Integrative Systems biology– Renal Diseases:
A road to a holist view of chronic disease mechanism

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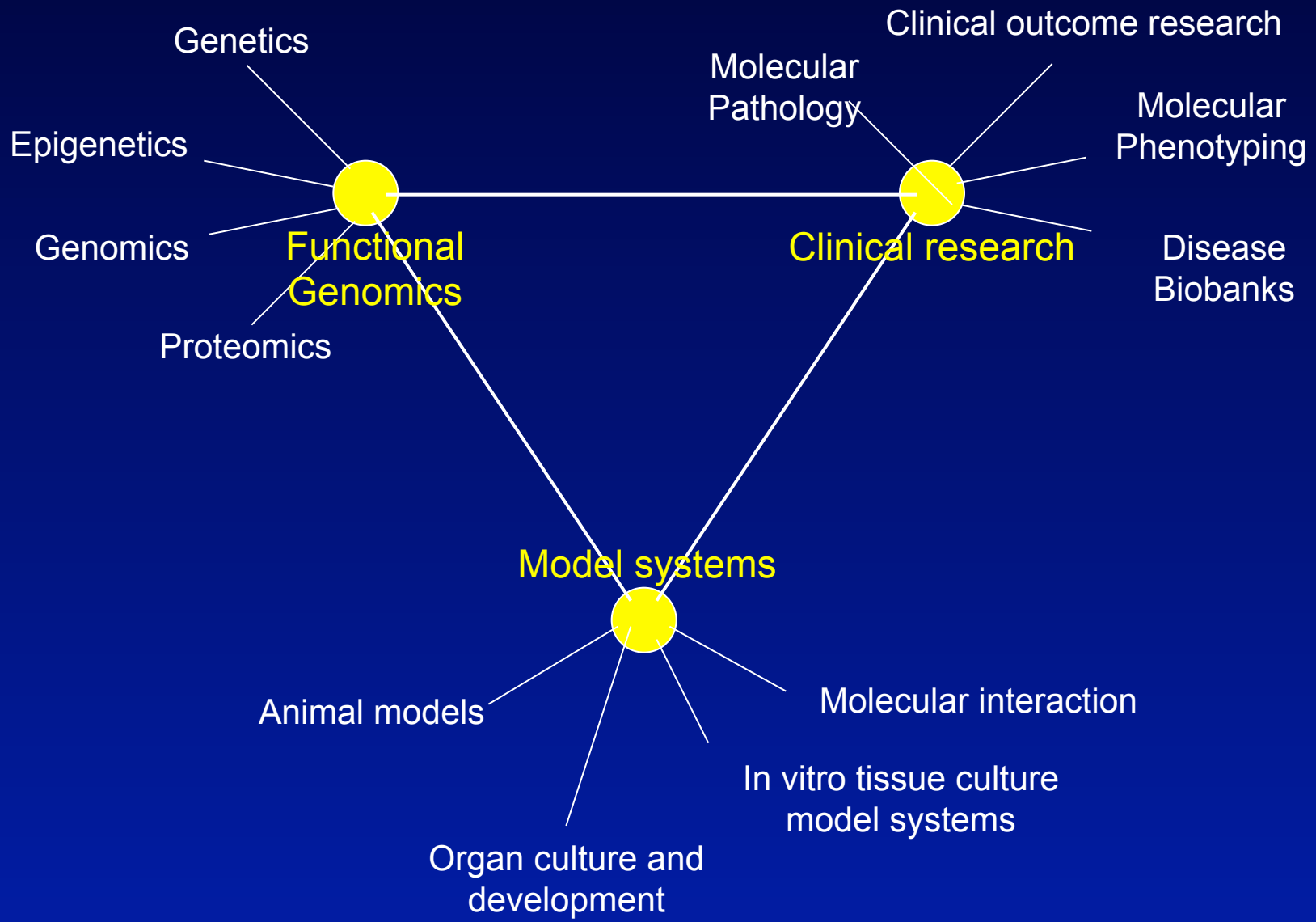
The challenge in chronic disease

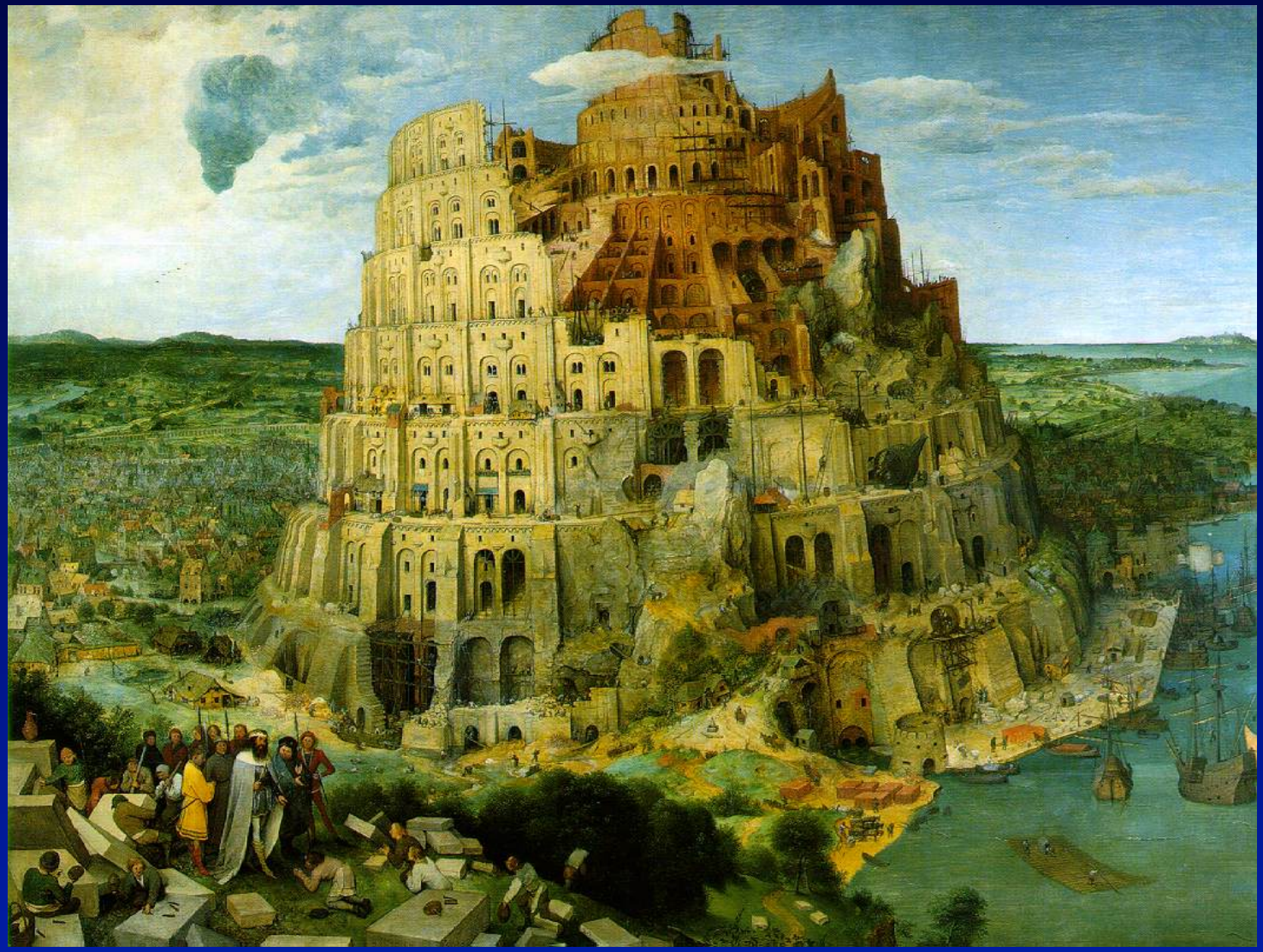
- Descriptive disease categorization with multiple pathogenetic mechanisms
  - Problems of ‘mixed bag’ diseases:
    - Unpredictable disease course and response to therapy
    - Nephrology as an *‘art of trial and error’*
- Shift in our disease paradigms:
  - Mechanism based patient management
    - Define the disease process active in the individual patient
      - Base prognosis on specific disease process
      - Target therapy to interfere with the mechanism currently destroying endorgan function

Molecular Nephrology approach



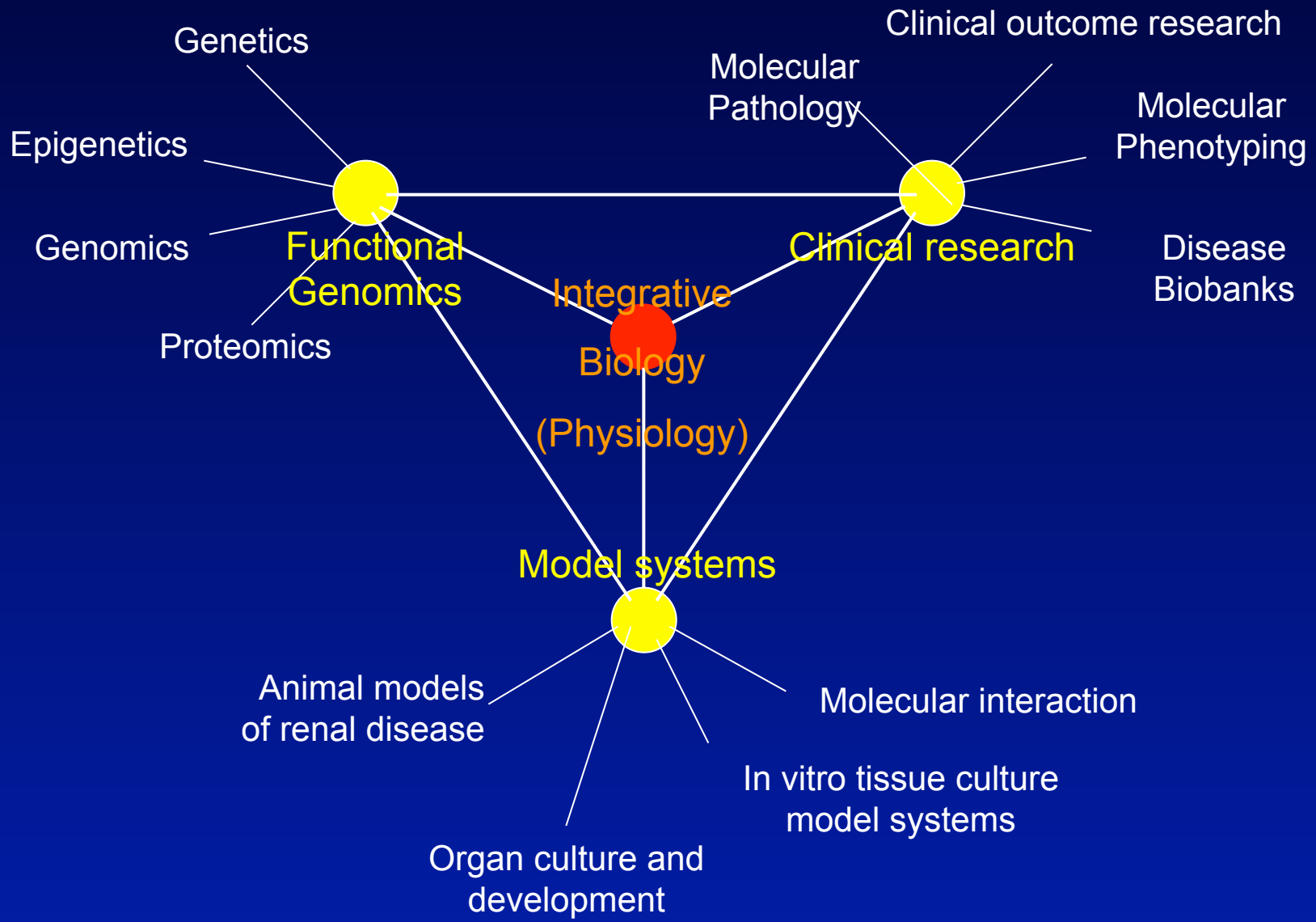
Tower of Babylon:

Search for the universal language for the medicine of the 21st century



Pieter Bruegl: 1563. Kunsthistorisches Museum Wien

Molecular Nephrology approach



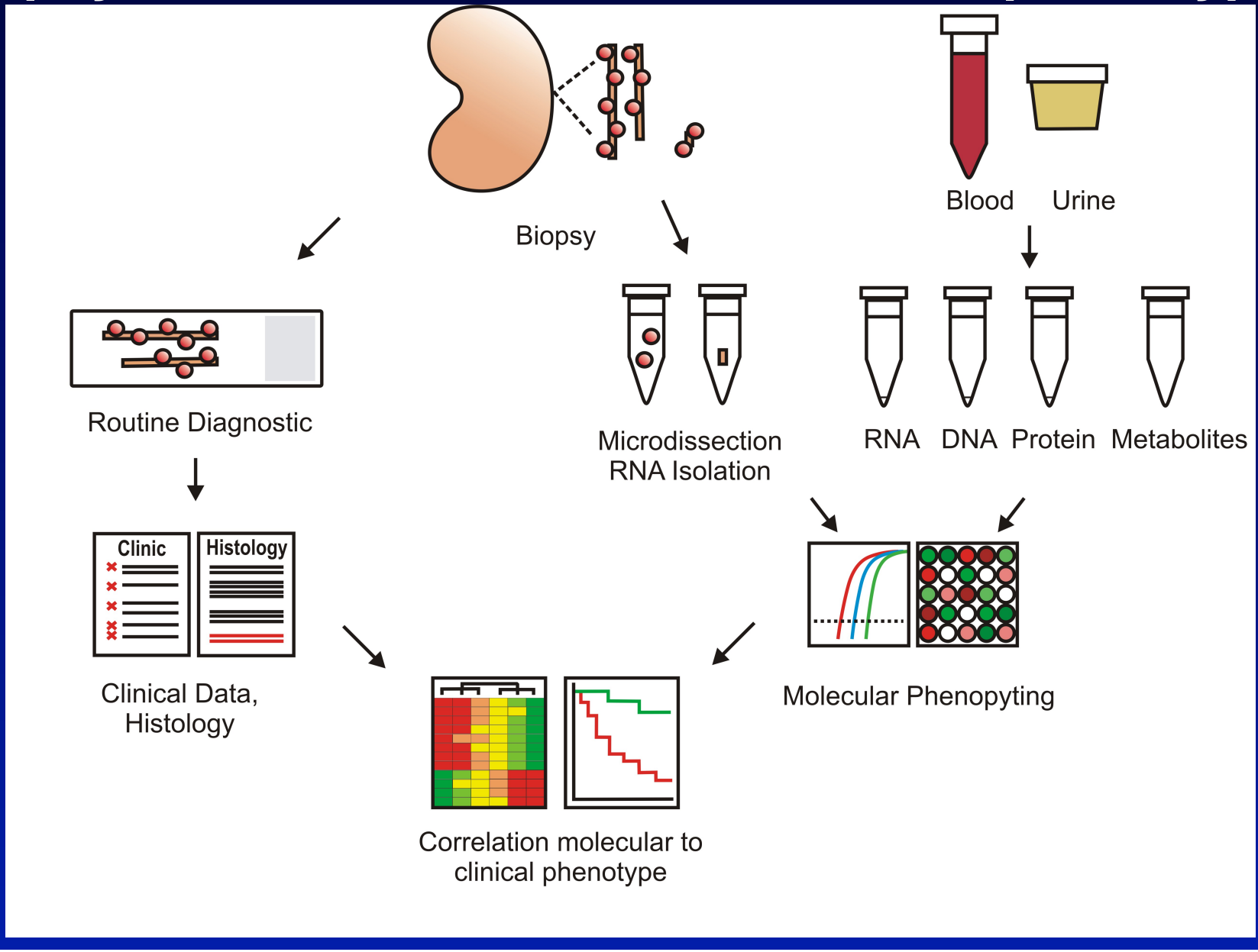
Systems analysis view of renal disease

Harness the capabilities of genome wide analyses for an integrated view of regulatory networks activated in glomerular disease:

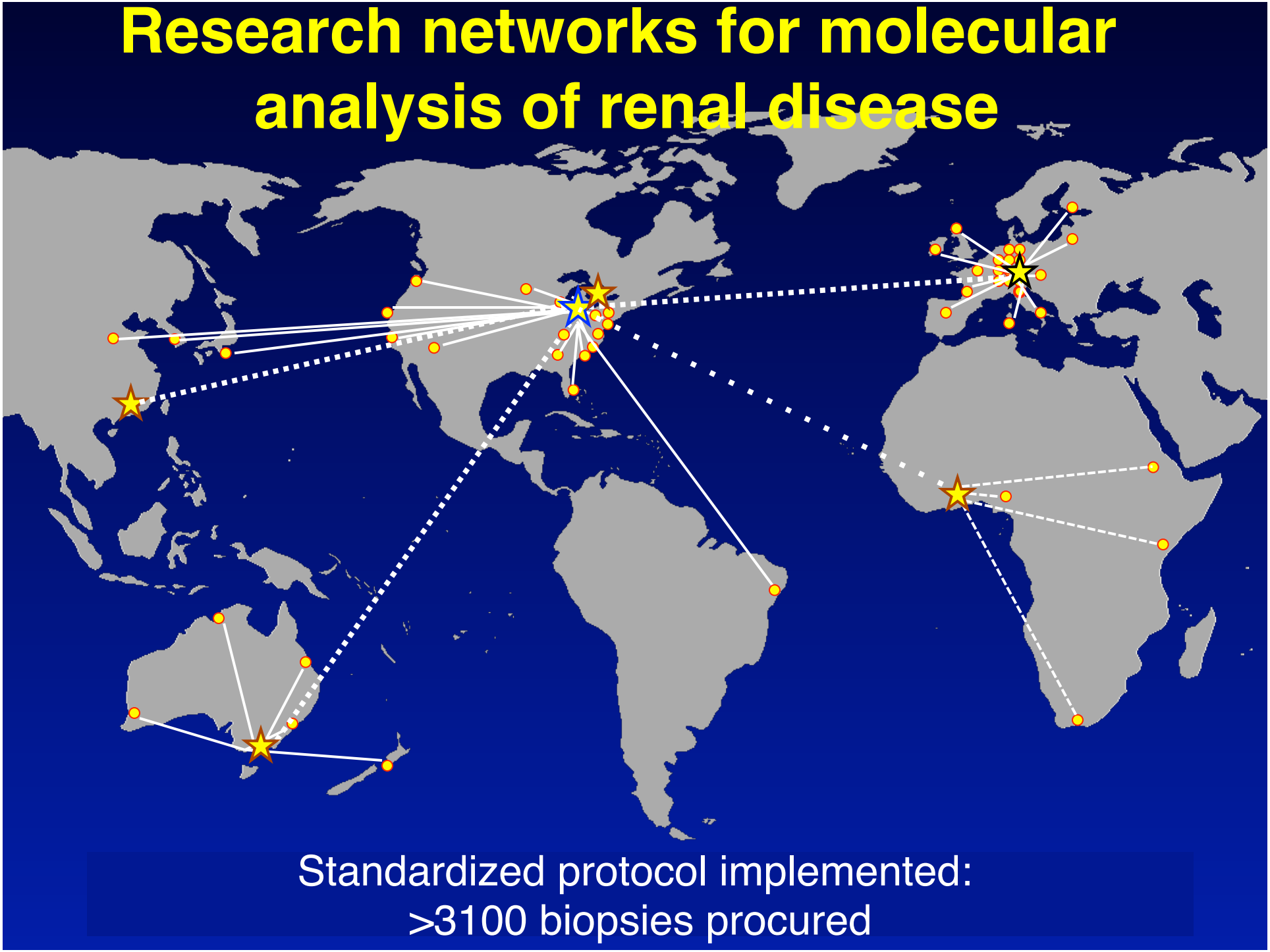
1. Develop cohorts for clinical and molecular phenotyping
2. Generate molecular map of renal disease
3. Integrate multi-level information
4. Develop strategies for outreach and clinical implementation

The advantage of being a Nephrologist:

Biopsy centered clinical and molecular phenotyping



Research networks for molecular analysis of renal disease



Standardized protocol implemented:
>3100 biopsies procured

Biorepositories for molecular analysis of chronic renal disease

ERCB

2560 renal biopsies for gene expression studies
24 European Centers

neptune

1165 Nephrotic Syndrome Patients in Registry
235 incipient Nephrotic syndrome Cohort
18 Centers in North-America

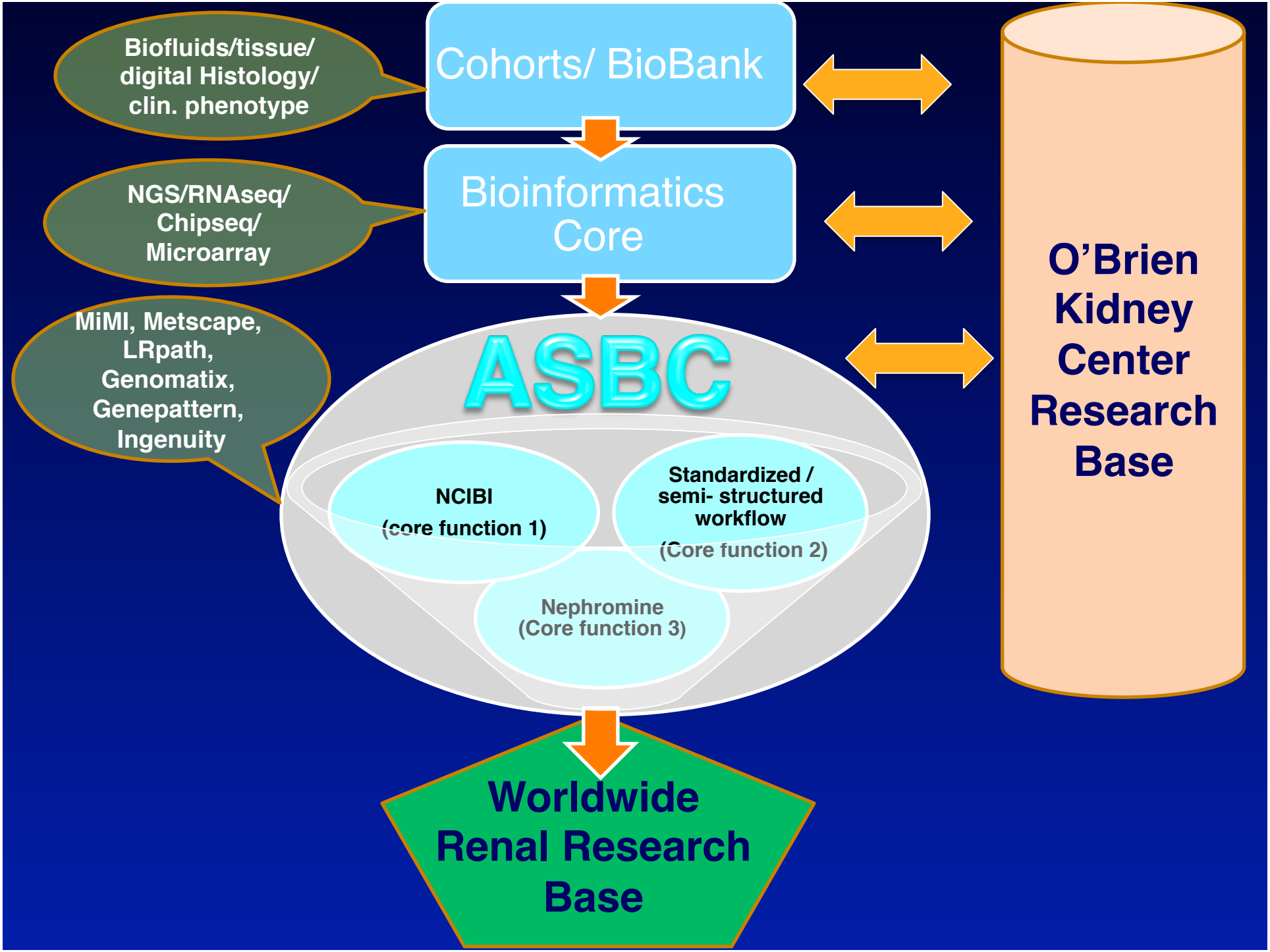
C-PROBE
clinical phenotyping resource biobank core

625 CKD patients in
5 Centers in Mid-West

60 years 1950 2010 NIDDK NATIONAL INSTITUTE OF DIABETES AND DIGESTIVE AND KIDNEY DISEASES
60 Years of Advancing Research to Improve Health
Research supported by NIDDK

180 Diabetic Nephropathy Cohort in Pima Interventional Trial
80 protocol biopsies available for molecular analysis

EURenOmics

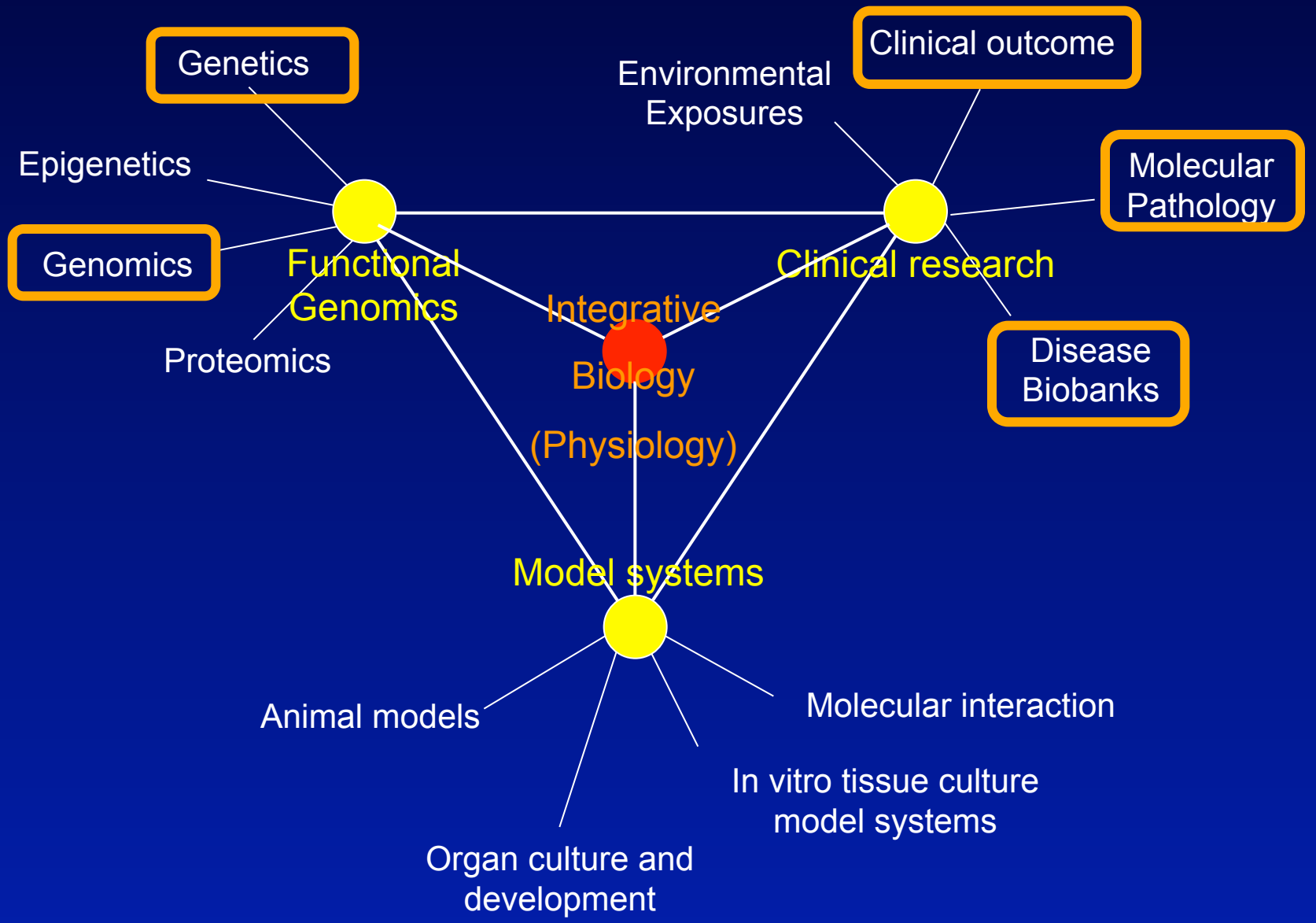

Biofluids/tissue/ digital Histology/ clin. phenotype
Cohorts/ BioBank
NGS/RNAseq/ Chipseq/ Microarray
Bioinformatics Core
MiMI, Metscape, LRpath, Genomatix, Genepattern, Ingenuity
ASBC
NCIBI (core function 1)
Standardized / semi- structured workflow (Core function 2)
Nephromine (Core function 3)
O'Brien Kidney Center Research Base
Worldwide Renal Research Base

Integrative Biology for target identification in CKD :

- **Case Study 1:**
  - The shared common pathway of CKD: Defining molecular context from genotype to phenotype
- **Case Study 2:**
  - Identify molecular mechanism and non-invasive correlates of fibrosis in CKD
- **Case Study 3:**
  - Molecular stratification of nephrotic syndrome

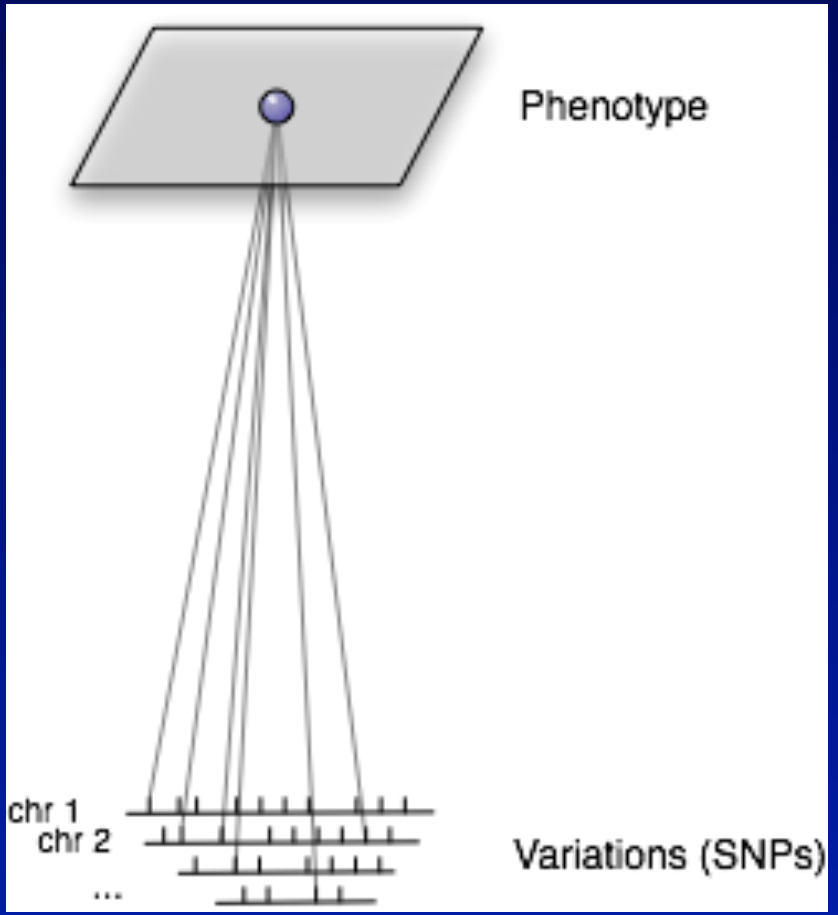
Case Study 1: *The shared common pathway of CKD:*

Defining molecular context from genotype to phenotype



Disease Causality:
Genetic variance can be linked to clinical phenotype

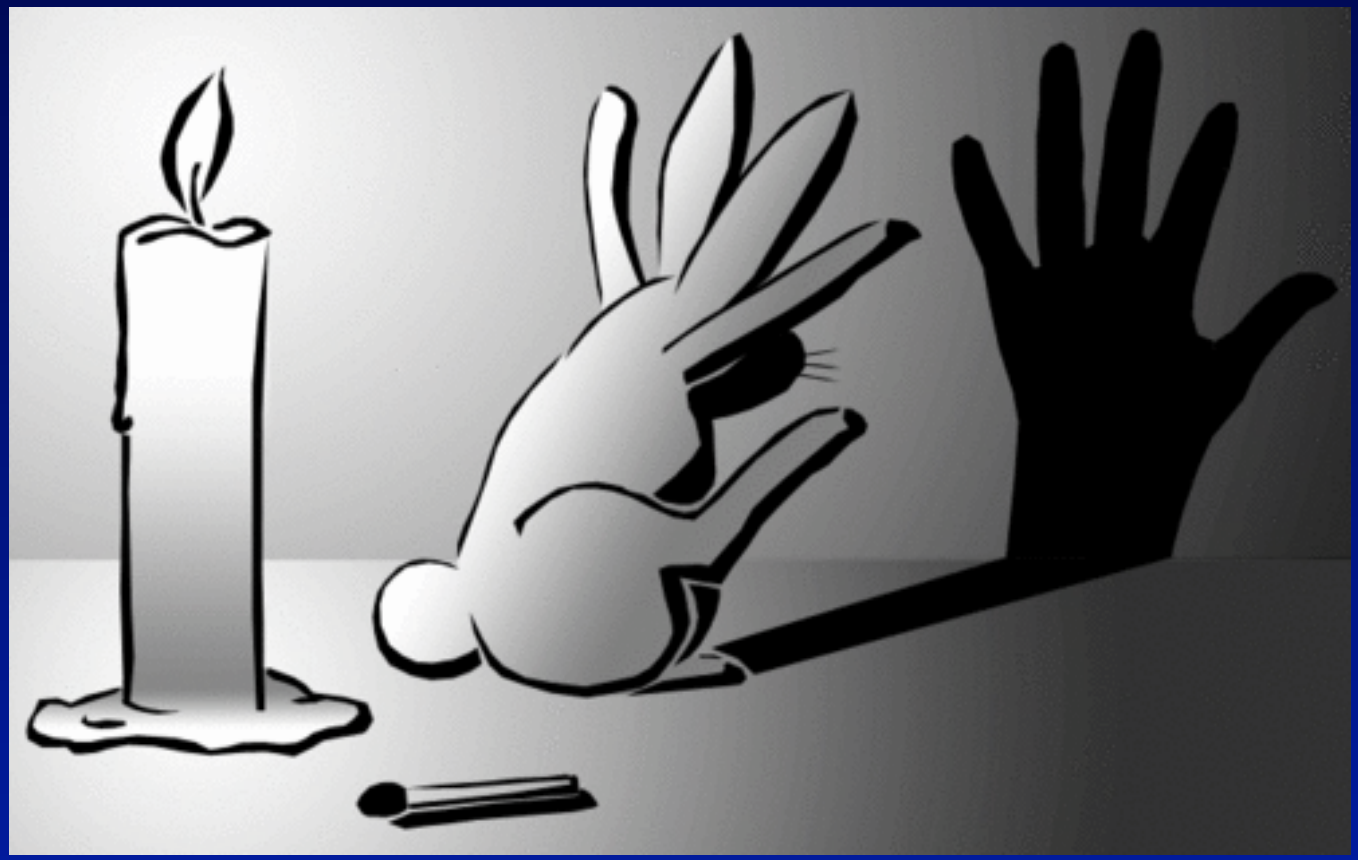
- Genetic studies identify genetic variances associated with clinical phenotypes.
- Genome Wide Association Studies (GWAS) gives lists of single nucleotide polymorphisms (SNPs) with genome wide significant *p*-values

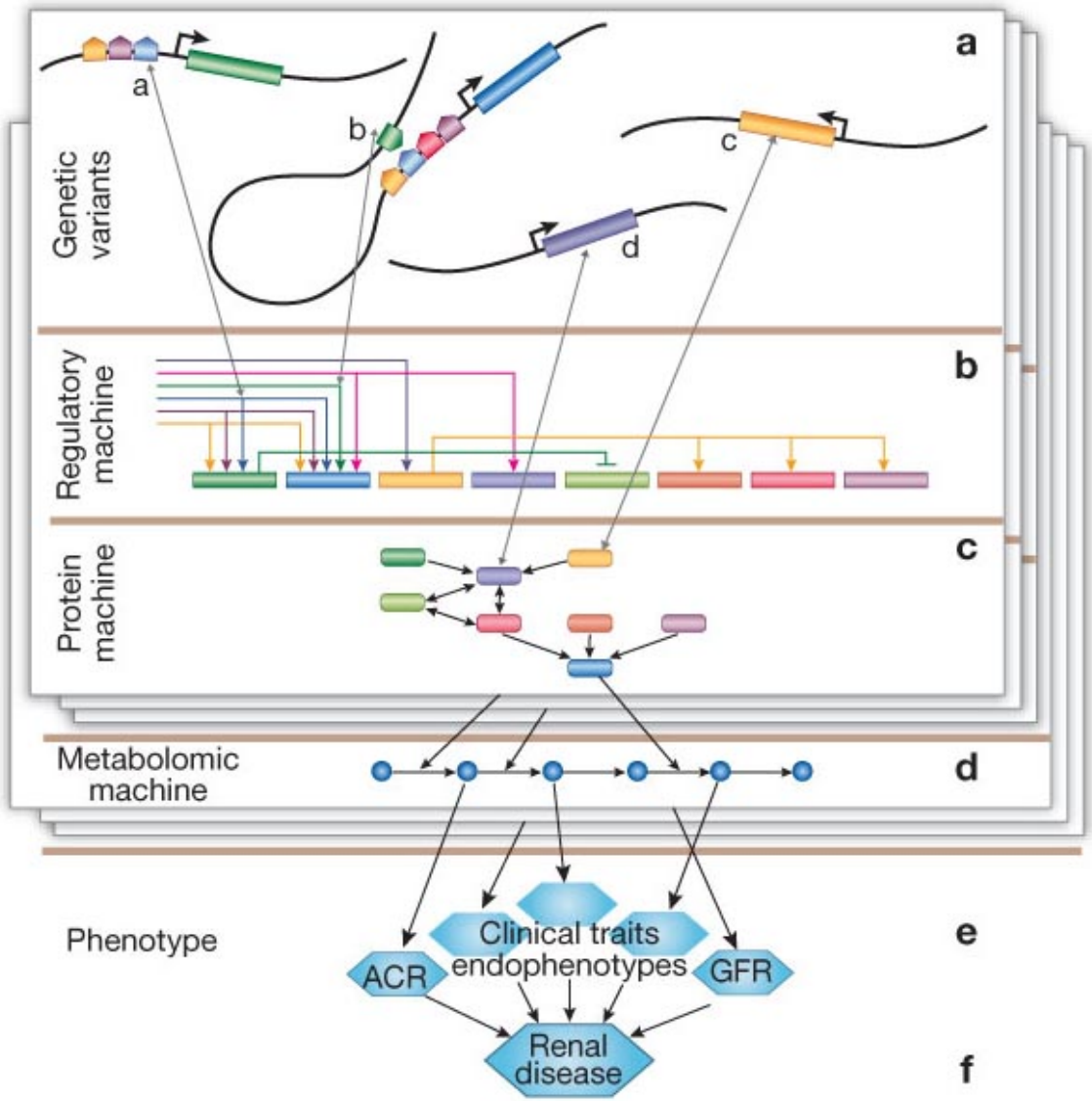


Association studies project SNPs onto Phenotype

What's the Biology in between?

Rethinking the Problem: Systems Genetics



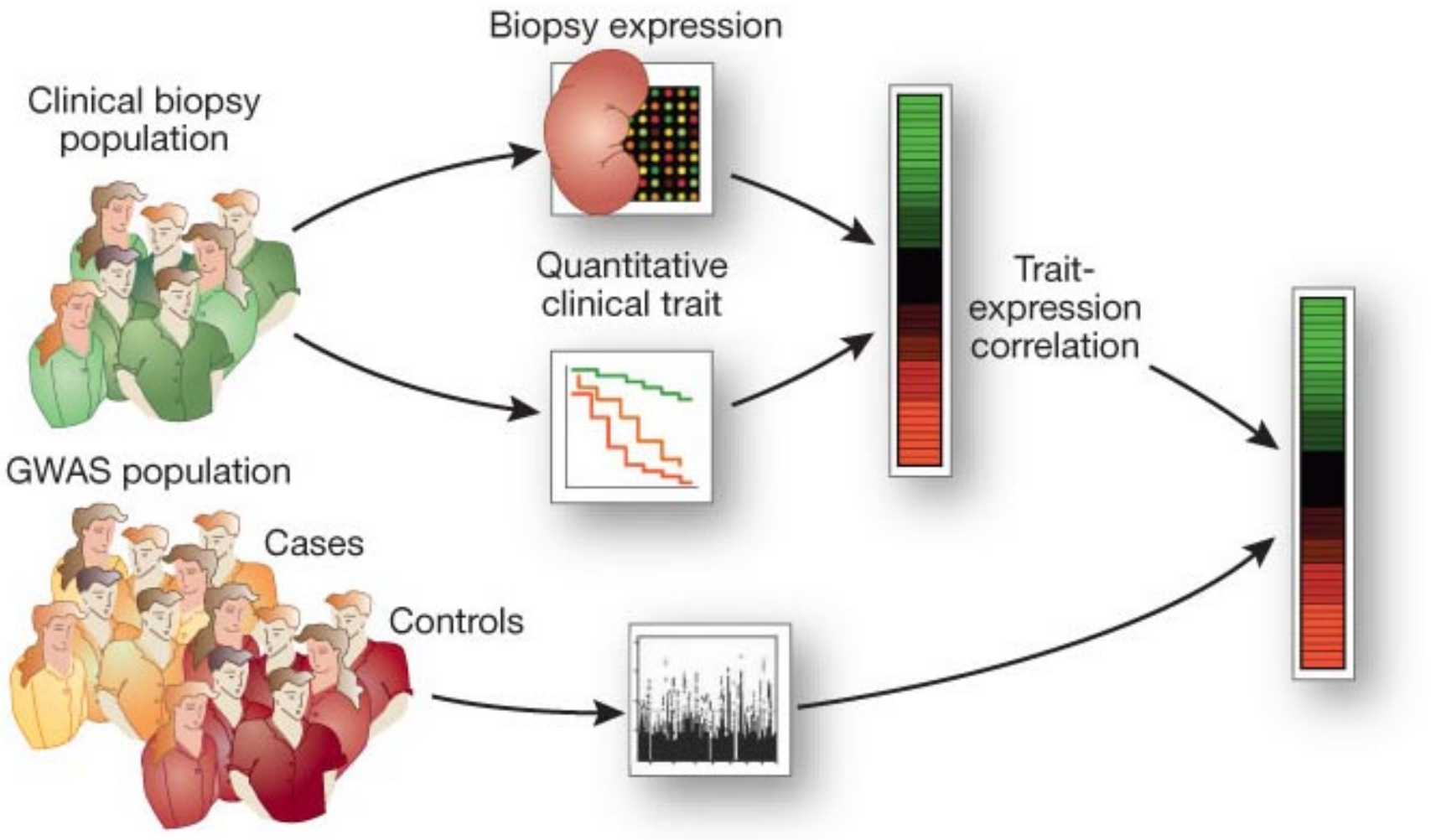


Systems genetics concepts

Genetic variants affect regulatory and proteomic machinery of the cell, leading to disruption in a metabolic pathway resulting in clinical trait / renal disease phenotype.

B. Keller et al. Kidney Int, 2012

Integration SNPs – transcripts-clinical traits

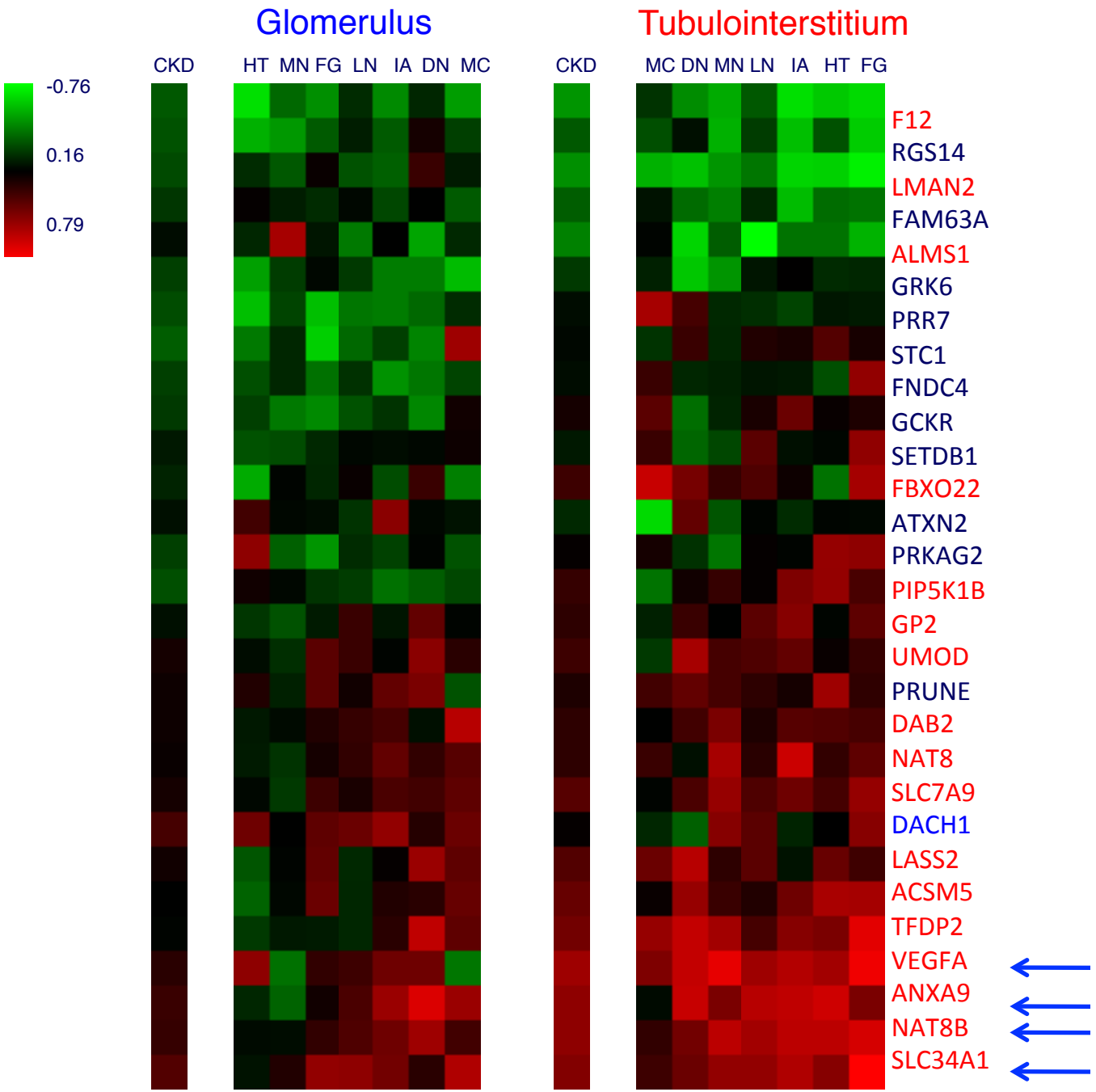


B. Keller et al. Kidney Int, 2012

Systems Genetics in CKD

Link polymorphism via regulatory networks to disease phenotypes

1. **Integration of SNP with mRNA levels (eQTL Concept):**
   Renal mRNA levels of CKDgen candidate genes
2. **Systems Genetics Concept:**
   CKD candidate genes are drivers in **pathways** associated with CKD.
3. **Network concepts:**
   CKD candidate genes, renal function analyses, and detection of shared transcript co-regulation
   => pathway enrichment analyses
   => **CKD pathway network**



Heatmap: GFR-correlation of candidate genes

29 CKDgen associated mRNAs:
Sig. correlation with eGFR ?

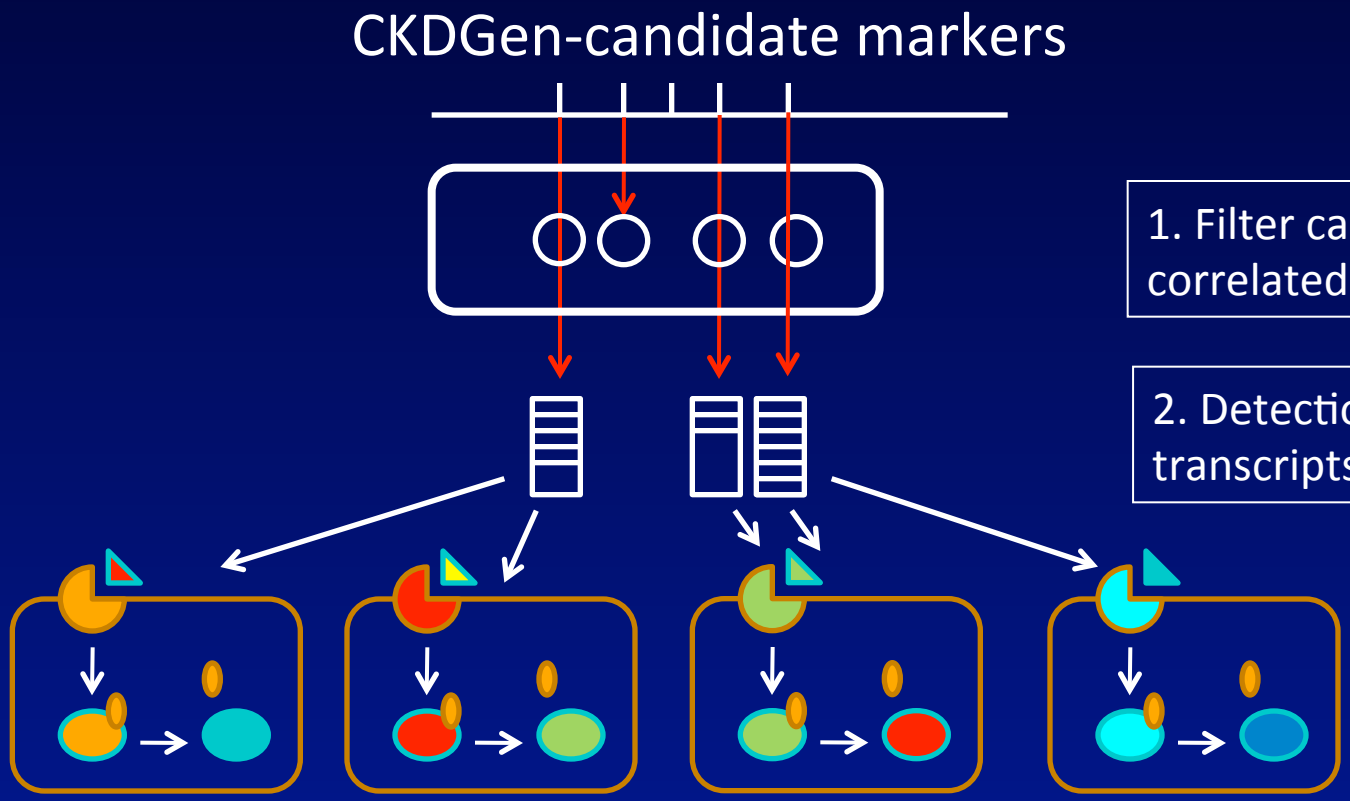
$|r| \geq 0.25$
FDR ≤ 0.01

Red: Tub-int (17)
Blue: Glom (5)

Range of GFR correlation:
-0.76 to 0.788

Martini et al. JASN, 2014

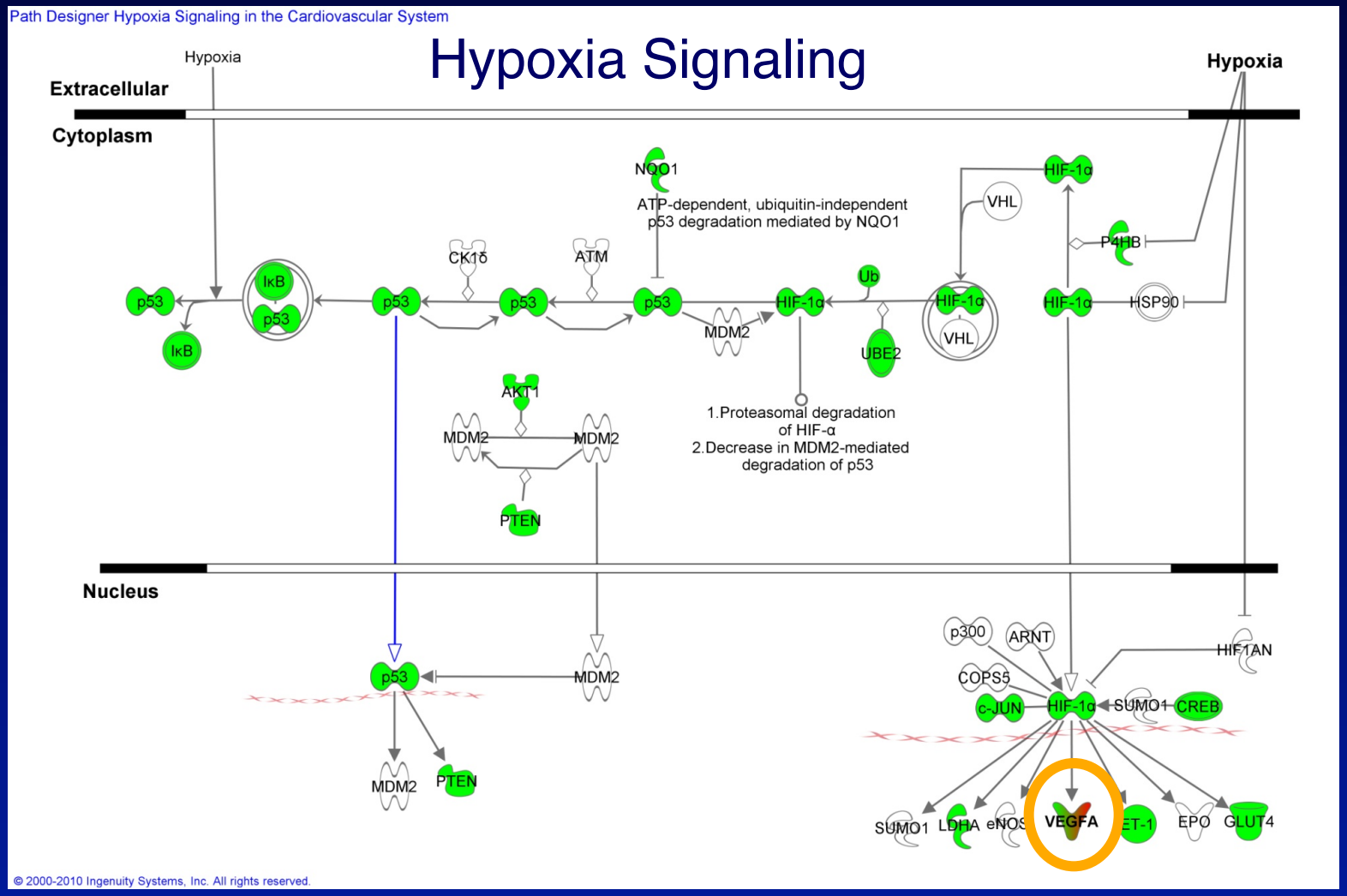
Systems Genetics of CKD



1. Filter candidate genes for GFR correlated mRNA expression

2. Detection of co-regulated transcripts for every candidate gene

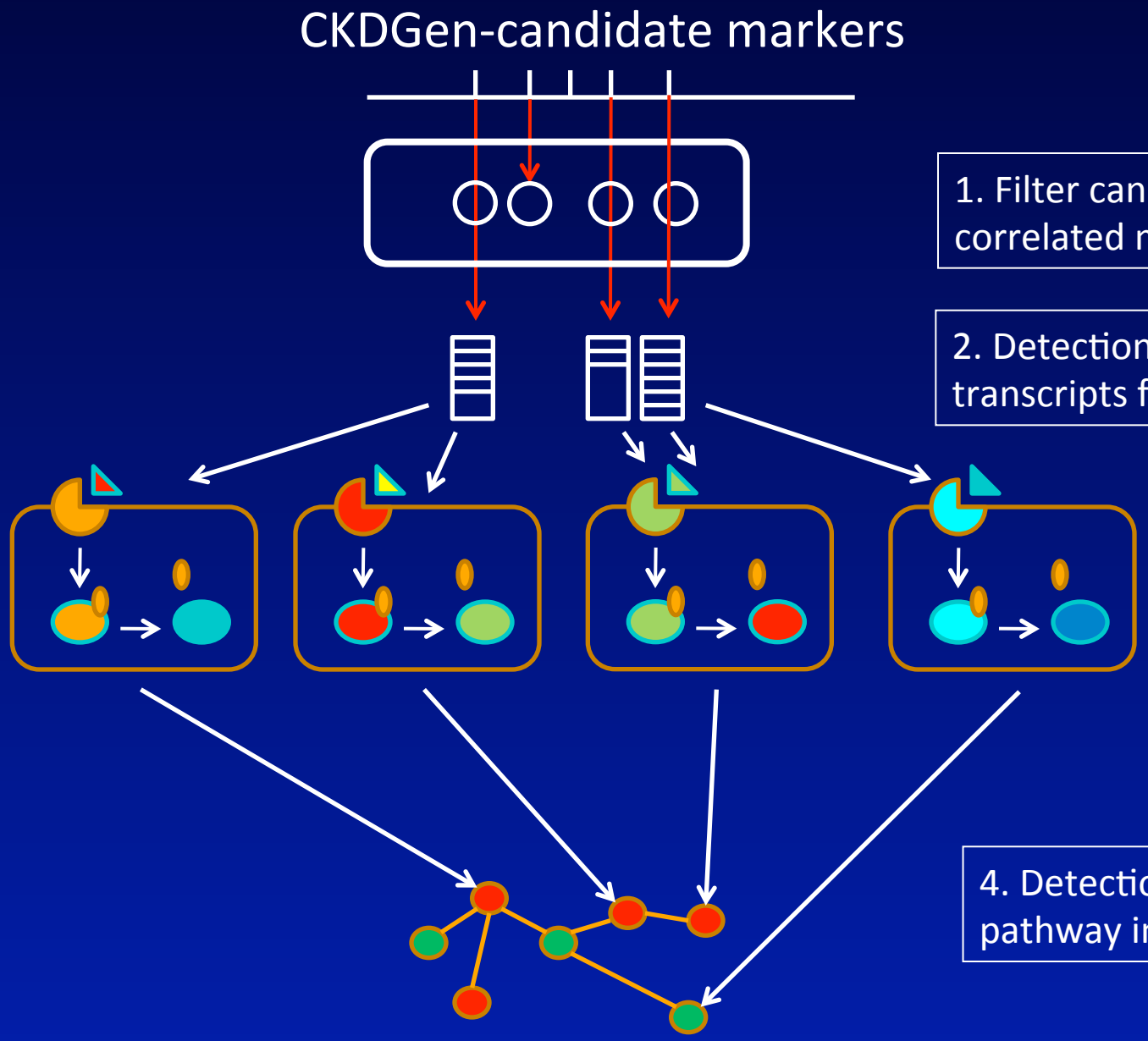
3. Detection of enriched pathways among co-regulated transcripts



see also: Neusser, Am J Path 2010
Higgins J Clin Invest 2007
Ding, Nature Med 2006

- GFR co-regulated mRNAs
- CKDGen associated transcript

Systems Genetics of CKD



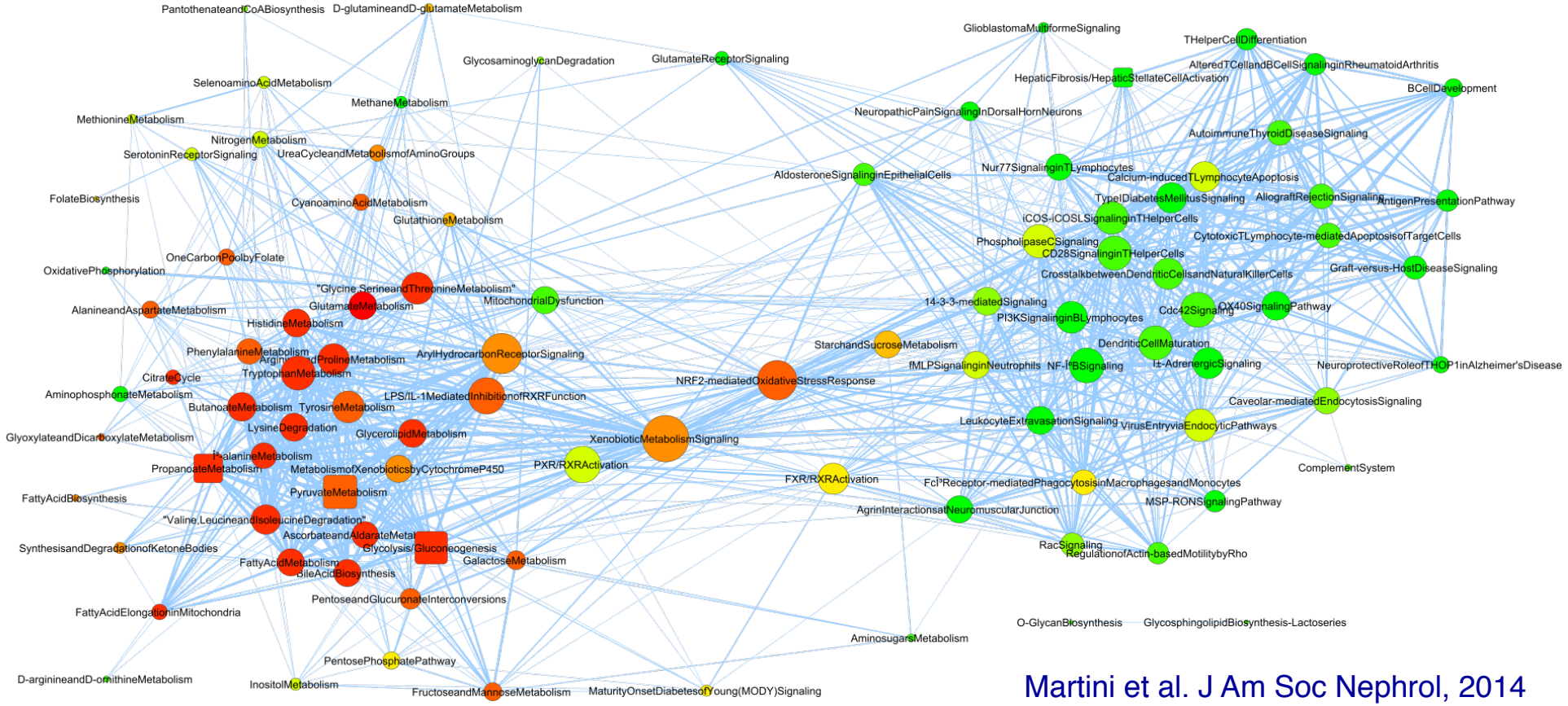
1. Filter candidate genes for GFR correlated mRNA expression

2. Detection of co-regulated transcripts for every candidate gene

3. Detection of enriched pathways among co-regulated transcripts

4. Detection CKD-associated pathway interdependencies

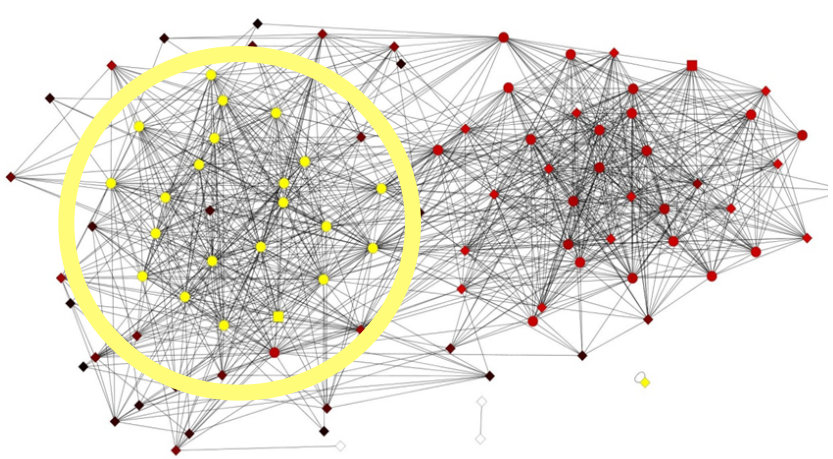
Systems genetics of CKD

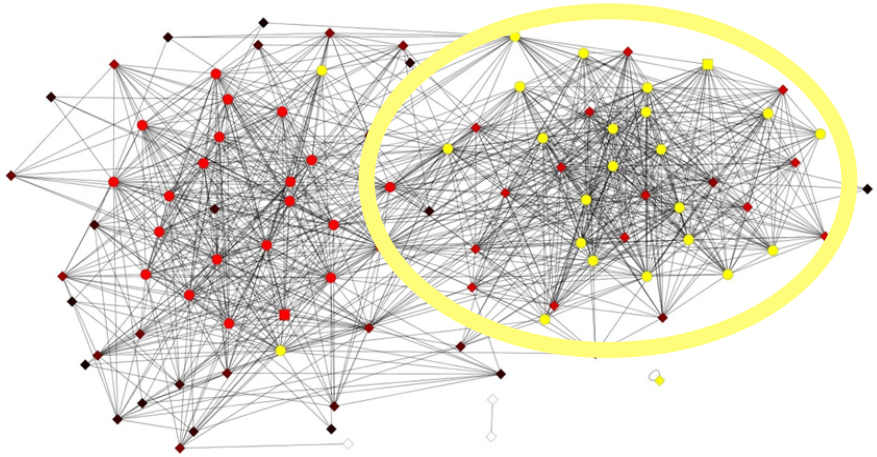


Martini et al. J Am Soc Nephrol, 2014

Pathway network associated with shared CKDgen co-regulated transcripts.
Spring embedded algorithm. Node size reflects degree of connectivity, edge thickness increasing with more genes shared among two pathways.
Node color reflects number of transcript associated with pathway: (multiple=red, few=green)

Definition of highly interconnected nodes (clusters)





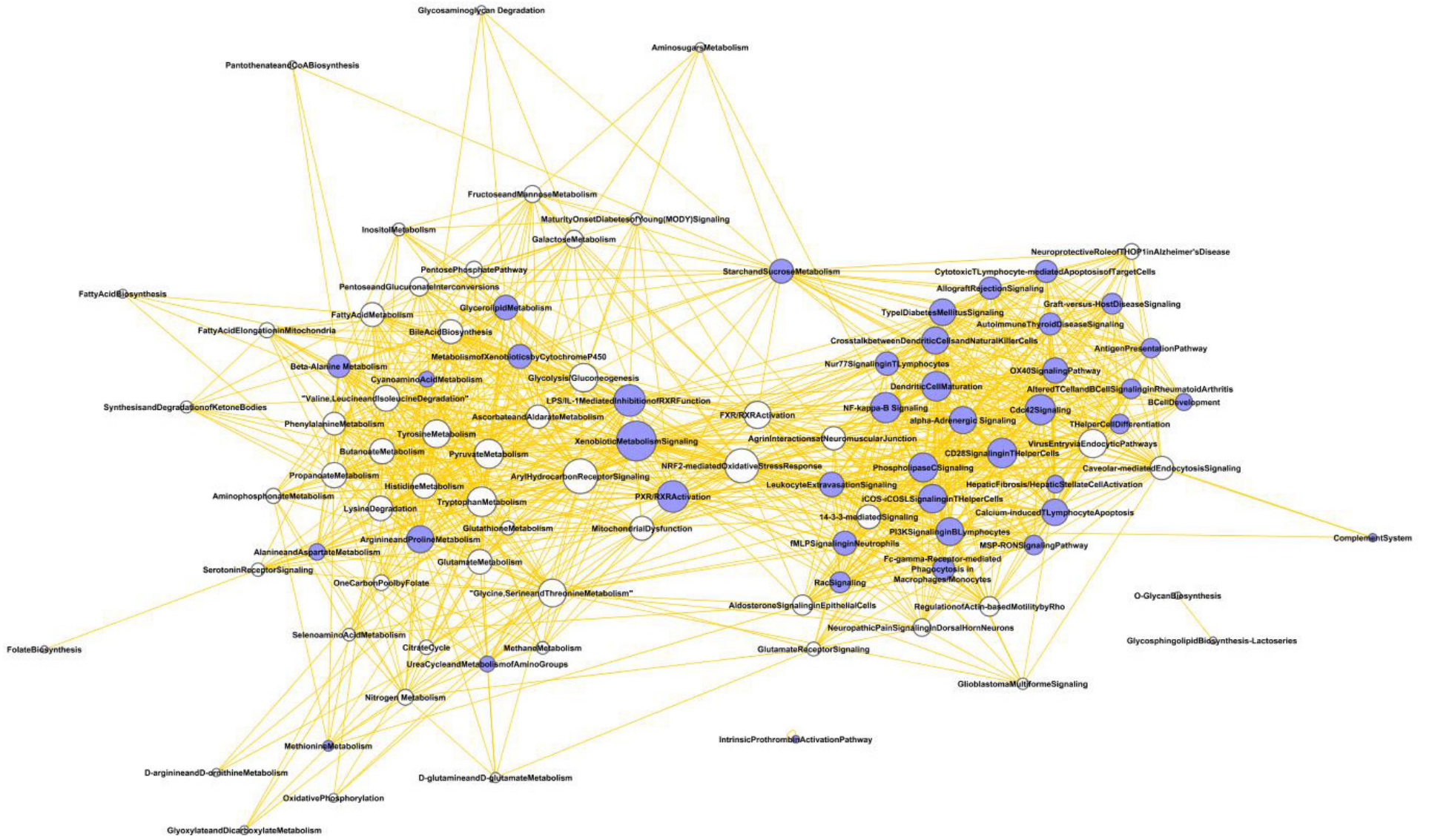
Metabolism

Xenobiotic Metabolism Signaling
Aryl Hydrocarbon Receptor Signaling
PPARgamma signaling
PXR/RXR Activation
LPS/IL-1Mediated Inhibition of RXRFunction
Tryptophan Metabolism…

Inflammation – Stress response

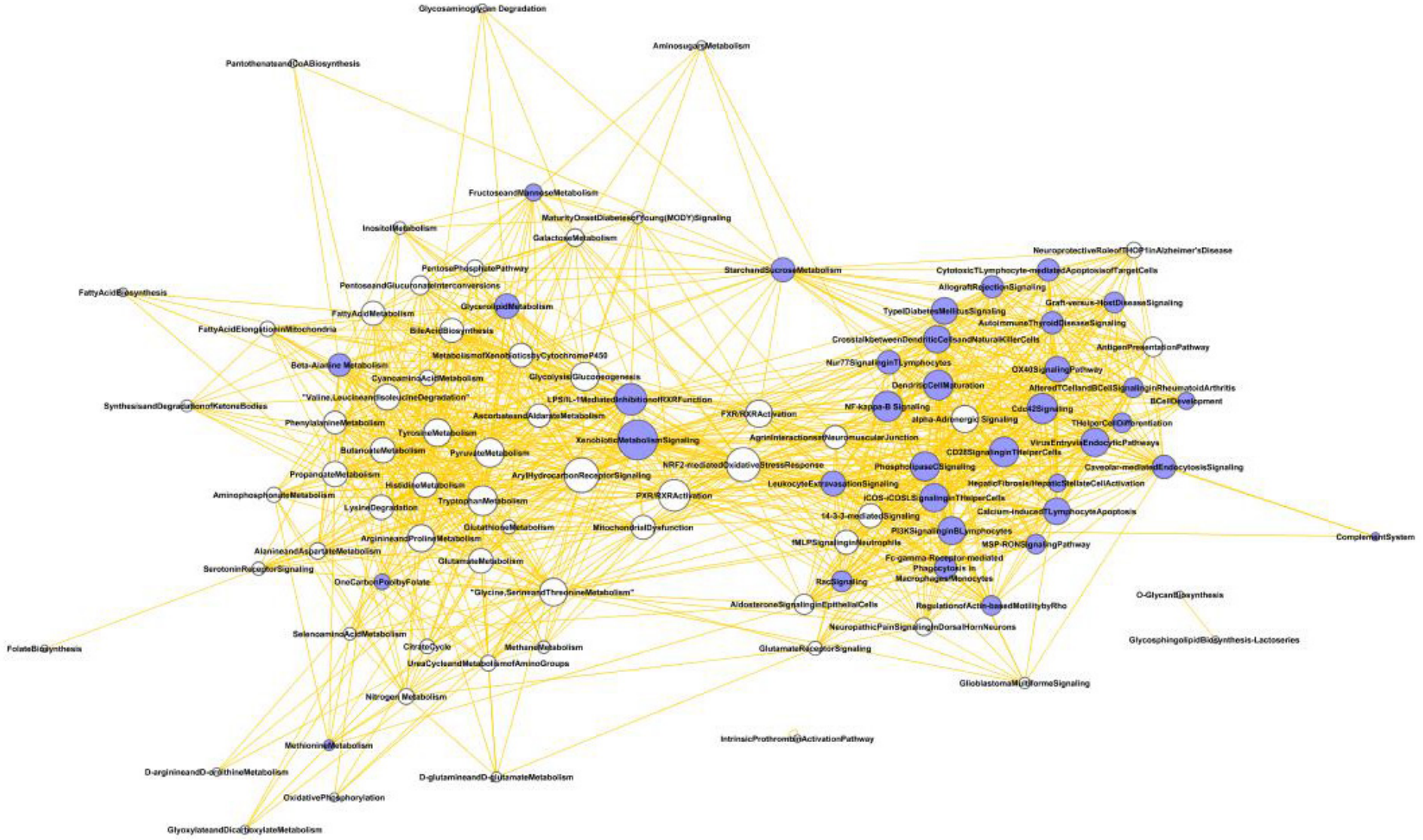
NRF2-mediated Oxidative Stress Response
Cdc42 Signaling
NF-kappaB Signaling
Dendritic Cell Maturation
CD28 Signaling in T helper Cells…

Lupus Nephritis pathways

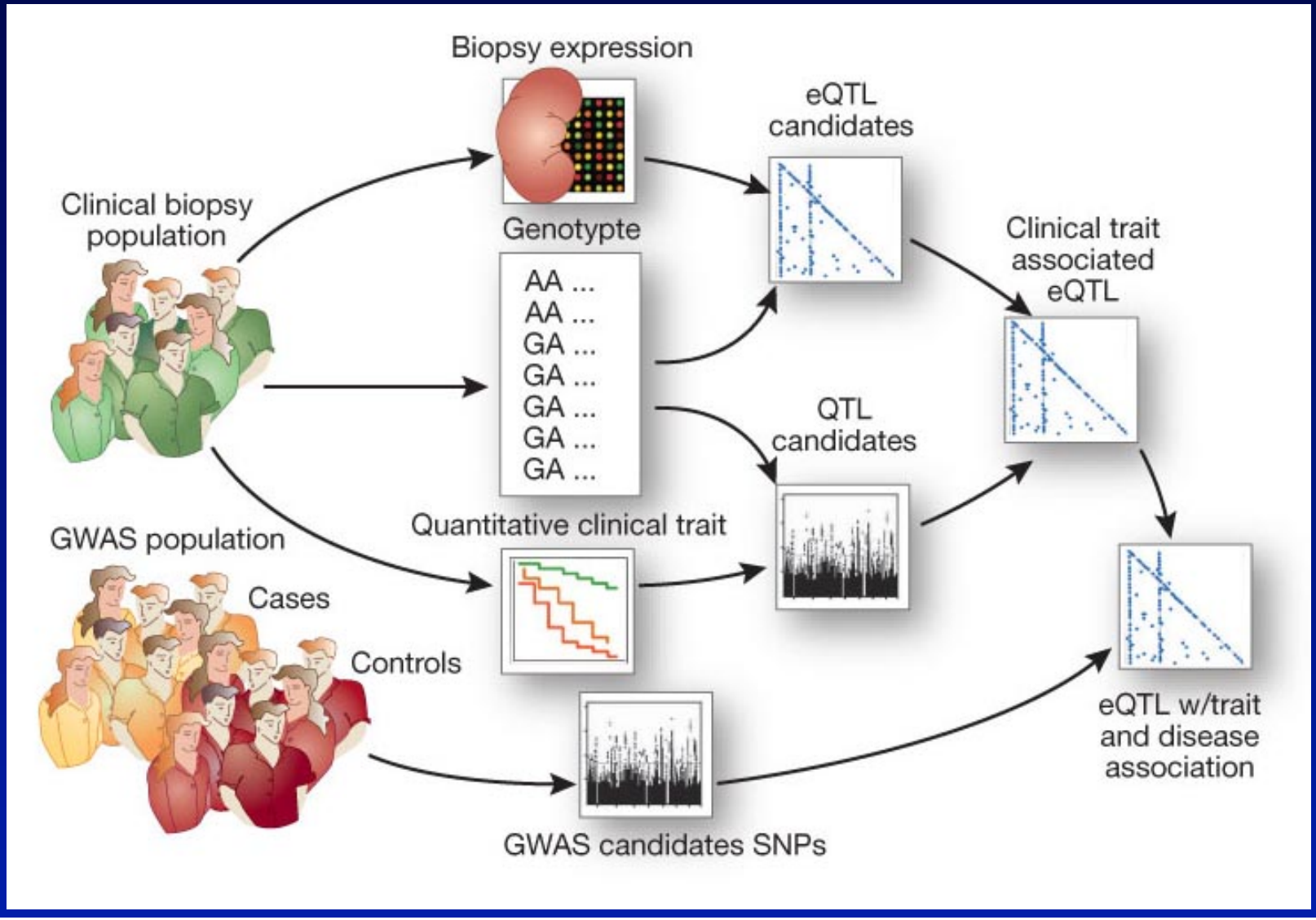


Differentially regulated genes were enriched in pathways indicated by the blue color.

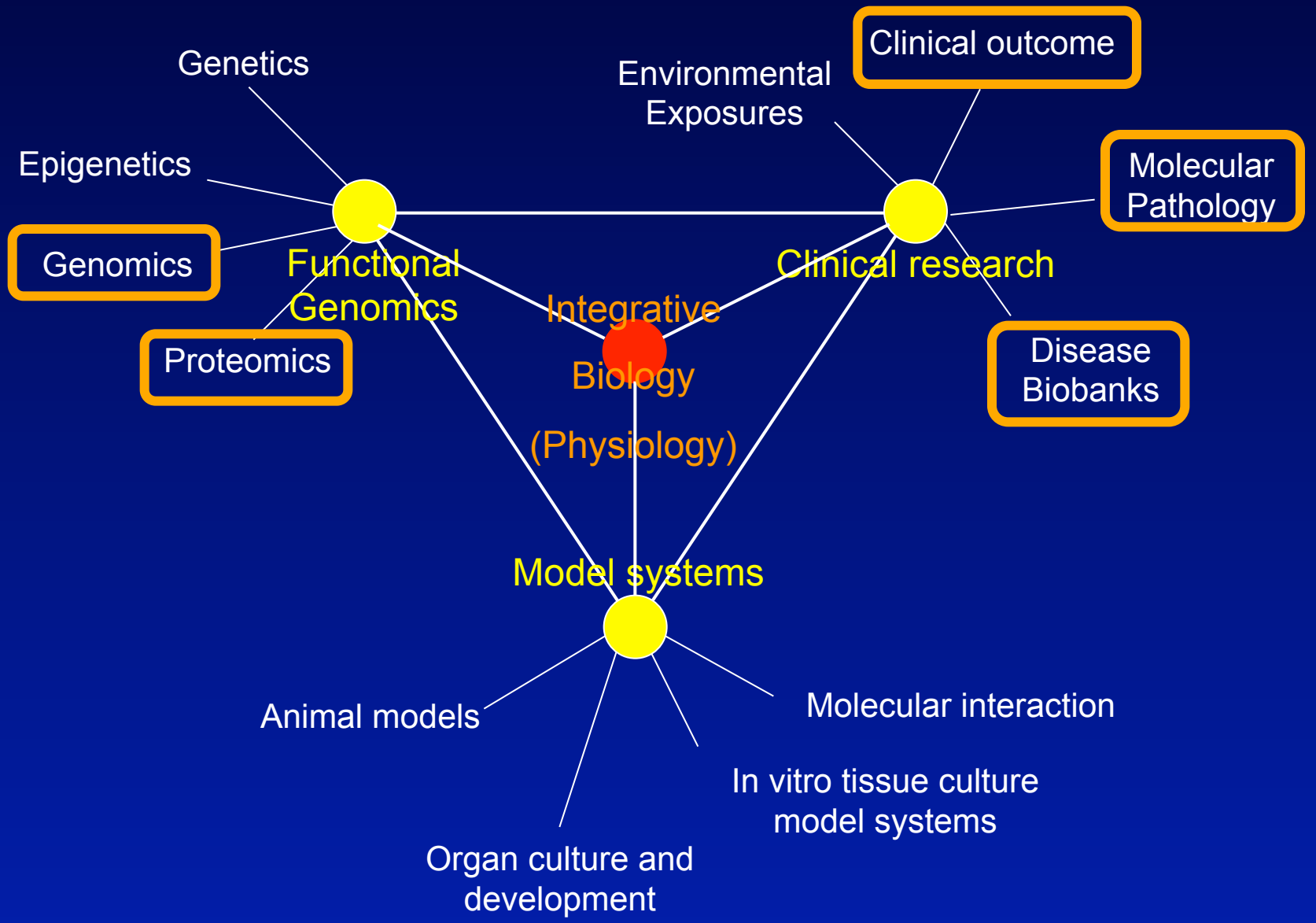
Diabetic Nephropathy pathways



eQTL – GWAS integration:
Tissue compartment specific eQTLs

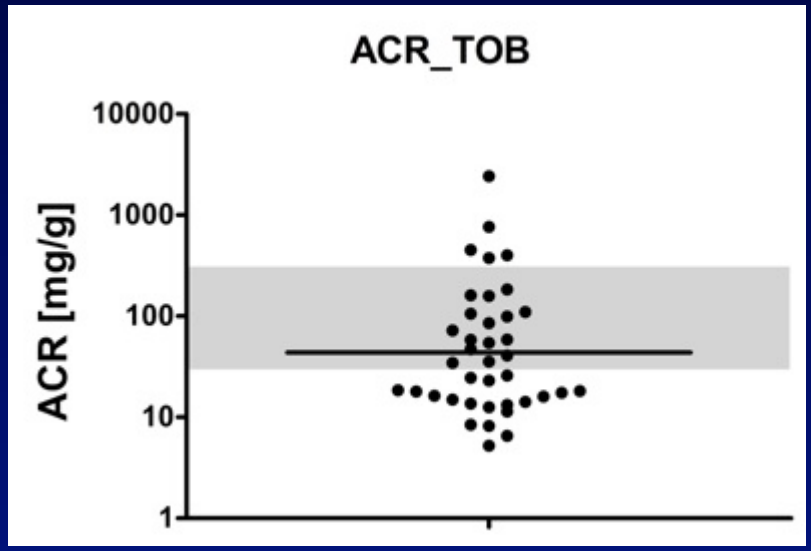


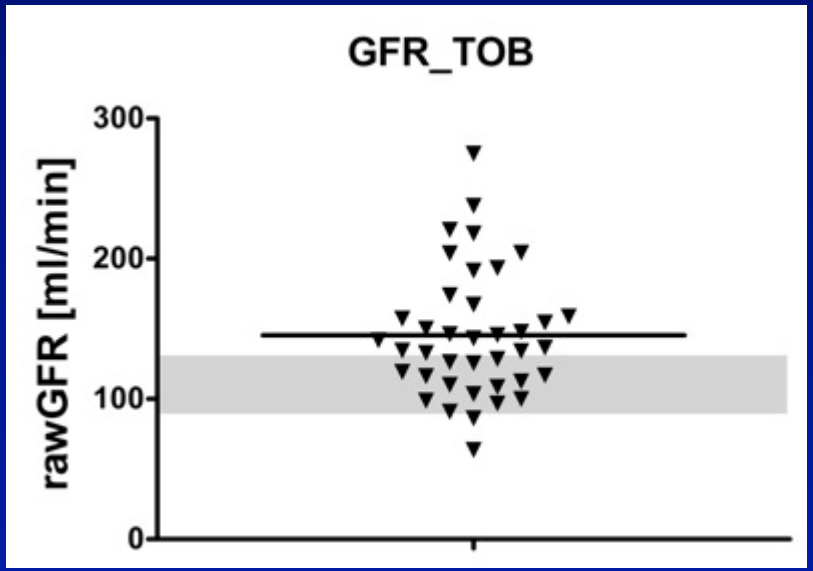
Study 2: Identify molecular mechanism and non-invasive correlates of fibrosis in CKD



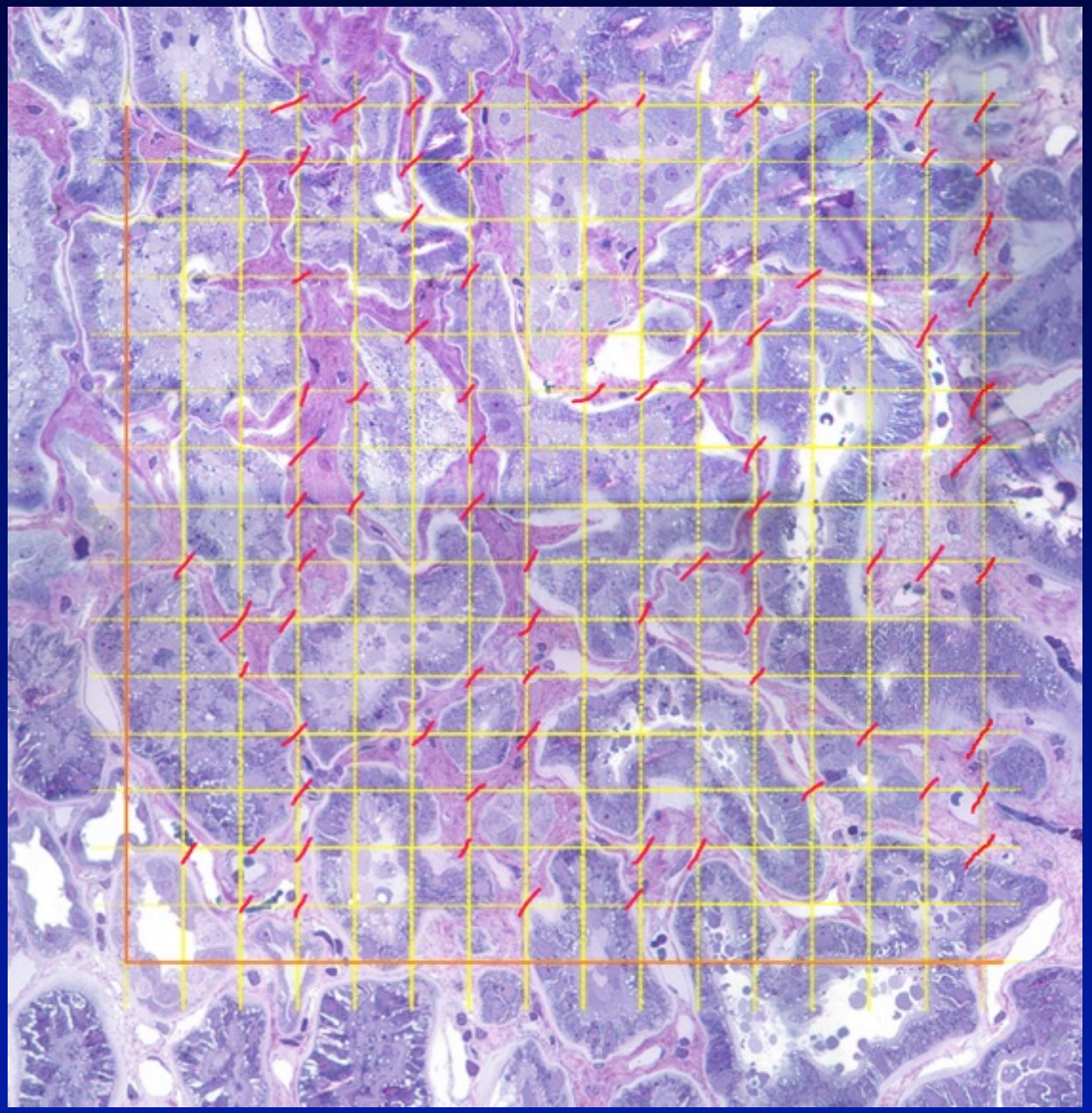
Pima protocol Biopsy Cohort:
Clinical Characteristics

Clinical Characteristics at Biopsy	
F/M (no.)	29/11
Age (yrs.)	45.8 (±9.4)
ACR(mg/g)	154.1(±403.9)
iGFR (ml/min)	144.2 (±45.4)
BMI (kg/m^2)	35.3(±8.3)
HbA1c (%)	8.9(±2.1)





Structure: Fractional Interstitial Area (FIA)



- Toluidine blue stained biopsies
- 15 x 15 μm yellow grid, 225 intersections on 40x image
- Grid intersections on interstitial tissue marked in red.
- Interstitial area= outside of tubular and vascular structures
- Repeated for a total of 10 grids for average fractional interstitial area

- **FIA:**

29.5% (±9.6) in Pima biopsies

vs

11.9% (±2.8) in living kidney donor biopsies

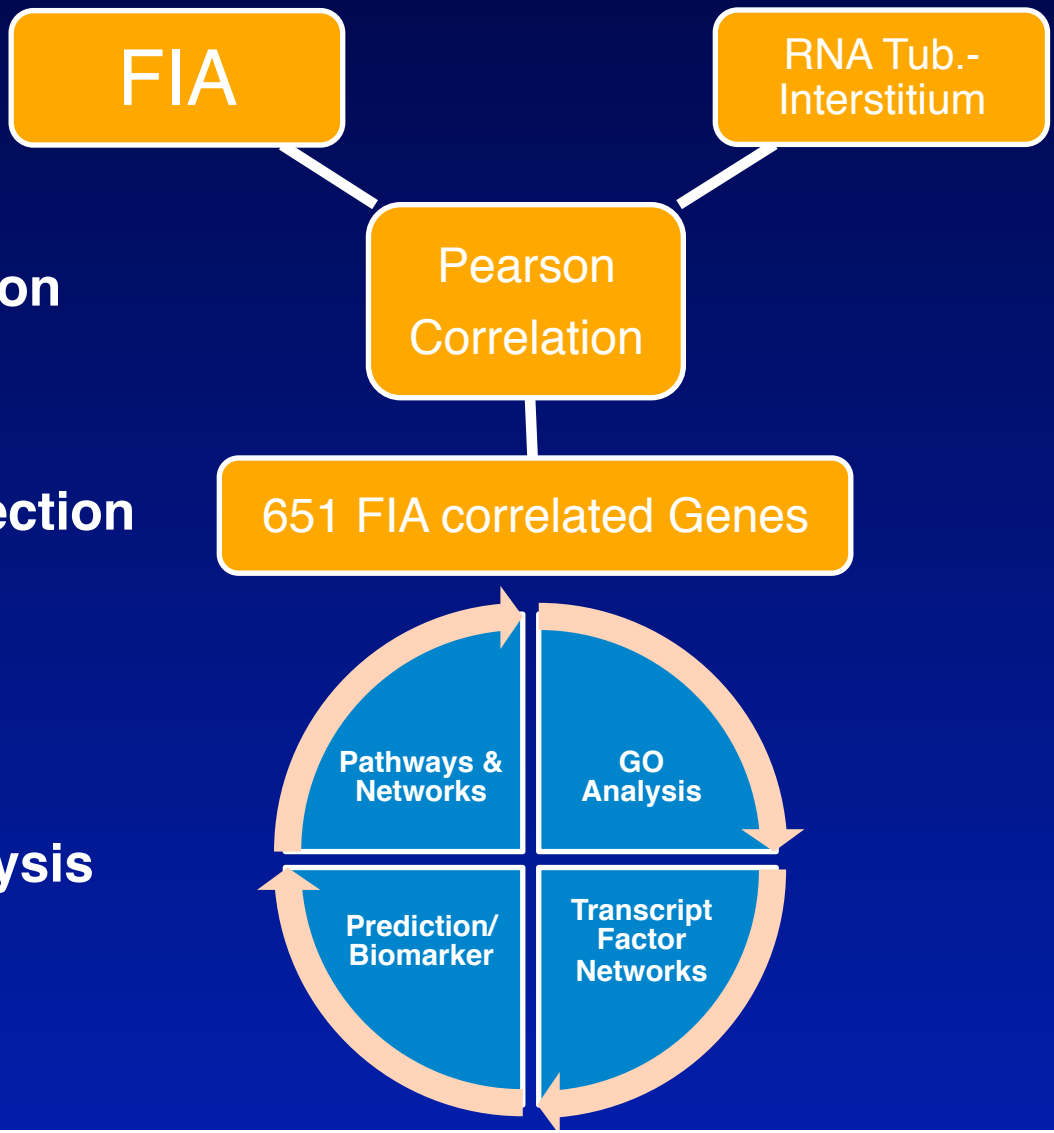
Linking gene expression and morphometry in early DN

1. Analysis Input

2. Variable association

3. Gene ranking/selection

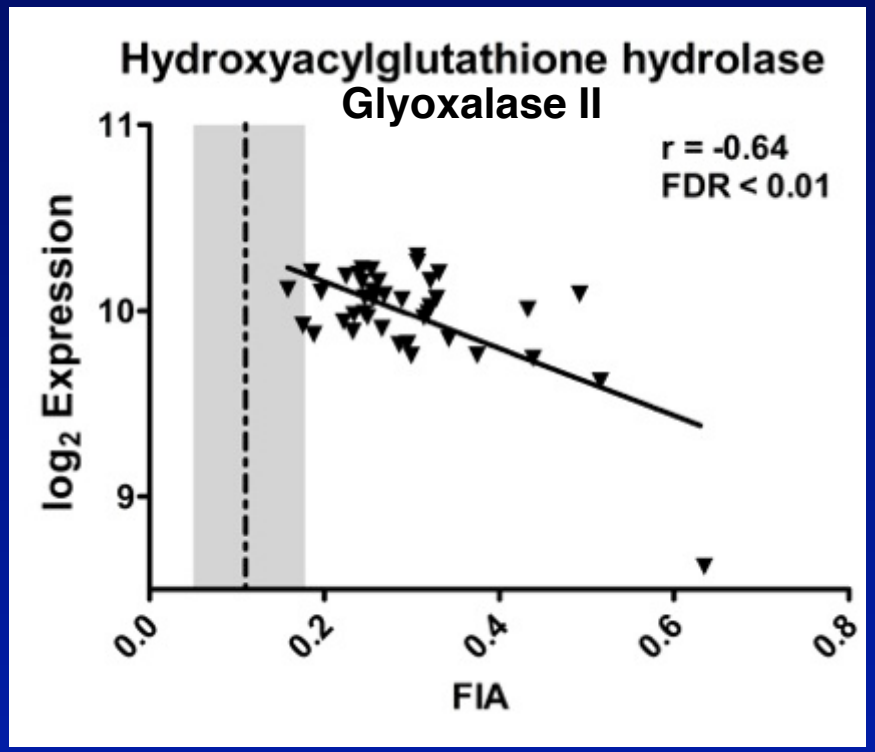
4. Downstream analysis

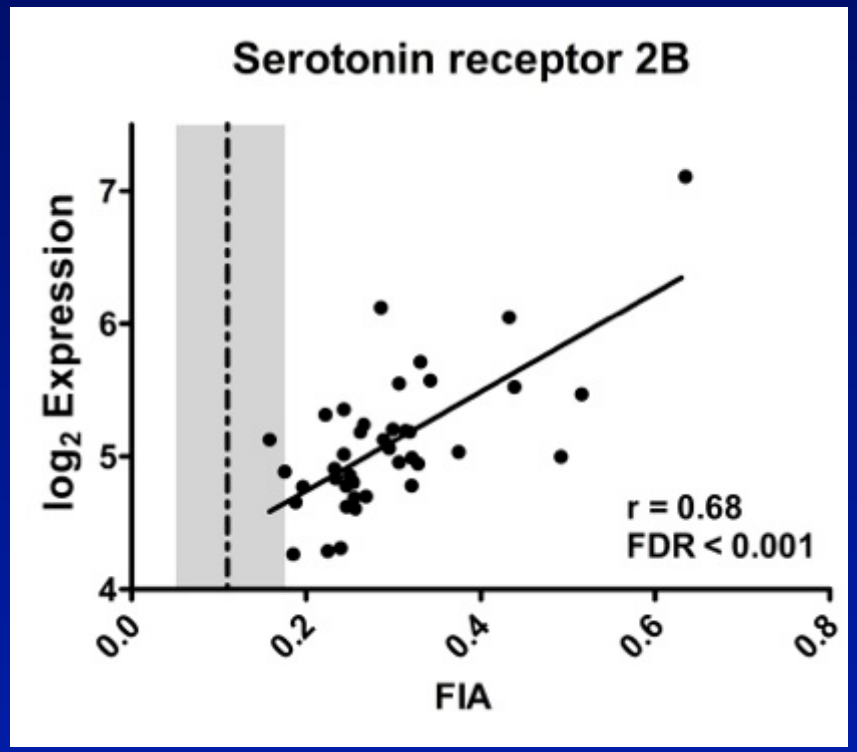


Transcript correlating with Fractional Interstitial Area

Tubulo-interstitial transcript correlated with FIA:

651 genes: FDR ≤ 0.05, | r | >0.36





Molecular Concepts associated with FIA in early DKD

Topological Mapping of enriched Gene Ontology Terms

	Biological Processes	Cellular Compartment
POS.COR.	Immune system process	Extracellular region
	Immune response	Extracellular matrix (ECM)
	Response to stimulus	Proteinaceous ECM
	Defense response	Extracellular space
	Response to stress and wounding	Integral to plasma membrane
NEG.COR.	Organic acid metabolic process	Mitochondrion
	Cellular ketone metabolic process	Cytoplasmic part
	Oxoacid metabolic process	Cytoplasm
	Carboxylic acid metabolic process	Mitochondrial lumen & matrix
	Cellular amino acid metabolic pro.	Cell fraction
	Amine metabolic process	Mitochondrial membrane

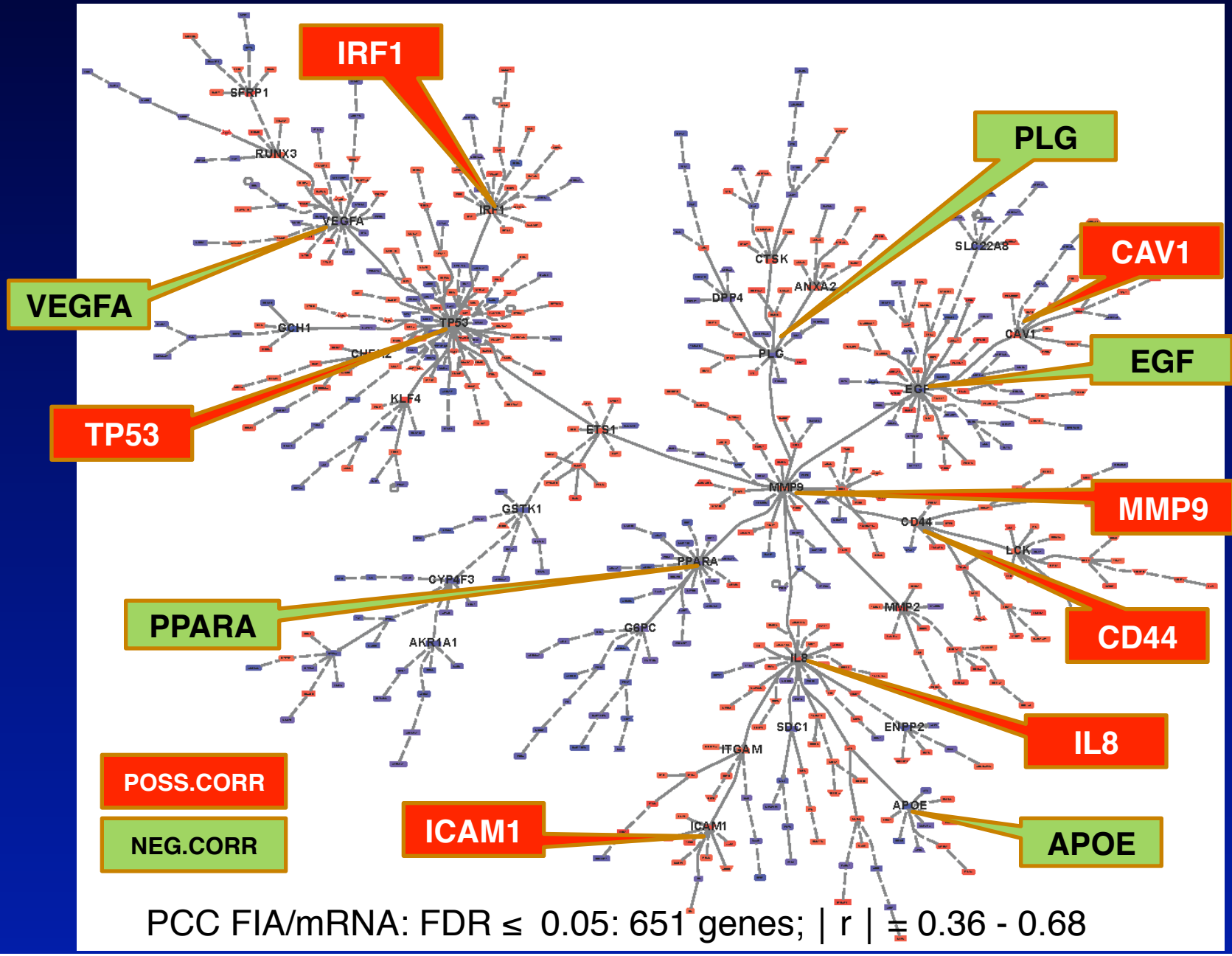
Integration into functional context: Morphogenomics networks

- Correlation of intrarenal structural lesions with gene expression in early DKD:
  - 651 genes: (FDR ≤ 0.05 | r | = 0.36 - 0.68)
  - Display of three levels of evidence
    - Correlated mRNAs
    - Prior knowledge
      - Natural language processing:
        - » Co-citation of genes in Pubmed abstract sentence
    - Unbiased sequence analysis:
      - Automated Promoter analysis defining Transcription Factor binding sites

Integration with multi-level evidence of gene function to identify underlying regulatory mechanism

- Gene (=Node) centred network displaying transcriptional dependencies as connections (=Edges)

Transcriptional network RNA ≈ FIA in early DKD



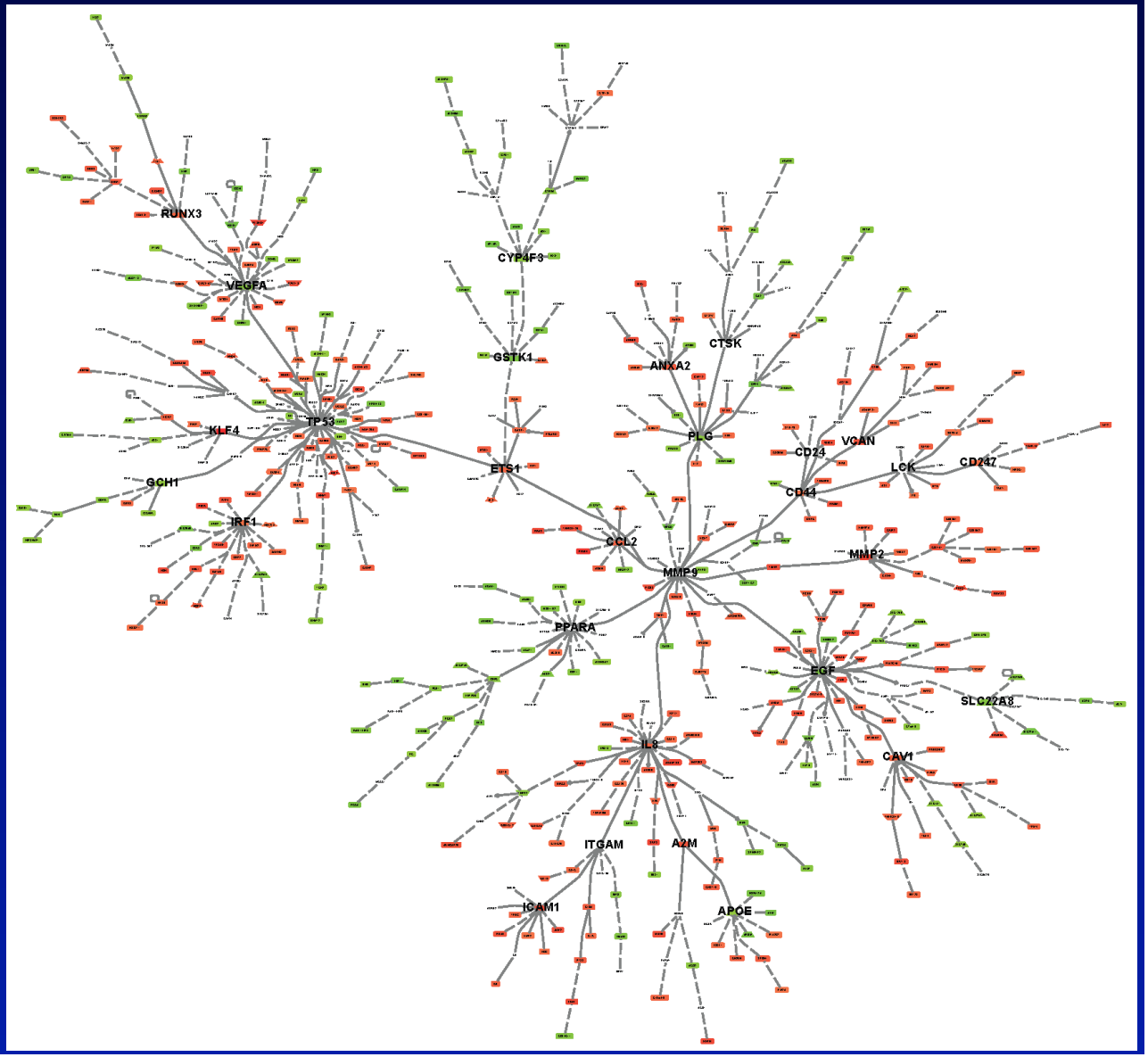
PCC FIA/mRNA: FDR ≤ 0.05: 651 genes; | r | = 0.36 - 0.68

FIA associated mRNA correlate with ACR 8 years after biopsy

FIA-mRNAs:
5 of 651 ACR correlation
at time 0 (biopsy)

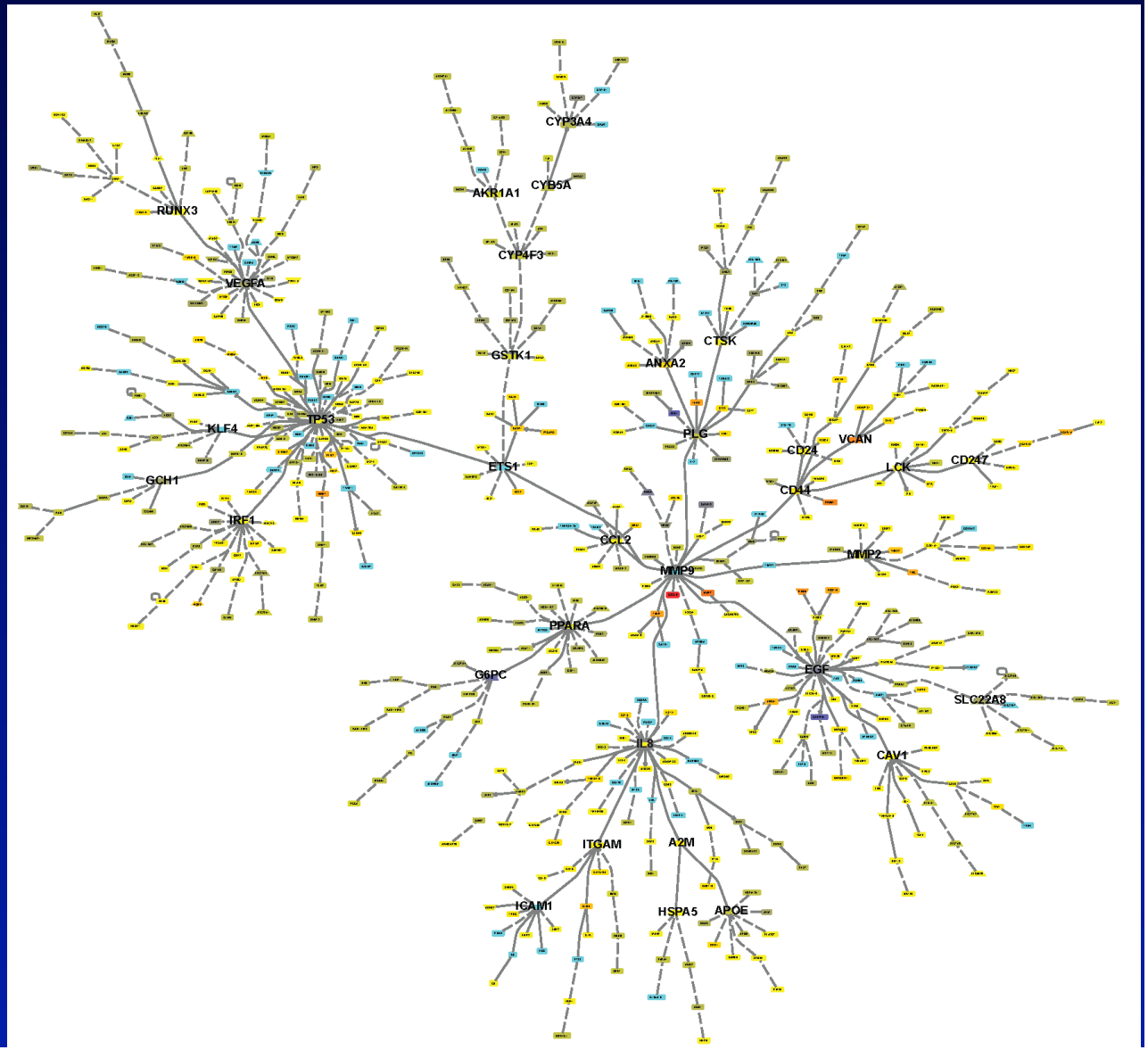
442 of 651 ACR correlation 8.25 years after biopsy.

All major network gene nodes retained

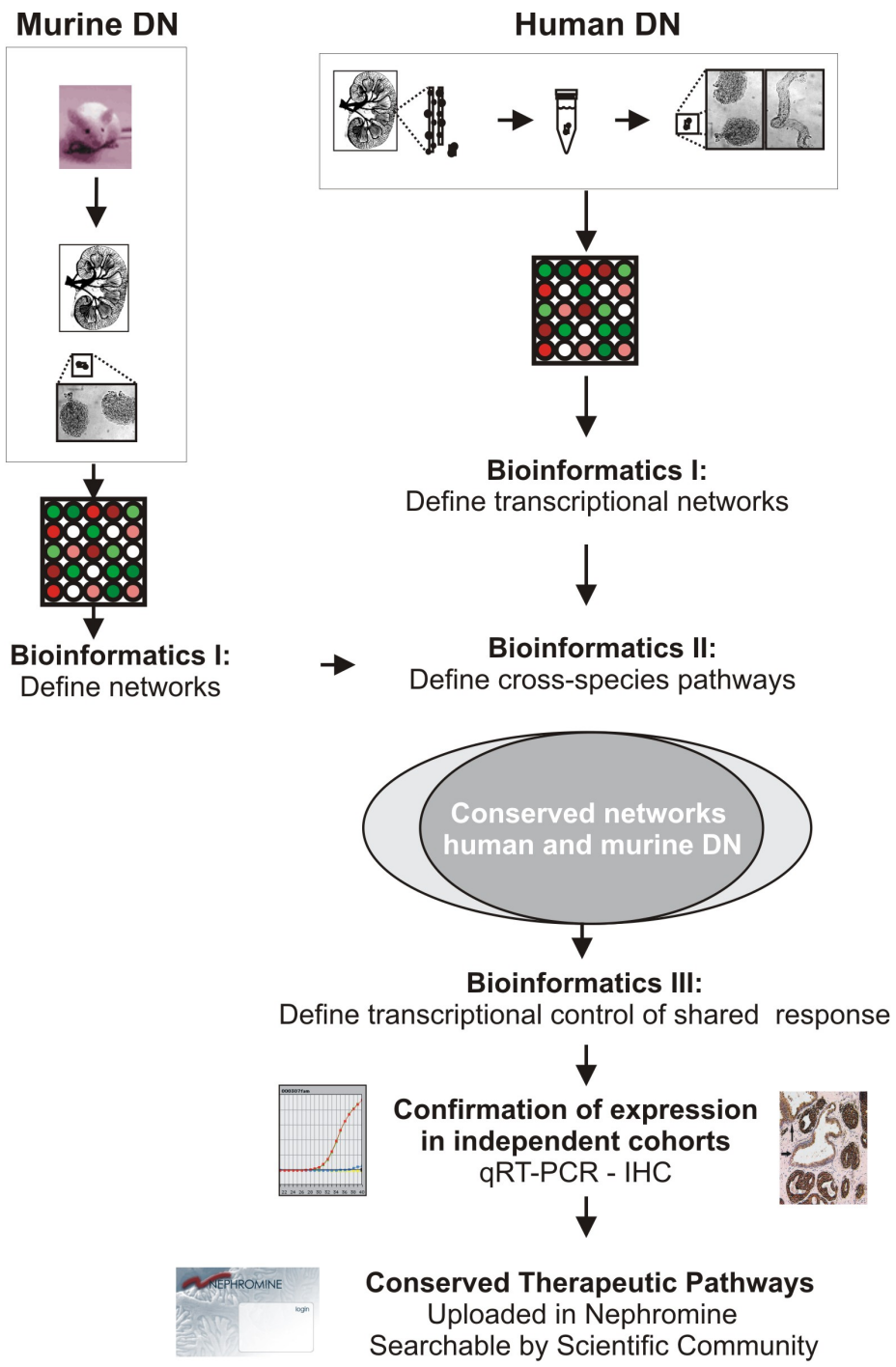


FIA transcript in progressive DKD

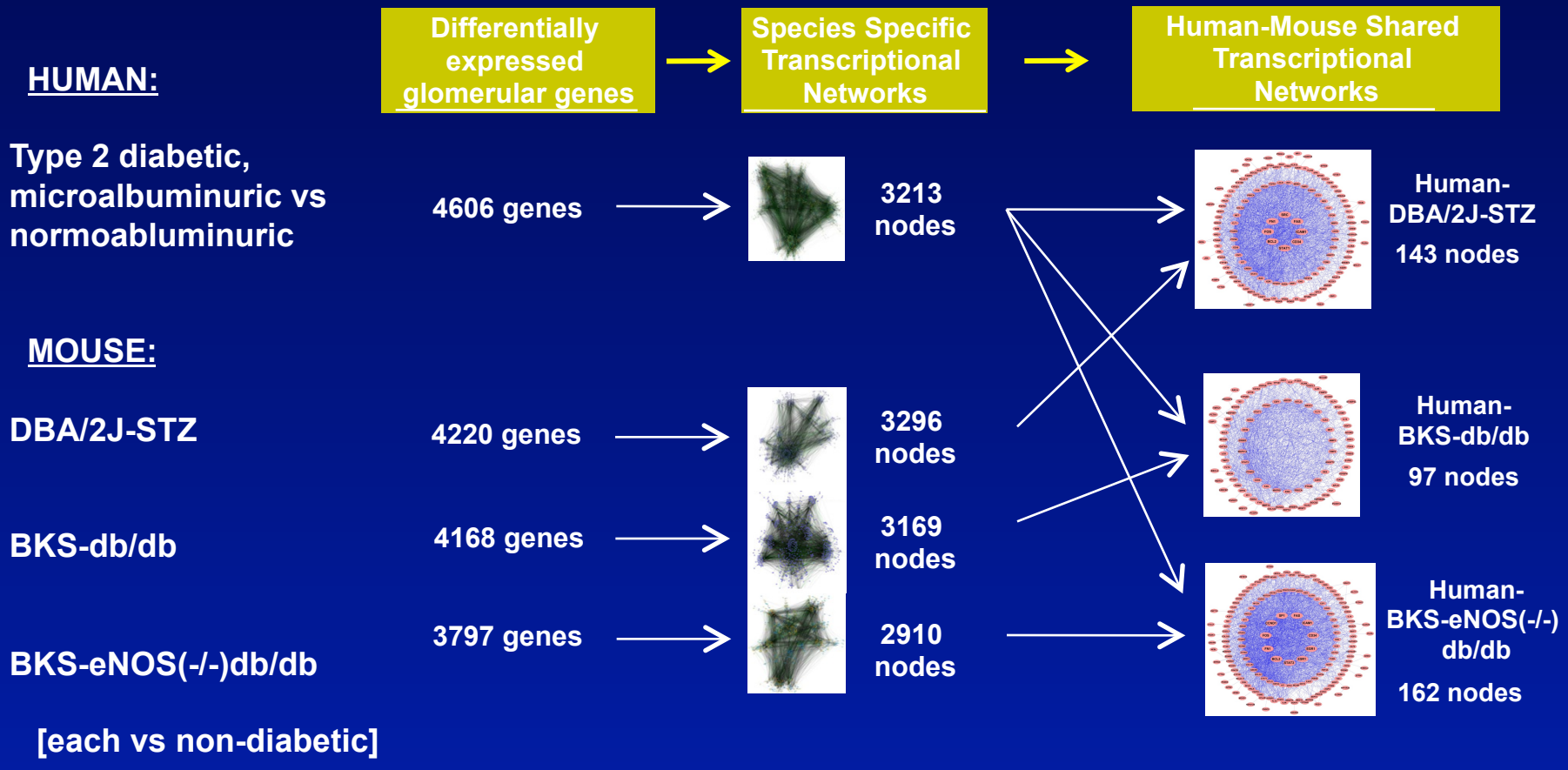
555 / 651 (85.3%) FIA-mRNAs regulated (q<0.05) in progressive DKD (European indication biopsies, N=17) vs living kidney donor biopsy (N=31)



Integration of human and murine transcriptomes in CKD



Cross-species regulatory networks in Diabetic Glomerulopathy

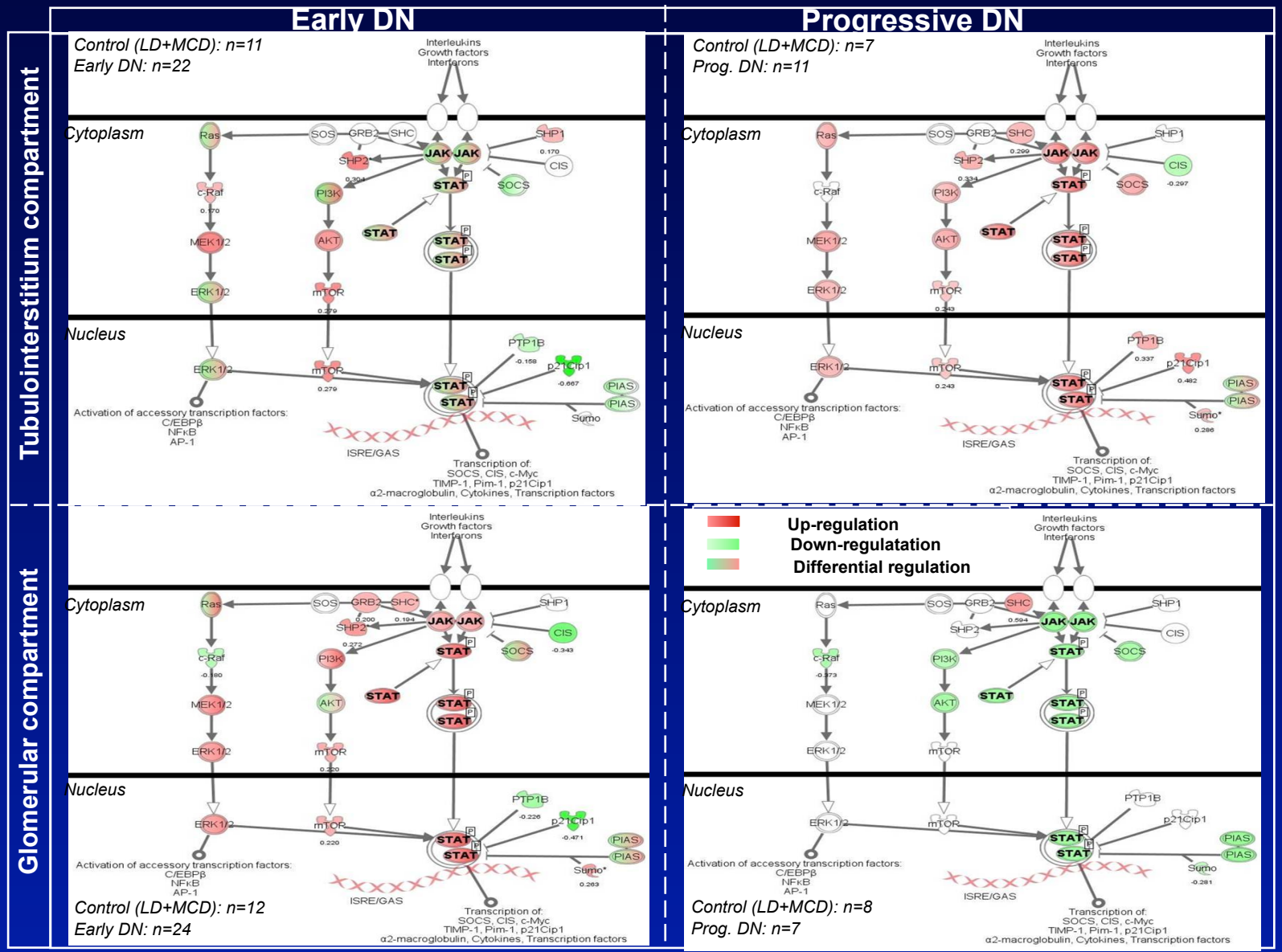


Hodgin et al, Diabetes, 2013

Human-mouse transcriptional networks: Shared pathways

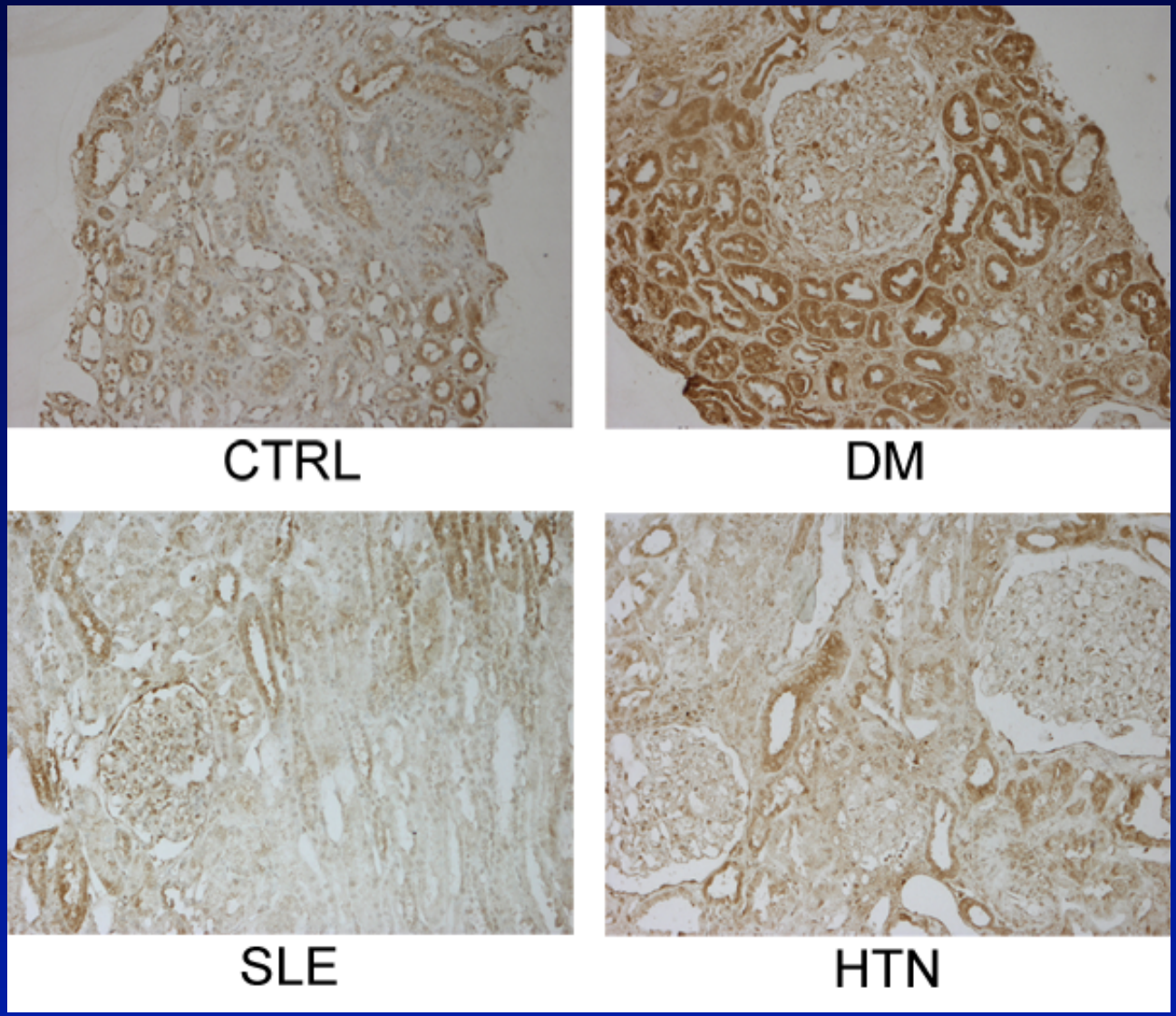
Canonical pathway	# genes observed in pathway		
	Human-DBA	Human-db/db	Human-eNOS-KO|db/db
Cytokine receptor degradation signaling (JAK-STAT pathway and regulation)	27	17	21
Migration (VEGF signaling)	15	9	11
VEGFR1 and VEGFR2-mediated signaling	11	8	8
HIF-1-alpha transcription factor network	8	4	7
Angiopoietin receptor Tie2-mediated signaling	6	5	---
HGF receptor (c-met) signaling	6	4	---
Regulation of nuclear SMAD2/3 signaling	---	5	9
Regulation of Androgen receptor activity	---	6	5
IL6-mediated signaling events	8	---	8
IL2 receptor beta chain in T cell activation	6	---	7
EGFR1	10	---	---
Signaling events mediated by PTP1B	7	---	---
Alpha6Beta4Integrin	---	5	---
Endothelin pathway	---	5	---
C-MYB transcription factor network	---	---	9
CDC42 signaling events	---	---	7

Hitting targets in DN: Jak-Stat Pathway as key driver



Berthier et al., Diabetes. 2009

Jak2 in Human Progressive DN and non-diabetic Kidney Diseases



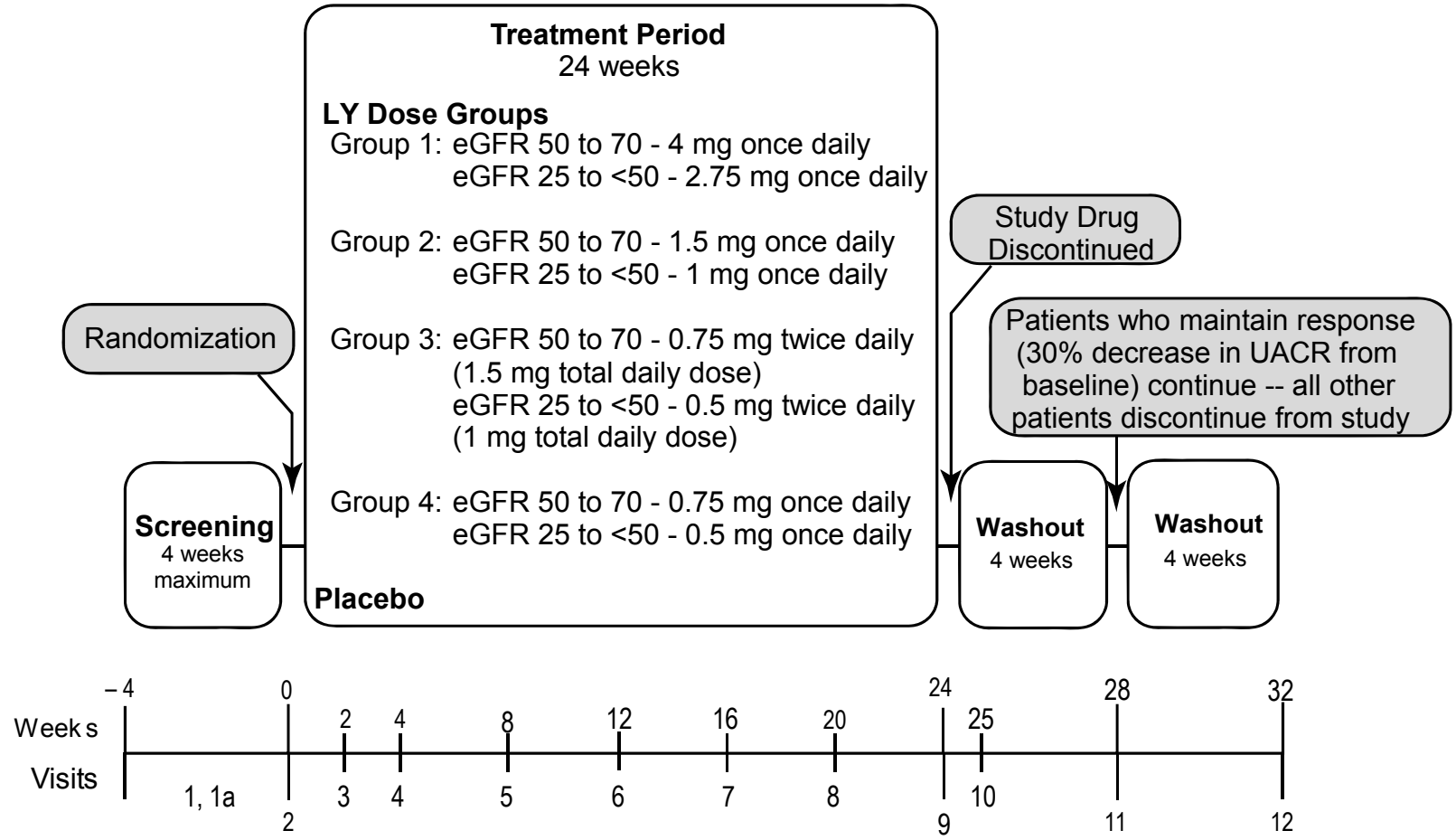
Berthier et al., Diabetes. 2009

Phase II trial of Jak 2 inhibition in diabetic nephropathy

Baricitinib, oral JAK2 inhibitor,
currently in Phase II for RA and Psoriasis
=> Repurposed in Diabetic Nephropathy

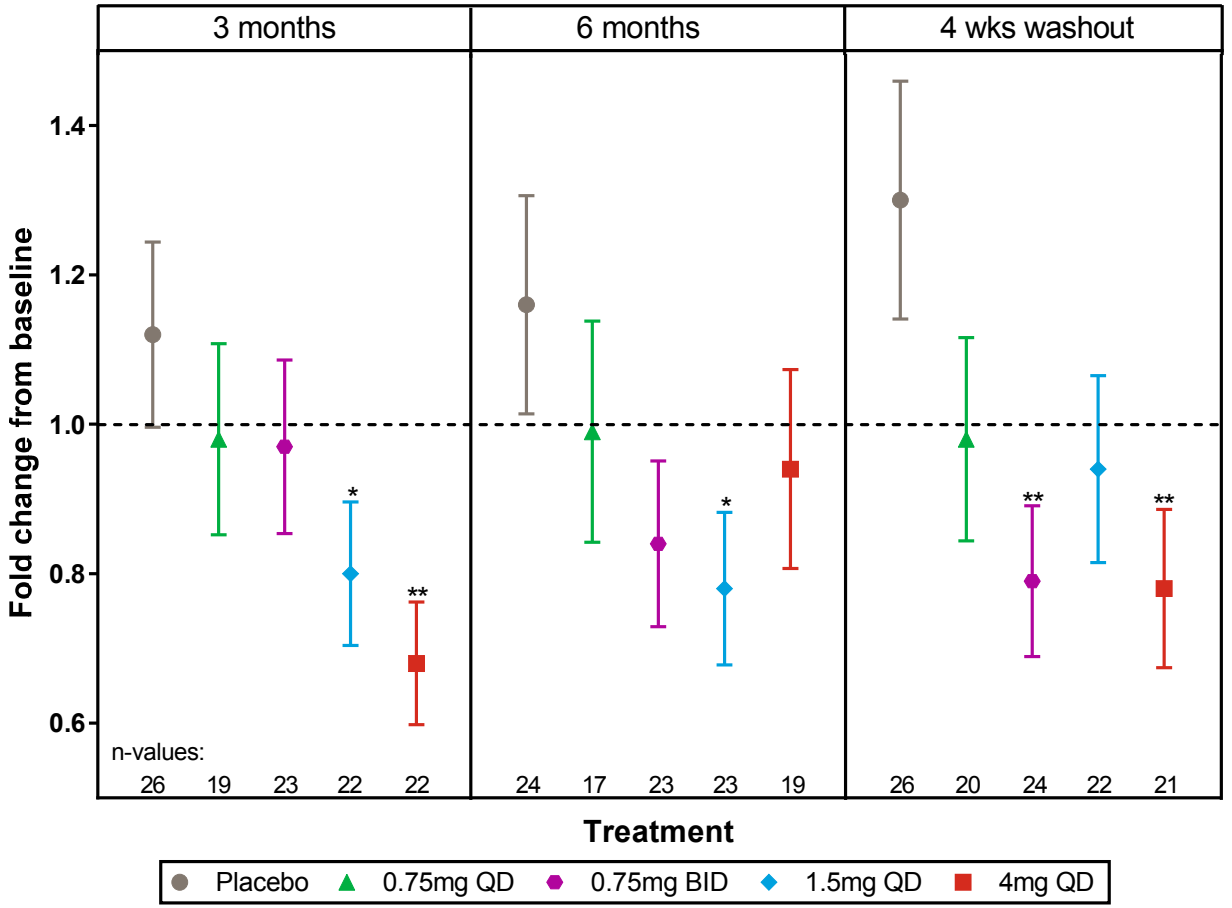
- RCT by Eli Lilly in DN
  - Primary outcome:
    - Change in urine ACR from baseline to 24 weeks
  - Study completed in Nov 2014
    - Late braking trial report at ADA in June 2015

From target identification to phase II completion in 42 months



Abbreviations: eGFR = estimated glomerular filtration rate; UACR = urinary albumin/creatinine ratio.

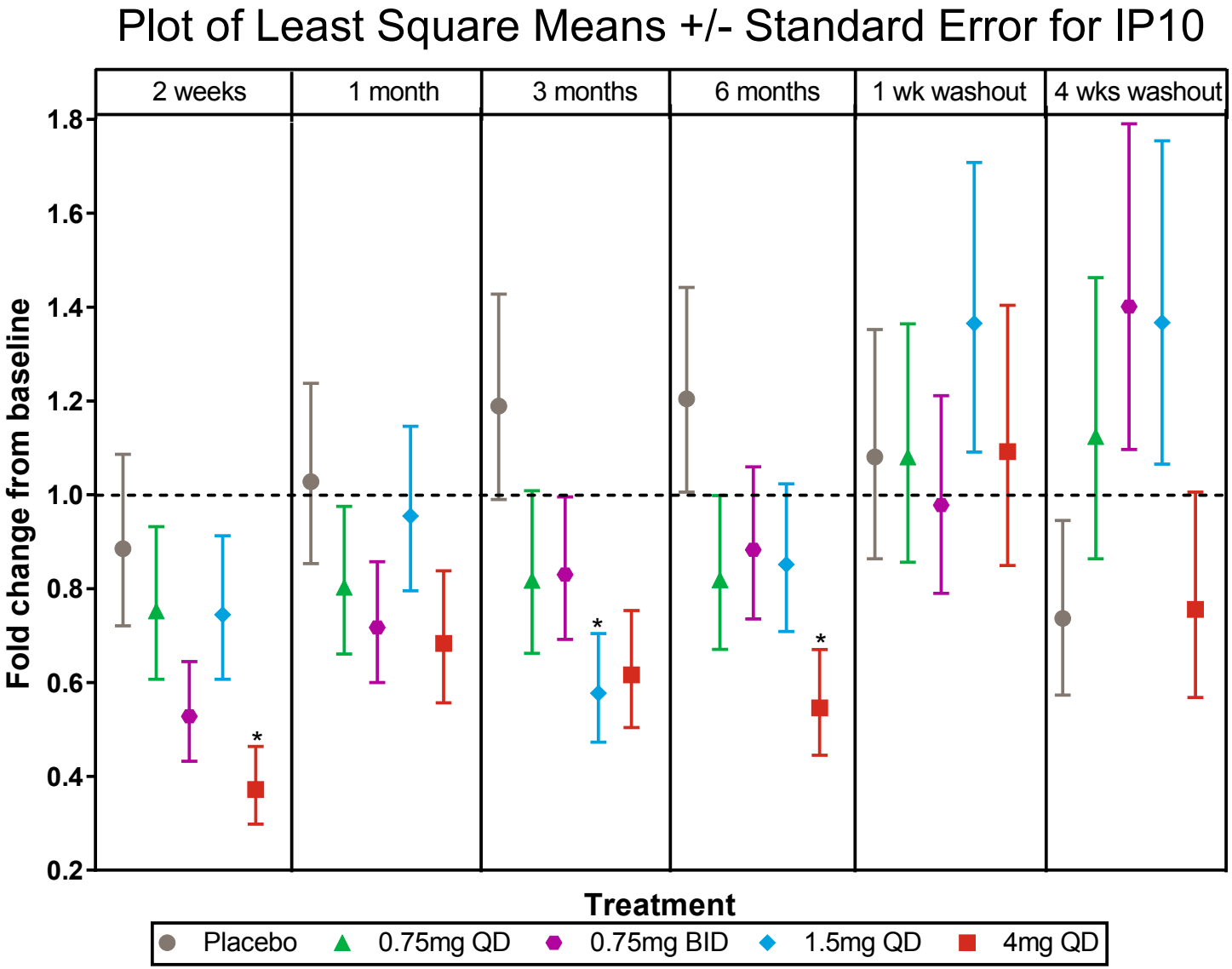
Plot of Least Square Means +/- Standard Error for 24-hour UACR



Mixed model repeated measures analysis of log-transformed data with results back transformed.
*p-value<0.05; **p-value<0.01 based on treatment difference compared to placebo.

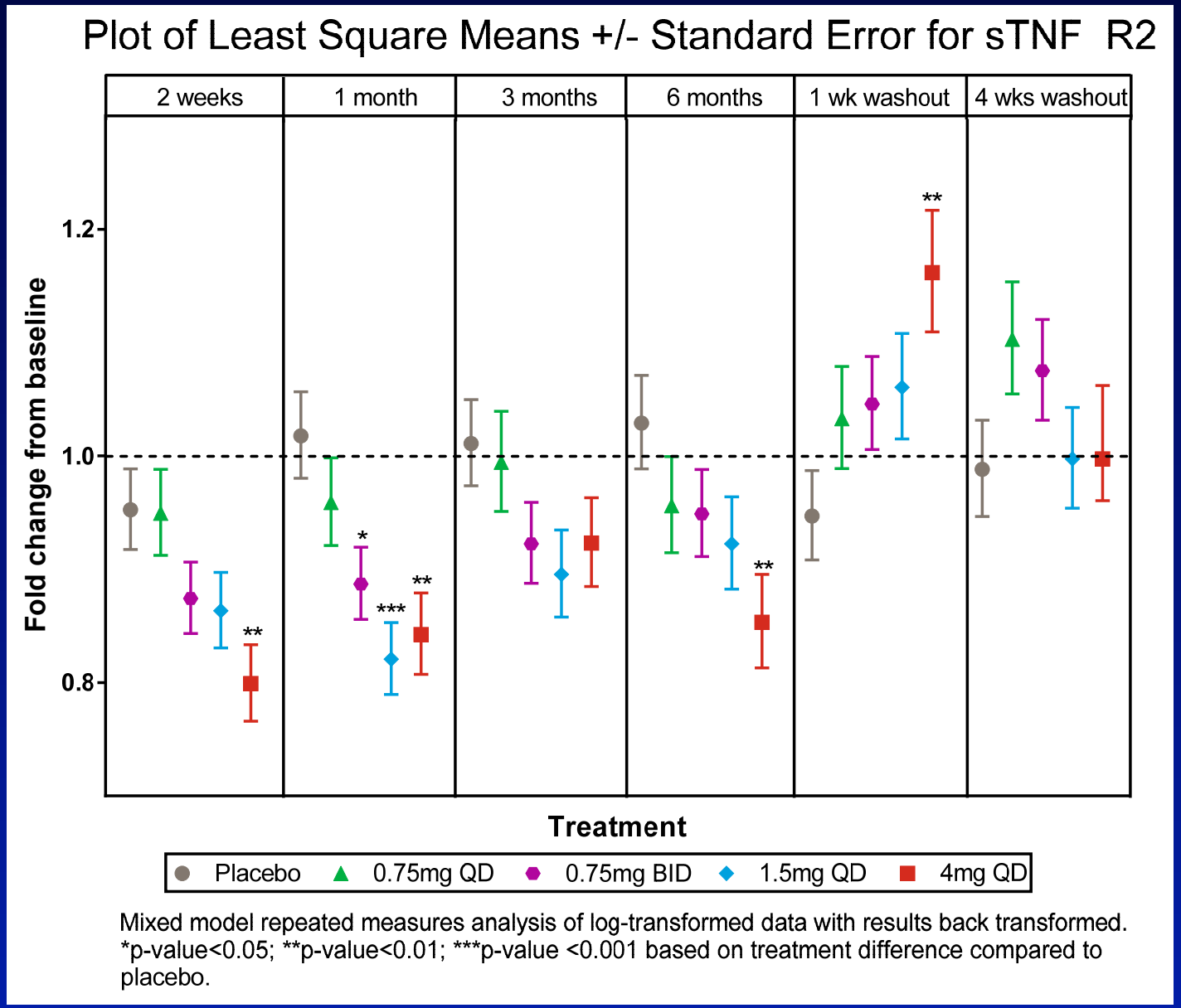
Reductions in 24-hour UACR were observed at 3 and 6 months (Figure 3).

Urine IP-10 (pg/mg Creatinine)



Mixed model repeated measures analysis of log-transformed data with results back transformed.
*p-value<0.05; **p-value<0.01 based on treatment difference compared to placebo.

Plasma sTNF R2 (pg/ml)



Mixed model repeated measures analysis of log-transformed data with results back transformed. *p-value<0.05; **p-value<0.01; ***p-value <0.001 based on treatment difference compared to placebo.

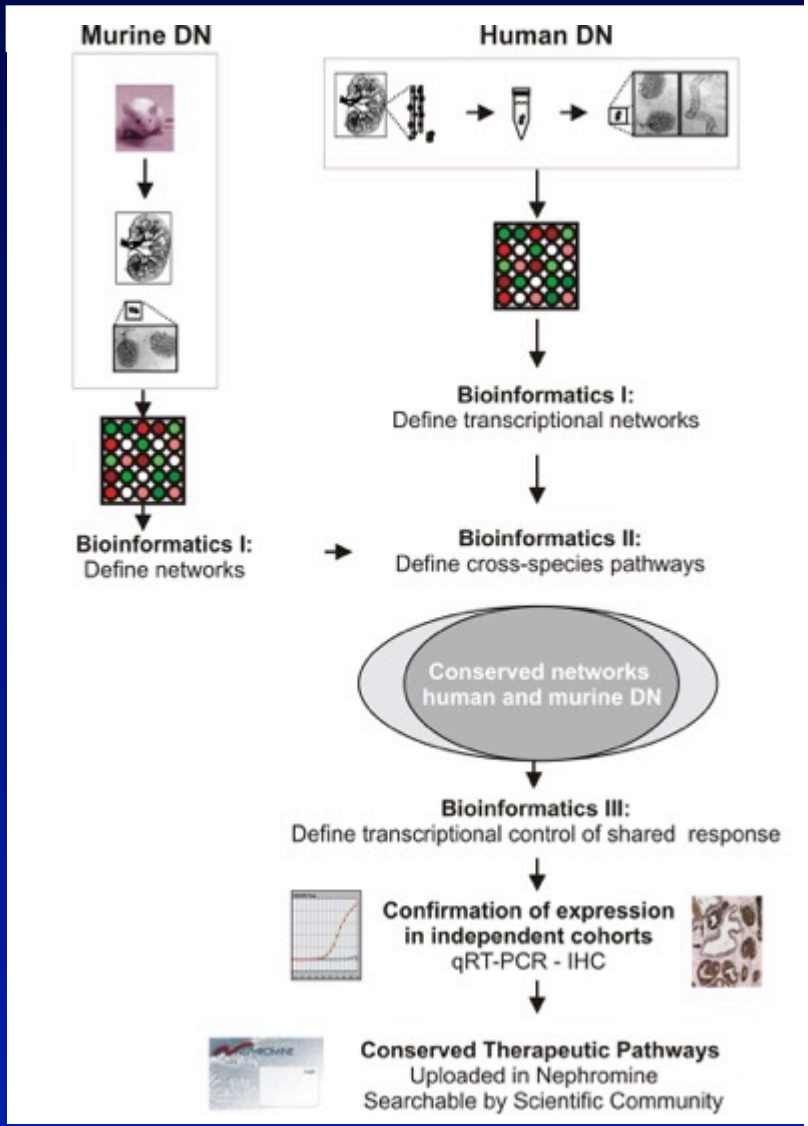
Analysis of diabetic endorgan damage across tissues, species and disciplines

Defining treatment response in Diabetic endorgan damage across

Species:
- Human - Mouse

Endorgans:
- Nerve – Kidney - Eye

Disciplines:
- Neurology (Feldman)
- Nephrology (Brosius, Pennathur)
- Ophthalmology (Gardner)
- Bioinformatics (Kretzler)
- Computer Science (Jagadish)

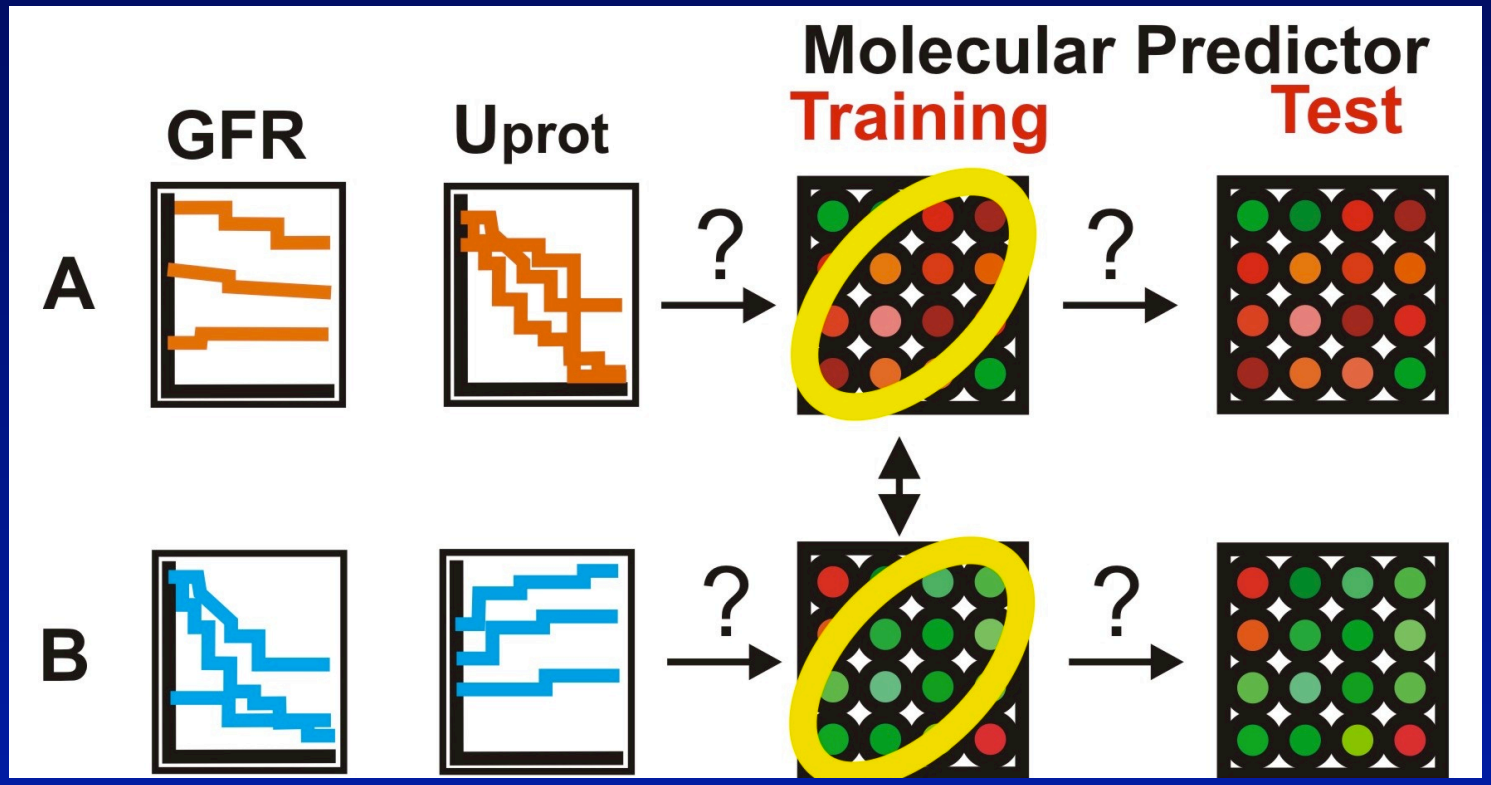


Predicton of CKD Progression

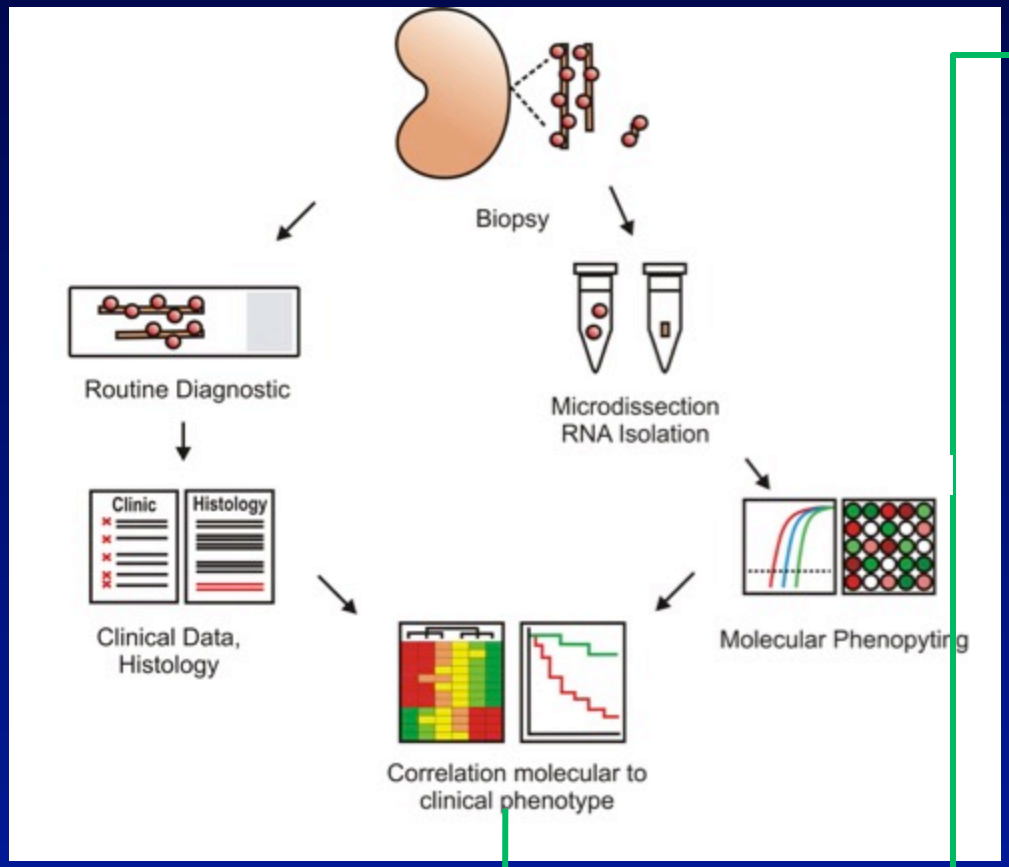
Selection of patients at risk

Risk Prediction:

- Use outcome to select predictor from genomic data set



From tissue to urine:
Non-invasive Biomarkers for CKD progression



A set of tissue based candidate markers

Validation markers in independent cohorts

Validated markers for testing in body fluids

Further validation in larger cohort

Biomarkers

Enrichment analysis: signaling pathways & Therapeutic targets

Treatment targets

Discovery and validation cohort for GFR prediction: intra-renal mRNA

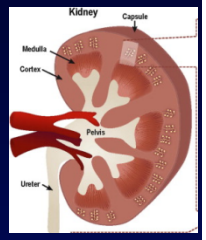


Table 1a. Demographic characteristics of participating CKD patients from the discovery ERCB cohort.

Disease type	CKD patients (n=164)	eGFR (ml/min per 1.73 m2)	Age (years)	Gender (male/female)
SLE	30	63.7±29.4	34.7±13.3	7m/23f
IgAN	24	75.9±37.9	36.4±14.6	18m/6f
MGN	18	88.9±41.4	53.4±19.3	10m/8f
FSGS	16	73.4±38.4	46.2±17.6	7m/9f
HTN	20	43.9±25.1	57.2±12.1	15m/5f
DN	17	44.3±24.9	58.3±10.7	12m/5f
MCD	12	100.7±33.9	35.8±16.8	8m/4f
RPGN	21	46.6±31.5	58.5±14.1	12m/9f
TMD	6	93.4±29.4	46.0±14.5	4m/2f
Total	**164**	**66.4±37.2**	**46.9±17.6**	**93m/71f**

Table 1b. Demographic characteristics of the first validation group of CKD patients from ERCB.

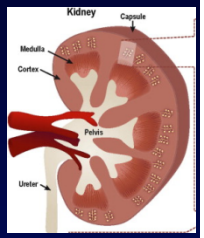
Disease type	CKD patients (n=55)	eGFR (ml/min per 1.73 m2)	Age (years)	Gender (male/female)
SLE	10	60.1±31.5	37.1±13.8	4m/6f
IgAN	17	50.8±34.1	46.0±17.5	12m/5f
MGN	4	54.4±32.4	58.7±23.6	2m/2f
MPGN	1	40.6	65	1m
FSGS	8	55.9±36.0	43.6±18.6	6m/2f
HTN	1	33.2	57.1	1f
DN	1	97.3	44.8	1m
MCD	4	86.0±44.5	44.4±19.3	4m
RPGN	5	20.9±15.0	50.4±21.7	4m/1f
Other	4	84.2±71.7	37.4±14.6	3m/1f
Total	**55**	**56.1±38.0**	**45.1±17.6**	**37m/18f**

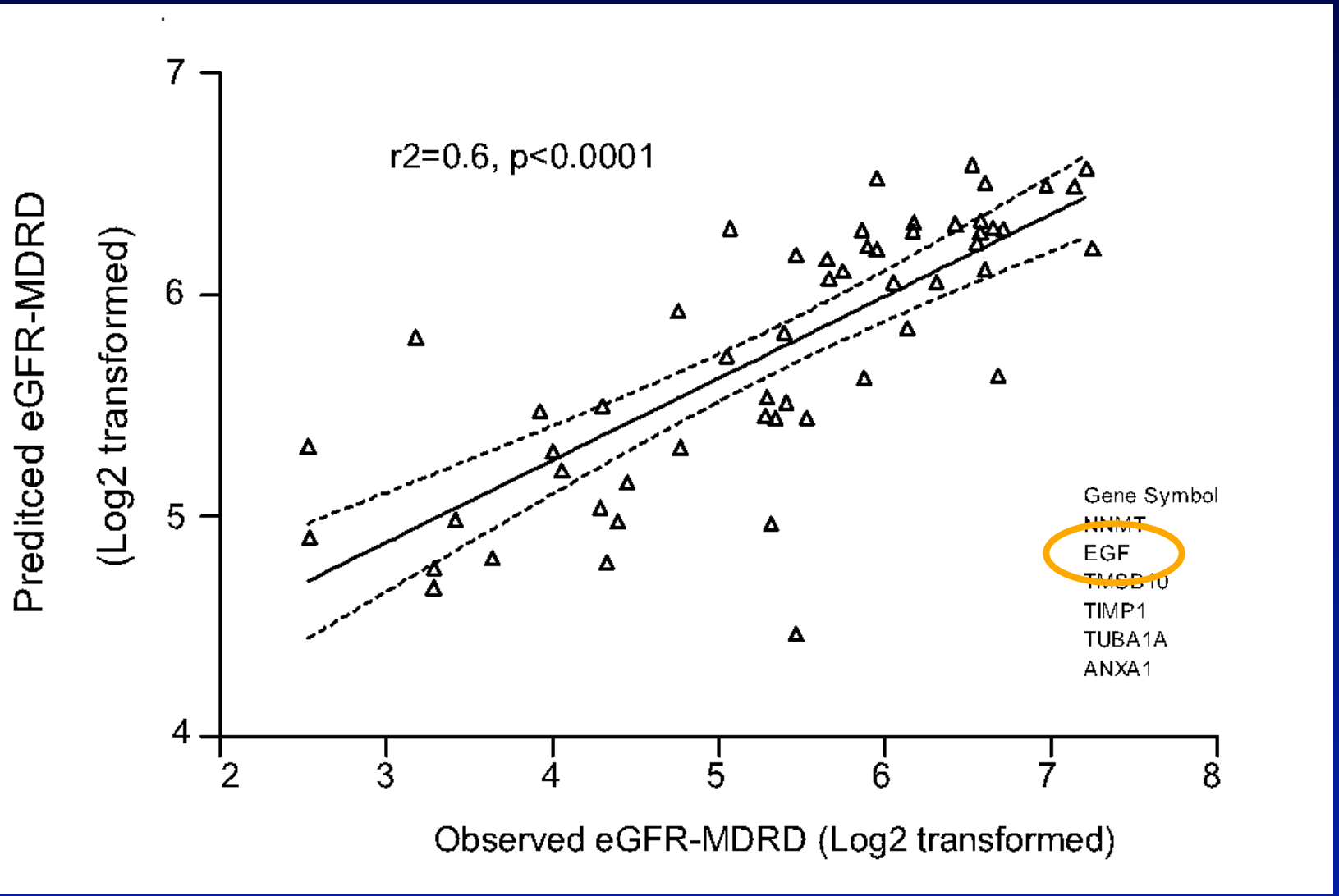
Affymetrix

The European Renal Biopsy cDNA Bank (ERCB)

TLDA (qRT-PCR)

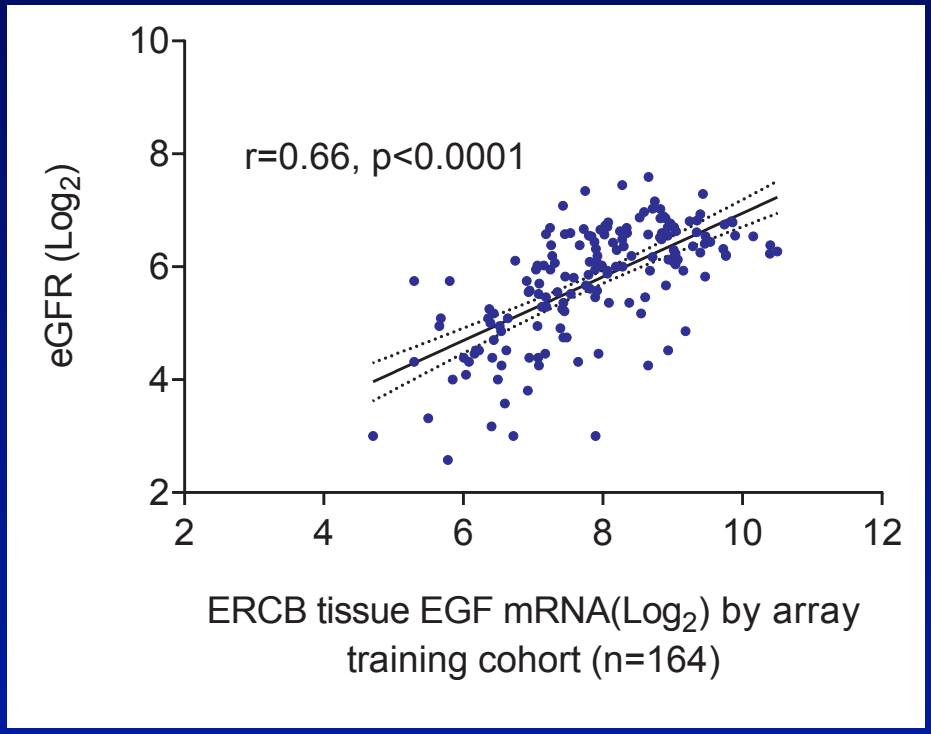
eGFR Predictor panel



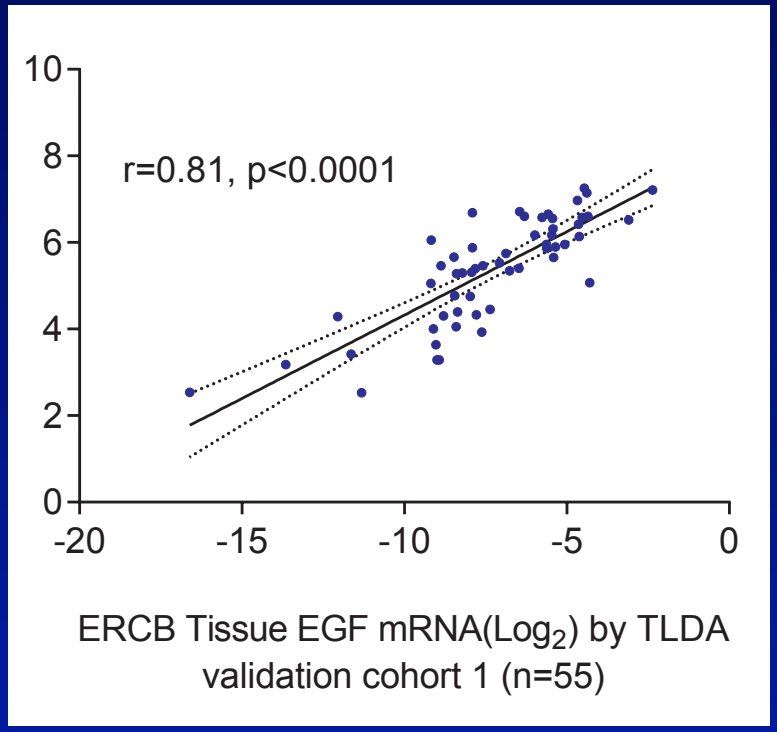


Intra-renal EGF correlation with eGFR in European CKD/DKD

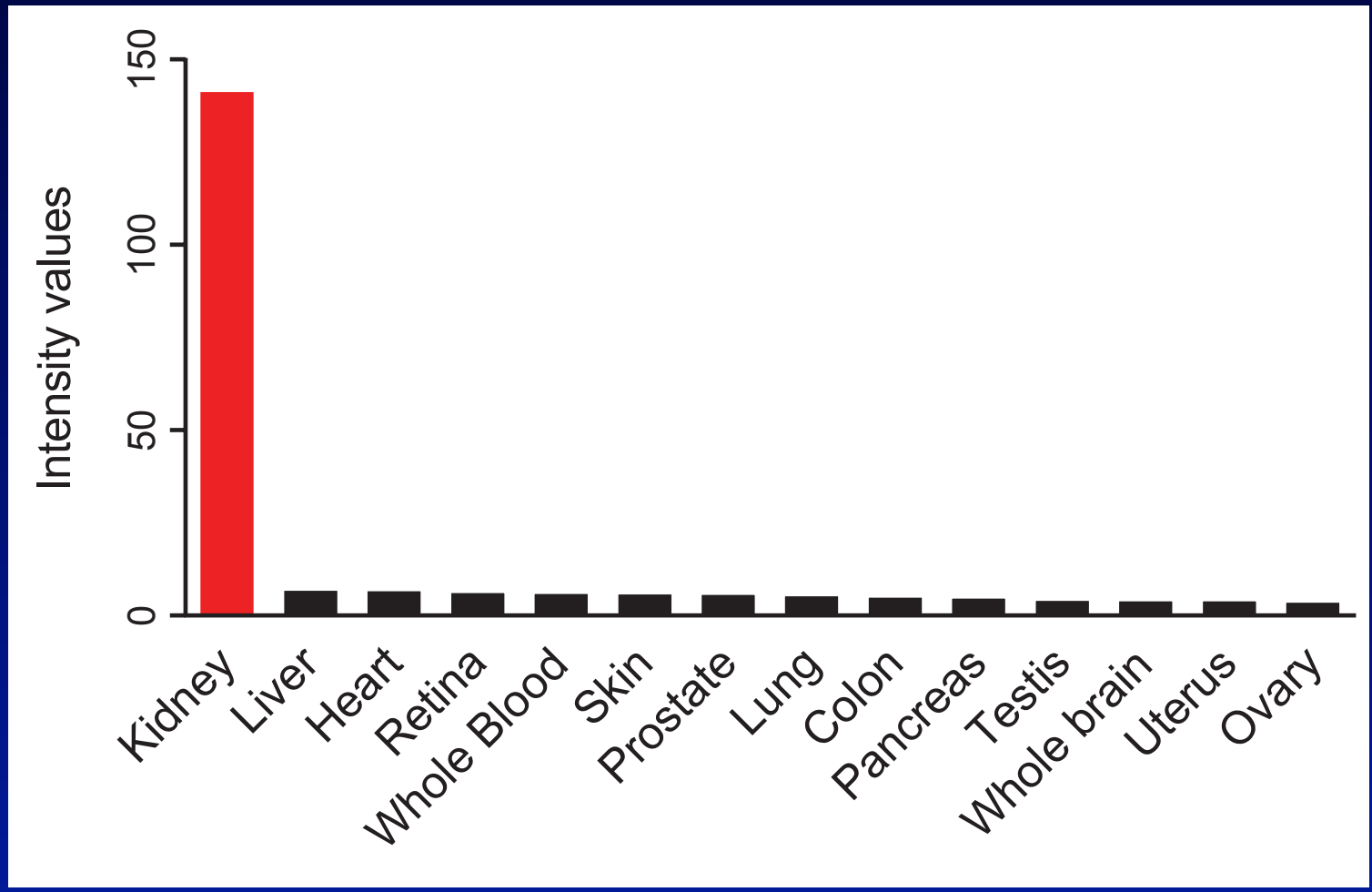
Training Cohort:
Affymetrix U 133



Test Cohort:
TILDA qRT-PCR

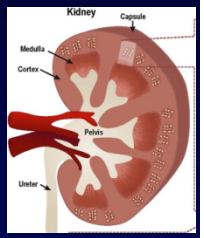


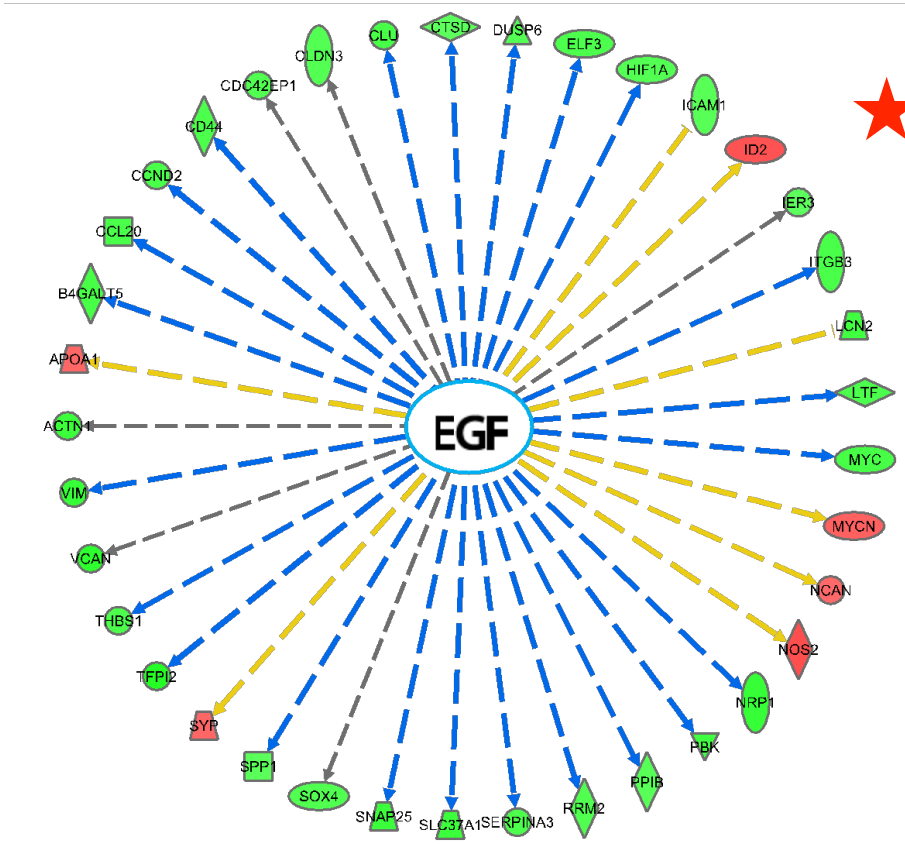
EGF expression in normal human tissue



Data derived from BioGPS portal
Wu et al., Genome Biology, 2009

EGF, top up-stream regulator of GFR slope correlated genes



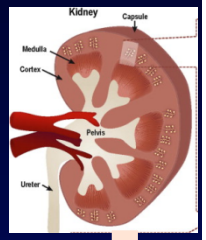


Figrue legend:
red node: positively corrlated with eGFR slope;
green node: negatively correlated with eGFR slope;
red edge: lead to activation;
blue edge: leads to inhibition;
yellow edge: findings incosistent with state of downstream molecule;

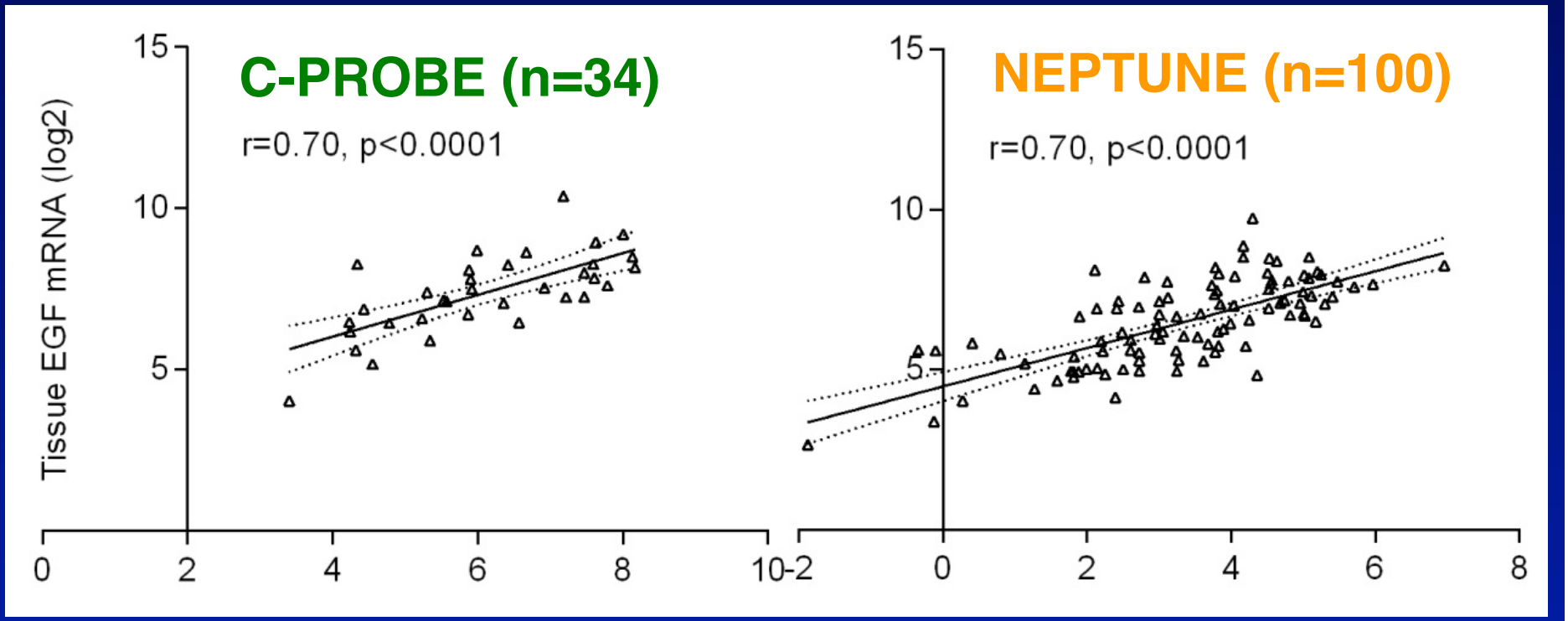
Top 10 upstream regulators of eGFR slope correlated genes.

Upstream Regulator	Molecule Type	p-value of overlap	Target molecules in dataset
EGF	growth factor	2.09E-12	ACTN1,APOA1,B4GALT5,CCL20,CCND2,C LCN2,LTF,MYC,MYCN,NCAN,NOS2,NRP1 VCAN,VIM
TP53	transcription regulator	4.83E-11	ACTN1,ALOX5,ANLN,ANTXR1,ANXA1,APA EIF4G3,ELF4,FHL1,FHL2,GDF15,GLIPR1, NRP1,PBK,PDLIM1,PFN1,PMEPA1,PPFIBI THBS2,TMSB10/TMSB4X,TNFSF9,TOP2A
IL1B	cytokine	3.45E-10	ADAMTS1,ANTXR1,ANXA1,CCL2,CCL20,C HSD11B1,ICAM1,IER3,ITGB3,ITGB8,LAMC SERPINA3,SNAP25,SOD2,SOX9,SPP1,TA
TGFB1	growth factor	1.36E-09	ACTN1,ALOX5,CCL2,CCL20,CCND2,CD2C FCER1A,FHL1,FNDC3B,FOSL2,GDF15,GC KDM5B,KITLG,KLF9,KRT18,LAMC1,LAMC OSM,PDLIM7,PKIG,PMEPA1,PNMT,SERP TSC22D3,TUBA1A,VCAN,VIM,ZYX
IL6	cytokine	1.28E-08	ADAMTS1,ANXA1,APOA1,ARL4C,CCL2,C LCN2,LTF,MET,MPO,MYC,NOS2,PSMB10 UBE2C,VIM,XRCC5
TNF	cytokine	2.54E-08	ALOX5,ANXA1,APAF1,APOA1,CCL2,CCL2 GDF15,HIF1A,HSD11B1,ICAM1,IDE,IER3,I MET,MMD,MMP7,MPO,MYC,NCAN,NFKBI SOX9,SPHK1,SPP1,TAC1,TAPBP,TFPI2,T
CSF2	cytokine	9.96E-08	ALOX5,ANLN,ANXA1,APAF1,CCL2,CD63,C NOS2,NRP1,OSM,RRM2,SOD2,SPP1,THB
CEBPA	transcription regulator	1.13E-07	ANXA1,ARL4C,CCL20,CCND2,FHL1,G0S2 PTPRE,SOD2,SPP1,TAC1,TGFB2,TRIB1,T
NFkB	complex	1.48E-07	CCL2,CCL20,CCND2,CD44,CD74,CFB,CL ITGB8,LCN2,MYC,NFKBIZ,NOS2,SENP2,S
ERBB2	kinase	3.46E-07	CCL20,CCND2,CLDN3,COL4A1,DHH,DUS MYCN,NNMT,NOS2,NRP1,PMEPA1,RRM2 VCAN,VIM

From tissue to urine: EGF and renal function in CKD

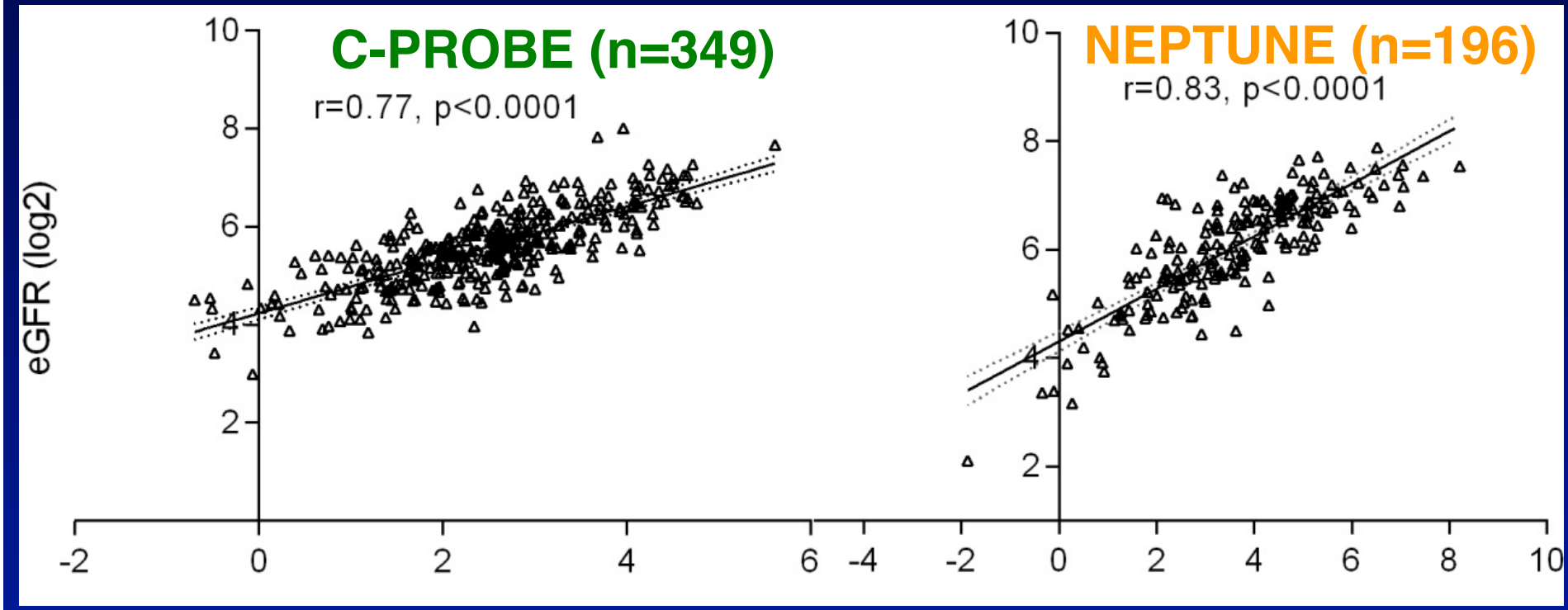


Urinary EGF protein correlates significantly with intrarenal EGF mRNA in matching samples



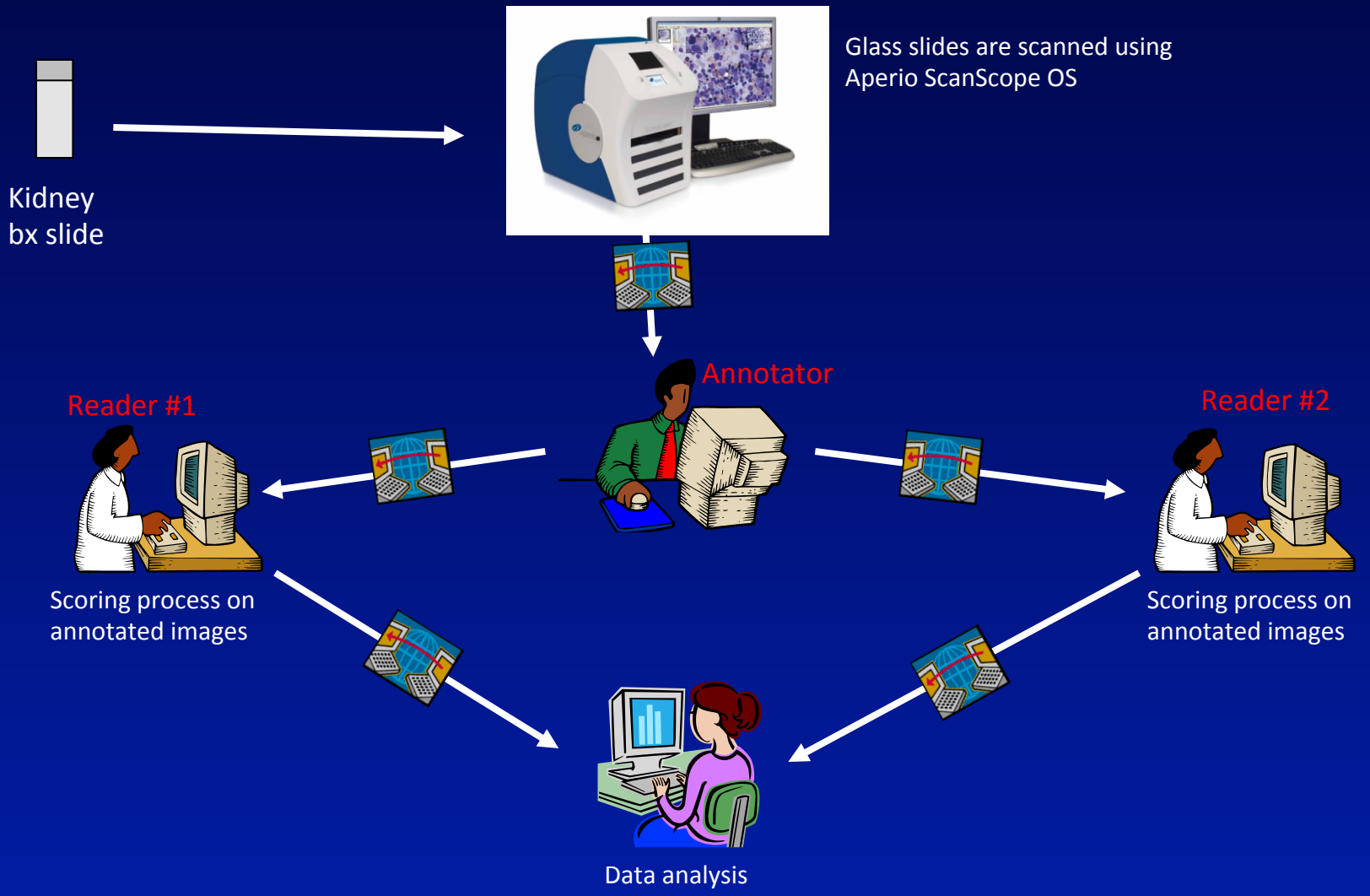
Urinary EGF/Cr. Protein (Log_2)

Urinary EGF protein significantly correlates with GFR



Urinary EGF/Cr. Protein (Log_2)

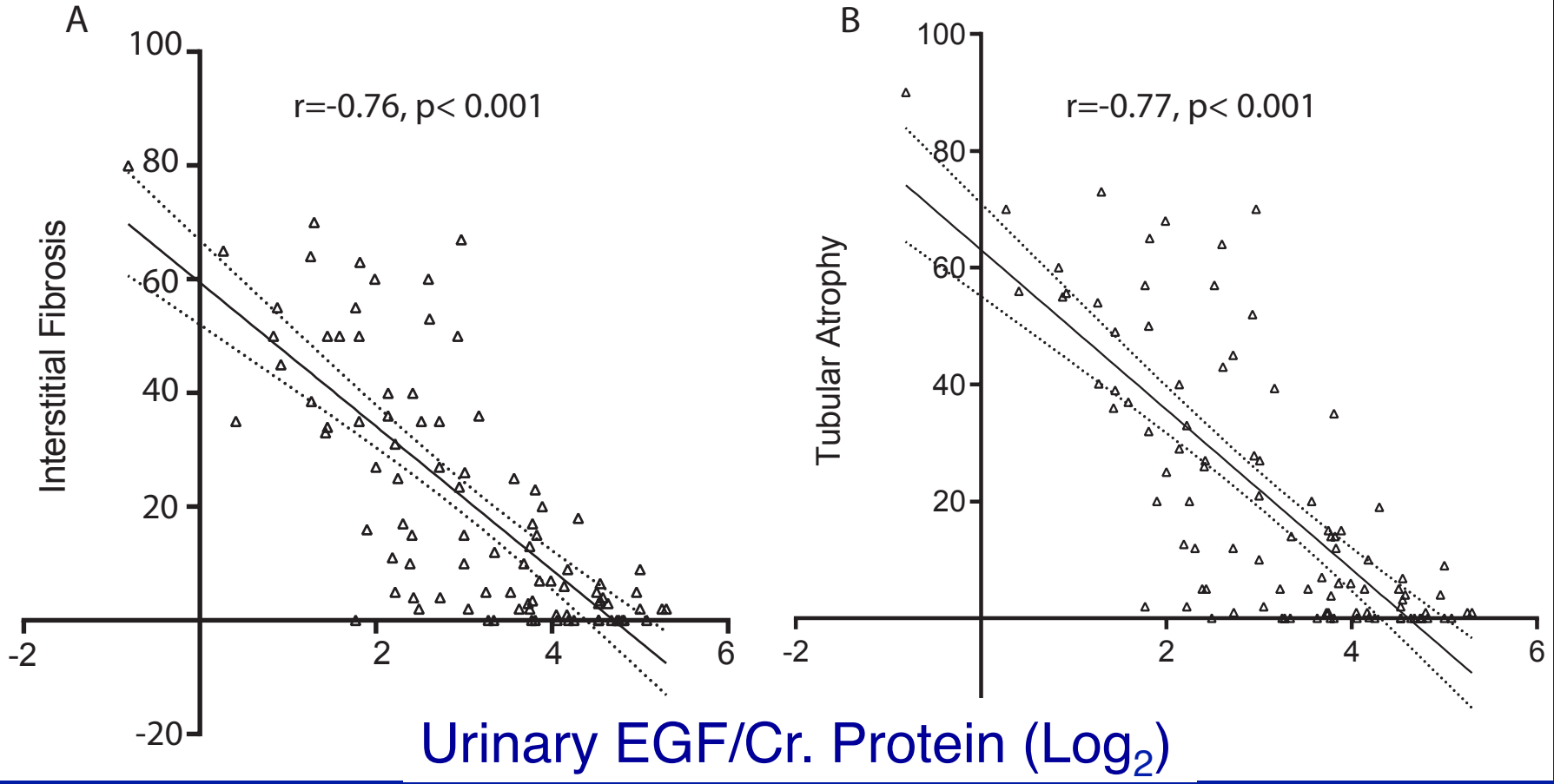
NEPTUNE Virtual Microscopy Archive of Nephrotic Syndrome



Barisoni et al. 2013

Urinary EGF protein and tubular damage

NEPTUNE: Interstitial Fibrosis / Tubular Atrophy



Association with disease progression

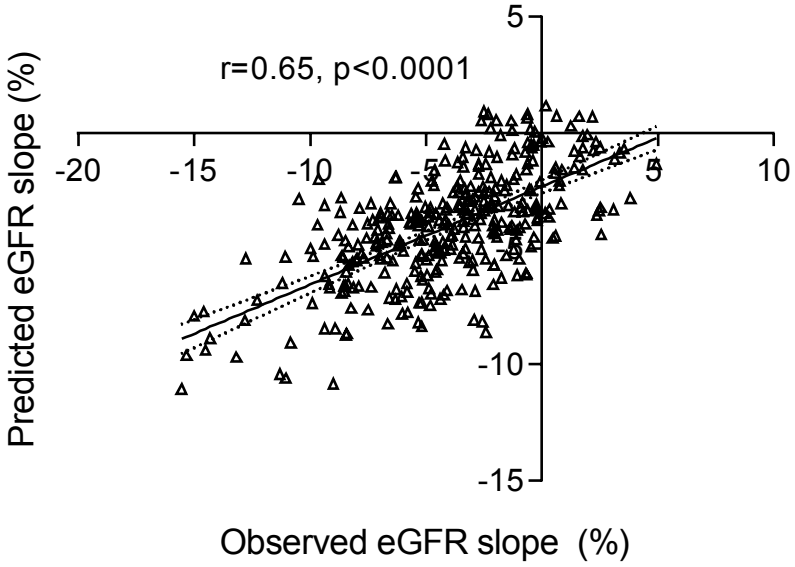
Slope of eGFR decline %/yr (mixed effects model)

&

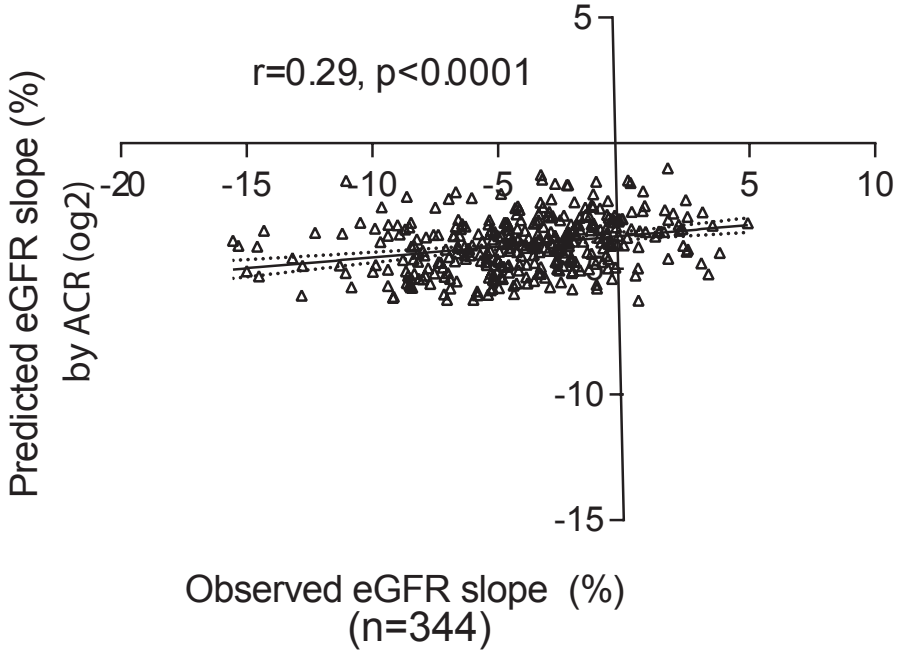
Time to renal event (ESRD or 40% reduction of baseline eGFR)

Urinary EGF predicts GFR slope%

C-PROBE

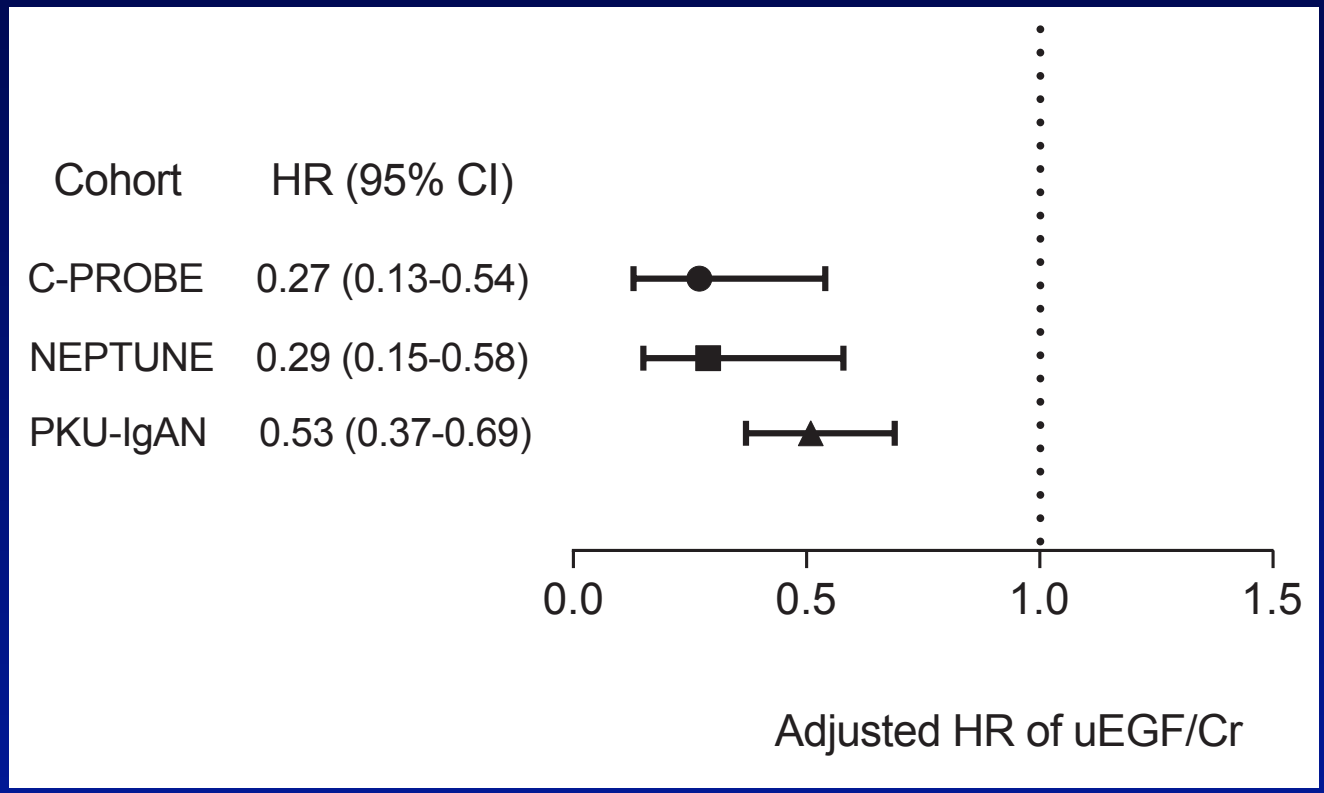


C-PROBE Albumin/Cr



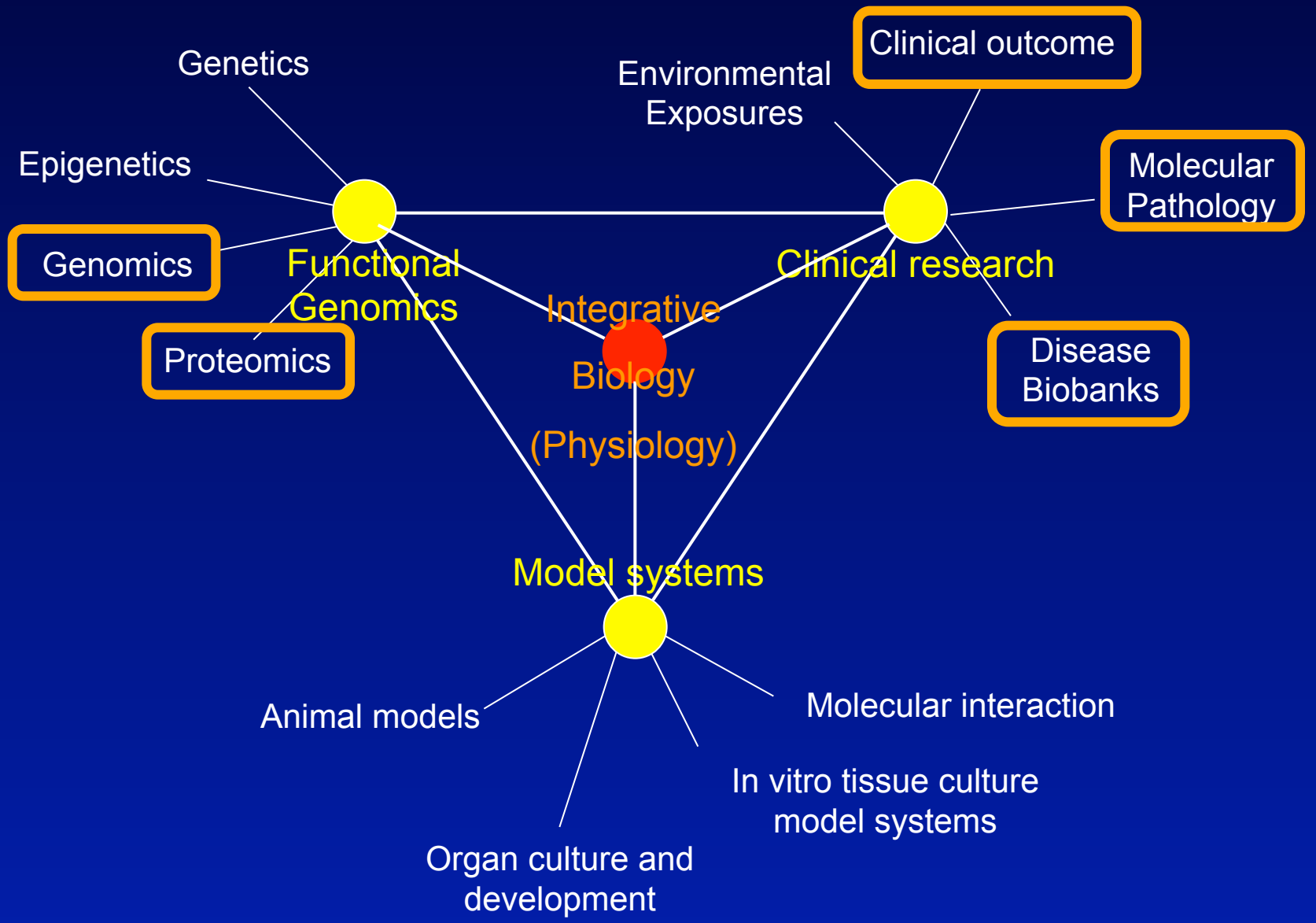
Correlation between ACR predicted eGFR slope versus the observed slope is r=0.25

uEGF: Hazard Ratio for time to event in glomerular disease



Multivariable-adjusted hazard ratios urinary EGF/Cr for outcomes. HRs adjusted by age, gender, eGFR and ACR and obtained by independent Cox regression models in each study cohort.

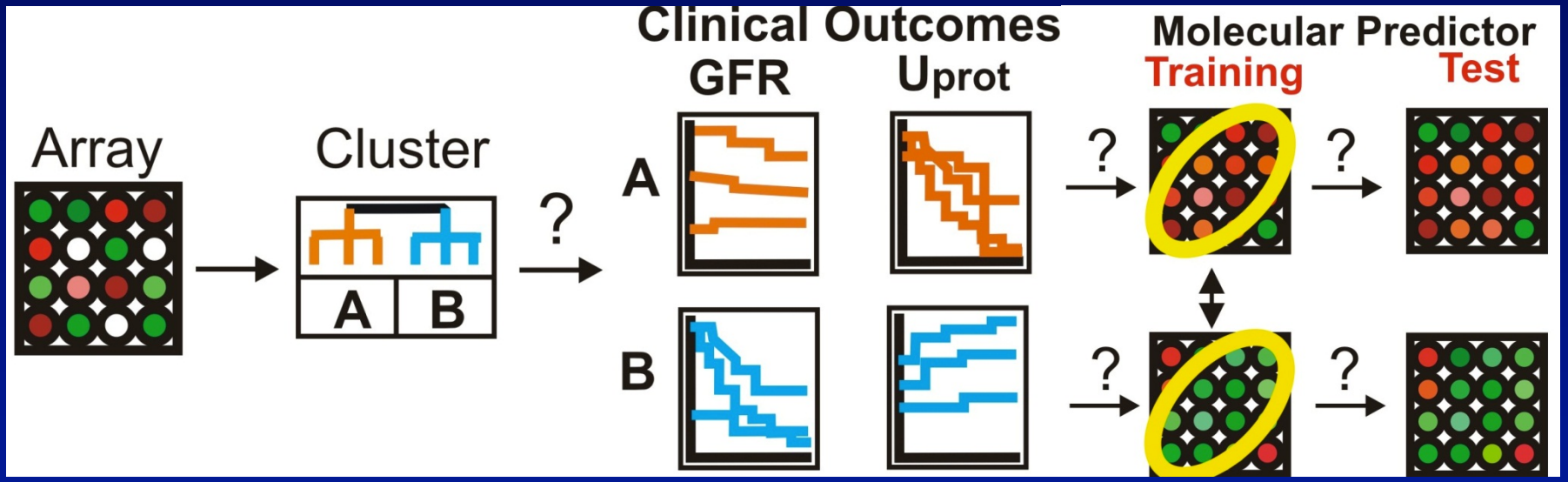
Case Study 3: *Molecular Subgroups for targeted treatment of FSGS/MCD*



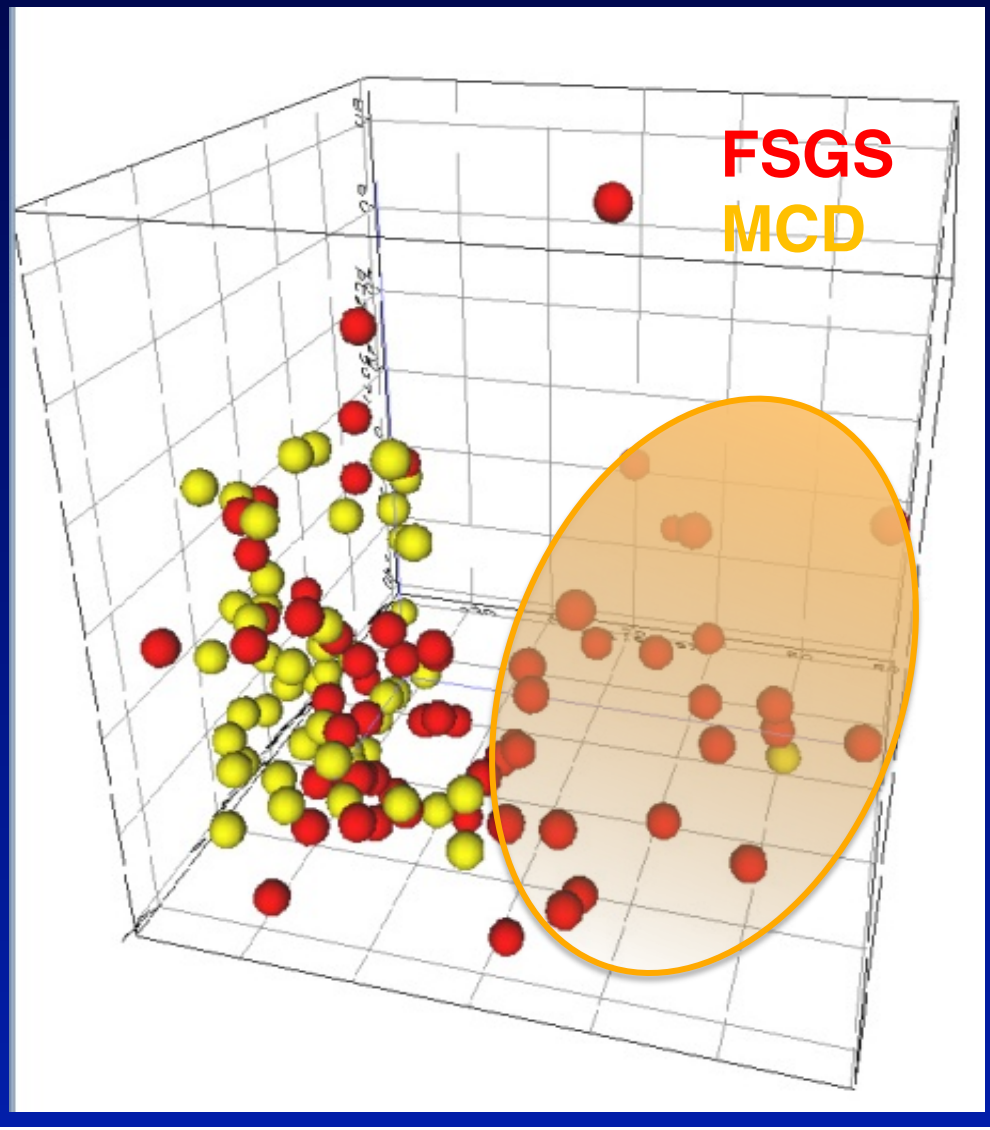
Molecular Phenotype - Clinical Outcome

Precision Medicine approach:

Define functional disease group => associate with outcome => predictors of group



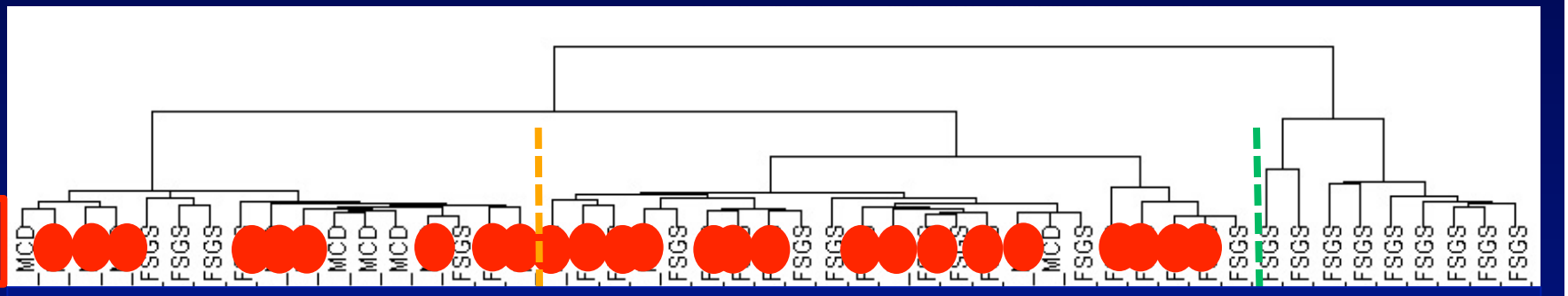
Tubulointerstitial gene expression PCA FSGS and MCD patients



PCA: Overlap of MCD and FSGS, but FSGS subgroup

PCA of normalized Affymetrix ST2.1 based gene expresssion data set of 68 FSGS and 51 MCD patients

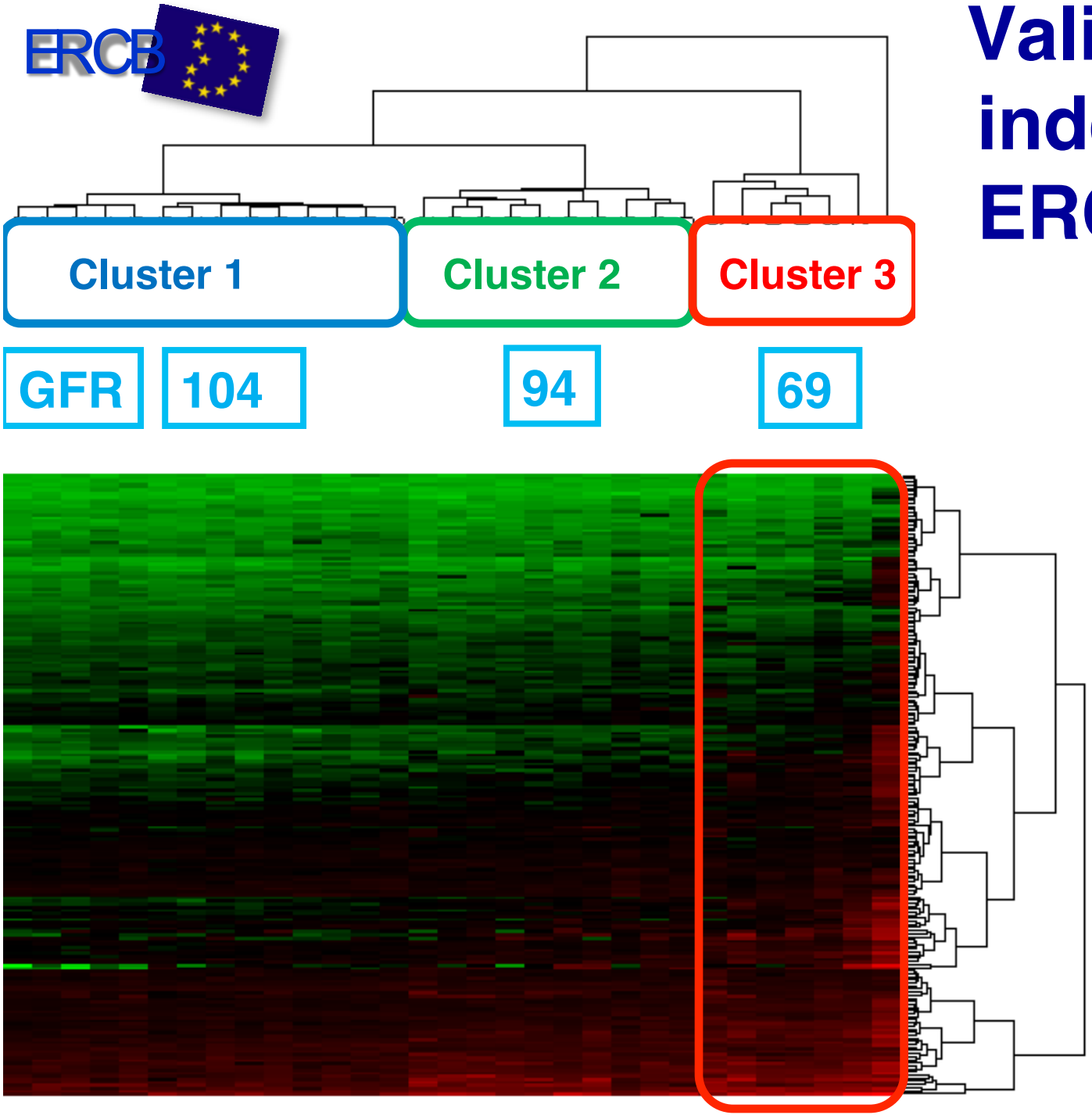
FSGS-MCD cluster - tubulointerstitial mRNA data



GFR*	108mL/min/m^2	79	42
UPCR	0.9	1.25	1.7

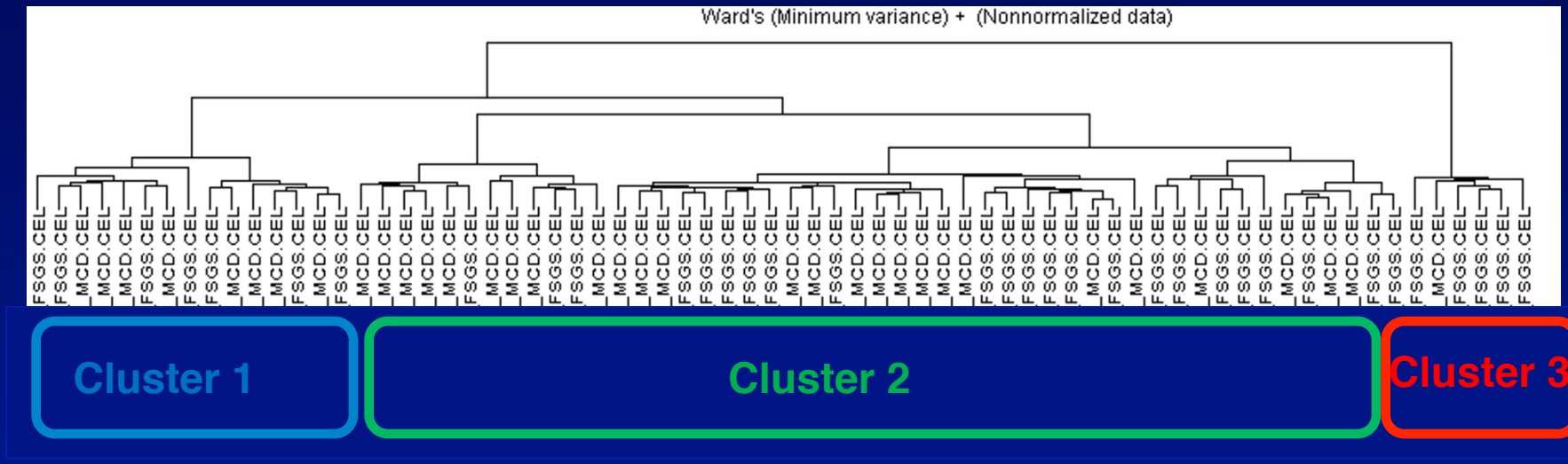
*=significant differences among clusters

Validation in independent ERCB cohort

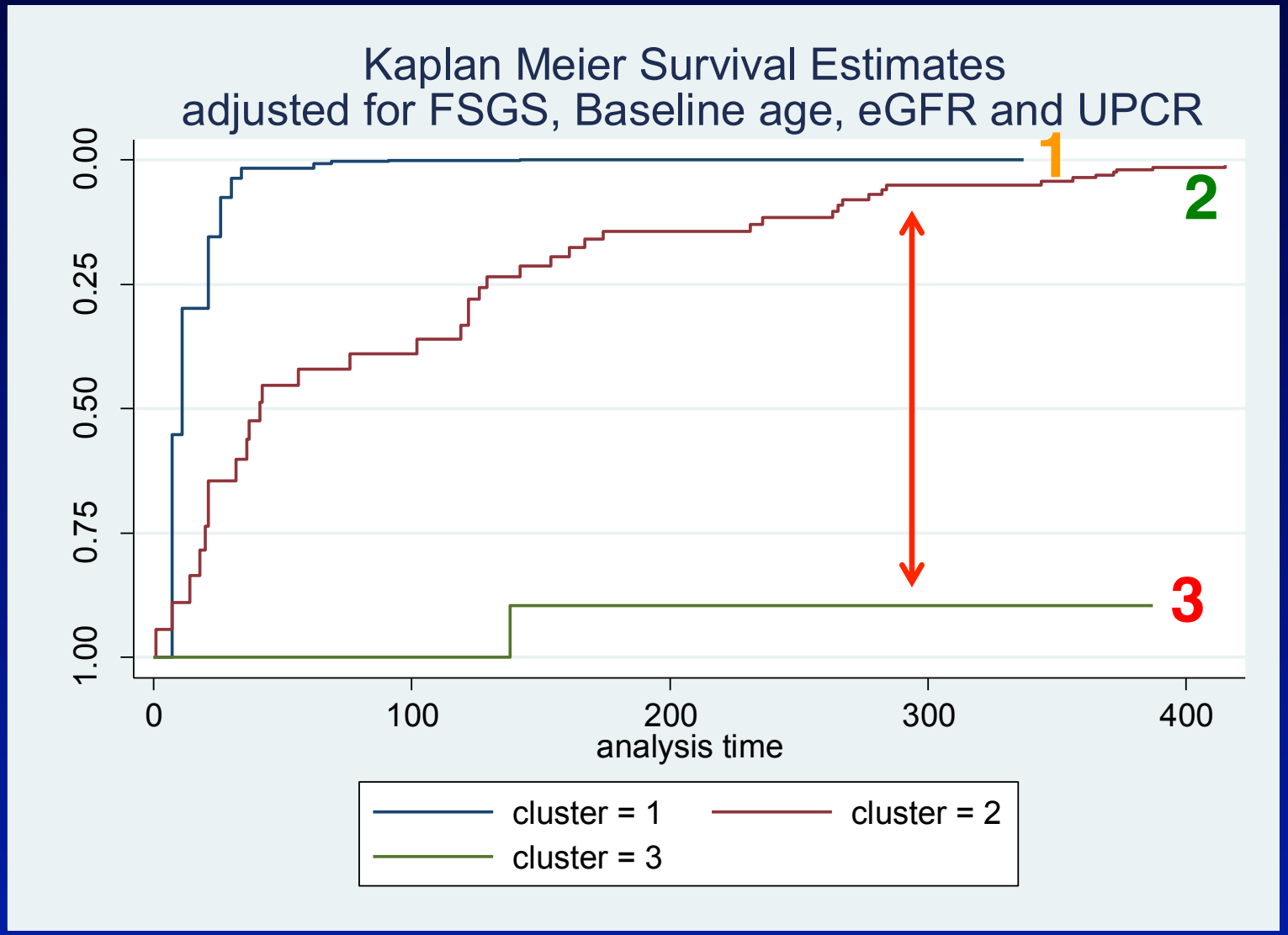


Concordant expression in 196/202 genes between ERCB and NEPTUNE cluster 3 vs 1+2

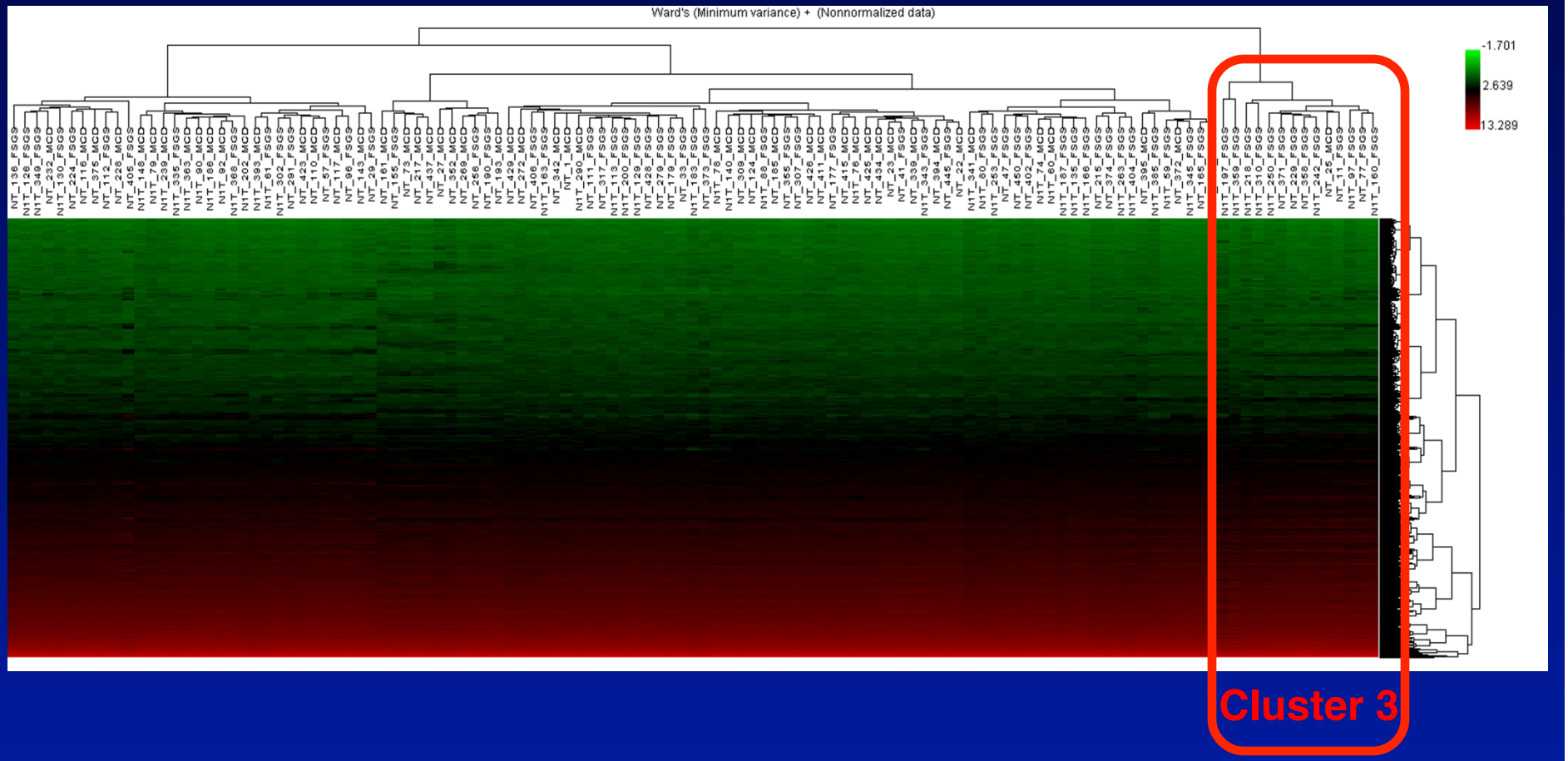
Replication in second NEPTUNE cohort



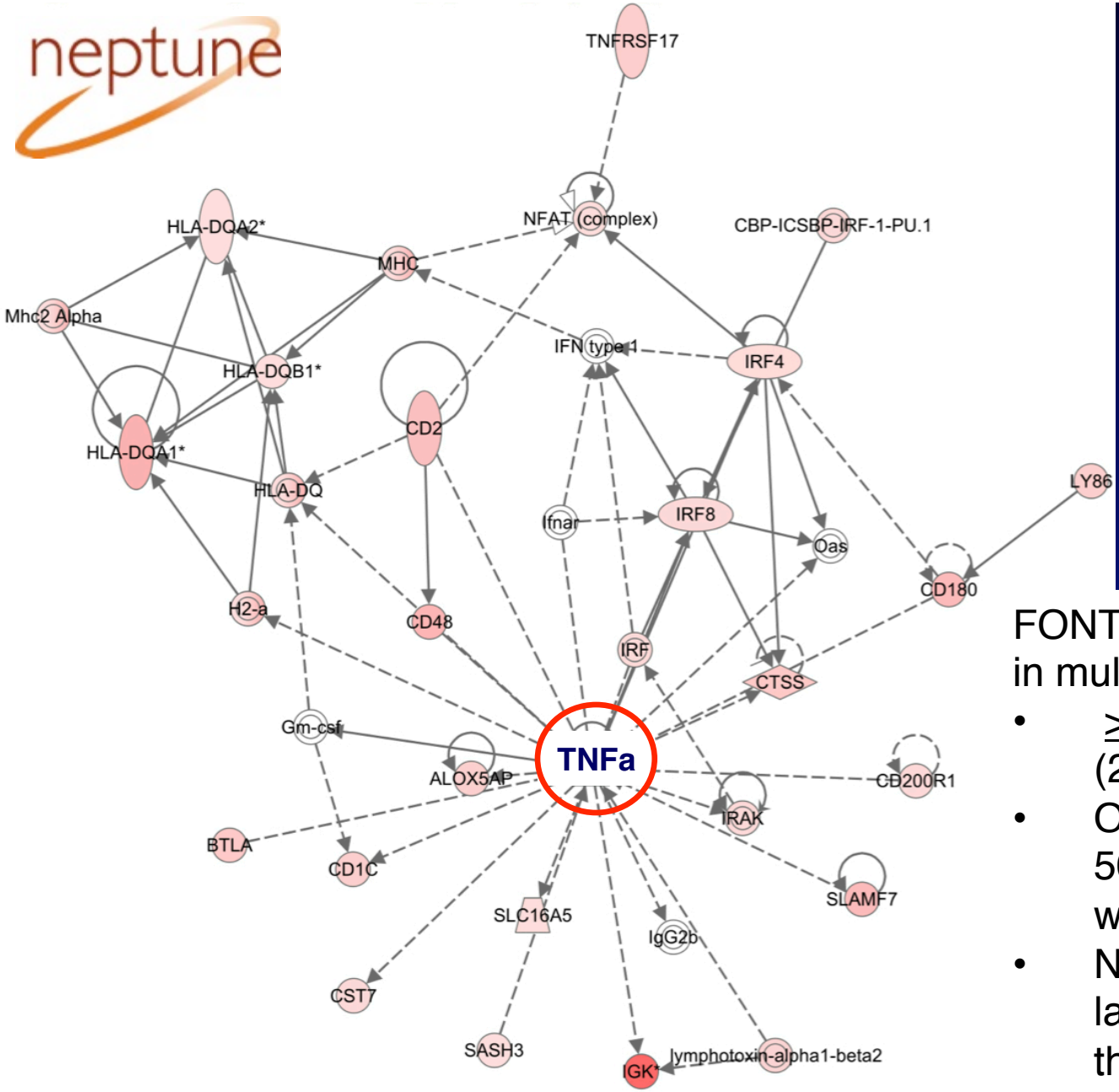
Time to Complete Proteinuria Remission per molecular subgroup



What transcript are responsible for molecular subgroups?



Transcriptional Networks in Cluster 3 vs 1+2

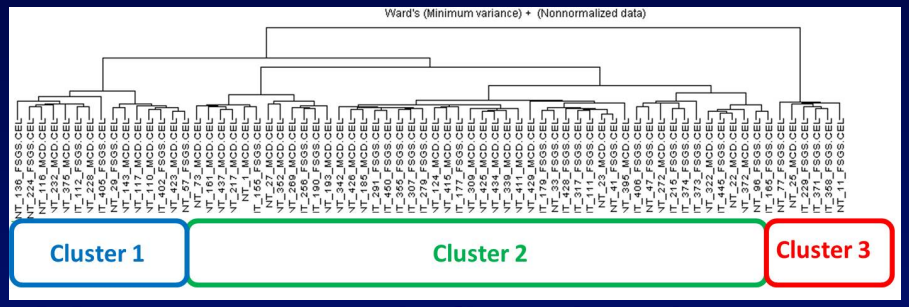


FONT II Clinical Trail
in multi-drug resistant FSGS:

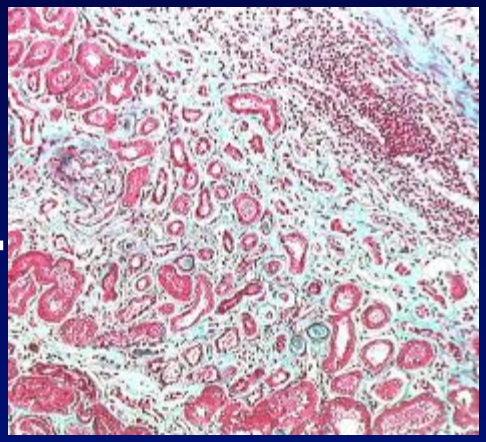
- ≥ 16 weeks of Adalimumab (24 mg/m^2, max 40)
- Outcome: 4/16 (25%) with 50% reduction in UPC with preserved eGFR
- No clinical or laboratory features that predicted response

309 probesets q<0.01 plus FC>2, co-expression interaction network (IPA 8.5)

Correlates of subgroups in urine and tissue

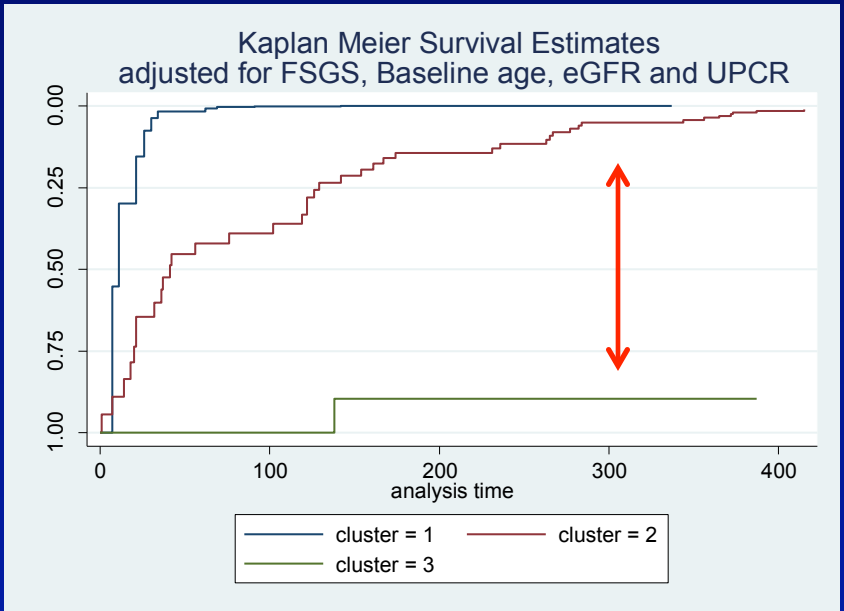


Molecularly defined subgroup – renal tissue

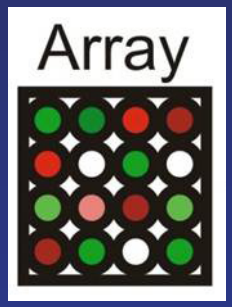


Identify a surrogate marker for patients with worse clinical outcome:

1. Reflects renal tissue mRNA
2. Urine ("liquid biopsy")
3. Histology



Association tissue transcripts encoded proteins in matching urine samples

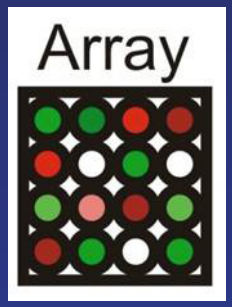


Transcripts of 13/24 of the urine biomarkers measured are also differentially expressed in the tubulointerstitium (q<5)

MMP7
CCL22
CCL5
CCL2
TIMP1
CXCL10
CCL4
TNF
CXCL1
TIMP2
IL8
PDGFA
VEGFA

Matching urinary proteins are concodant regulation in Cluster 3 vs. Cluster 1+2 (p<0.05)

Association tissue transcripts encoded proteins in matching urine samples

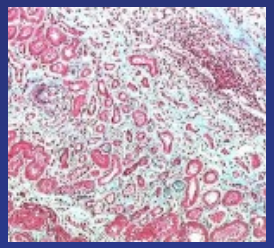


Transcripts of 13/24 of the urine biomarkers measured are also differentially expressed in the tubulointerstitium (q<5)

MMP7
CCL22
CCL5
CCL2
TIMP1
CXCL10
CCL4
TNF
CXCL1
TIMP2
IL8
PDGFA
VEGFA

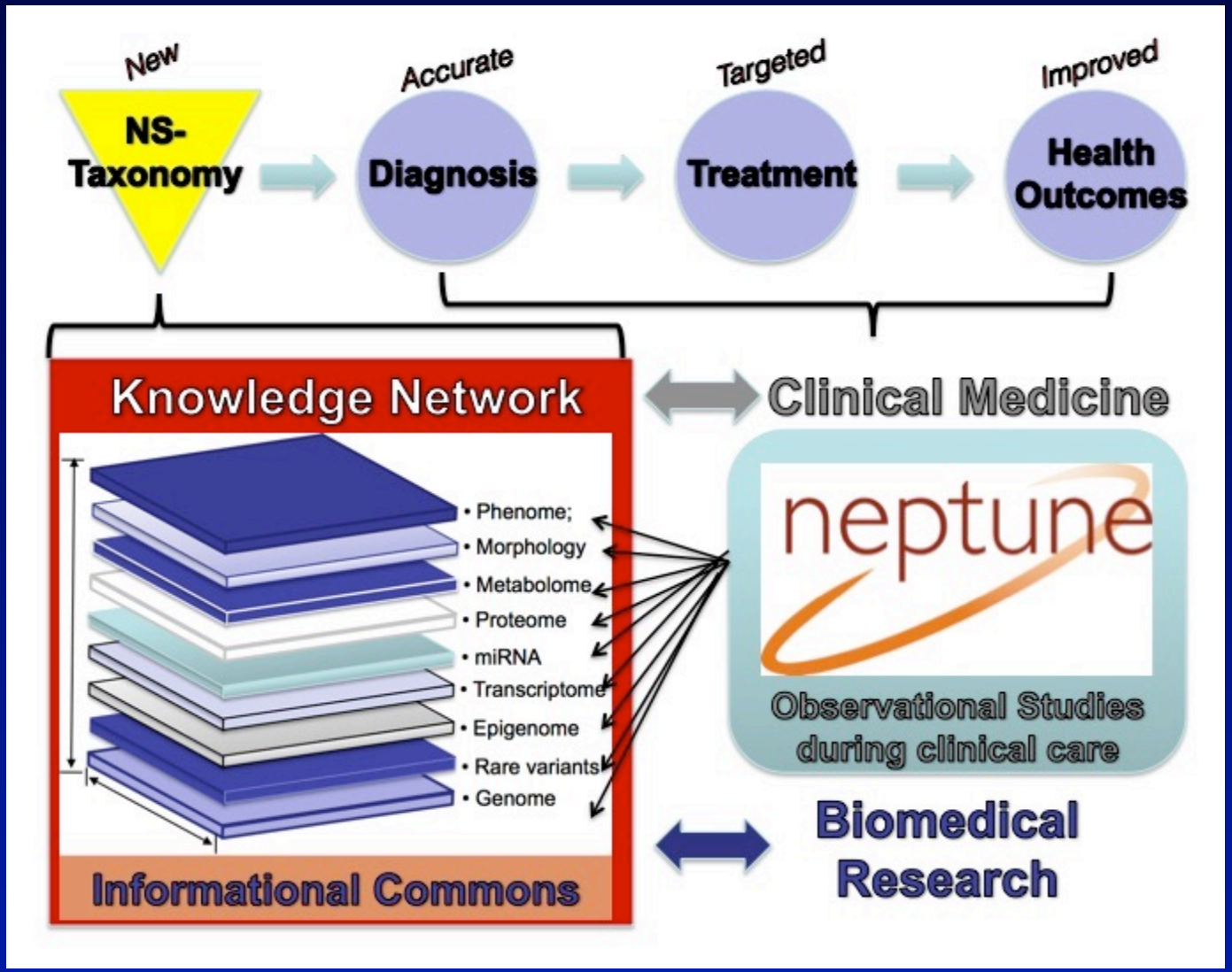
0.56
0.62
0.58
0.51
0.59
0.36
0.34
0.49
0.20
0.59
0.46
0.36
-0.53

Histology



Pearson Correlation with Interstitial Fibrosis/ Tubular Atrophy Scores

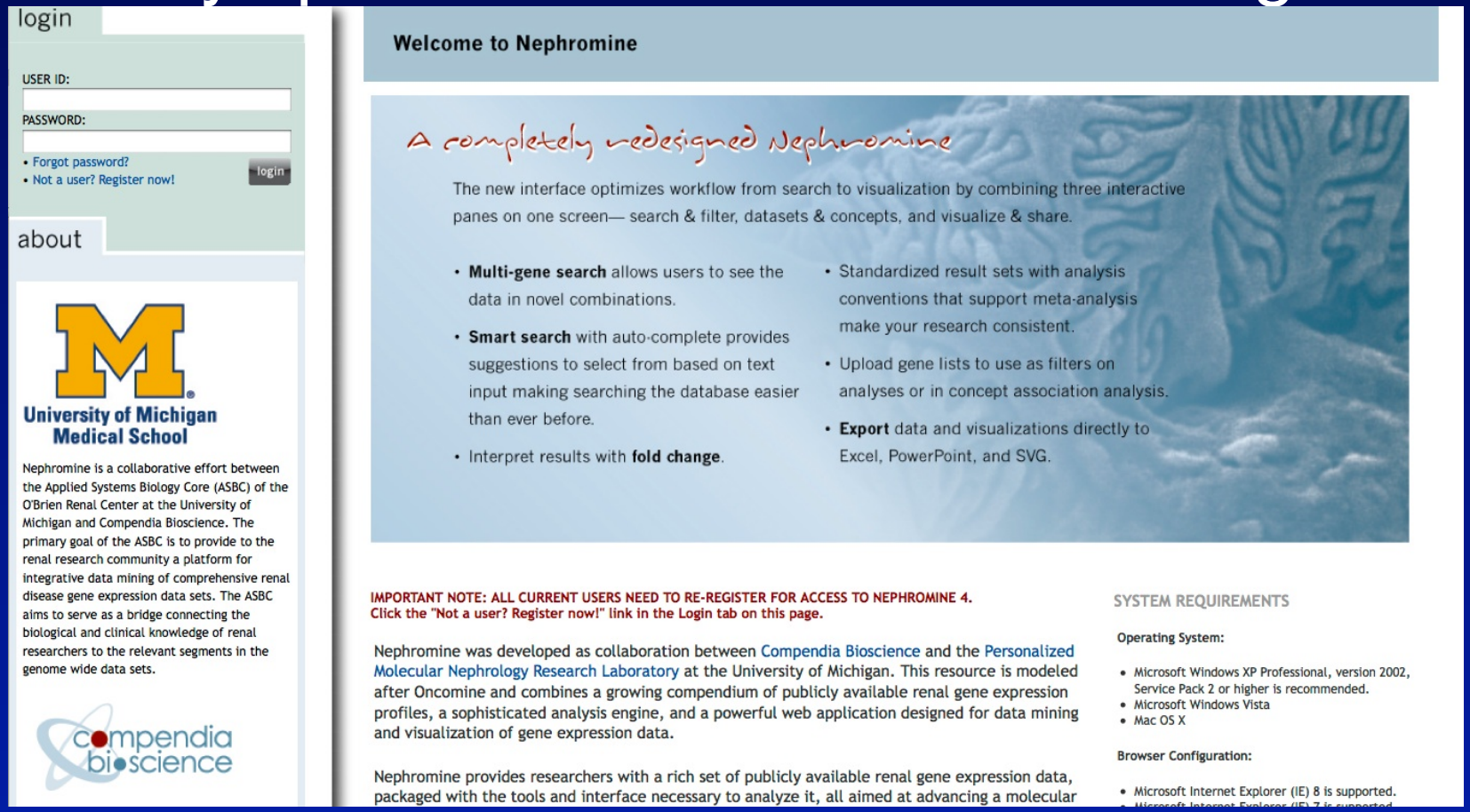
Precision Medicine for Nephrotic Syndrome

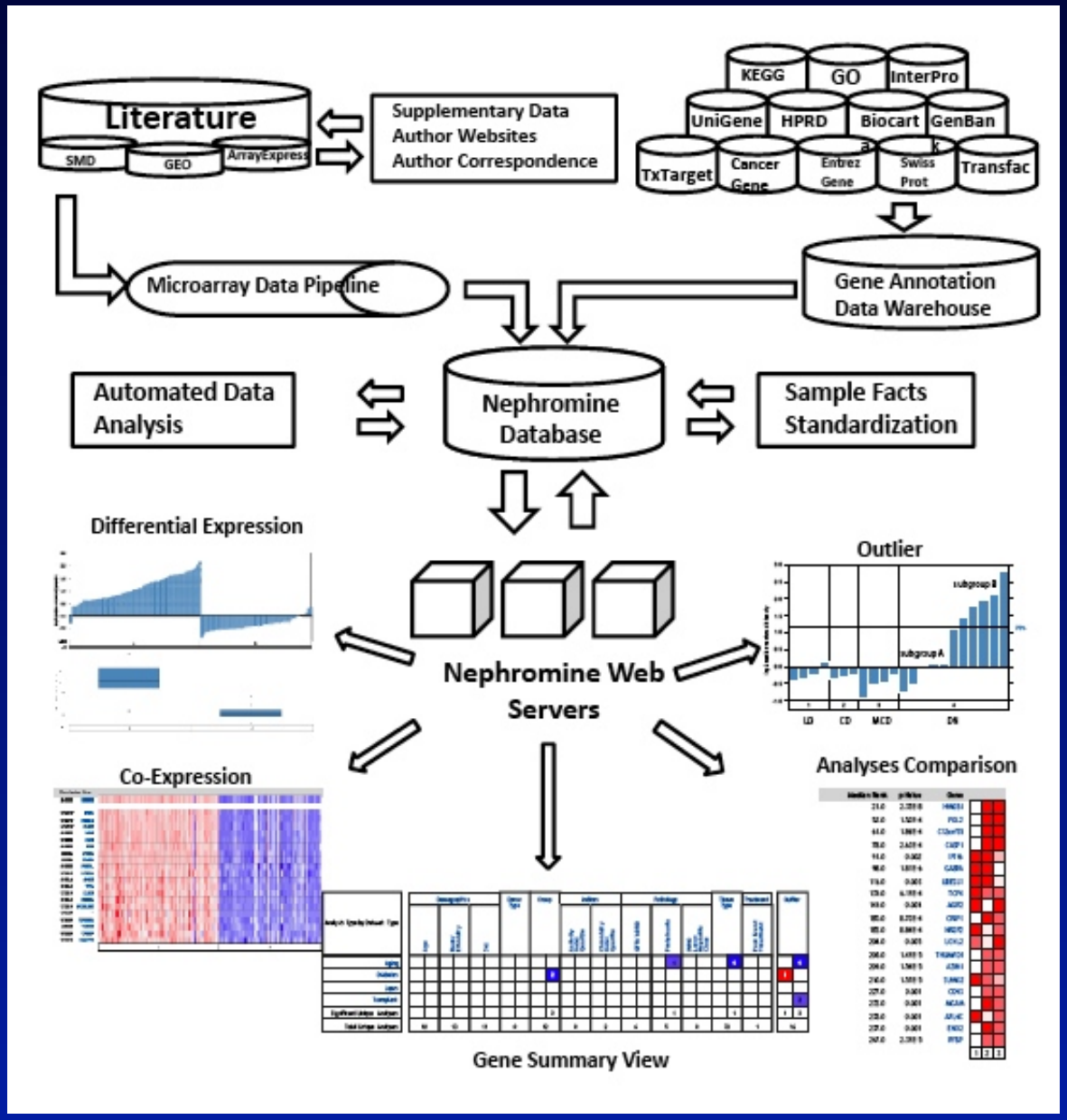


(mod. National Research Council, 2011)

Sharing Knowledge in the Informational Commons

- Nephromine:
  Kidney specific web based search engine:



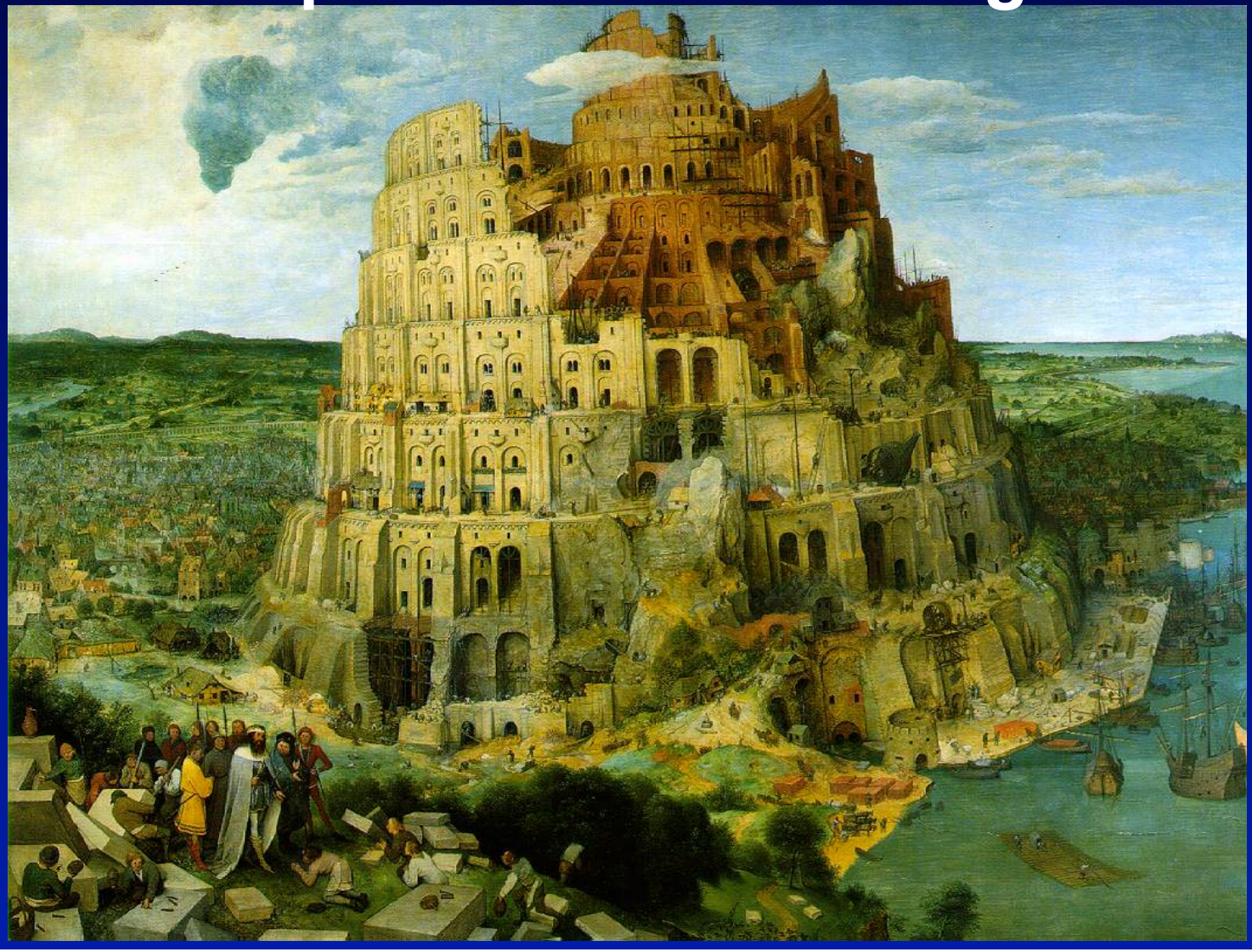


Nephromine 4.0

Combined data base and systems biology search engine for standardized analysis by the renal research community

Empower Participatory Research

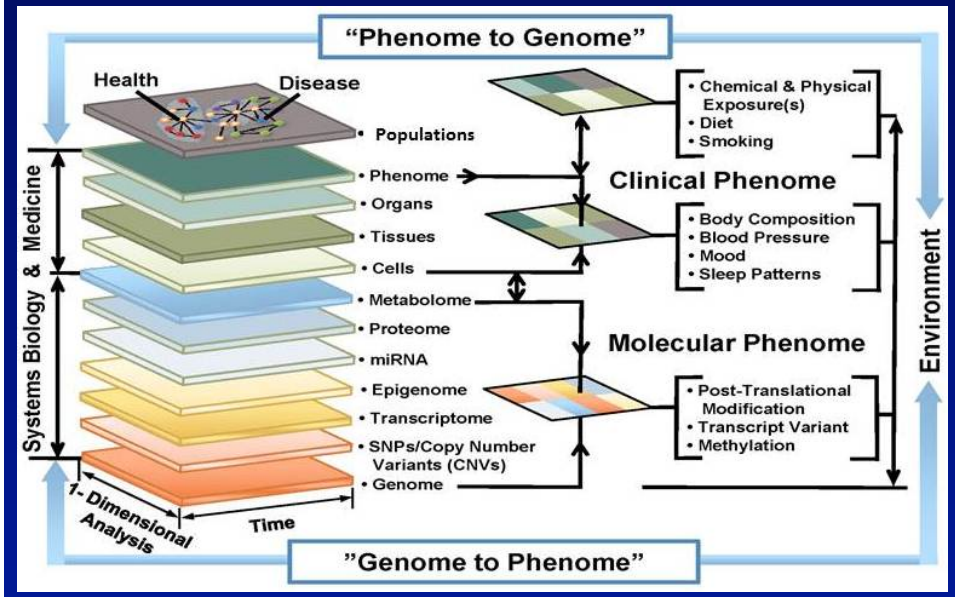
From predefined analyses to domain expert driven knowledge discovery



Translational Research: Data Integration & Analysis

The Challenge:

- Data Integration & Analysis



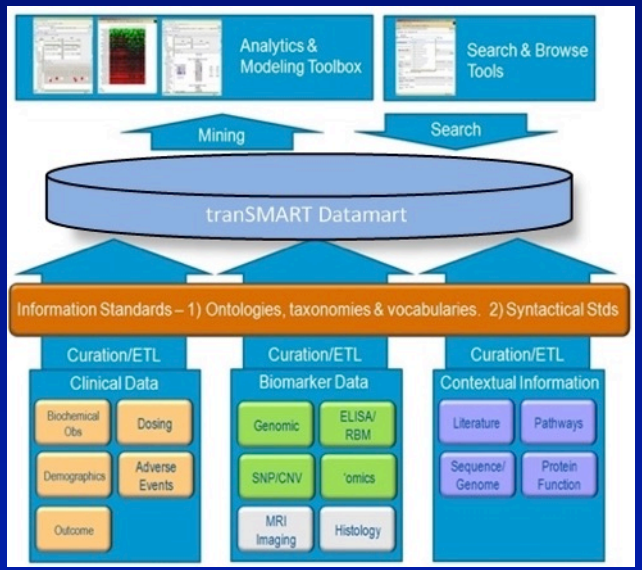
Athey and Omenn, 2009

A solution:

- tranSMART

tranSMART FOUNDATION

Open-source solution for sharing, integration, standardization and analysis of heterogeneous data from collaborative translational studies supported by an open-data biomedical research community

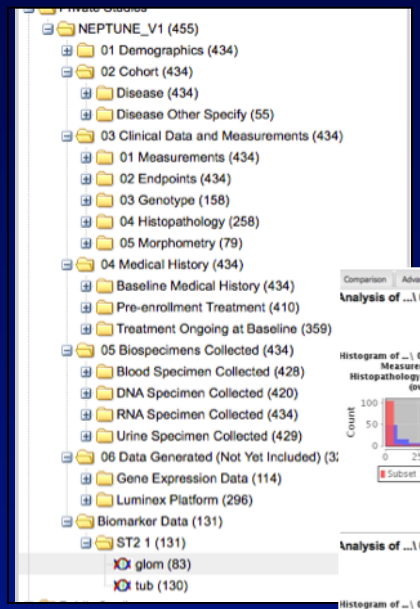


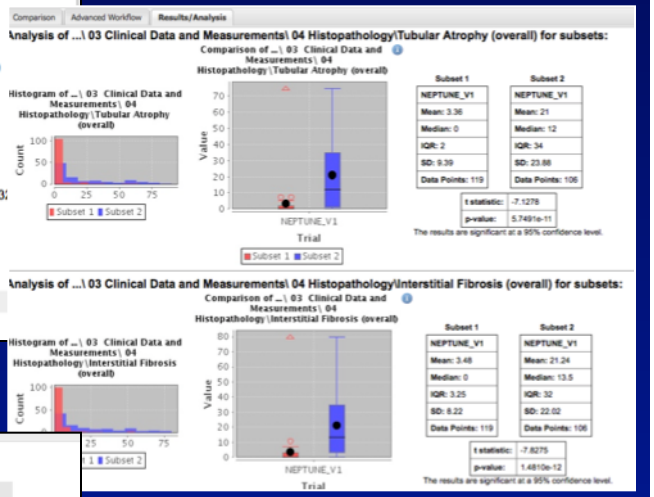
Overview at http://lanyrd.com/2014/transmart/sdfqkf/

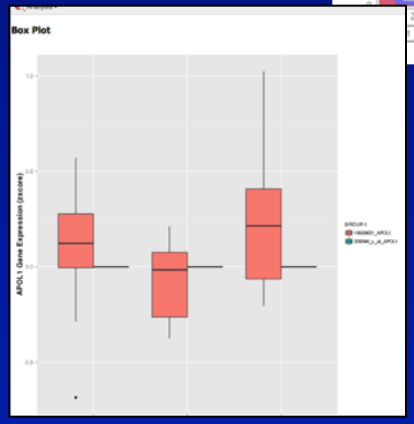
tranSMART in renal disease

Implemented for NEPTUNE consortium 09/2014:

- Data exploration
  - *Combining diverse data sets and studies with my unique background*
- Hypothesis generation
  - *Leveraging the unpredicted observations for disruptive insights*
- Develop ancillary study concepts
  - *Using live cohorts to test hypotheses, and enrich core data set with ancillary data in the process*







Translational Medicine in Renal Disease

Molecular mechanism emerging:

- Prognostic and predictive biomarkers
- Integration along all steps of the Genotype-Phenotype continuum using data sets rapidly becoming available

$\Rightarrow$ **Novel Therapeutic Targets**

Identified intervention points to be tested:

- Molecular characterized cohorts in place to test identified targets across diseases and continents

Team Science in Renal Research


… and our patients and their families