Maßgeschneiderte Therapie von Nierenerkrankungen

One size does not fit all!

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Medizinische Klinik 4
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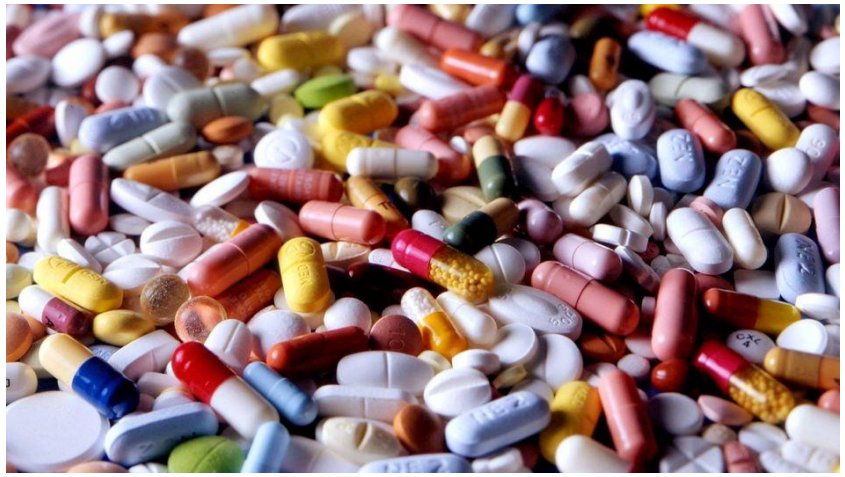
Heidelberger Nephrologie Seminar 2022

Interessenkonflikte bestehen mit diesem Thema keine.

Definition of personalized medicine

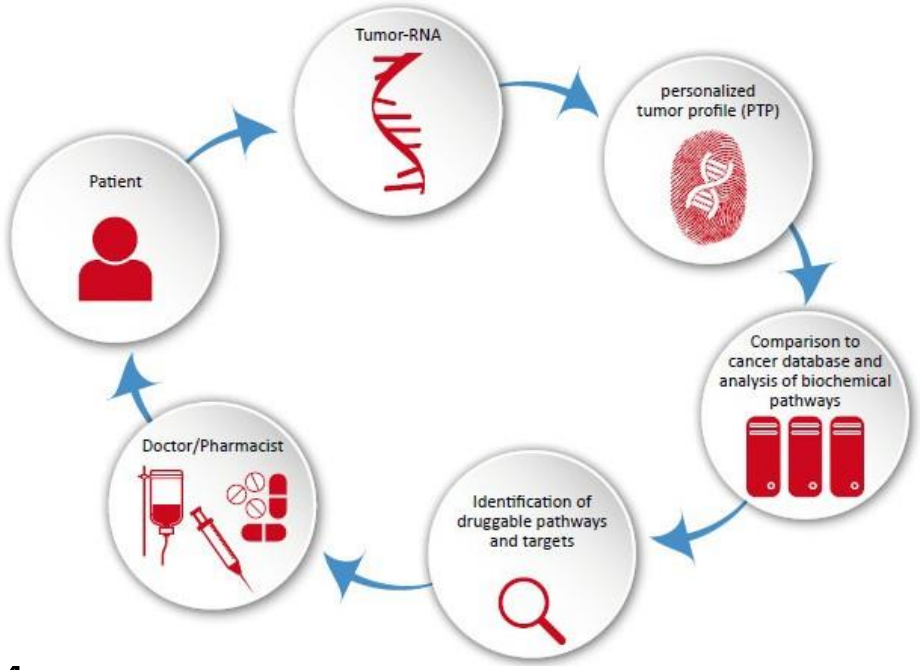
- The goal of personalized medicine is to determine the right drug, for the right patient, at the right time.
- Taking into account an individual's unique underlying biology and genetics, lifestyle, and environment.

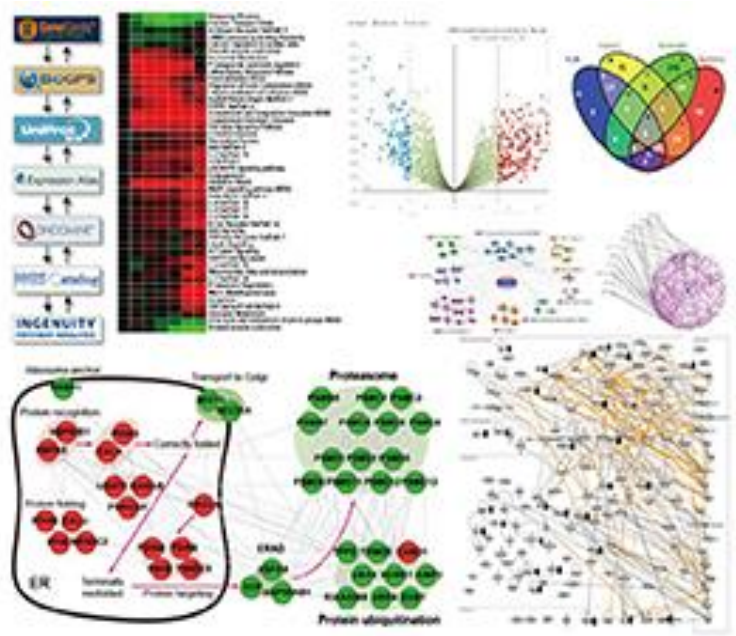


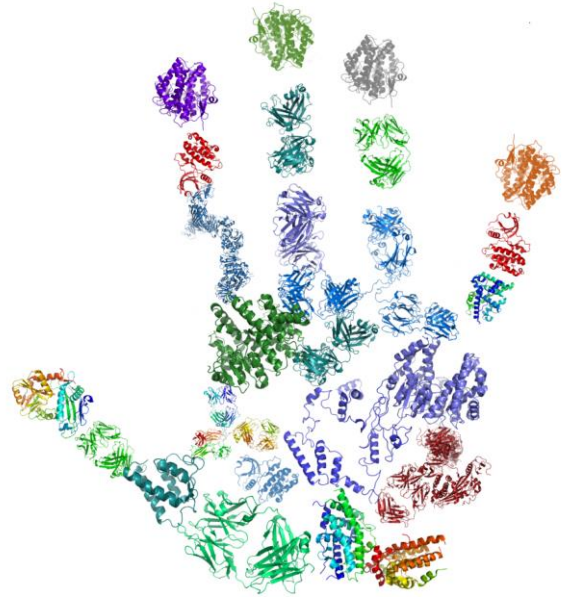
Definition of precision medicine

- **Treatments targeted to the needs of individual patients on the basis of genetics, novel biomarker, phenotypic or psychosocial characteristics.**

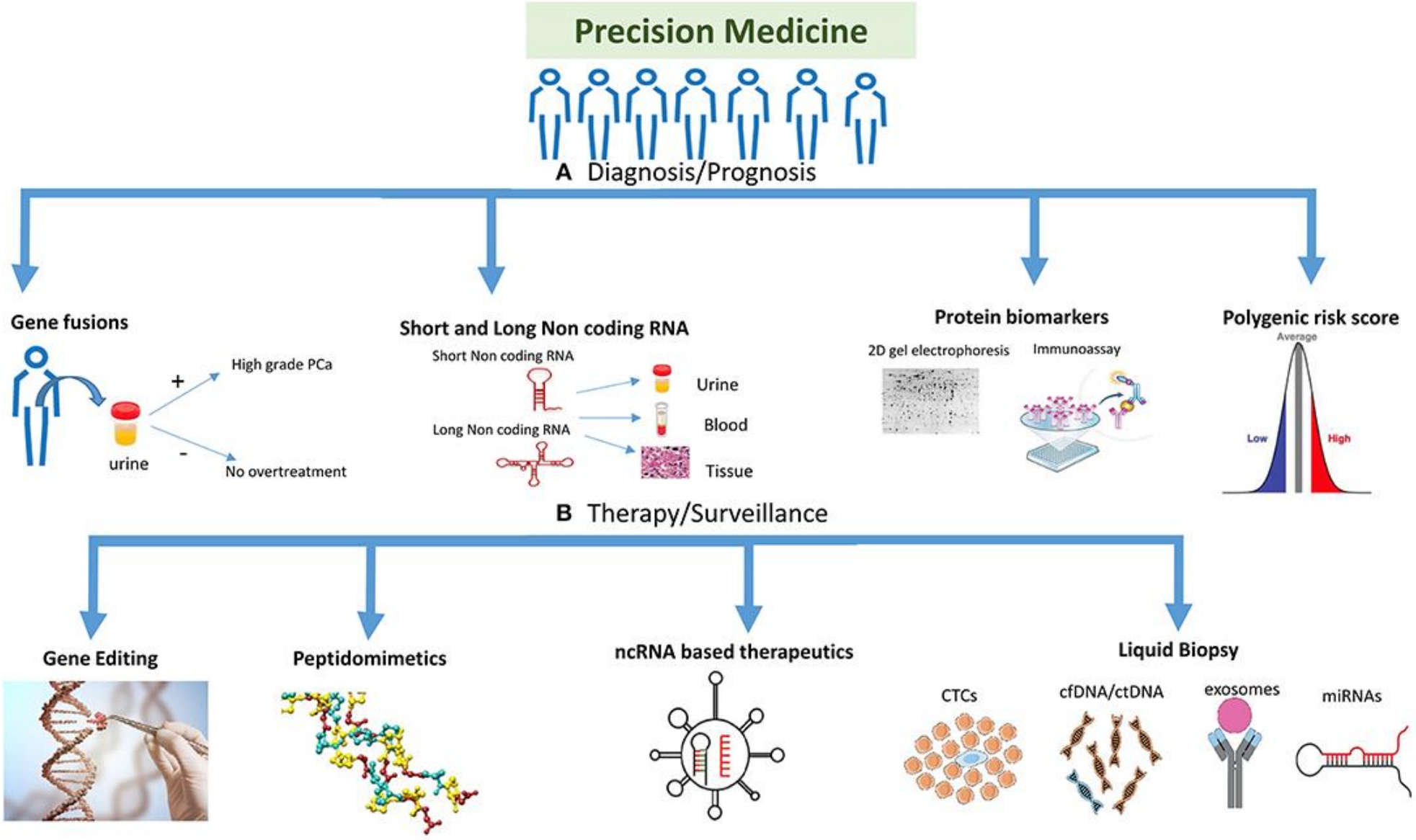
- **Stratify patients into novel subgroups for more precise therapeutic solutions.**







Precision medicine in oncology

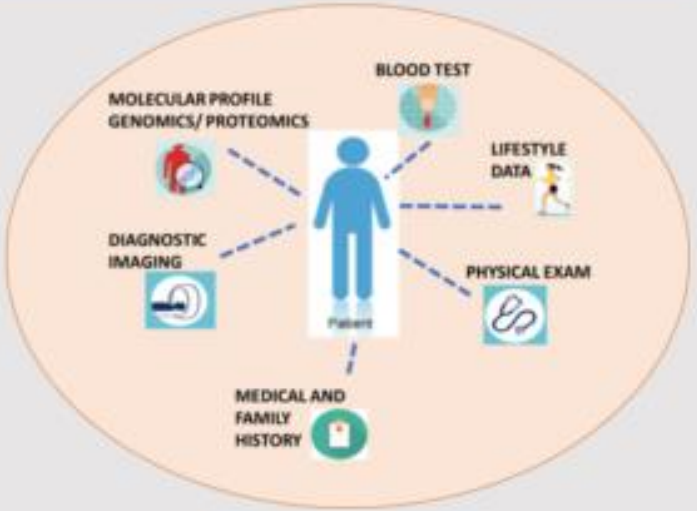


Precision and personalized medicine

PREVENTION

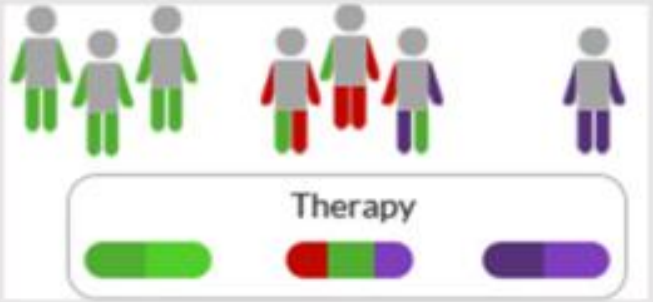
Early detection of patients at risk, Improve preventive measures (individual/collective)

DIAGNOSIS



Accurate disease diagnosis enabling individualized treatment strategy

TREATMENT

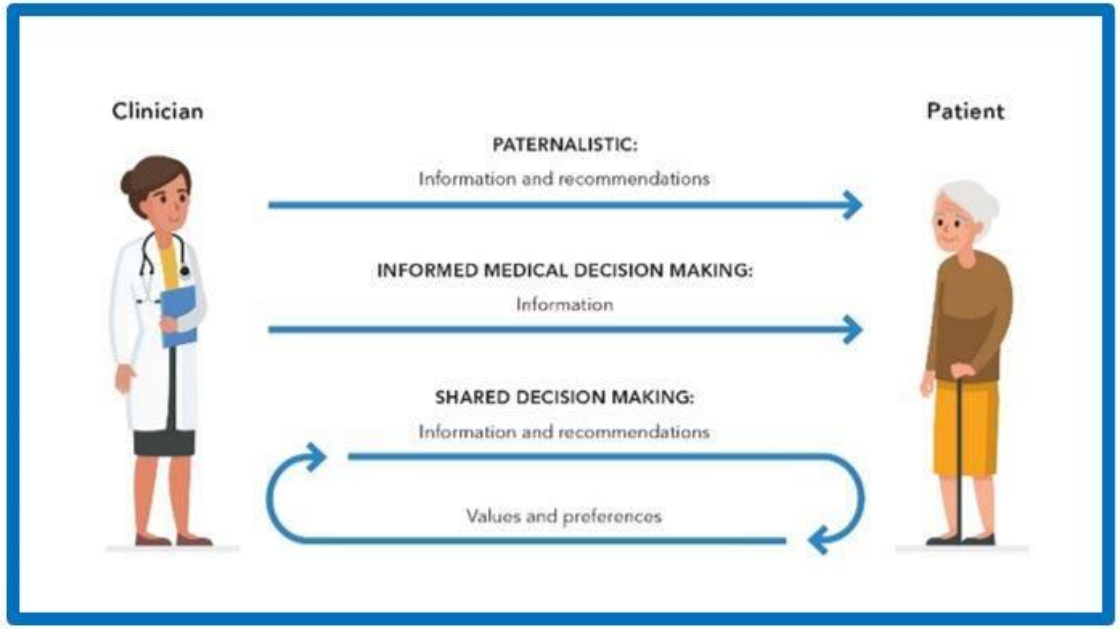


Improved outcomes through targeted treatments and reduced side effects

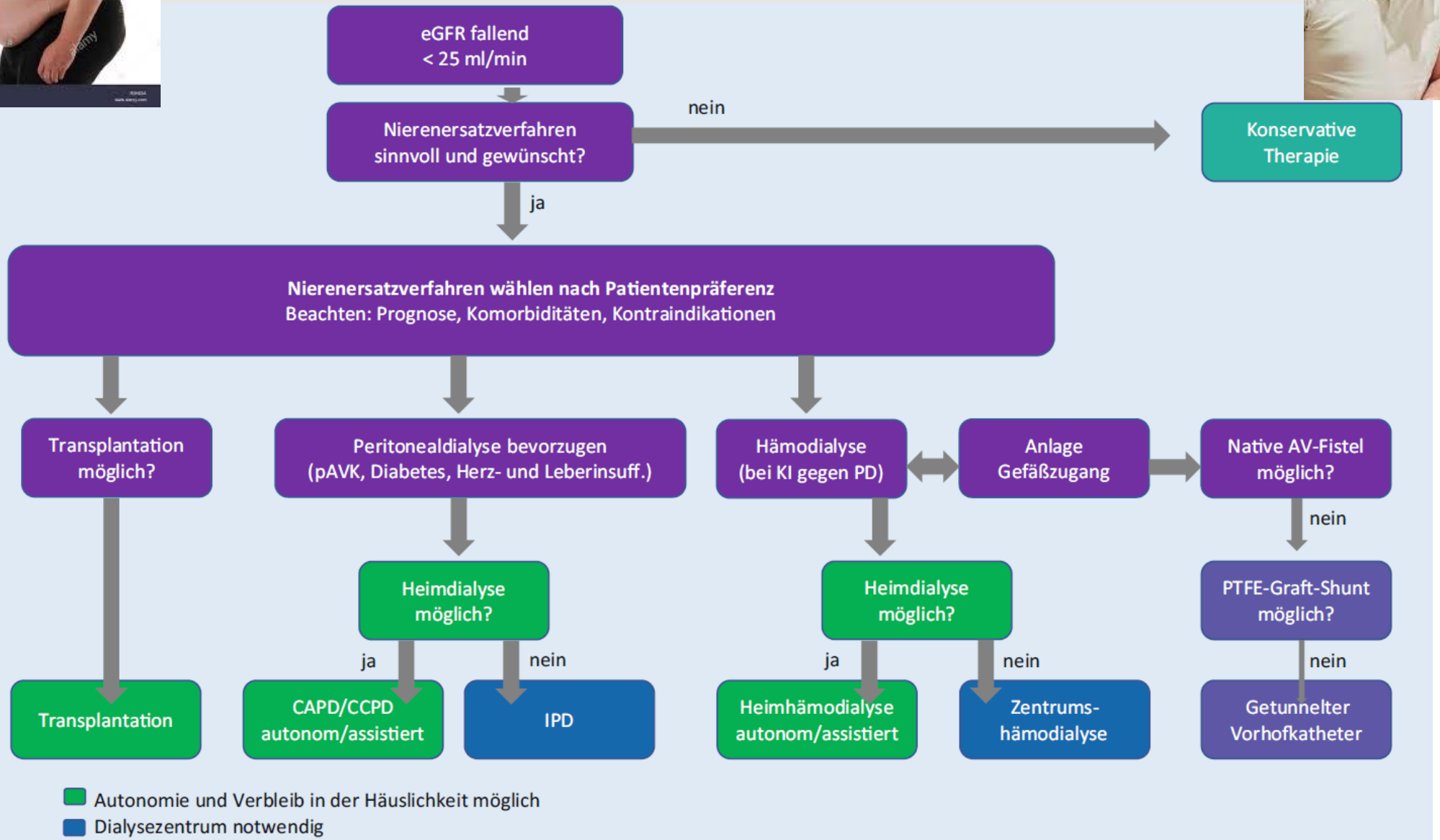
What we already do in nephroplogy

(is more personalized not that much precision medicine)

- **Dose adjustment of durgs on eGFR, drug level, body weight, age, special risks**
- **Individualized blood pressure control based on age, proteinuria, comorbidities**
- **Individualized blood sugar control base on age, comorbidities**
- **Shared desicion making on therapy**



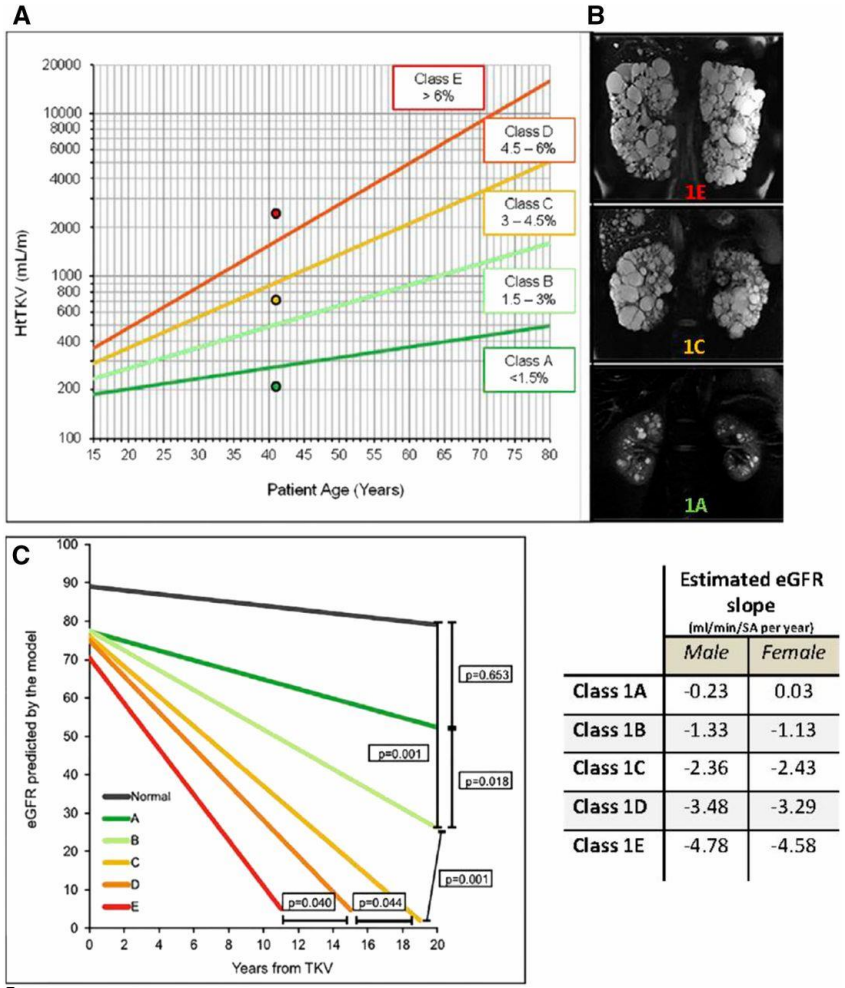
Personalized renal replacement therapy
Exempel 1



Personalized Tolvaptan treatment in ADPKD
Exempel 2

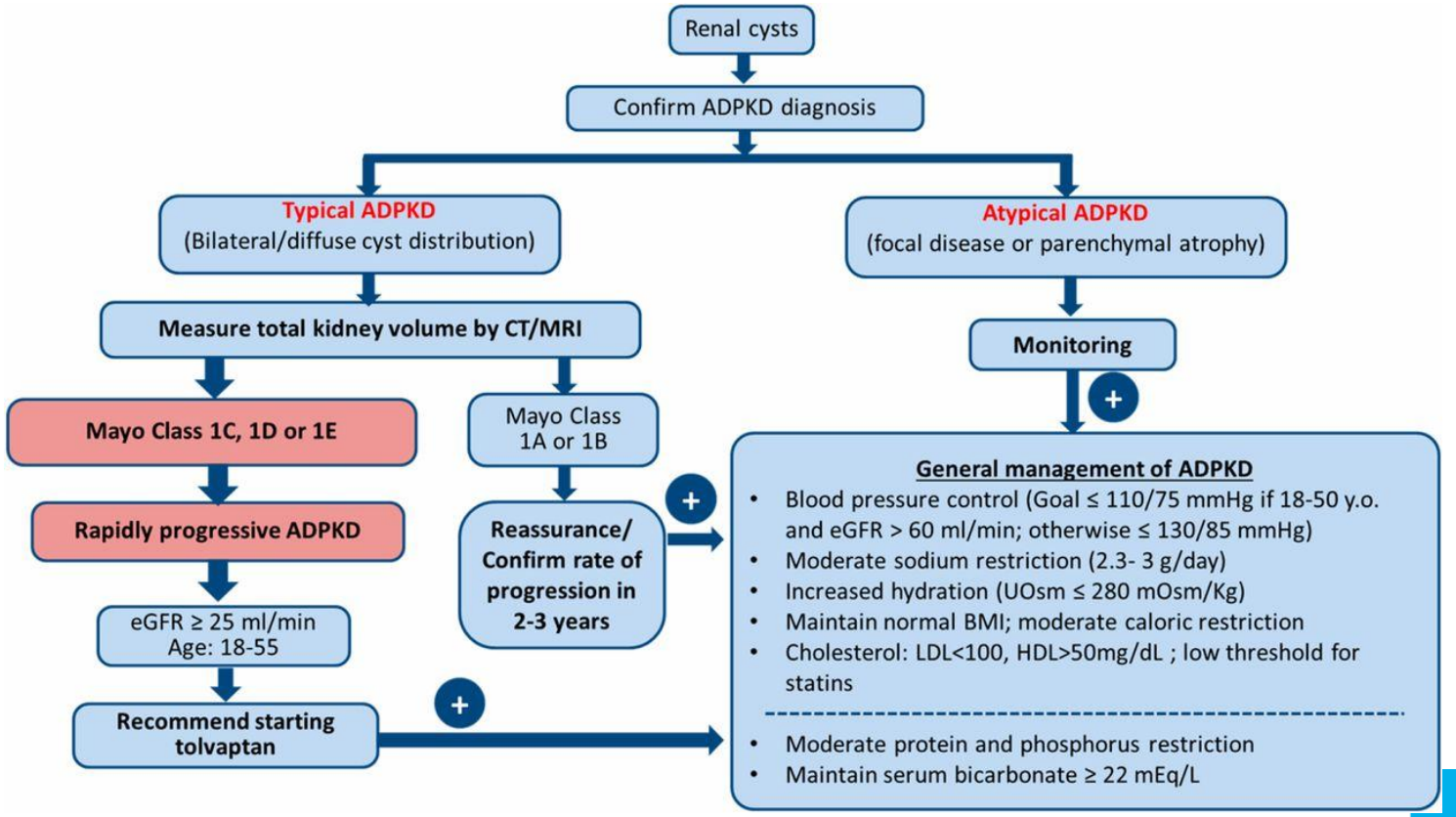
Fouad T. Chebib et al. JASN 2018

Mayo imaging classification

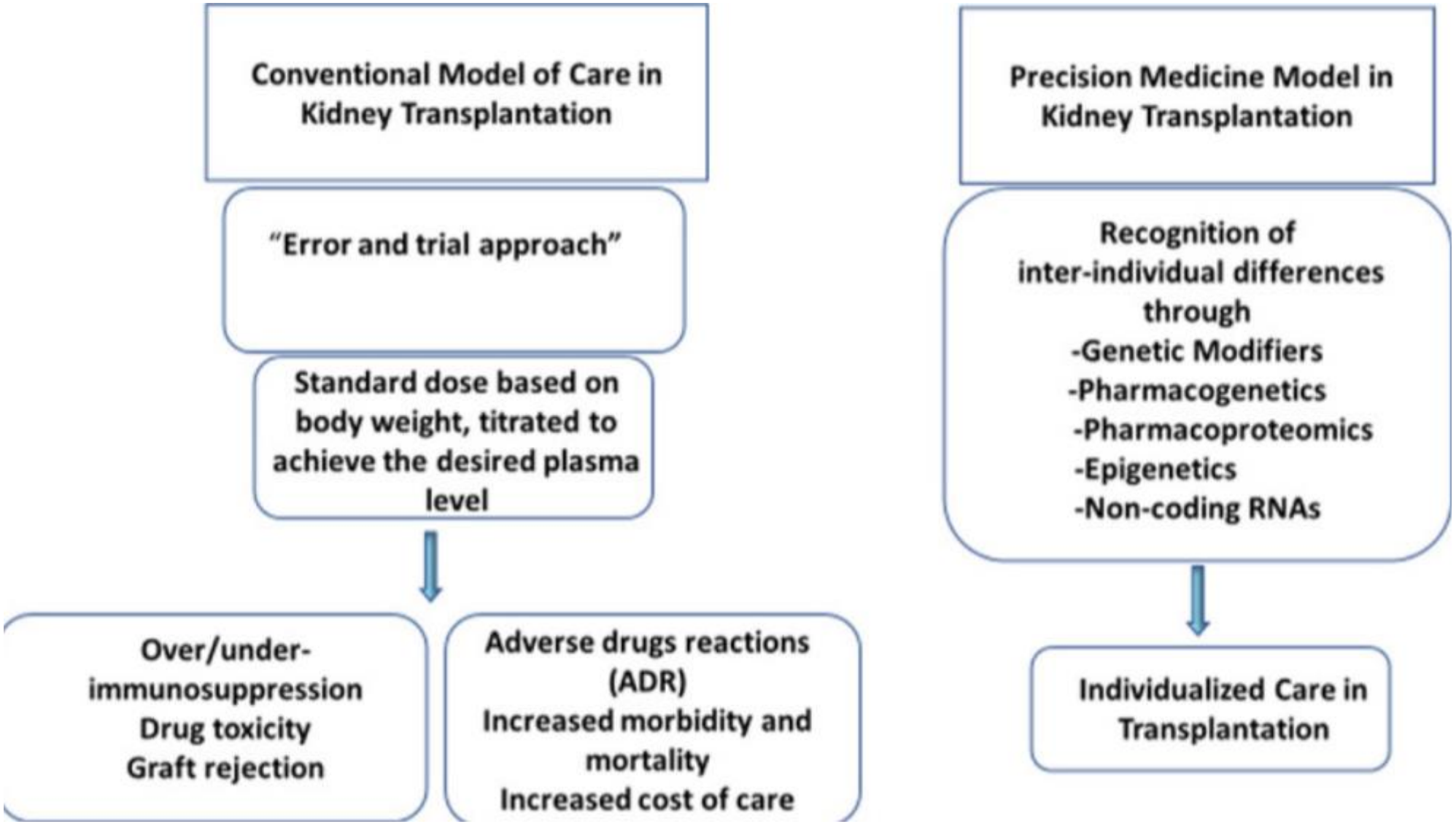


	Estimated eGFR slope (ml/min/SA per year)	
	Male	*Female*
Class 1A	-0.23	0.03
Class 1B	-1.33	-1.13
Class 1C	-2.36	-2.43
Class 1D	-3.48	-3.29
Class 1E	-4.78	-4.58

Identification of patients more likely to benefit from tolvaptan



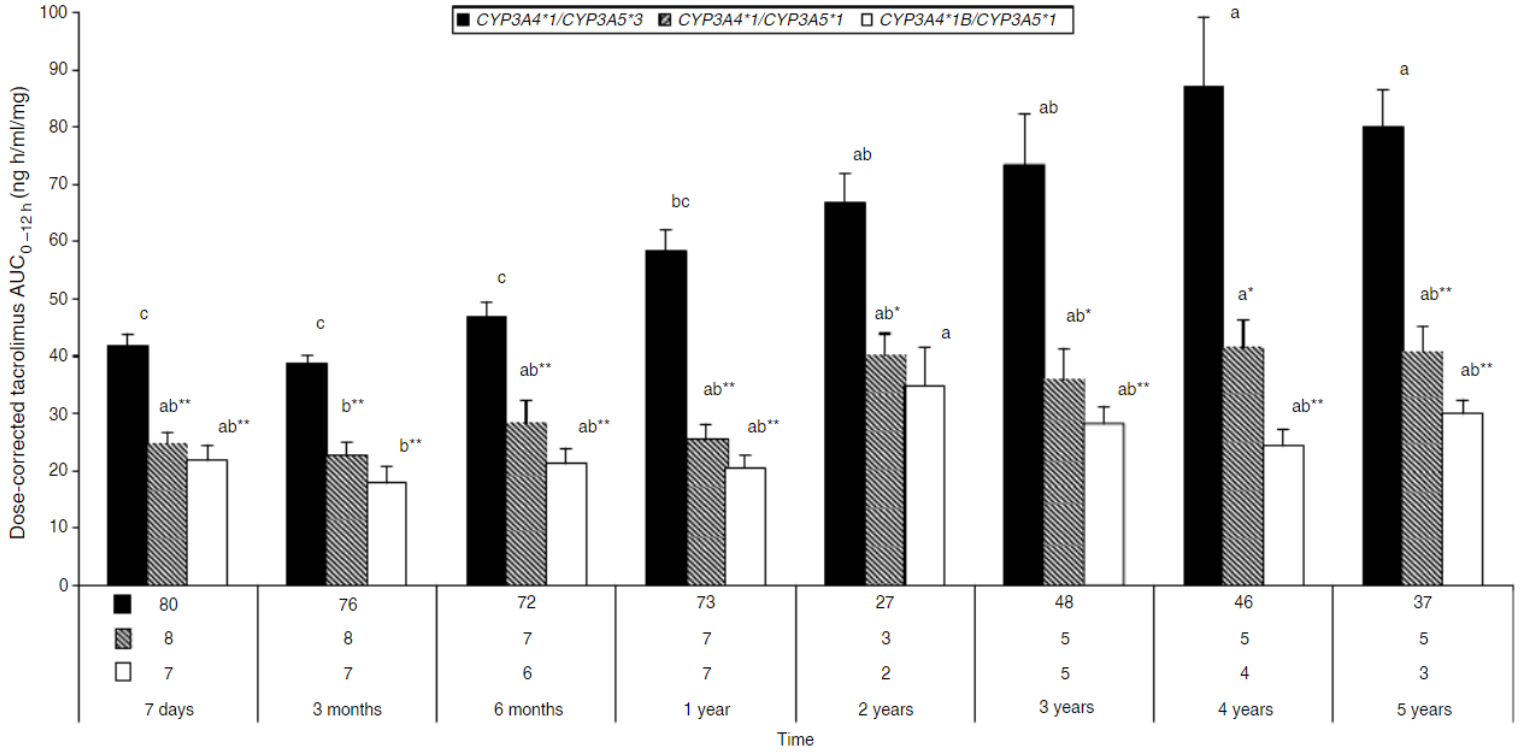
Precision Medicine in Kidney Transplantation



Therapy based on genetic variants in drug metabolic pathways
Exempel 3

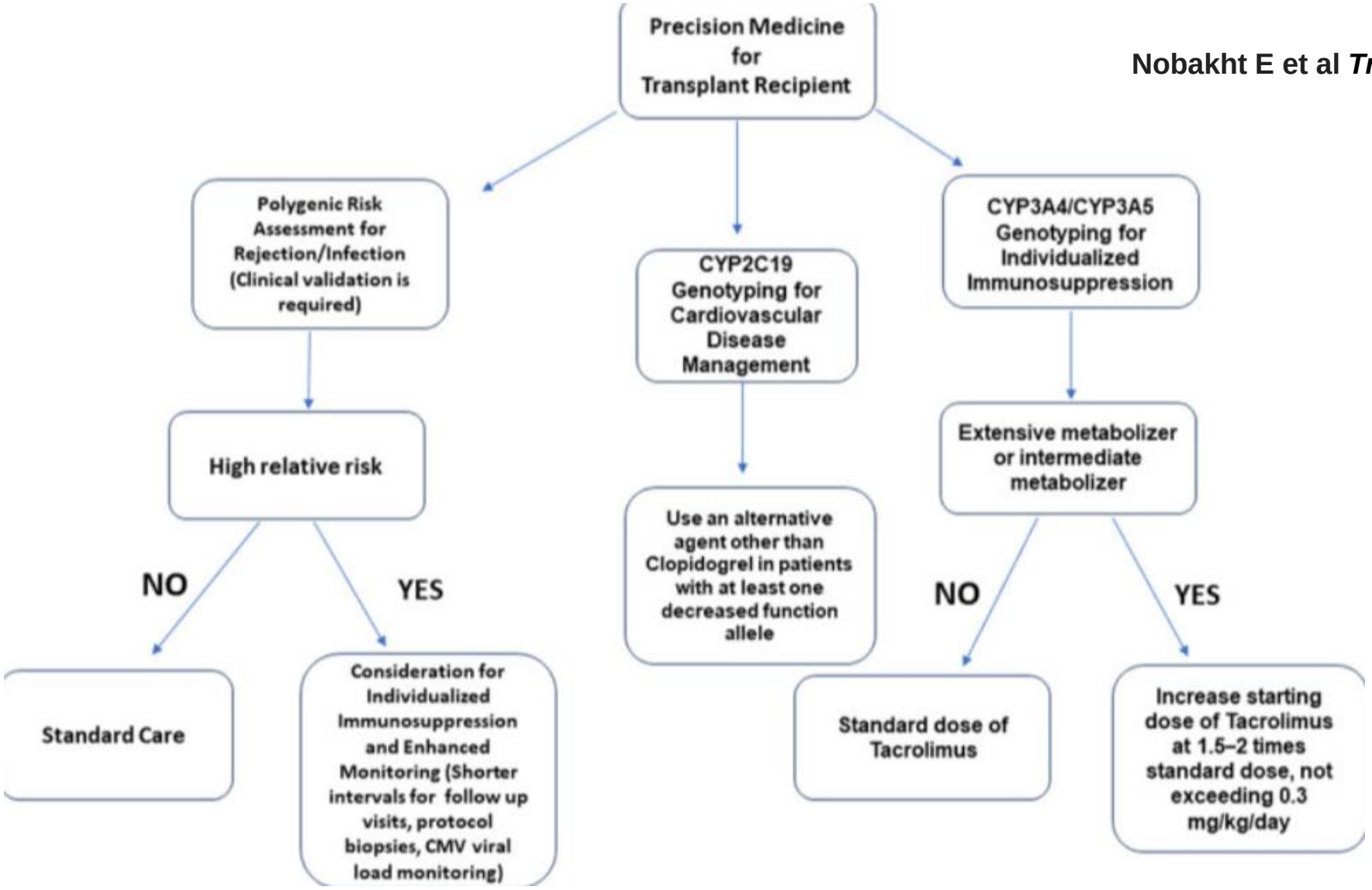
- **Significant inter-individual variation in the expression and function of CYP3A5, CYP3A4, and P-gp is caused by SNPs**

- CYP3A4*1/CYP3A5*1 and CYP3A4*1B/CYP3A5*1 genotypes were significantly more frequently associated with **tacrolimus-related nephrotoxicity** than the CYP3A4*1/ CYP3A5*3 genotype



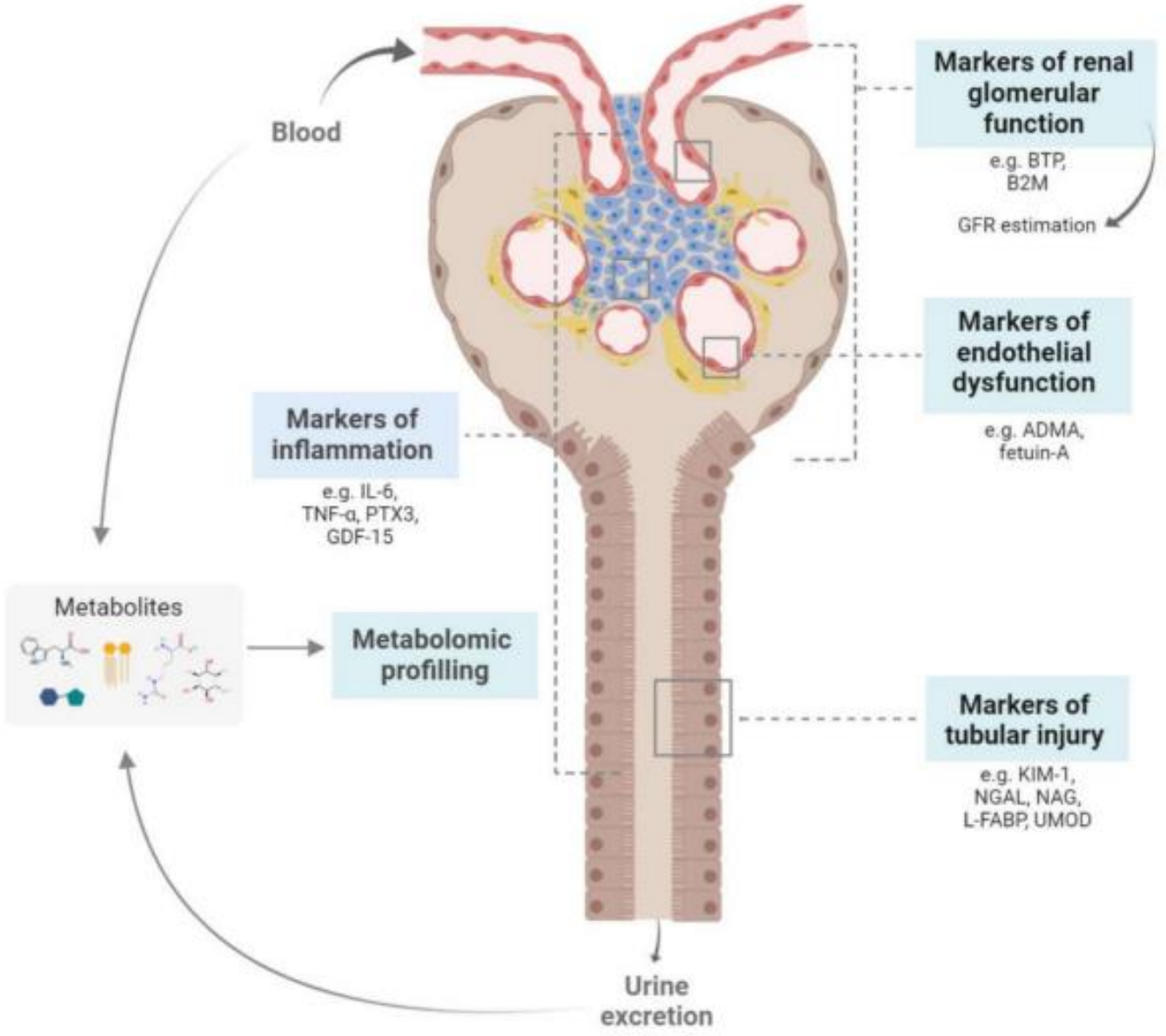
Kuypers DR et al. *Clin Pharmacol Ther*. 2007

Precision Medicine in Kidney Transplantation



Nobakht E et al *Transplant Direct*. 2021

Therapy based on biomarkers



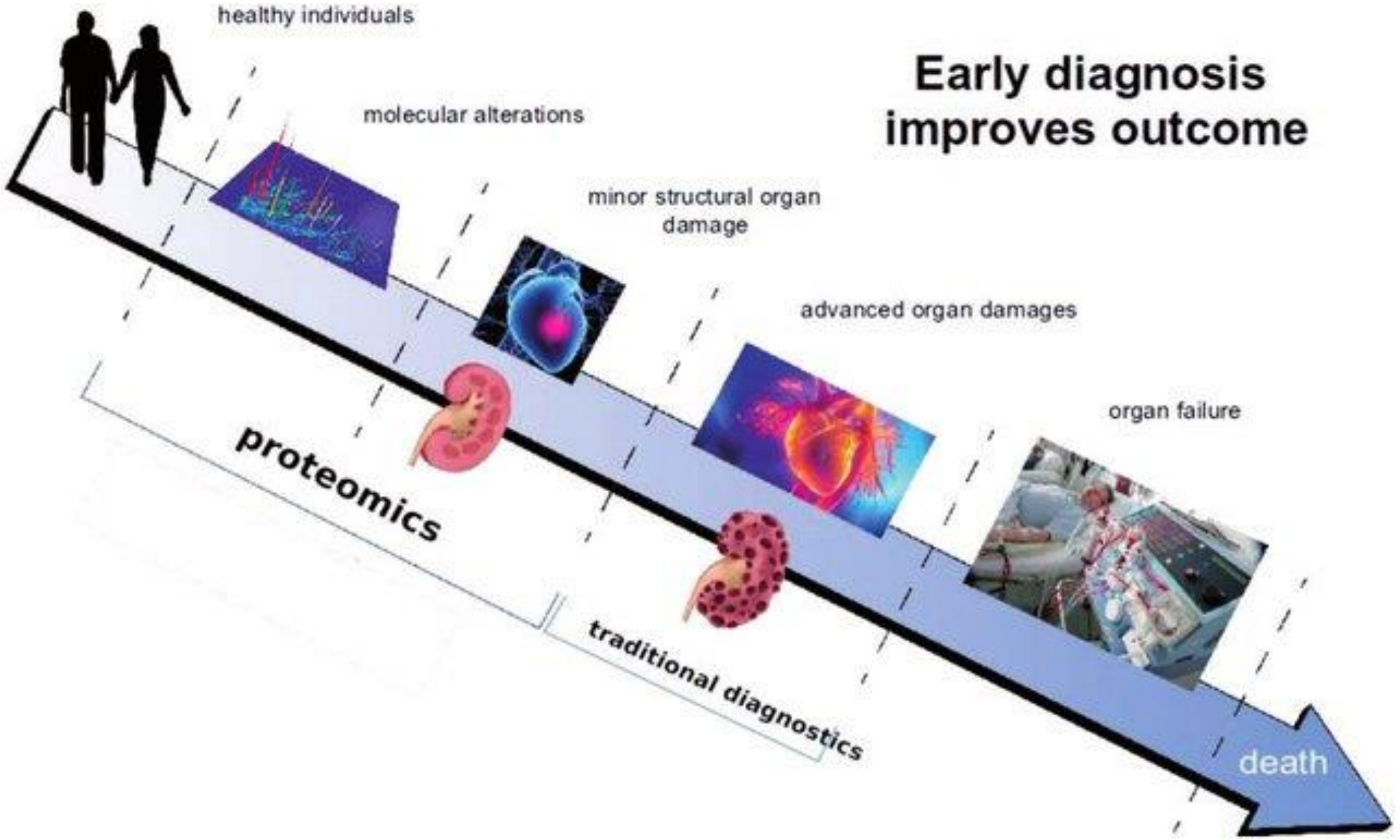
Therapy based on biomarkers

Needs for novel biomarker in nephrology:

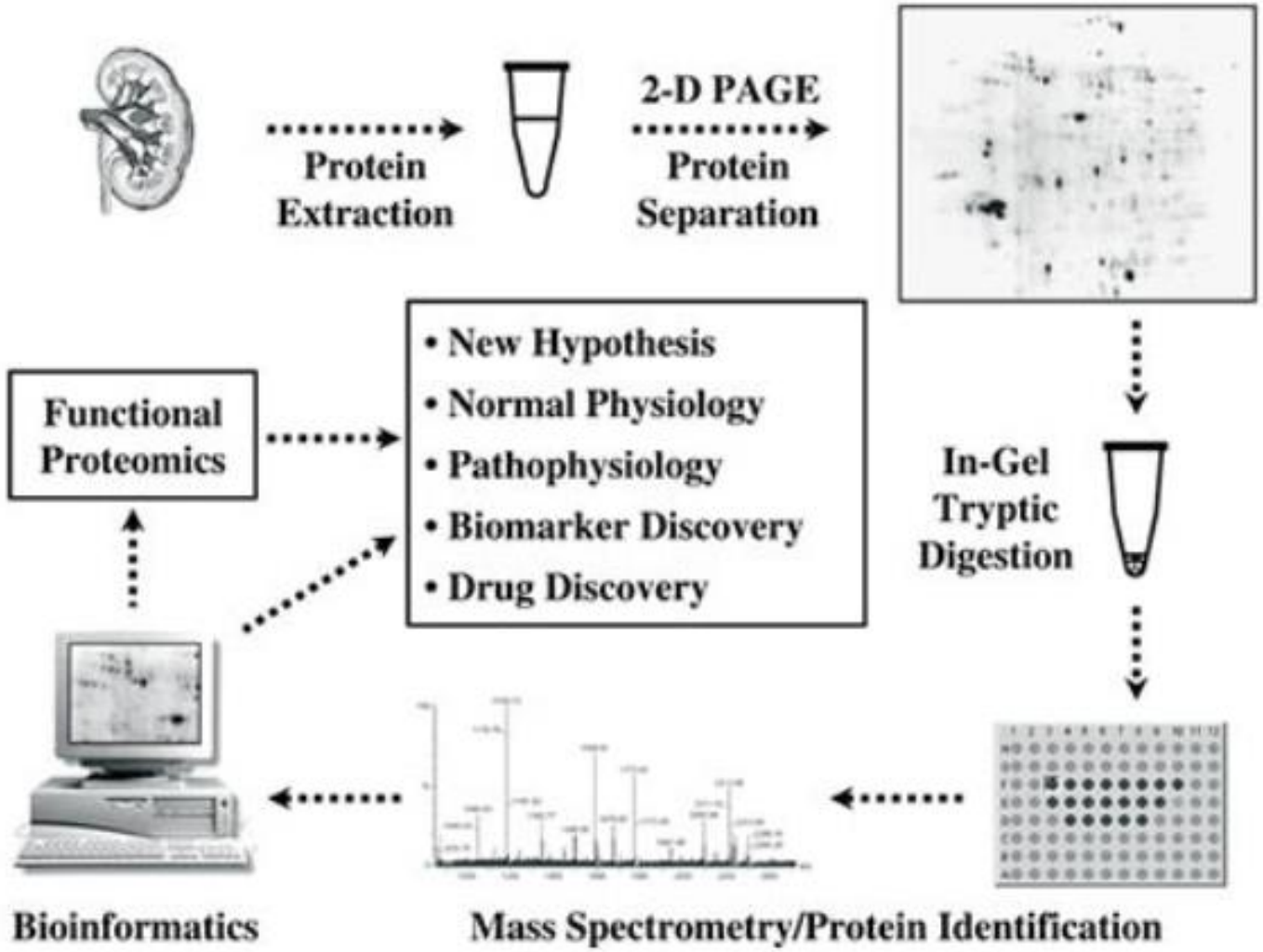
- Renal specificy
- Kinetics, that reflect the dynamic of the disease
- Easy and cost efficient analysis in biological liquids like serum or urin
- Significant better predicition

Non of these biomarkers are in clinical use

Precision medicine



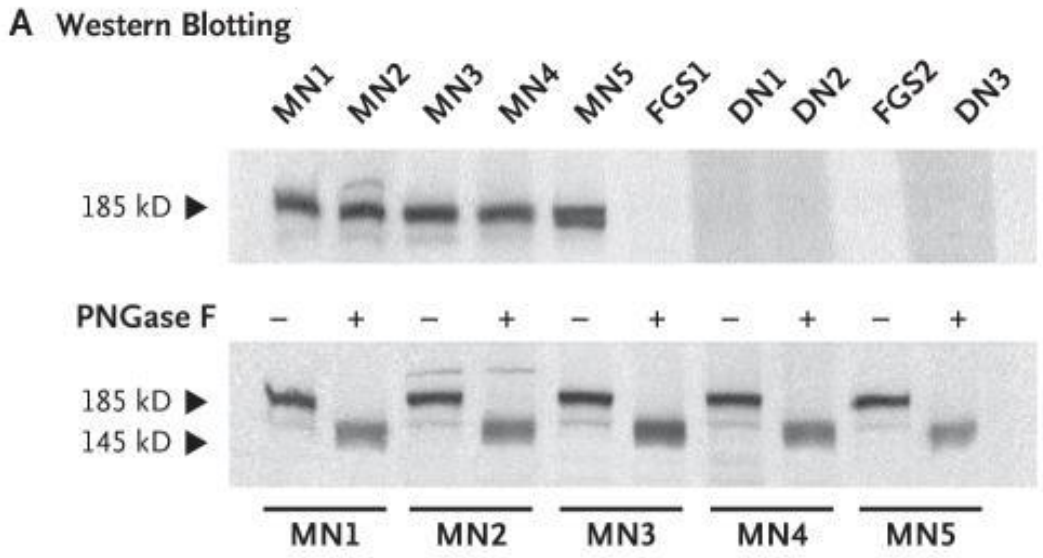
Clinical proteomics

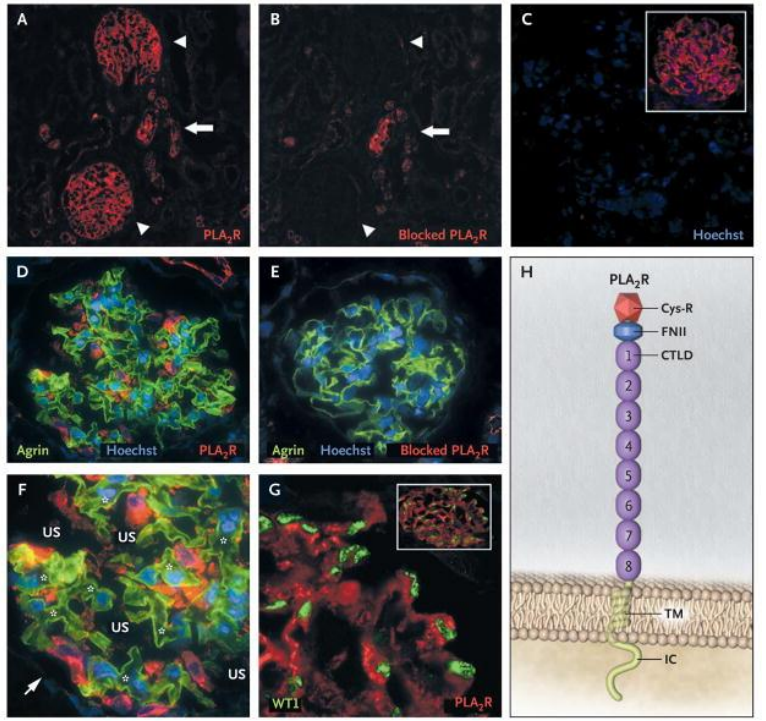


Proteomic approaches in Membranous Nephropathy
Example 4

Beck et al. *N Engl J Med*. 2009

- Western blotting of protein extracts from normal h. glomeruli with serum from MGN.
- Mass spectrometry confirmed the identity of the target antigen with a monospecific antibody
- Reactive serum specimens recognized recombinant PLA_2R
- PLA_2R was expressed in podocytes in normal glomeruli and colocalized with IgG4 in immune deposits in glomeruli with MGN





Proteomic approaches in Membranous Nephropathy

Example 4

Prognostic Biomarker

Created: December 22, 2016.

Definition

A biomarker used to identify likelihood of a clinical event, disease recurrence or progression in patients who have the disease or medical condition of interest.

→ Natural course, untreated

Predictive Biomarker

Created: December 22, 2016.

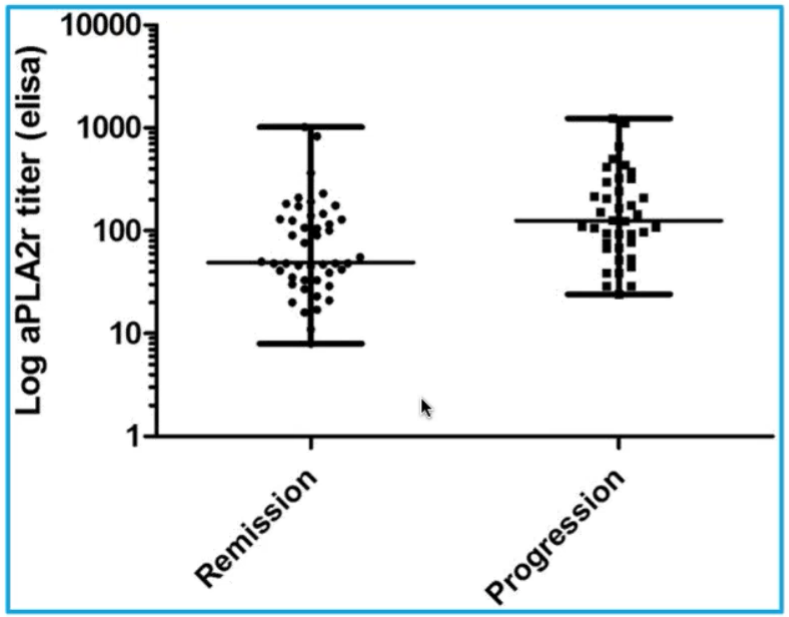
Definition

A biomarker used to identify individuals who are more likely than similar individuals without the biomarker to experience a favorable or unfavorable effect from exposure to a medical product or an environmental agent.

→ Response to therapy

Proteomic approaches in Membranous Nephropathy
Example 4

PLA2Rab as prognostic biomarker



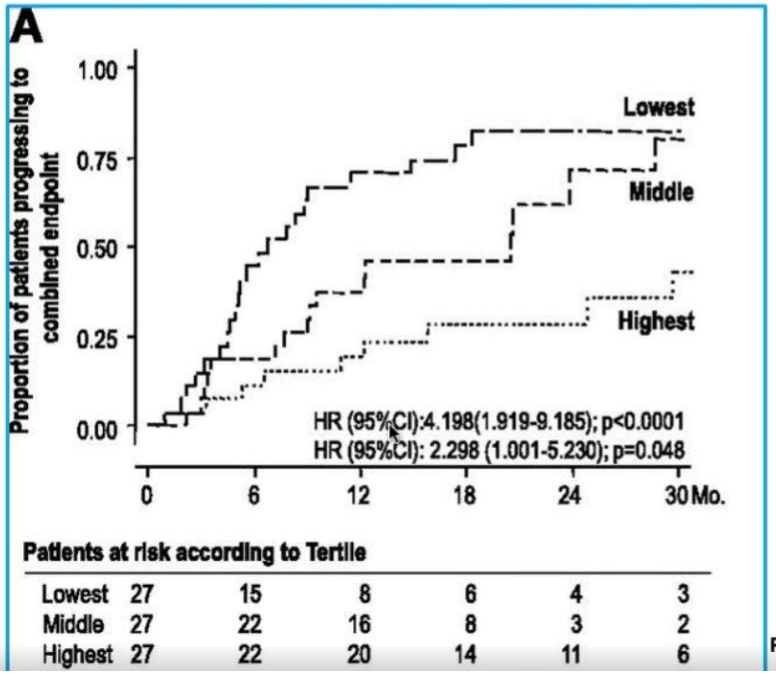
aPLA2R1ab levels at baseline of patients with normal serum creatinine with progression (n = 39) and or spontaneous remission (n = 46).

PLA2Rab levels:

Limited prognostic value

Logt van de AE, Anti-PLA2R1 Antibodies as Prognostic Biomarker in Membranous Nephropathy. Kidney Int Rep. 2021 Apr 22;6(6):1677-1686.

PLA2R antibodies as predictive biomarker



Predictive =

Response to therapy

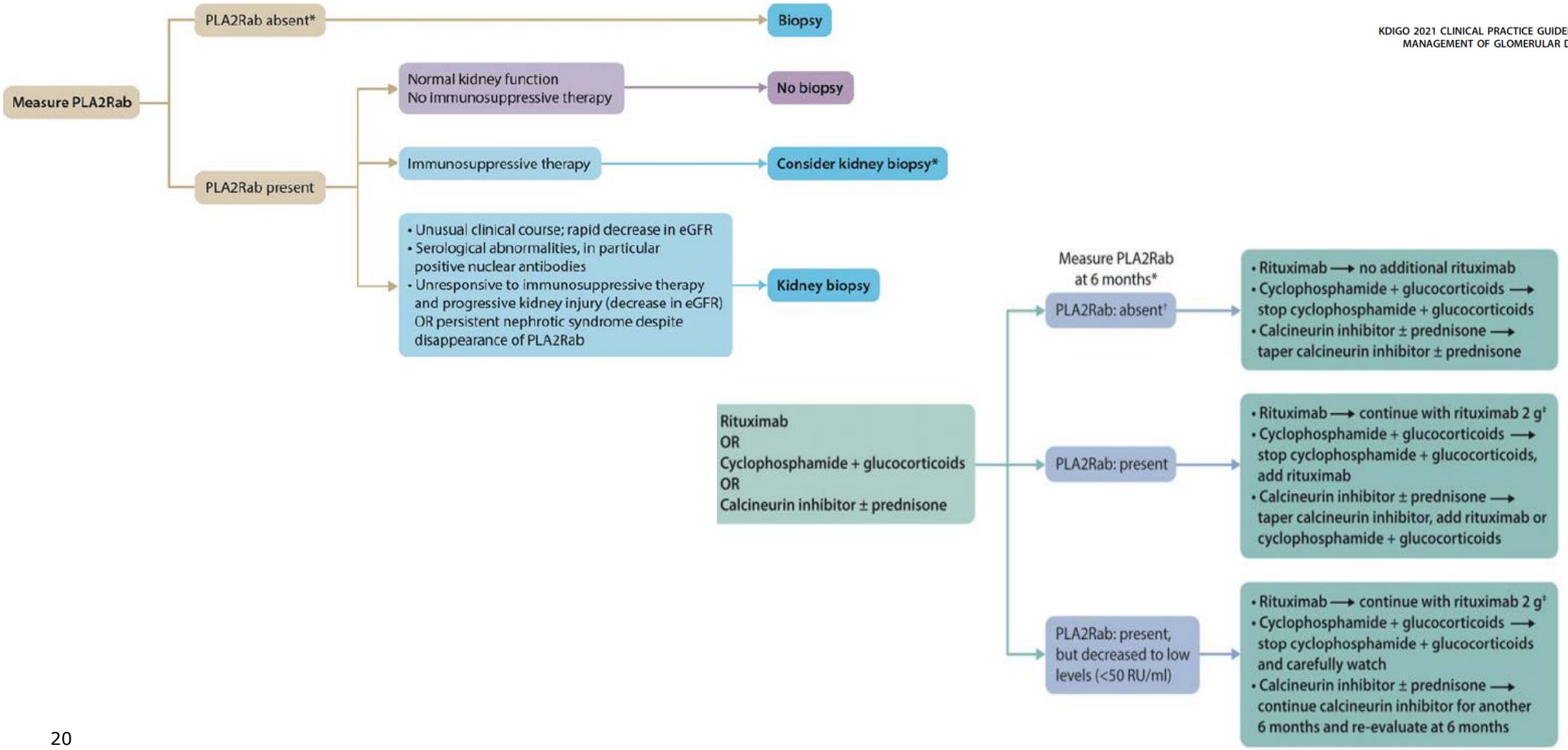
(Rituximab)

(Confirmed in MENTOR)

Piero Ruggenenti et al. JASN 2015;26:2545-2558

Proteomic approaches in Membranous Nephropathy
Example 4

KDIGO 2021 CLINICAL PRACTICE GUIDELINE FOR THE MANAGEMENT OF GLOMERULAR DISEASES



Lipidomics for precision medicine in diabetic nephropathy

Exempel 5

American Diabetes Association. Diabetes Care

Circulating Free Fatty Acid and Phospholipid Signature Predicts Early Rapid Kidney Function Decline in Patients With Type 1 Diabetes

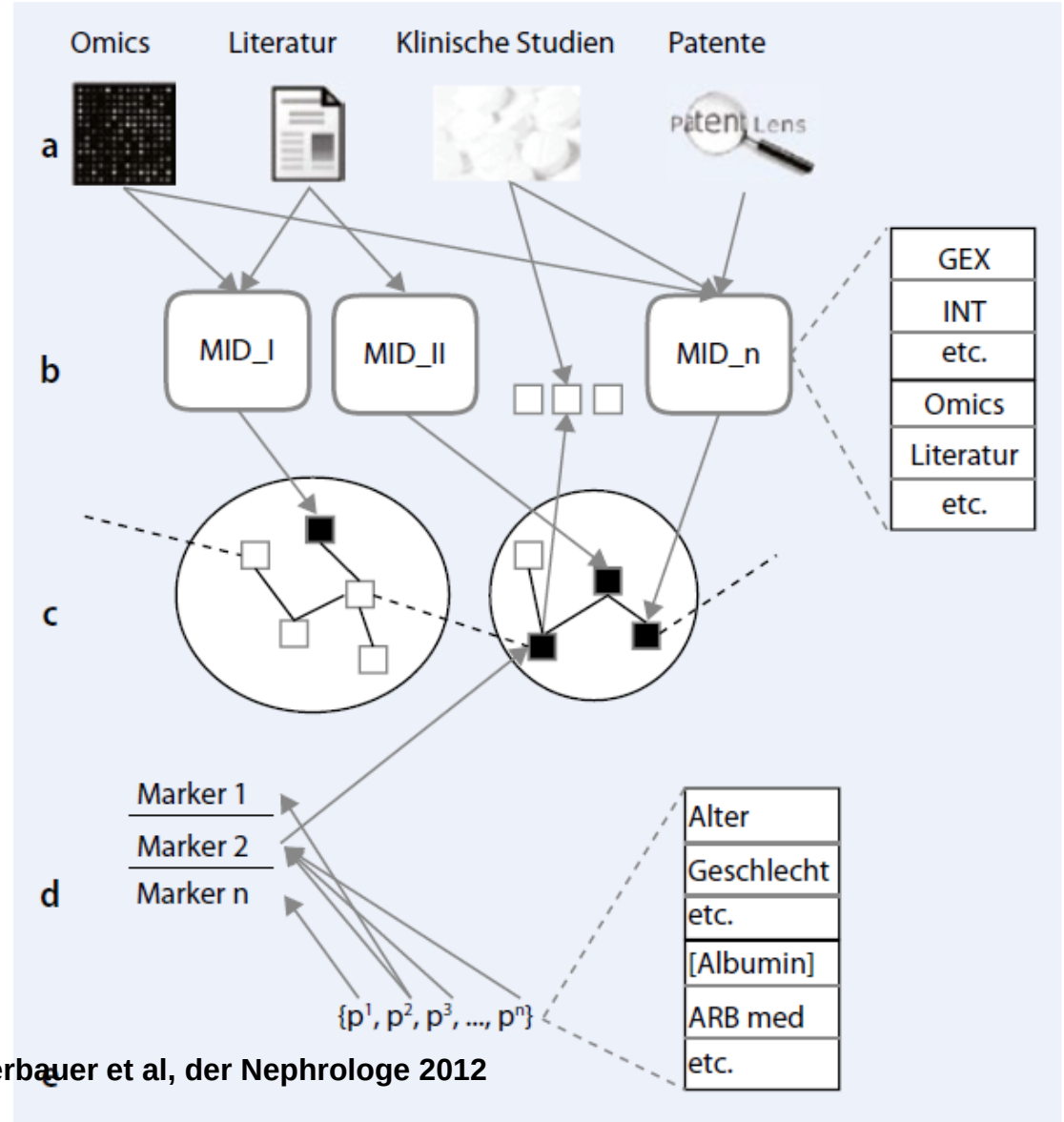
Farsad Afshinnia[1⇑], Thekkelnaycke M. Rajendiran[2,3], Chenchen He[1], Jaeman Byun[1], Daniel Montemayor[4,5], Manjula Darshi[4,5], Jana Tumova[4,5], Jiwan Kim[4,5], Christine P. Limonte[6,7], Rachel G. Miller[8], Tina Costacou[8], Trevor J. Orchard[8], Tarunveer S. Ahluwalia[9,10], Peter Rossing[11,12], Janet K. Snell-Bergeon[12], Ian H. de Boer[6,7,13], Loki Natarajan[14], George Michailidis[15], Kumar Sharma[4,5⇑] **and** Subramaniam Pennathur[1,2,16⇑]

OBJECTIVES Patients with type 1 diabetes (T1D) exhibit modest lipid abnormalities as measured by traditional metrics. This study aimed to identify lipidomic predictors of rapid decline of kidney function in T1D.

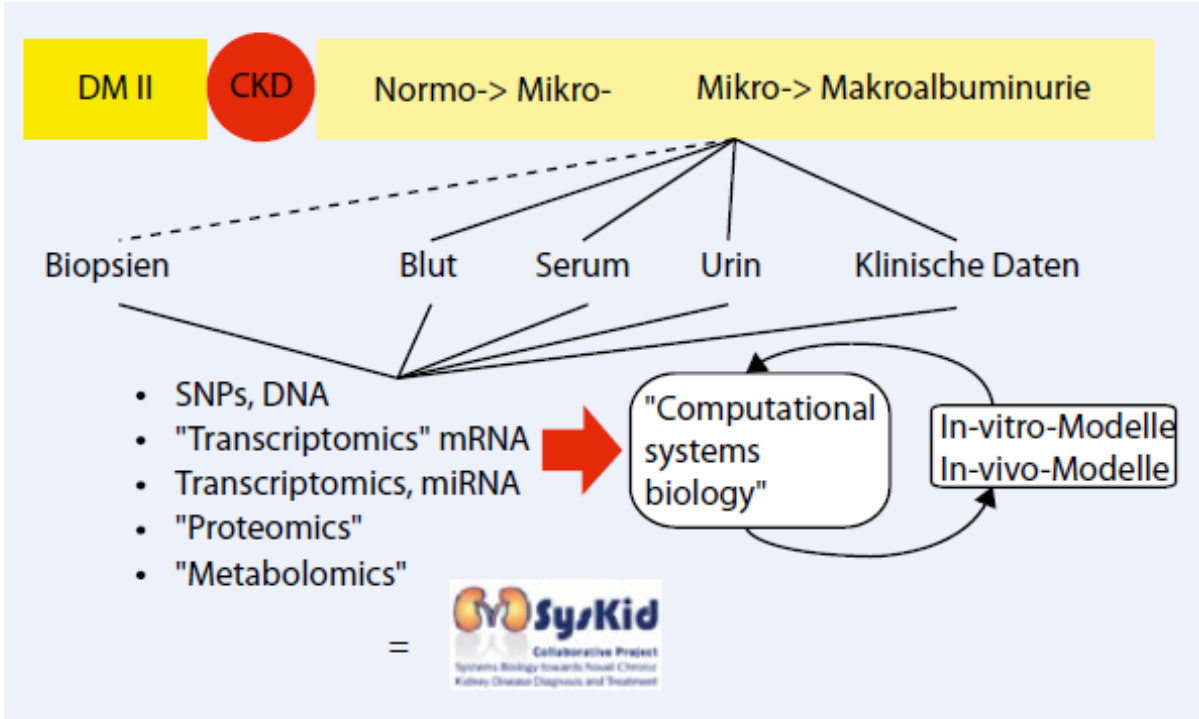
RESEARCH DESIGN AND METHODS In a case-control study, 817 patients with T1D from three large cohorts were randomly split into training and validation subsets. Case was defined as >3 mL/min/1.73 m² per year decline in estimated glomerular filtration rate (eGFR), while control was defined as <1 mL/min/1.73 m² per year decline over a minimum 4-year follow-up. Lipids were quantified in baseline serum samples using a targeted mass spectrometry lipidomic platform.

RESULTS At individual lipids, free fatty acid (FFA)20:2 was directly and phosphatidylcholine (PC) 16:0/22:6 was inversely and independently associated with rapid eGFR decline. When examined by lipid class, rapid eGFR decline was characterized by higher abundance of unsaturated FFAs, phosphatidylethanolamine (PE)-Ps, and PCs with an unsaturated acyl chain at the sn1 carbon, and by lower abundance of saturated FFAs, longer triacylglycerols, and PCs, PEs, PE-Ps, and PE-Os with an unsaturated acyl chain at the sn1 carbon at eGFR ≥90 mL/min/1.73 m². A multilipid panel consisting of unsaturated FFAs and saturated PE-Ps predicted rapid eGFR decline better than individual lipids (C-statistic, 0.71) and improved the C-statistic of the clinical model from 0.816 to 0.841 (P = 0.039). Observations were confirmed in the validation subset.

Integration of molecular and clinical data



Oberbauer et al, der Nephrologe 2012

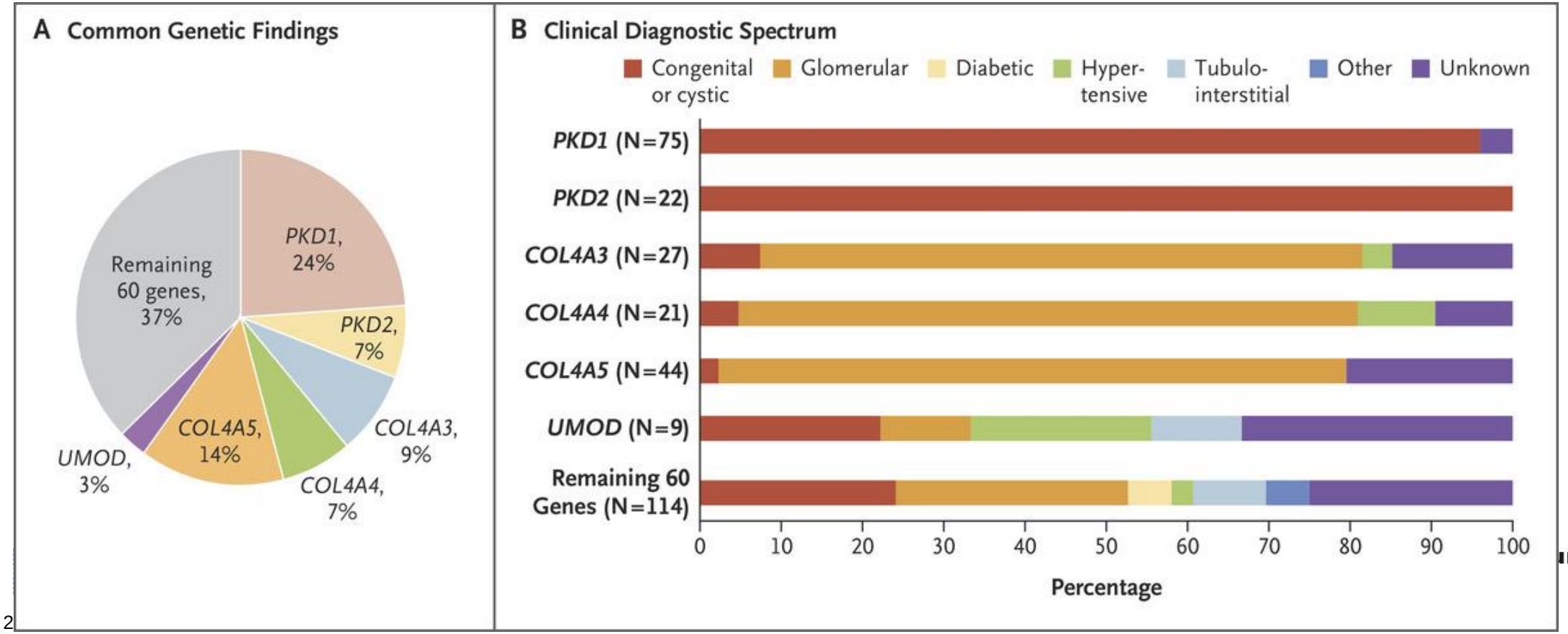


Omics-Datennetz aus Gewebe, Blut und Harn
>Integration dieser Daten im Zusammenhang mit klinischen Daten **(„computational systems biology“)** > **Hypothesen** zur Beschreibung der Pathophysiologie der Erkrankung **> Validierung in Modellsystemen**

Diagnostic utility of exome sequencing for kidney disease
Exempel 6

EE Groopman et al. N Engl J Med 2019

Exome sequencing in a combined cohort of more than 3000 patients with chronic kidney disease yielded a genetic diagnosis in ~10% of cases.



WES for precision medicine in transplantation

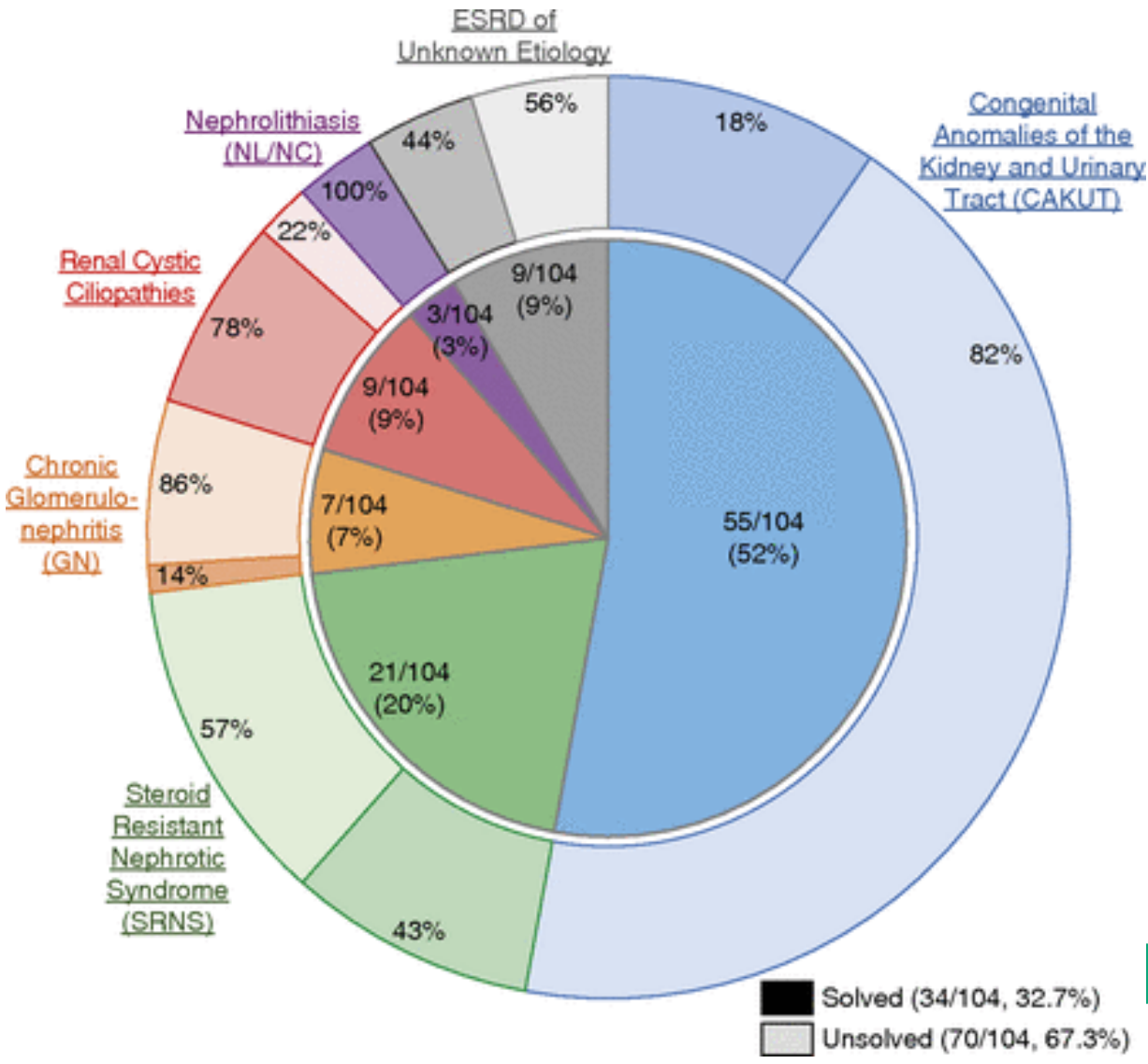
Exempel 7

Whole-Exome Sequencing Enables a Precision Medicine Approach for Kidney Transplant Recipients

Mann et al. JASN, 2019

1/3 of pediatric renal transplant recipients had a genetic cause

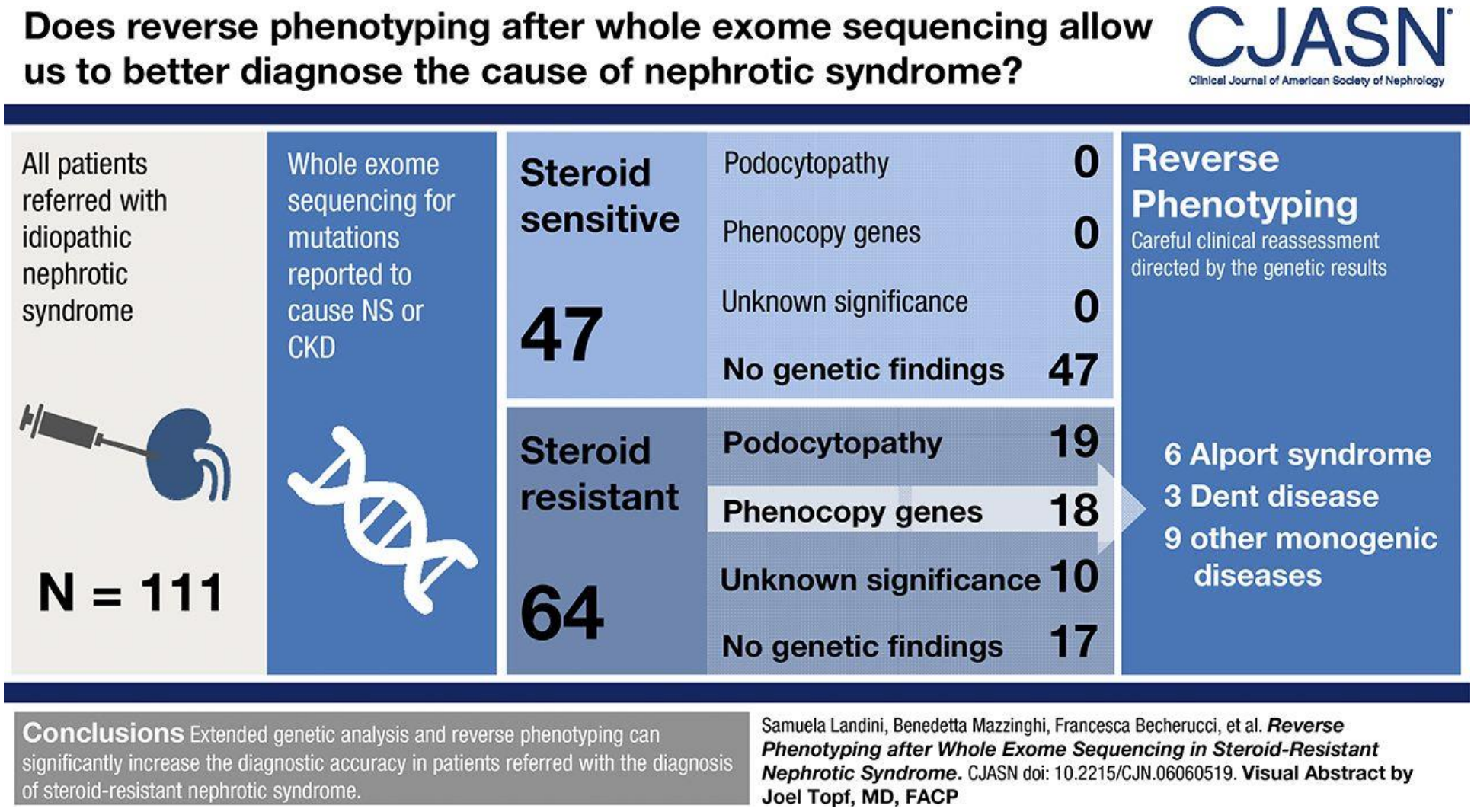
> guide management of both transplant patients and potential living related donors.



WES for precision medicine SNS

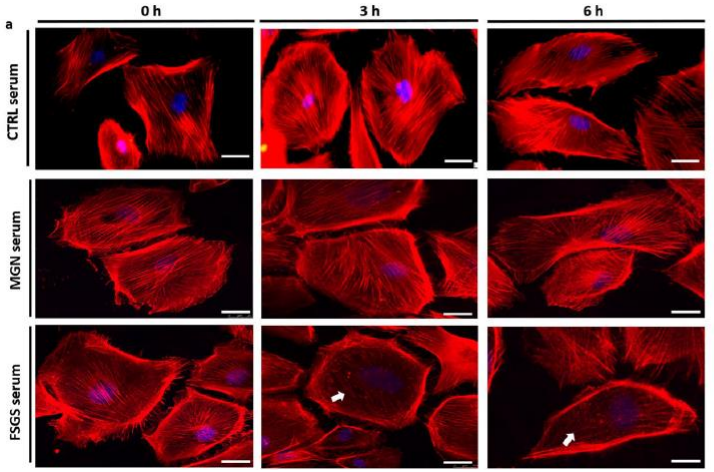
Exempel 8

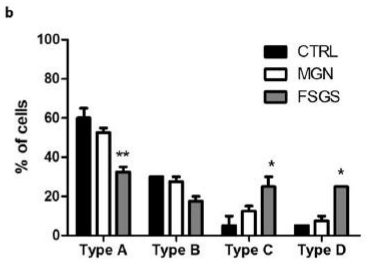
SRNS > genetic podocytopathy
occasionally other genetic nephropathies present as clinically indistinguishable phenocopies

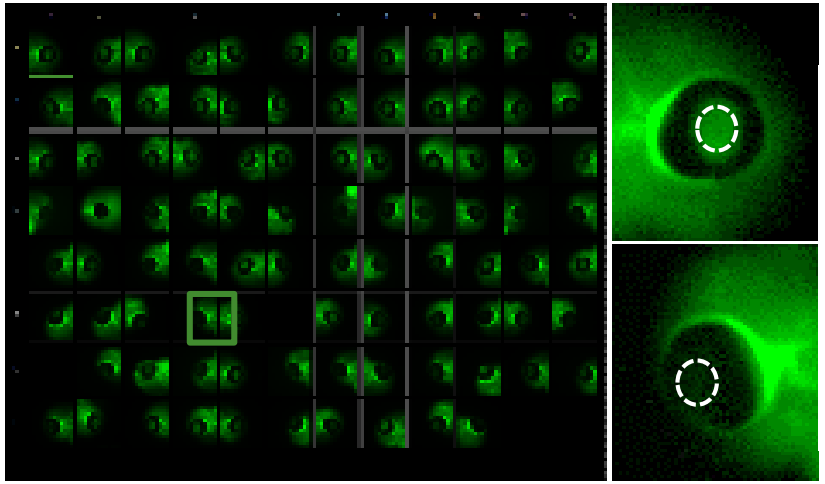


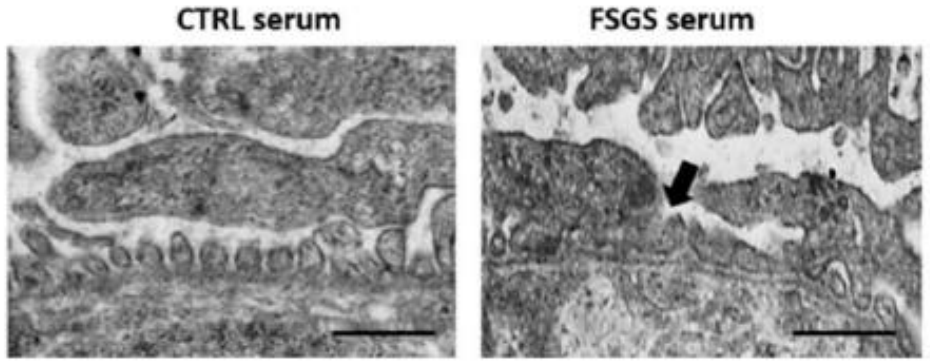
Personalized models for FSGS

Personalized in vitro and in vivo assay for early detection of soluble factors in primary FSGS









iPSCs for personalized podocytes ex vivo

+ Oct4
+ c-Myc
+ Sox2
+ Kfl4

Selection

2d

+ CHIR99021
+ Activin A

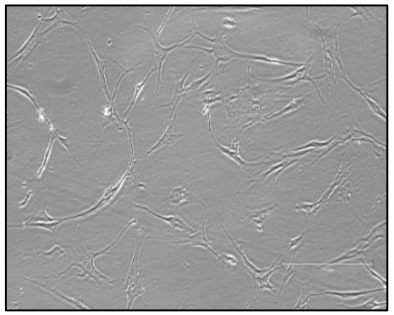
14d

+ CHIR99021
+ BMP7

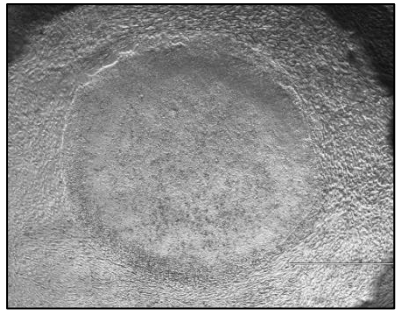
5d

+ BMP7, VEGF,
Activin A,
CHIR99021, Retinoic Acid

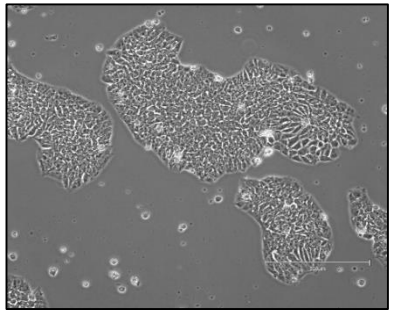
Primary fibroblasts



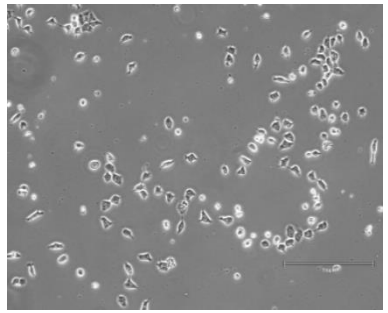
Episomal reprogramming



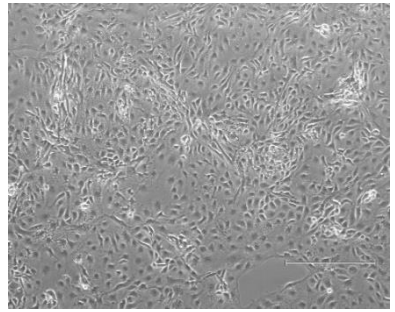
HiPSC



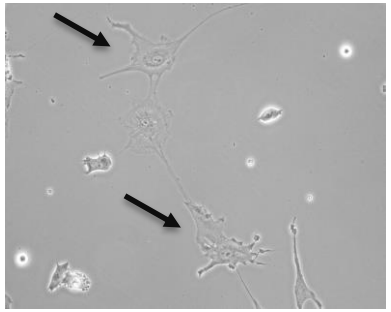
Mesoderm



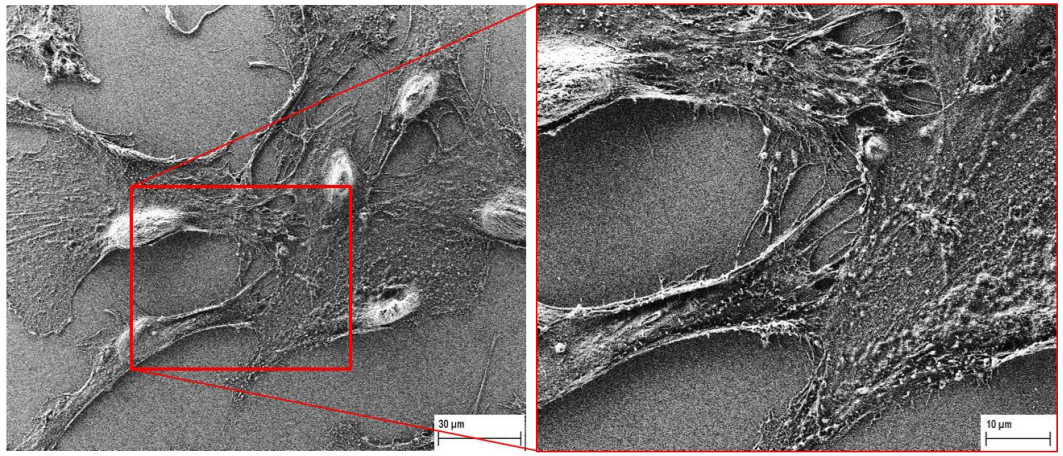
Intermediate Mesoderm



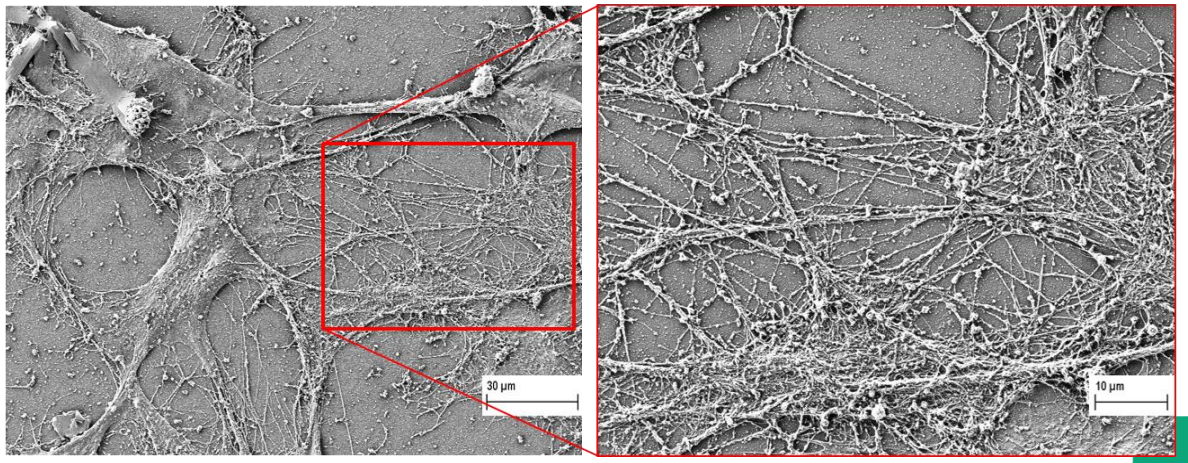
hiPSC-Podocytes



Immortalized podocytes

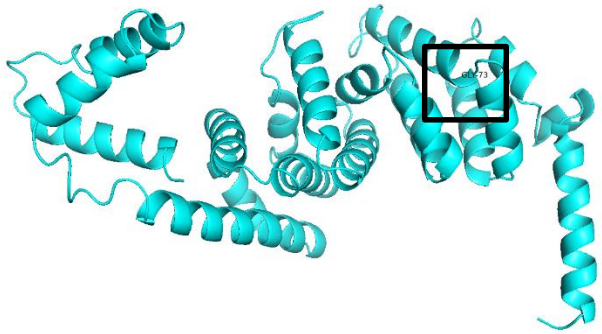


Human induced pluripotent stem cell-derived podocytes

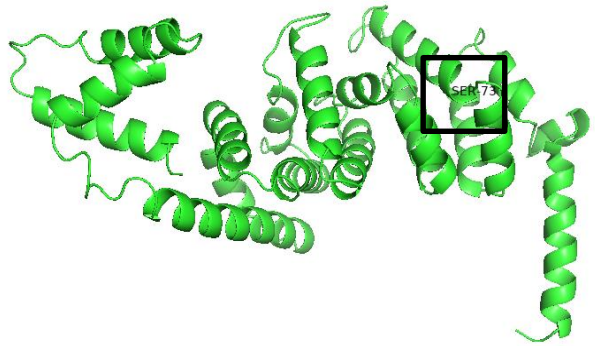


iPSCs for personolized podocytes ex vivo

Wildtype pos. 73 glycine

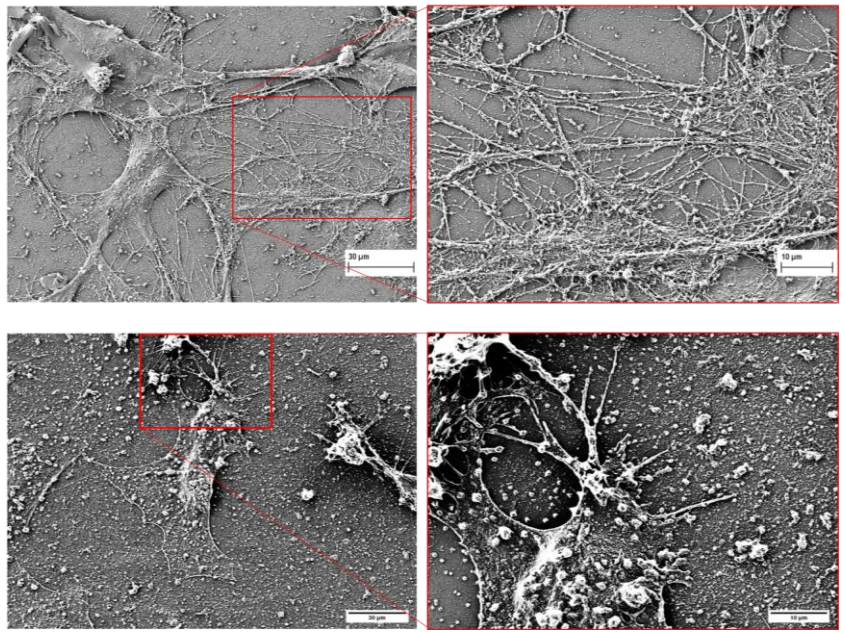


INF2 mutant pos. serine (G73S)

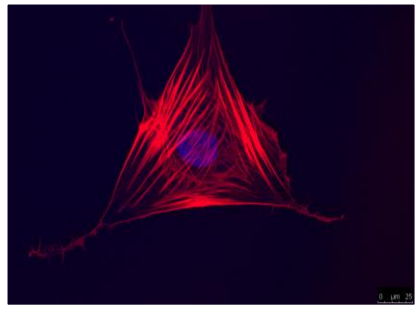


HiPSC-podocytes wildtype

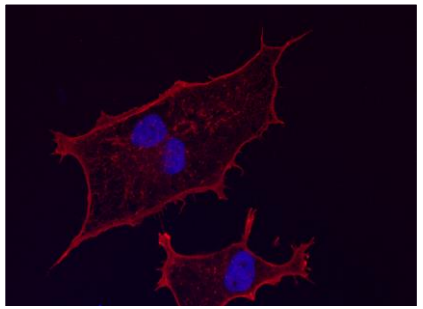
HiPSC-podocytes INF2 mutant



HiPSC-podocytes wildtype



HiPSC-podocytes INF2 mutant

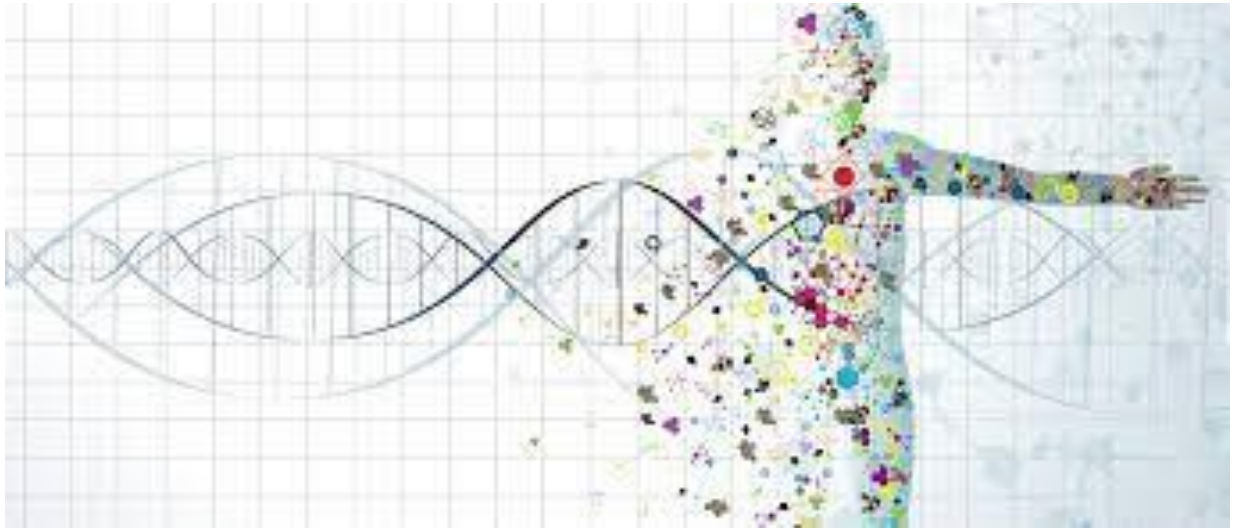


Critics on personalized medicine

- **Interpretation of data:**
  > 200 gene polymorphisms associated with CKD identified by GWAS of >1million people

  - **most implicated genes do not appear “drug able”**
  - **their link to the pathogenesis of CKD remains unclear**

- **Costs**
- **Infrastructure/ technology**
- **no large clinical studies possible any longer with multiple subgroups of a disease**



Conclusion

- **The goal of personalized medicine is to determine the right drug, for the right patient, at the right time.**
- **Taking into account an individual's unique underlying biology and genetics, lifestyle, and environment.**
- **Integration of genetic sequencing, omics, experimental assays and clinical data to understand phenotypic complexity of different forms of CKD > precision medicine.**

Thank you for your attention

One size does not fit all

Heidelberger Nephrologie Seminar **2021**