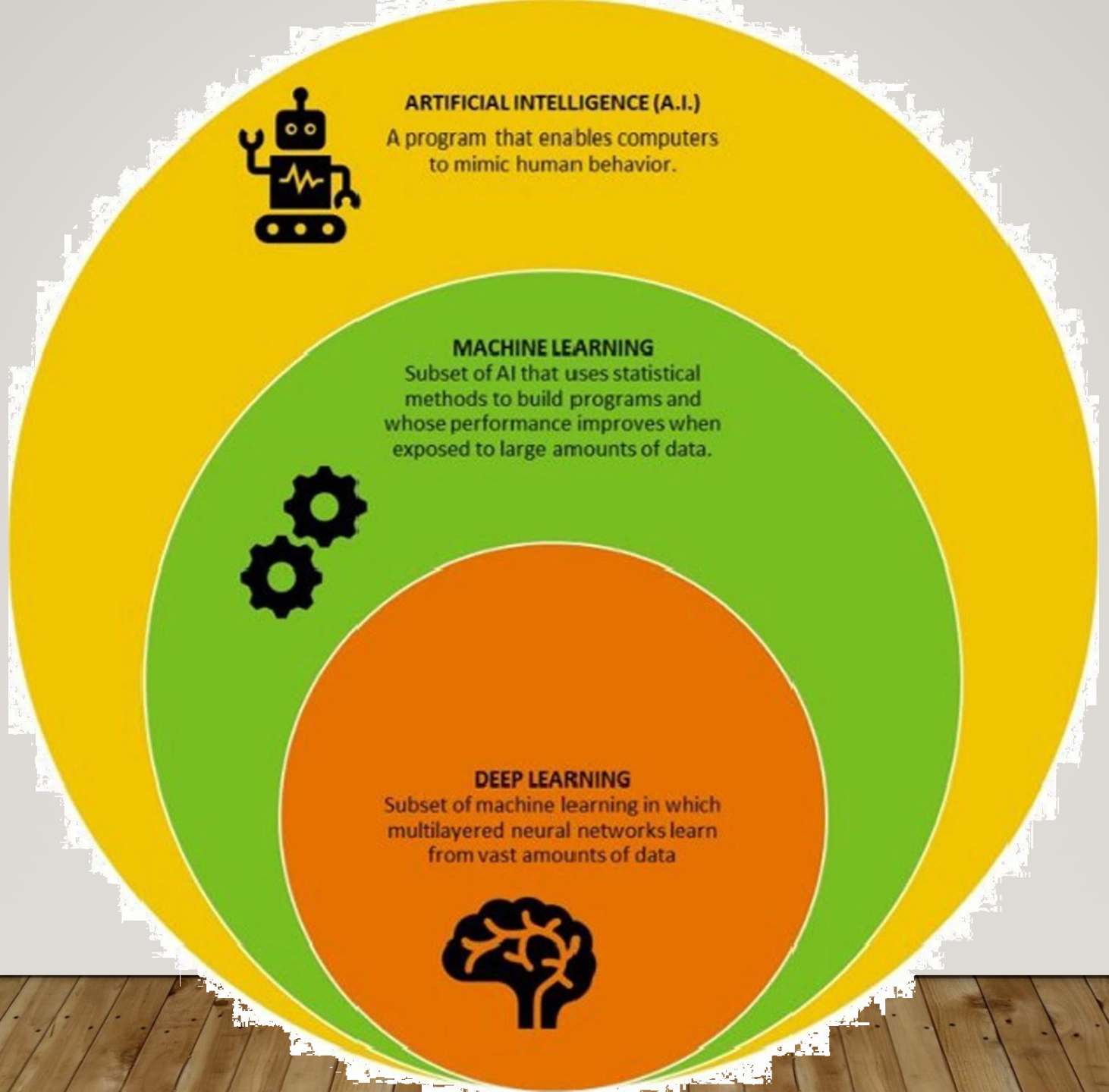
Differentially methylated genes associated with diabetic kidney disease

Gene	Ensembl ID	P value	DMR coordinates	Diabetes associated pathways
GAB1	ENST00000262995	1.69E-04	4:144404420-144404861	Insulin signaling
IRS2	ENST00000375856	1.58E-03	13:110443347-110443786	Insulin signaling
FGF1	ENST00000494579	6.39E-03	5:142078293-142078636	Insulin signaling
FGF18	ENST00000274625	6.63E-03	5:170909699-170911557	Insulin signaling
RPTOR	ENST00000537330	7.71E-03	17:78549200-78549666	Regulates insulin release and signaling
MTOR	ENST00000361445	8.79E-03	1:11307862-11309107	Regulates insulin release and signaling
PIP4K2A	ENST00000376573	9.05E-05	10:22874619-22875118	Lipid metabolism
NCOR2	ENST00000405201	2.82E-04	12:124864792-124865295	Lipid metabolism
SMPD3	ENST00000219334	5.86E-04	16:68399936-68400660	Lipid metabolism
AGPAT6	ENST00000396987	4.00E-03	8:41470262-41470706	Lipid metabolism
MED15	ENST00000425759	4.69E-03	22:20918886-20919334	Lipid metabolism
FIG4	ENST00000441478	5.14E-03	6:110104322-110104932	Lipid metabolism
LCAT	ENST00000264005	5.37E-03	16:67975360-67975797	Lipid metabolism
MED13L	ENST00000281928	5.99E-03	12:116716013-116716425	Lipid metabolism
TXNRD1	ENST00000525566	6.44E-03	12:104687048-104687537	Lipid metabolism
MGLL	ENST00000434178	7.76E-03	3:127416330-127417102	Lipid metabolism
PLA2G4A	ENST00000367466	7.77E-03	1:186955914-186956703	Lipid metabolism
MVK	ENST00000539696	8.82E-03	12:110033681-110035595	Lipid metabolism
GPD1L	ENST00000282541	9.67E-03	3:32185089-32185514	Lipid metabolism
COL1A2	ENST00000297268	1.34E-04	7:94025128-94026206	Integrin cell interaction
ITGA11	ENST00000315757	5.44E-03	15:68608377-68609157	Integrin cell interaction
AMICA1	ENST00000356289	6.90E-03	11:118069845-118070106	Integrin cell interaction
COL4A4	ENST00000396625	8.02E-03	2:227972698-227973120	Integrin cell interaction



Genes implicated in DN are differentially methylated




ARTIFICIAL INTELLIGENCE (A.I.)
A program that enables computers to mimic human behavior.
MACHINE LEARNING
Subset of AI that uses statistical methods to build programs and whose performance improves when exposed to large amounts of data.
DEEP LEARNING
Subset of machine learning in which multilayered neural networks learn from vast amounts of data

- Indicated for DKD Stages 1-3b (excluding G1&A1 and G2&A1)
- NY state-approved for clinical use
- Granted Breakthrough Device designation by the US Food and Drug Administration (FDA)

Standard blood draw

Biomarkers sTNFR-1, sTNFR-2, and KIM-1

Standard Clinical Data Elements

eGFR, UACR, serum calcium, HbA1c, systolic BP, platelets, AST

Machine Learning Algorithm Harmonizes Disparate Data

Actionable Risk Assessment

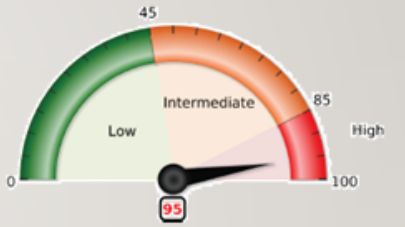
Test Report

Ordered by	Dr. Fran Lake
Collection Date	8/14/2020
Report Date	8/19/2020
Specimen ID	665544

PATIENT INFORMATION

NAME	SEX	DATE OF BIRTH	MEDICAL RECORD #
Jane Lee	F	1/1/1960	00998877

RISK OF PROGRESSIVE DECLINE IN KIDNEY FUNCTION



95

Patients with a **high** score have an elevated risk of progressive decline in kidney function

score ranges from 0-100 and correlates with the probability of progressive decline in kidney function in the study population. Risk classification is provided to guide interpretation of the risk score using cut-offs related to clinical outcomes.

SIGNED	DATE	TIME

Laboratory Director Michael T. Donovan PhD, MD, CLIA: Renalytix AI, 101 6th Ave 3rd Floor, Room 32, New York, NY 10013, CLIA Number 33D2156875

This test was developed and its performance characteristics determined by Renalytix AI Inc. It has not been cleared or approved by the FDA nor is it currently required to be. The laboratory is regulated under CLIA as qualified to perform high-complexity testing. The test is used for clinical purposes. It should not be regarded as investigational or for research. See page 2 for further details.

EXAMPLE OF CLINICAL PATHWAY

Frequency of Monitoring / Referral[1]		Comprehensive Strategy to Maximize Protection for Diabetic Kidney Disease Progression and Cardiovascular Disease[2,3]	
Monitoring 3x/year	Nephrology Referral	Titrate ACEi or ARB to maximally tolerated dose	Strongly consider SGLT2 inhibitor therapy unless contraindicated

[1] KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease https://kdigo.org/wp-content/uploads/2017/02/KDIGO_2012_CKD_GL.pdf
[2] Executive Summary of the 2020 KDIGO Diabetes Management in CKD Guideline. https://doi.org/10.1016/j.kint.2020.06.024
[3] ADA guidelines. https://care.diabetesjournals.org/content/43/Supplement_1/S135

RENALYTIX AI

KidneyIntelX