SUPPLEMENTARY INFORMATION for:

A Signature of Circulating Inflammatory Proteins and Development of End Stage Renal Disease in Diabetes

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Supplementary Information

Additional information regarding the examination of the Joslin Cohorts:

Ascertainment of onset of ESRD: All subjects included in this study were queried against rosters of the United States Renal Data System (USRDS) and the National Death Index (NDI). USRDS maintains a roster of US patients receiving renal replacement therapy, which includes dates of dialysis and transplantation. The NDI is a comprehensive roster of deaths in the US that includes date and cause of death. ESRD was defined either by a match with the USRDS roster or a listing of renal failure among the causes of death on an NDI death certificate[1,2]. 10-year risk of ESRD was evaluated in the Joslin Kidney Study. Subjects who reached 10 years of follow-up from their recruitment date and did not develop ESRD were censored.

All-cause and cardiovascular (CVD) mortality – competing outcome: In the T1D Cohort, there were 15 deaths among the 219 subjects (7%) within the follow-up period, and CVD was listed as a primary cause of death for 9 of the 15 cases. In the T2D Cohort, 8 deaths occurred among the 144 subjects (5%) during the follow-up period, and CVD was listed as a primary cause of death for two of them. In the Cox models, these subjects were censored at the time of death. Given the low frequency of competing outcome events (<10%), no competing risk modelling was performed in our prospective study.

Ascertainment of the renal function decline based on GFR slope: A total of 4,721 calibrated serum creatinine determinations from clinic visits in 364 study subjects were used to estimate GFR with the CKD-EPI formula in the cohort of subjects with T1D and proteinuria. The trajectories, characterized with linear regression-based spline models, are linear or nearly linear for 87% of study subjects. Therefore, linear trajectories were estimated further with least-

squares regression as previously described[3]. Similar protocols were followed to estimate GFR slopes in subject with T2D.

Joslin Diabetic Retinopathy Study in T1D: The retinopathy study data were collected through a retrospective chart review at the Beetham Eye Institute, Joslin Diabetes Center between November 2010 and March 2012. Dates of first diagnosis of each event (mild, moderate, severe non-proliferative retinopathy [NPDR] and proliferative retinopathy [PDR]) were recorded as per the ophthalmologists' clinical examination generally consisting of anterior segment exam, fundus ophthalmoscopy, fundus photography and/or optical coherence tomography (OCT). NPDR severity was determined according to standard Early Treatment Diabetic Retinopathy Study (ETDRS) modified grading criteria based on the presence and extent of key retinal lesions (retinal hemorrhages/micro-aneurysms, venous beading and intra-retinal microvascular abnormalities). PDR was characterized by presence, location and extent of retinal neovascularization and/or vitreous/pre-retinal hemorrhage. Quiescent PDR (qPDR) indicates fully inactive PDR at the time of evaluation. DR severity was based on each patient's worse eye. Categories included NPDR (collapsing no DR, mild, moderate and severe NPDR), and PDR (collapsing PDR and qPDR). For our cross-sectional analyses, patients were categorized as follows: 1) "PDR" if they had PDR at any time before or within six months after the SOMAScan; 2) "NPDR" if they were diagnosed with NPDR before the SOMAScan and the severity of NPDR remained the same after the SOMAScan, and 3) "NPDR" if they were diagnosed with NPDR any time after the SOMAScan.

For the purpose of the Joslin Retinopathy study analysis, we included all Joslin Kidney Study participants with T1D who had SOMAscan measurements, i.e. subjects from the exploratory cohorts as well as those with proteinuria but with normal renal function. That resulted in final inclusion of 180 subjects (131 subjects with PDR and 49 subjects with NPDR). Clinical characteristics of these sub-groups are provided in Supplementary Table 5.

Supplementary Table 1: Global proteomic profiling data of the circulating inflammatory proteins not associated with ESRD or not replicated in both types of diabetes in the Joslin Cohorts.

Assay precision and proteins' associations with ESRD risk in T1D and T2D Joslin Cohorts for the 177 (non-KRIS) proteins are presented in alphabetical order according to protein HGNC name. Effect sizes (fold change) and strengths of the associations (as logarithmically base 10 transformed p values) are shown. See also legend below.

			T1D COHORT N=219		T2D COHORT N=144	
Protein name		**Precision**	**Effect size**	**Significan-ce**[¶]	**Effect size**	**Significan-ce**[†]
HGNC (gene) name	**Alternate Name**	**median inter-assay CV (%)**	**Fold change**	**(- log 10 p)**	**Fold change**	**(- log 10 p)**
AIF1	**AIF1**	5.7	0.71	2.5	0.92	0.3
C1QA C1QB C1QC	**C1q**	9.7	0.97	0.1	0.98	0.1
C1QBP	**C1QBP**	2.6	0.97	1.5	0.91	1.3
C1R	**C1r**	3.2	0.97	0	1	0.1
C1S	**C1s**	14.9	1.03	1	0.96	0.9
C2	**C2**	7.6	1.04	0.9	1.03	0.4
C3	**C3**	8.6	1.02	0.4	0.96	0.5
C3	C3a	37.5	1	0.1	0.87	1.1
C3	**C3adesArg**	22.5	0.98	0.3	0.98	0.3
C3	**C3b**	17.9	0.99	0.3	1.02	0.1
C3	**C3d**	15.8	1.03	0.2	0.8	1
C3	**iC3b**	17.2	1.04	0.6	0.98	0.1
C4A C4B	**C4**	9.3	1.02	0.3	0.96	0.6
C4A C4B	**C4b**	10.3	1.02	0.2	1	0.1
C5	**C5**	3.7	1.05	2.3	1.03	0.4
C5	**C5a**	6.4	0.89	0.3	1.04	0.3
C5 C6	**C5b, 6 Complex**	2.7	1.04	1.1	1.07	0.7
C6	**C6**	5.0	0.99	0.4	0.89	**2.3***
C7	**C7**	6.8	1.04	0.7	1.08	0.6
C8A C8B C8G	**C8**	6.0	1.05	0.9	1.01	0.5
C9	**C9**	4.7	1.08	1.9	1.04	0.6
CCL1	**I309**	3.0	0.94	0.4	1.07	0.1
CCL2	**MCP1**	2.5	0.93	0.3	0.96	0.1
CCL3	**MIP1a**	7.4	1.05	0.3	0.95	0.5
CCL3L1	**LD78beta**	6.2	0.95	0.9	0.95	0.6

CCL4L1	**LAG1**	3.5	0.68	0.4	1.05	0.9
CCL5	**RANTES**	3.7	0.86	1.5	0.88	0.6
CCL7	**MCP3**	3.1	1.04	0.6	1.24	1.9
CCL8	**MCP2**	2.7	1.05	1.4	1.05	0.6
CCL11	**Eotaxin**	6.5	1.2	2.98	1.04	0.6
CCL13	**MCP4**	3.4	0.94	0.3	1.02	0
CCL16	**HCC4**	1.1	1.16	1.8	1.02	0.2
CCL17	**TARC**	2.1	0.89	0.9	0.99	0.1
CCL18	**PARC**	4.1	0.94	0.4	1.01	0.1
CCL19	**MIP3b**	6.9	1.18	1.3	0.72	0.4
CCL20	**MIP3a**	1.3	0.83	2.3	1.05	0.5
CCL21	**6Ckine**	3.5	0.99	0.1	1.07	0.3
CCL22	**MDC**	6.2	1.06	0.5	0.97	0.1
CCL23	**Ckb81**	8.0	1.14	**3.4***	1.05	0.2
CCL23	**MPIF1**	6.7	1.11	1.9	1	0.1
CCL24	**Eotaxin2**	9.2	0.9	1.5	1.17	0.1
CCL25	**TECK**	19.7	1.17	1.1	0.95	0.2
CCL27	**CTACK**	3.9	1.06	0.2	0.96	0.4
CCL28	**CCL28**	8.3	0.92	0.9	1.04	0.4
CD163	**sCD163**	2.9	1.01	0	1.1	0.4
CD200	**OX2G**	2.2	1.31	2.7	1.12	**2.4***
CD209	**DCSIGN**	2.0	1.04	0.9	0.99	0
CD4	**sCD4**	5.1	1.05	2.97	1.06	1.1
CD48	**CD48**	2.4	1.12	**4.8***	1.09	1.6
CD84	**SLAF5**	3.6	1.09	2.8	1.11	1.8
CFB	**Factor B**	3.4	1	0	0.97	0.5
CFD	**Factor D**	5.2	1.02	0.5	1.01	0
CFH	**Factor H**	4.7	1.04	1.8	1.01	0.1
CFHR5	**CFHR5**	5.7	0.94	0.6	0.95	0.5
CFI	**Factor I**	2.8	1	0.1	0.98	0.6
CRLF1 CLCF1	**CLF1/CLC Complex**	3.5	0.97	0.1	1.04	0
CRLF2	**TSLP R**	5.2	0.93	2	0.92	0.9
CRTAM	**CRTAM**	1.8	0.88	2.5	0.87	1.7
CSF1R	**MCSF R**	21.0	0.98	0.1	1.09	0.4
CSF2	**GMCSF**	2.4	1.93	1.9	0.91	0.8
CSF3	**GCSF**	5.7	1.59	**5.0***	1.47	1.3
CSF3R	**GCSFR**	1.9	1.05	0.5	1.67	**2.1***
CX3CL1	**Fractalkine**	5.2	1.18	**3.6***	1.16	1.1
CXCL1	**Groa**	5.0	0.93	1.2	1.12	0.1
CXCL3 CXCL2	**Grob/g**	5.8	0.79	2.8	0.71	1.7
CXCL5	**ENA78**	2.1	0.93	2.3	0.94	0.6
CXCL6	**GCP2**	9.4	1.04	0	0.9	0.8

CXCL8	**IL8**	3.2	0.89	0.6	1.24	0.2
CXCL10	**IP10**	3.2	0.94	0.7	1.05	0.2
CXCL11	**ITAC**	10.9	1.04	0.2	0.93	0.1
CXCL12	**SDF1**	7.5	0.95	1.2	0.99	0.1
CXCL13	**BLC**	8.7	0.96	0.1	0.92	0.2
CXCL16	**CXCL16**	1.6	1.13	**3.9***	1.08	0.8
FASLG	**Fas ligand**	4.2	0.96	0	0.72	0.1
FCER2	**CD23**	2.5	1.21	**4.9***	1.17	1.3
GRN	**GRN**	2.9	1.09	**3.9***	1.01	0.2
ICOS	**ICOS**	15.0	1.3	**5.3***	1.02	0.3
ICOSLG	**B7H2**	5.1	0.5	2.2	0.83	0.5
IFNG	**IFNg**	5.2	0.79	2.4	0.77	1.9
IFNL1	**IFNlambda 1**	3.9	0.93	1.3	0.88	1
IL1A	**IL1a**	6.4	0.88	0.7	0.83	0.4
IL1B	**IL1b**	6.1	1.08	0.6	1.52	1.4
IL1RAP	**IL1 R AcP**	1.9	1.06	0.6	0.96	0.2
IL1RAPL2	**IL1 sR9**	2.4	1.01	0.1	0.93	0.7
IL1RL1	**IL1 R4**	5.2	1.1	1.8	1.06	0.2
IL1RL2	**IL1Rrp2**	1.3	0.98	0.6	0.94	1.3
IL2	**IL2**	6.7	1.05	0.9	1.1	0.6
IL2RA	**IL2 sRa**	4.7	1.1	0.7	0.98	0.7
IL2RG	**IL2 sRg**	2.2	0.82	1.4	0.76	1.9
IL3	**IL3**	6.0	0.92	0.7	0.88	1.7
IL3RA	**IL3 Ra**	5.6	0.99	1.2	0.89	1
IL4	**IL4**	1.7	0.91	2.1	1	0.3
IL4R	**IL4 sR**	4.0	1.07	0.2	0.76	0.1
IL5	**IL5**	6.0	0.99	0.2	0.89	**2.5***
IL5RA	**IL5 Ra**	4.2	0.97	0	1.04	0.2
IL6	**IL6**	14.0	1.05	0	1.24	1.6
IL6R	**IL6 sRa**	2.9	1.07	1.4	0.98	0.2
IL6ST	**gp130**	4.9	1.07	2.99	1.11	1.9
IL7	**IL7**	3.1	1	0	1.05	0.4
IL7R	**IL7 Ra**	6.9	1.11	0.1	1.37	1.7
IL10	**IL10**	3.5	1.54	0.8	1.02	0.3
IL10RB	**IL10 Rb**	5.3	1.09	**4.2***	1.01	0.2
IL11	**IL11**	1.6	0.98	0.5	0.97	0.1
IL11RA	**IL11 RA**	2.9	1.06	1.1	1.02	0.4
IL12A IL12B	**IL12**	9.5	0.88	1.8	0.98	0.2
IL12B IL23A	**IL23**	3.0	1.03	0.1	2.67	1.3
IL12RB1	**IL12 Rb1**	7.0	1.01	0.5	1.02	0.3
IL12RB2	**IL12 RB2**	2.7	0.8	0.1	0.57	0
IL13	**IL13**	6.6	0.96	0.5	1	0.2
IL13RA1	**IL13 Ra1**	3.8	1.24	**6.5***	1.17	1.3

IL16	**IL16**	6.7	0.77	1	0.94	0.2
IL17A	**IL17**	3.2	0.99	0.5	1.11	0.9
IL17B	**IL17B**	1.8	0.99	0.3	0.85	0.2
IL17D	**IL17D**	4.8	1.01	0.1	0.98	0.2
IL17RA	**IL17 sR**	3.5	0.96	0.2	0.92	0.6
IL17RB	**IL17B R**	2.4	1.18	2.1	0.88	0.5
IL17RC	**IL17 RC**	6.9	1.05	**3.4***	1.05	0.5
IL17RD	**IL17 RD**	1.3	0.87	0.3	0.96	0.2
IL18BP	**IL18 BPa**	6.0	1.23	**8.4***	1.17	1.9
IL18RAP	**IL18 Rb**	3.6	0.93	0.9	0.83	0.3
IL19	**IL19**	4.0	1.05	1.2	1.01	0.1
IL20	**IL20**	6.9	1.02	0.5	1.08	0.7
IL20RA	**IL20 Ra**	2.6	1.29	1	1.05	1.5
IL22	**IL22**	2.3	0.91	0	1.27	0.1
IL22RA1	**IL22RA1**	10.0	0.82	**3.3***	1.05	0
IL22RA2	**IL22BP**	3.4	1.12	1.3	1.19	1.1
IL23R	**IL23 R**	2.7	0.93	1.3	0.93	0.8
IL24	**IL24**	7.5	1.17	0.6	1.31	0.7
IL25	**IL17E**	3.7	0.74	0.4	0.92	0.6
IL27 EBI3	**IL27**	2.2	1.47	1.9	1.05	1
IL27RA	**TCCR**	3.9	1.04	1.1	0.97	0.2
IL34	**IL34**	10.6	0.98	0	0.86	0.4
IL37	**IL1F7**	5.5	0.82	1	0.8	**2.6***
KLRK1	**NKG2D**	7.2	1.31	2.92	2.49	0.8
LAG3	**LAG3**	3.1	1.13	1.3	1	0
LTA4H	**LKHA4**	18.3	1.04	0.8	1.39	**2.1***
LY9	**LY9**	5.5	1.18	2.8	1.2	**2.1***
MIF	**MIF**	3.2	0.86	1.6	0.87	1.1
NCR1	**NKp46**	5.7	1.19	**5.8***	0.73	0.3
NCR3	**NKp30**	11.7	1.17	**5.3***	1.06	0.7
PDCD1LG2	**PDL2**	2.9	1.13	**3.7***	1.07	0.8
PPBP	**CTAPIII**	7.1	0.75	2.3	0.91	1
PPBP	**NAP2**	3.3	0.75	2.4	0.9	1
SLAMF6	**SLAF6**	3.3	1.06	2.4	1.15	**2.1**
SLAMF7	**SLAF7**	6.8	1.09	0.4	1.09	0.2
TNFRSF3	**Lymphotoxin b R**	5.9	0.94	0	0.94	0.4
TNFRSF4	**TNR4**	3.3	1.21	**6.2***	1.13	1.8
TNFRSF6B	**DcR3**	6.7	1.04	1.1	1.15	0.2
TNFRSF8	**CD30**	6.1	1.11	2.91	1.11	**2.1***
TNFRSF9	**41BB**	3.6	1.31	**8.2***	0.45	1
TNFRSF10A	**TRAIL R1**	4.5	1.09	0	1.05	0.1
TNFRSF11A	**RANK**	4.3	0.99	0.1	1.05	0

TNFRSF11B	**OPG**	4.7	0.95	0.8	0.92	1.5
TNFRSF12A	**TWEAKR**	6.3	1.82	1.6	1.07	0.8
TNFRSF13B	**TACI**	1.8	0.99	0.1	0.94	0.4
TNFRSF13C	**BAFF Receptor**	2.0	0.98	0.7	0.88	1.4
TNFRSF14	**HVEM**	1.7	1.14	**4.9***	0.97	0.3
TNFRSF17	**BCMA**	4.5	1.03	0	1.01	0.1
TNFRSF18	**GITR**	2.8	0.94	1.5	0.88	0.4
TNFRSF25	**DR3**	1.8	0.91	1.7	0.91	0.8
TNFRSF27	**CD27**	4.9	0.93	0.5	0.96	0.8
TNFRSF: EDAR	**EDAR**	2.2	0.95	0.1	1.06	0.4
TNFSF1	**TNFbeta**	3.3	1.07	0.2	0.93	0.7
TNFSF2	**TNFalpha**	5.8	0.68	0	1.43	0.1
TNFSF4	**OX40 Ligand**	5.3	0.99	0.3	5.45	1.5
TNFSF5	**CD40 ligand**	6.4	0.85	1.7	0.55	1.7
TNFSF7	**CD70**	5.8	1.26	**10.3***	1.08	1.3
TNFSF8	**CD30 Ligand**	3.6	1.09	1.6	1.19	1.5
TNFSF9	**41BB ligand**	2.0	1.07	0.2	1.05	0.3
TNFSF11	**sRANKL**	6.4	0.89	0.7	0.86	1.2
TNFSF12	**TWEAK**	3.1	0.9	**5.1***	0.95	1
TNFSF13B	**BAFF**	7.0	1.1	1.7	1.04	0
TNFSF14	**LIGHT**	3.8	0.51	1.7	0.93	0.5
TNFSF18	**TNFSF18**	4.2	1.02	0.6	0.86	1
TNFSF: EDA	**EDA**	4.4	1.19	0.9	0.89	0.6
TNFSF: LTA LTB	**Lymphotoxin a1/b2**	5.4	1.19	2.87	1.19	2
TNFSF: LTA LTB	**Lymphotoxin a2/b1**	4.4	1.04	0.5	0.99	0

Legend: HGNC - protein name according to the HUGO Gene Nomenclature Committee. CV - coefficient of variation.

Fold change is a ratio of mean concentration of a protein in subjects who developed ESRD over mean concentration of the same protein in subjects who did not develop ESRD during 10 year follow-up.

Significance was tested in the generalized linear model (two-sided p value). Significant thresholds used: ¶ in exploratory T1D cohort $-\log_{10}p > 3.6$ (i.e. $p<0.05$ after Bonferroni correction) and † in validation T2D cohort $-\log_{10} p > 2.0$ (i.e. $p < 0.01$).
P values marked with an asterisk (*) point to associations significant in either T1D or T2D cohorts according to above thresholds.

Supplementary Table 2: Effect of circulating KRIS proteins on 10-year risk of development of ESRD according to Cox proportional hazard models adjusted for different covariates in Joslin Cohorts (**A**) and in Pima Cohort (**B**).

KRIS proteins		**A. JOSLIN COHORTS (n= 363) - Cox models**		
		Model #1	**Model #2**	**Model #3**
HGNC name	**Alternate name**	HR (95% CI)	HR (95% CI)	HR (95% CI)
TNFRSF members				
TNFRSF1A	TNF-R1	2.99 (2.24, 3.99)	2.40 (1.77, 3.24)	2.78 (2.02, 3.83)
TNFRSF1B	TNF-R2	2.22 (1.73, 2.85)	1.72 (1.32, 2.23)	1.86 (1.42, 2.43)
TNFRSF21	DR6	1.69 (1.35, 2.12)	1.39 (1.10, 1.76)	1.38 (1.08, 1.76)
TNFRSF19	TROY	2.07 (1.63, 2.62)	1.74 (1.35, 2.24)	1.68 (1.31, 2.16)
TNFRSF27	XEDAR	2.18 (1.75, 2.70)	1.92 (1.54, 2.39)	1.99 (1.59, 2.50)
TNFRSF19L	RELT	1.68 (1.33, 2.13)	1.43 (1.13, 1.83)	1.46 (1.13, 1.88)
Other proteins				
IL15RA	IL15RA	2.37 (1.85, 3.04)	1.89 (1.47, 2.43)	1.83 (1.42, 2.37)
IL17F	IL17F	1.92 (1.51, 2.44)	1.52 (1.20, 1.93)	1.65 (1.29, 2.11)
CD55	DAF	1.69 (1.34, 2.13)	1.36 (1.06, 1.74)	1.36 (1.06, 1.73)
CD300C	CLM6	1.84 (1.46, 2.32)	1.46 (1.15, 1.85)	1.57 (1.23, 2.00)
TNFSF15	TL1A5	1.83 (1.47, 2.26)	1.50 (1.20, 1.86)	1.53 (1.23, 1.91)
CCL14	HCC1	1.38 (1.11, 1.70)	1.34 (1.08, 1.66)	1.53 (1.21, 1.93)
CCL15	MIP5	1.54 (1.24, 1.92)	1.44 (1.15, 1.80)	1.43 (1.14, 1.78)
CSF1	M-CSF	1.35 (1.10, 1.65)	1.21 (0.98, 1.48)	1.24 (1.01, 1.51)
HAVCR2	TIMD3	1.64 (1.32, 2.04)	1.32 (1.06, 1.65)	1.39 (1.11, 1.74)
IL1R1	IL1R1	1.47 (1.20, 1.82)	1.15 (0.93, 1.43)	1.14 (0.92, 1.41)
IL18R1	IL18R1	1.41 (1.14, 1.73)	1.24 (1.01, 1.53)	1.28 (1.04, 1.58)

KRIS proteins		B. PIMA COHORT (n=162) - Cox models		
		Model #1	**Model #2**	**Model #3**
HGNC name	**Alternate name**	HR (95% CI)	HR (95% CI)	HR (95% CI)
TNFRSF members				
TNFRSF1A	TNF-R1	1.89 (1.21, 2.95)	1.67 (1.06, 2.64)	1.71 (1.07, 2.72)
TNFRSF1B	TNF-R2	2.75 (1.62, 4.67)	2.08 (1.19, 3.61)	2.32 (1.33, 4.06)
TNFRSF21	DR6	2.60 (1.54, 4.39)	2.00 (1.13, 3.54)	2.24 (1.25, 4.01)
TNFRSF19	TROY	1.92 (1.26, 2.91)	1.75 (1.10, 2.77)	1.76 (1.09, 2.83)
TNFRSF27	XEDAR	1.55 (1.02, 2.34)	1.60 (1.07, 2.39)	1.83 (1.17, 2.86)
TNFRSF19L	RELT	2.40 (1.43, 4.01)	2.34 (1.33, 4.11)	2.46 (1.38, 4.40)
Other proteins				
IL15RA	IL15RA	1.90 (1.21, 2.96)	1.78 (1.09, 2.89)	1.89 (1.14, 3.15)
IL17F	IL17F	2.22 (1.39, 3.54)	1.05 (0.58, 1.90)	1.09 (0.59, 2.01)
CD55	DAF	2.93 (1.72, 4.98)	2.49 (1.39, 4.46)	2.73 (1.49, 5.02)
CD300C	CLM6	2.03 (1.30, 3.15)	2.11 (1.29, 3.43)	2.34 (1.41, 3.87)
TNFSF15	TL1A	1.76 (1.15, 2.70)	1.86 (1.09, 3.15)	1.94 (1.16, 3.26)
CCL14	HCC1	1.67 (1.11, 2.51)	1.88 (1.23, 2.86)	1.93 (1.24, 3.01)
CCL15	MIP5	1.30 (0.87, 1.94)	1.34 (0.87, 2.06)	1.54 (0.94, 2.52)
CSF1	M-CSF	2.08 (1.31, 3.31)	1.56 (1.00, 2.43)	1.68 (1.04, 2.71)
HAVCR2	TIMD3	2.28 (1.43, 3.64)	1.66 (1.02, 2.69)	1.98 (1.19, 3.29)
IL1R1	IL1R1	1.44 (0.97, 2.15)	1.12 (0.71, 1.76)	1.18 (0.71, 1.95)
IL18R1	IL18R1	0.81 (0.54, 1.24)	1.01 (0.66, 1.54)	0.96 (0.63, 1.47)

Legend: Model #1 is adjusted for age, GFR and HbA1c; model #2 is adjusted for age, GFR, HbA1c and ACR; model #3 is adjusted for age, GFR, HbA1c, ACR, gender, diabetes duration, systolic blood pressure and BMI.
Additionally analysis of the Joslin Study includes an indicator of diabetes type and estimated GFR, whereas the Pima study reports direct GFR. Effect (hazard ratios) and 95% confidence intervals are shown per one tertile change of concentration of examined protein.

Evaluation of changes in beta estimates following an adjustment of covariates one at a time was performed. In the Joslin Kidney Study KRIS proteins were not confounded by age, gender, HbA1c, diabetes duration, systolic bp, or BMI; in the Pima Indian Study KRIS proteins were not confounded by age, gender, diabetes duration, systolic bp, or BMI.KRIS proteins were not confounded by HbA1c in the Pima Study except for RELT, CCL14 and IL1R1.GFR – glomerular filtration rate, ACR – albumin to creatinine ratio, HbA1c – hemoglobin A1c, BMI – body mass index, HR – hazard ratio, CI – confidence intervals, ESRD – End Stage Renal Disease.

Supplementary Table 3. KRIS proteins and albuminuria involvement in the mediation analysis. Albuminuria-mediated and albuminuria-independent (independ) effects of 17 KRIS proteins on renal function slope.

		JOSLIN COHORTS					PIMA COHORT				
		Total effect		Decomposed effect		Proportion	Total effect		Decomposed effect		Proportion
Protein name **HGNC**	**Alternate**	β+SE	(-log 10 p)	**Albuminuria - independ** β	**Albuminuria-mediated** β	**Albuminuria - independ %**	β+SE	(-log 10 p)	**Albuminuria - independ** β	**Albuminuria-mediated** B	**Albuminuria - independ %**
TNFRSF1A	TNF-R1	-14.1± 2.5	7.9	-9.3	-4.8	66	-18.9± 5.5	3.2	-9.3	-8.5	55
TNFRSF1B	TNF-R2	-11.4± 2.6	4.8	-6.3	-5.1	55	-25.6± 5.6	5.4	-16.5	-9.1	64
TNFRSF21	DR6	-11.0± 3.0	3.7	-5.6	-5.4	51	-23.0± 5.7	4.3	-15.2	-7.8	66
TNFRSF19	TAJ	-6.7± 1.7	3.9	-3.4	-3.3	51	-8.3± 4.0	1.4	-5.3	-2.9	
TNFRSF27	XEDAR	-8.9± 1.9	5.4	-7.0	-1.9	79	-10.3± 7.3	0.8	-3.3	-6.9	
TNFRSF19L	RELT	-7.0± 2.2	2.7	-3.4	-3.6	48	-20.7± 5.8	3.4	-12.2	-8.6	59
			0.0								
IL15RA	IL15RA	-10.3± 2.6	4.1	-5.2	-5.0	51	-25.1± 7.9	2.9	-18.7	-6.4	
IL17F	IL17F	-7.8± 1.6	6.2	-4.7	-3.2	60	-13.0± 3.3	4.0	-7.4	-5.7	57
CD55	DAF	-9.5± 2.9	3.0	-3.3	-6.2	35	-21.9± 5.7	3.9	-13.1	-8.8	60
CD300C	CLM6	-10.0± 2.6	3.9	-5.4	-4.6	54	-17.4± 5.4	2.9	-11.9	-5.5	69
TNFSF15	TNFSF15	-7.9± 2.2	3.5	-4.4	-3.5	55	-19.9± 5.1	4.0	-14.3	-5.5	72
CCL14	HCC1	-4.0± 1.9	1.4	-2.7	-1.2		-11.7± 5.3	1.6	-10.5	-1.2	
CCL15	MIP5	-4.6± 2.1	1.5	-4.1	-0.5		-4.8± 2.9	1.0	-3.8	-1.0	
CSF1	M-CSF	-3.0± 1.7	1.1	-0.9	-2.1		-13.9± 3.6	3.9	-7.9	-6.0	
HAVCR2	TIMD3	-6.5± 2.1	2.7	-3.0	-3.5	46	-15.6± 4.9	2.8	-9.6	-6.0	62
IL1R1	IL1R1	-1.5± 1.2	0.6	0.7	-2.2		-12.0± 4.3	2.3	-8.6	-3.4	
IL18R1	IL18R1	-2.6± 2.1	0.7	0.1	-2.7		-2.8± 8.1	0.1	-12.5	9.7	

Legend. Etiological model is adjusted for age, HbA1c, baseline GFR, whereas ACR is entered as a mediator of the effect. Effect estimate represents an annual loss of estimated GFR in ml/min/1.73m^2/yr (Joslin Cohorts, n=363) and direct GFR in ml/min/yr (Pima Cohort, n=162) per an increase in one unit of a KRIS protein transformed to its base$_{10}$ logarithm. P value is two sided. For example, an increase in one log$_{10}$ unit of TNFR1 is associated with a rapid eGFR loss of 14ml/min/1.73m^2/ yr in Joslin Study that in a typical study subject with proteinuria and CKD stage 3 would lead to ESRD in 3 years. Please see a corresponding Figure 2 in the main body of the manuscript.

Supplementary Table 4: Characteristics of subjects with T1D and with T2D selected from the Joslin Cohorts into the nested case-control study whose urines obtained at baseline were subjected to the urinary proteomics analysis.

	T1D Control (n = 31)	**T1D Cases (n = 29)**	**T2D Control (n = 26)**	**T2D Cases (n = 26)**
At baseline:				
Male, n (%)	16 (52)	13 (45)	8 (31)	8 (31)
Age, (yr)	43±7	41±8	57±5	60±7
Duration of diabetes, (yr)	30±7	29±9	14±8	19±10
HbA_1C (%)	8.5±1.4	9.4±1.8	7.9±1.9	7.9±1.7
ACR (mg/mg creatinine)	0.6 (0.3, 1.0)	1.5 (0.8, 2.0)	0.2 (0.1, 0.5)	0.5 (0.2, 2.2)
eGFR (ml/min/1.73m^2)	46±9	38±10	50±11	45±11
Within 5-year follow up:				
eGFR slope, (mL/min/1.73 m^2/yr)	-1.9±1.1	-7.6±5.0	-1.0±1.9	-7.0±3.3
eGFR loss >40%, n (%)	(-) (by design)	29 (100)	(-) (by design)	26 (100)
ESRD cases, n (%)	-	18 (62)	-	11 (42)

Legend: Mean and standard deviation or median (25^{th}, 75^{th} percentile) have been provided for the continuous variables. Abbreviations: ACR – albumin to creatinine ratio; eGFR - estimated Glomerular Filtration Rate; ESRD – End Stage Renal Disease onset during the 10 year of follow-up.

Supplementary Table 5: Subjects with T2D included in the 1K Kidney Genome Project (1KGP) from whom kidney specimens were analyzed in this study: clinical characteristics and histology indices.

Clinical and histology characteristics	**Subjects for whom kidney expressions of genes encoding KRIS proteins were available**	
	In Glomeruli	**In Tubules**
Subjects (n)	23	37
Clinical characteristics		
Age	62.6 (12.5)	66.3 (11.7)
Female	13 (56.5%)	17 (45.9%)
Race n (%)		
Asian	4 (17.4%)	7 (18.9%)
Caucasian	4 (17.4%)	7 (18.9%)
African American	8 (34.8%)	12 (32.4%)
Hispanic	5 (21.7%)	3 (8.1%)
Multiracial	1 (4.3%)	6 (16.2%)
Unknown	1 (4.3%)	2 (5.4%)
BMI (kg/m^2)	29.5 (9.0)	29.4 (8.6)
eGFR ($ml/min/1.73m^2$)	48.5 (34.57)	53.5 (27.4)
Proteinuria: dipstick (range: 0-5), median IQR	2 (0, 3)	1 (0, 3)
Histology indices		
Glomerular sclerosis (%)	9.7 (15.3)	16.0 (21.3)
Tubulo-Interstitial Fibrosis (%)	16.6 (25.4)	21.7 (24.6)
Lymphocytic Infiltrate (range: 0-3)	1.0 (0.9)	1.1 (0.9)

Legend: Characteristics of subjects for whom glomerular and tubular RNAseq-based expression were determined for genes encoding KRIS proteins. Abbreviations: 1K Kidney Genome Project – 1KGP, eGFR – estimated glomerular filtration rate, BMI - body mass index.

Supplementary Table 6: Comparison of clinical characteristics of subjects with T1D in the Joslin Kidney Study who had SOMAscan measurements and at that time had either Proliferative Diabetic Retinopathy (PDR) or Non-Proliferative Diabetic Retinopathy (NPDR).

	PDR (n = 131)	**NPDR (n = 49)**	**p**
Clinical characteristics			
Male, n (%)	66 (50%)	21 (43%)	0.367
Age, (yr)	40 ± 9	37 ± 10	0.087
ACR (µg/mg creatinine)	1184 ± 1275	829 ± 1280	8.9×10^{-4}
eGFR (ml/min/1.73m^2)	71 ± 32	99 ± 28	5.9×10^{-7}
HbA1c (%)	9.2 ± 1.2	8.8 ± 1.0	0.026
eGFR Slope (ml/min/1.73m^2/yr)	-3.2 (-7.3, -1.5)	-2.2 (-3.3, -1.2)	0.018

Legend: Mean ± standard deviation or median (25th, 75th percentile) measures are provided as applicable. Abbreviations: T1D – Type 1 Diabetes, ACR – albumin-creatinine ratio, eGFR – estimated glomerular filtration rate, HbA1c – Hemoglobin A1c. Categorical variables compared by Chi square test and the continuous variables were compared in the analysis of variance for an unbalanced design. Two sided p value.

Supplementary Table 7: Current and future clinical treatments targeting pathways that involve KRIS proteins. **(A)** Indications for diabetic kidney disease (DKD) or chronic kidney disease (CKD), **(B**) Other indications.

A.

Target protein	MOA: DRUG (generic name)	Indications	Status	References for human interventional studies in DN
IL15RA, CCL14, CCL15, TNF-R1, TNF-R2	JAK1, JAK2 -STAT inhibitor: baricitinib	T2D, DKD	completed RCT, phase II	NCT01683409, PMID: 27333885; PMID: 27230798; PMID: 24802062
IL1RA	IL1Ra: rilonacept	CKD stage 3-4	completed RCT, phase II	PMID: 27647856
IL1RA	IL1Ra: anakinra	gout, T2D, DKD	post hoc analysis	PMID: 26126095

B.

Target protein	MOA: DRUG (generic name)	Indications	Status	References for animal studies in DN of other fibrotic kidney diseases
TNF-R1, TNF-R2	TNFR2-Fc: etanercept; anti-TNF mAb: infliximab, adalimumab, golimumab; anti-TNF Fab: certolizumab pegol	RA and other rheumatoid diseases	approved	PMID: 17767370, PMID: 24647715
IL15RA	anti-IL15 Ab: rituximab; anti-IL15 Ab: mIKBETAi; anti-IL15 Ab: HuMax-IL15; Syk inhibitor: fostamatinib	RA and other rheumatoid diseases	ongoing RCT	
IL17F	anti-IL17A/mAb: secukinumab; anti-IL17RA mAb: brodalumab; anti-IL17A/F mAb: ixekixumab	RA and other rheumatoid diseases	ongoing RCT	PMID: 27852609,
CCL14, CCL15	CCR1 antagonist (targeting CCL14, CCL15 among others): BAY 86-5047, MLN3897, BX471, AZD-4818, CP-481,715	RA, endometriosis, multiple sclerosis, COPD	completed RCT - uncertain benefit	PMID: 11805137, PMID: 15569315; PMID: 17392166

CCL15	CCR3 antagonist (targeting CCL15 among others): GW766944	asthma	completed RCT - uncertain benefit	PMID: 24286456,
TIMD3	anti-TIMD3 Ab: TSR-022	solid tumors	ongoing RCT	
IL1RA	IL1Ra: anakinra; IL1R1/IL1RAcP: rilonacept; anti-IL1 beta mAb: canakinumab	RA, CAPS, gout, CVD	approved/ongoing RCT	
IL18RA	anti-IL18 Ab: GSK1070806	obese T2D, IBD	completed RCT	

Legend: Additional references for human interventional studies on compounds approved for other clinical indications: PMID: 24679538; PMID: 28275260; PMID: 19950299; PMID: 28168715; PMID: 24286456; PMID: 26930607, NCT02817633, NCT01648153, NCT01035645 (www.clinicaltrials.gov accessed on Sept 15, 2017); Abbreviations: T2D – Type 2 Diabetes, RA – rheumatoid arthritis, RCT – randomized clinical trial, MOA – mechanism of action.

Supplementary Table 8: Predictive performance of the Cox proportional hazards models evaluating 10-year ESRD risk in the three cohorts.

	Model			Model comparisons	
	1	**2**	**3**	**2 vs 1**	**3 vs 2**
Predictive metrics					
C statistics ± SE	0.807 ±0.016	0.843 ±0.014	0.857 ±0.014		
p				*0.0010*	*0.0071*
–2 log likelihood (2LL)	1915	1822	1788		
P				*$5.2x10^{-22}$*	*7.4×10^{-7}*
Akaike Information Criterion (AIC)	1929	1838	1812		
Covariates					
Clinical	+	+	+		
TNFRSF1A (TNF-R1)		+	+		
Forward selected additional KRIS proteins			+		
Effect estimates					
TNFRSF1A (TNF-R1) HR (95% CI)		2.91 (2.31, 3.66)	1.87 (1.41 ,2.46)		
TNFRSF27 HR (95% CI)			1.57 (1.26 ,1.94)		
IL17F HR (95% CI)			1.23 (0.97 ,1.50)		
TNFSF15 HR (95% CI)			1.21 (1.00 ,1.50)		
CCL15 HR (95% CI)			1.23 (1.00 ,1.50)		
Significance					
TNFRSF1A1 p		*1.4×10^{-19}*	*9.2×10^{-6}*		
TNFRSF27 p			*4.2×10^{-5}*		
IL17F p			*0.0776*		
TNFSF15 p			*0.0658*		
CCL15 p			*0.0459*		

Legend: Three cohorts comprise T1D Joslin (n=219) and T2D Joslin (n=144) and T2D Pima (n=162). Forward selected clinical covariates include age, gender, HbA1c, ACR, BMI and cohort indicator (Model #1). The Model #1 has been compared to the model with the same clinical covariates in the presence of TNF-R1 (Model #2) or to the model with the same clinical covariates and TNF-R1, but considering the remaining 16 KRIS proteins (Model #3). Forward selection to Model #3 results in the inclusion of 5 KRIS

proteins listed above including TNFR1. Entry criterion, p=0.1. Effects are shown as hazard ratios (95% confidence intervals) per one tertile change of the KRIS protein distribution. Two sided p values. Null values for C-statistics are 0.5 and 2148 for AIC, respectively. Higher values for C-statistics, less negative values for 2LL and lower values for AIC indicate better performing models. HR – hazard ratios, CI – confidence intervals, ESRD – End Stage Renal Disease.

References for Supplementary Information

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