RENAL FUNCTION

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ARGENTINA

2015

NOVARTIS
PHARMACEUTICALS

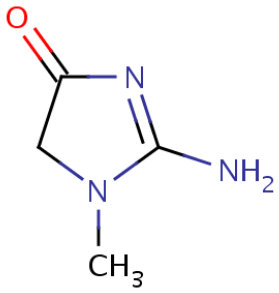
DISCLOSURES

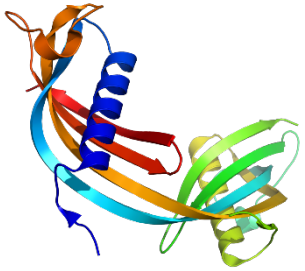
- Served as a consultant and/or has received lecture honoraria from:

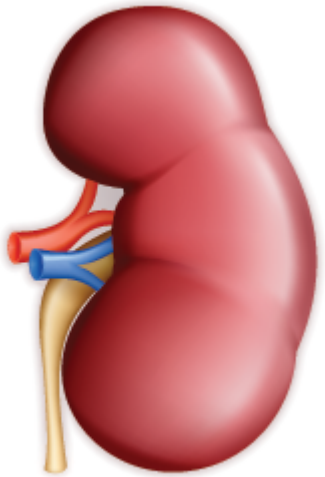
- ALEXION
- BRISTOL MYERS SQUIBB
- GENZYME
- NOVARTIS
- PFIZER

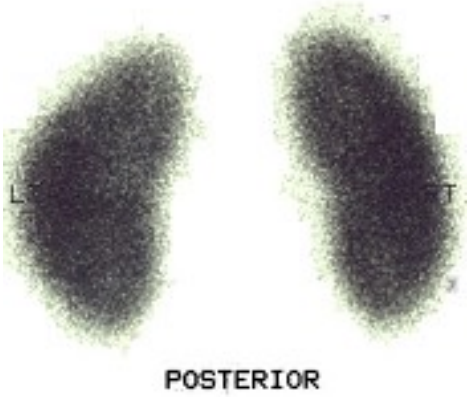
NOVARTIS PHARMACEUTICALS

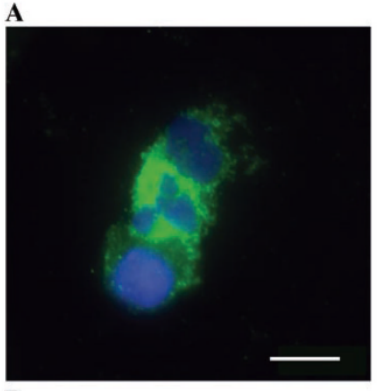
HOW CAN WE ASSESS RENAL FUNCTION?

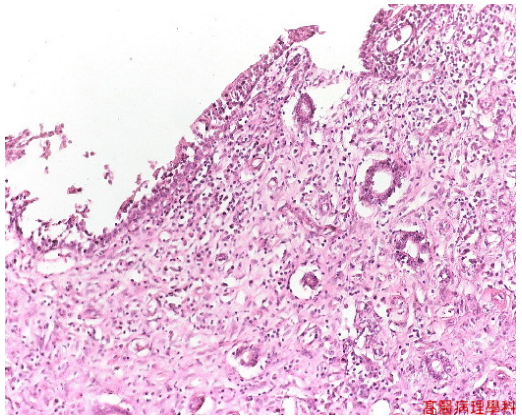


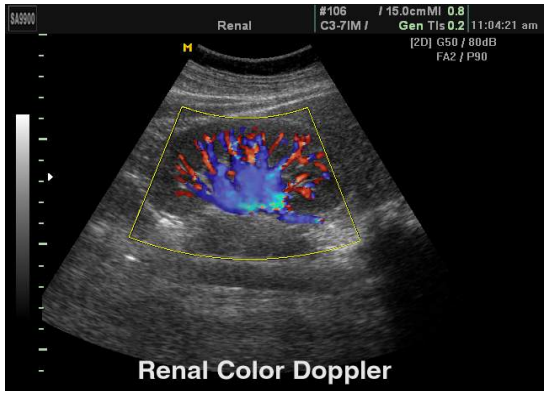












NOVARTIS PHARMACEUTICALS

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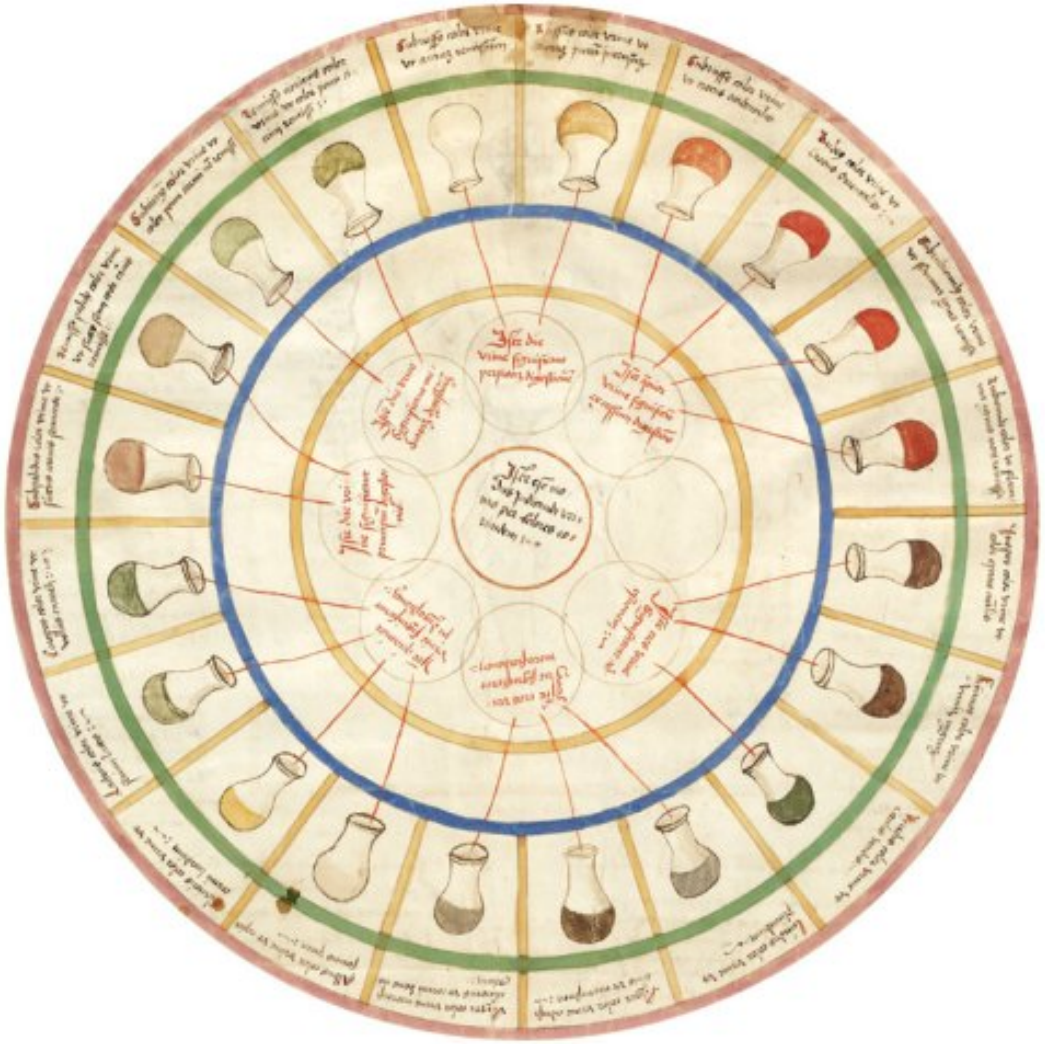

"This urine wheel was published in 1506 by Ullrich Pinder, in his book Epiphanie Medicorum. It describes the possible colours, smells and tastes of urine, and uses them to diagnose disease." *Jeremy K. Nicholson & John C. Lindon Nature 2008 455(7216): 1054-1056*

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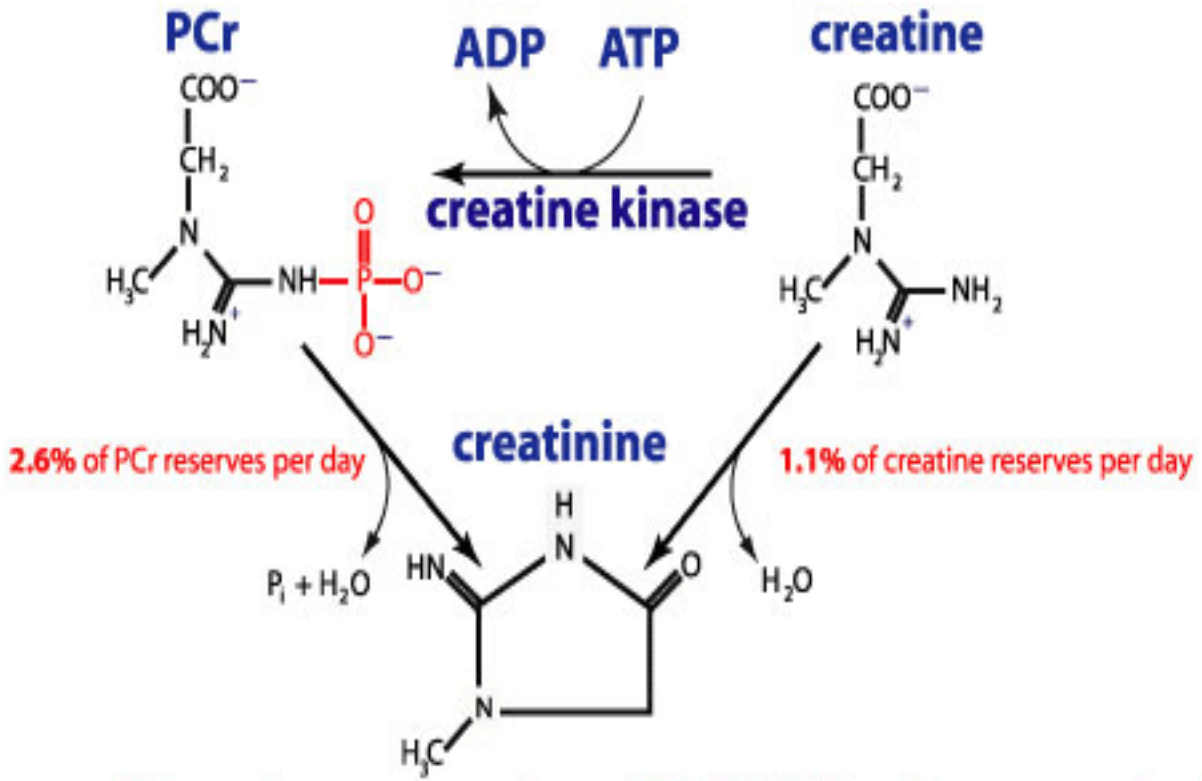

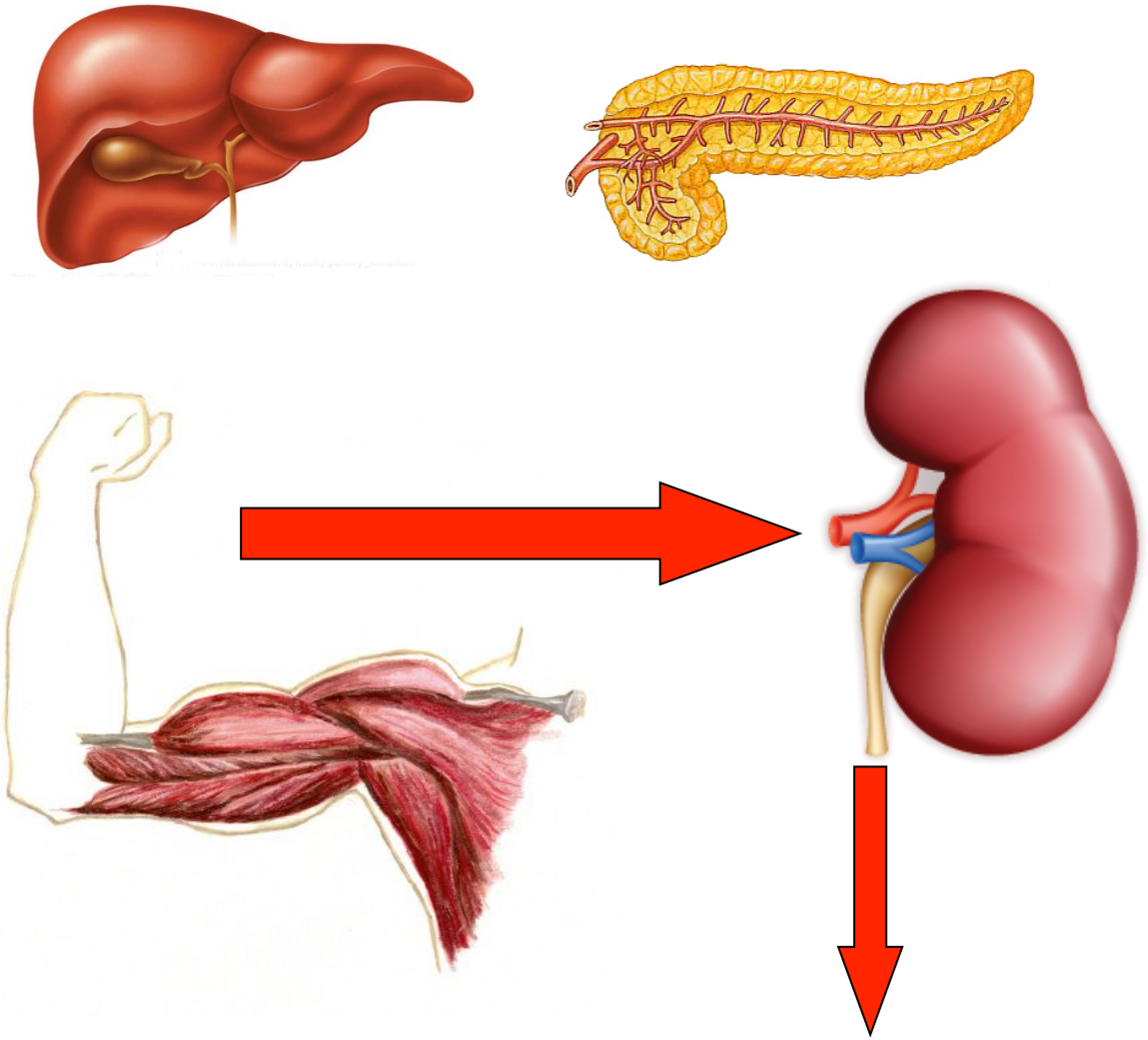

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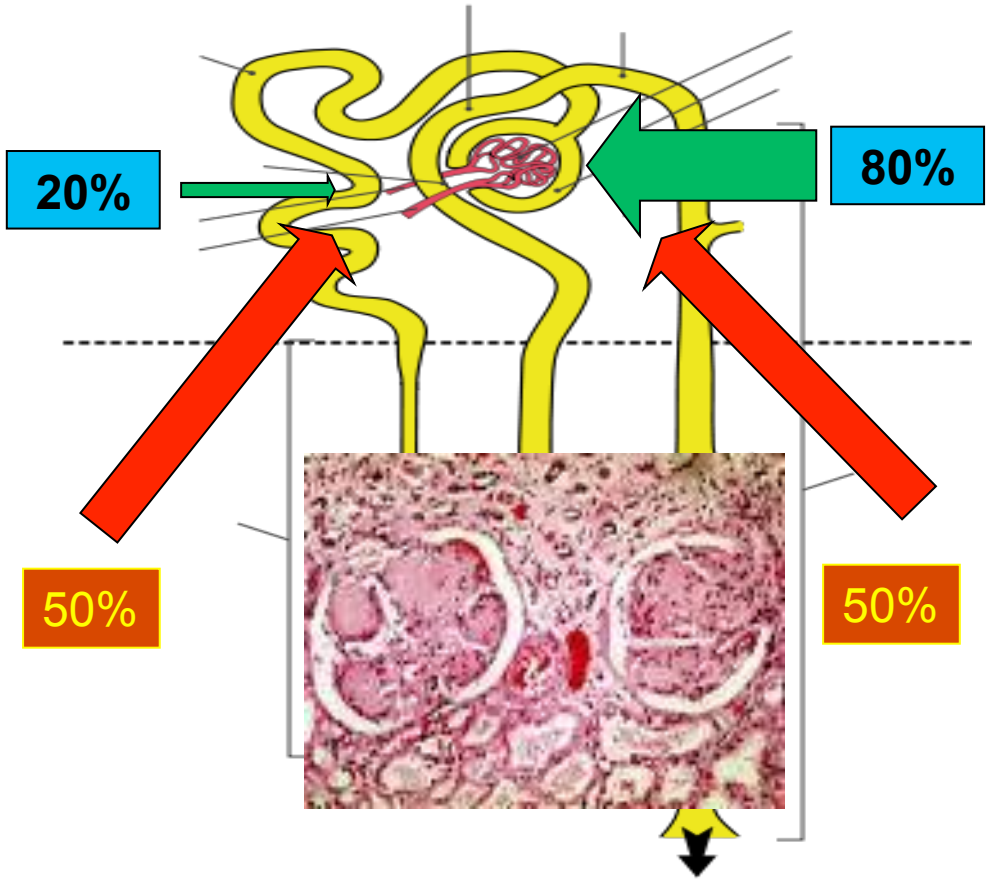
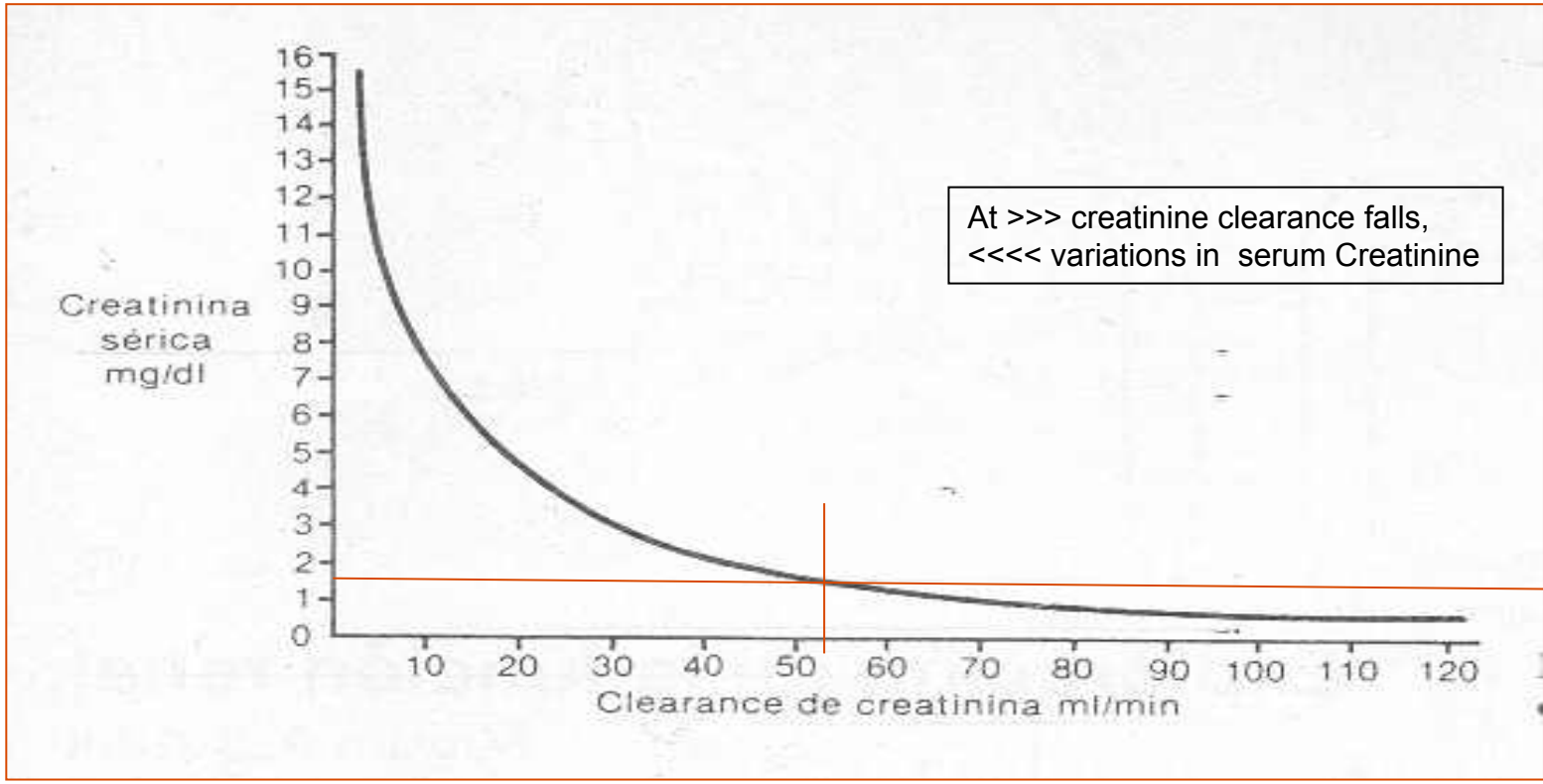
HOW CAN WE ASSESS RENAL FUNCTION?

CREATININE CLEARANCE IS NOT A SYNONIMUS OF GFR





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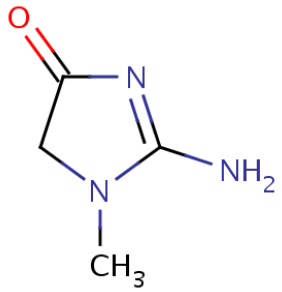
HOW CAN WE ASSESS RENAL FUNCTION?

In absence of other markers of kidney disease (proteinuria, hematuria, histology > 3 months or past medical records) GFR must be reported in its specific values only if < 60 ml/min/1.73 m^2

National Kidney Foundation®
KDOQI

Equations:
Must employ creatininemia, age, gender, race and body mass



PITFALLS

Creatinine is decreased in:

Old individuals
Low muscular mass
Liver disease
Pancreas disease
Low protein intake

Levey AS, Coresh J, Balk E, et al; National Kidney Foundation. National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Ann Intern Med. 2003;139(2):137-147.

NOVARTIS PHARMACEUTICALS

HOW CAN WE ASSESS RENAL FUNCTION?

National Kidney Foundation®
KDOQI *Kidney Disease Outcomes Quality Initiative*

CKD is stratified into 5 stages according to the GFR estimated through the depuration of creatinine:

"Slight" Stages 1 and 2; GFR >60 ml/min per 1.73 m^2

"Moderate" * Stage 3; GFR 59-30 ml/min per 1.73 m^2

"Severe" * Stage 4; GFR 29-15 ml/ min per 1.73m^2

Stage 5; GFR <15 ml/ min per 1.73 m^2 (end-stage renal disease)

Stages of CKD – KDOQI 2002 Definitions

Stage 1: eGFR ≥ 90 ml/min/1.73m^2 and ACR ≥ 30 mg/g
Stage 2: eGFR 60-89 ml/min/1.73m^2 and ACR ≥ 30 mg/g
Stage 3: eGFR 30-59 ml/min/1.73m^2
Stage 4: eGFR 15-29 ml/min/1.73m^2
Stage 5: eGFR < 15 ml/min/1.73m^2

*Defined as CKD, independently of renal damage

Levey AS, Coresh J, Balk E, et al; National Kidney Foundation. National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Ann Intern Med. 2003;139(2):137-147.

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HOW CAN WE ASSESS RENAL FUNCTION?

Twenty-four hour urine creatinine clearance:

$$GFR = \frac{\text{urinary creatinine}}{\text{serum creatinine}} \times \frac{\text{daily urinary output}}{1{,}440} \times \frac{\text{DuBois BSA}}{1.73\ m^2}$$

where urinary and serum creatinine is measured in mg/dL.

Cockcroft-Gault:

$$GFR = \frac{(140 - age) \times weight}{72 \times \text{serum creatinine}} \times (0.85, \text{if female}) \text{ per } 1.73\ m^2 \text{ BSA}$$

where weight is in kg.

MDRD-4: $GFR = 186 \times (\text{creatinine}/88.4)^{-1.154} \times (age)^{-0.203} \times (0.742, \text{if female})$

CKD EPI: In males, if creatinine <0.9

$$GFR = 141 \times \left(\frac{\text{plasmatic creatinine}}{0.9}\right)^{-0.411} \times 0.993^{age}$$

In males, if creatinine >0.9

$$GFR = 141 \times \left(\frac{\text{plasmatic creatinine}}{0.9}\right)^{-1.209} \times 0.993^{age}$$

In females, if creatinine <0.7

$$GFR = 144 \times \left(\frac{\text{plasmatic creatinine}}{0.7}\right)^{-0.329} \times 0.993^{age}$$

In females, if creatinine >0.7

$$GFR = 144 \times \left(\frac{\text{plasmatic creatinine}}{0.7}\right)^{-1.209} \times 0.993^{age}$$

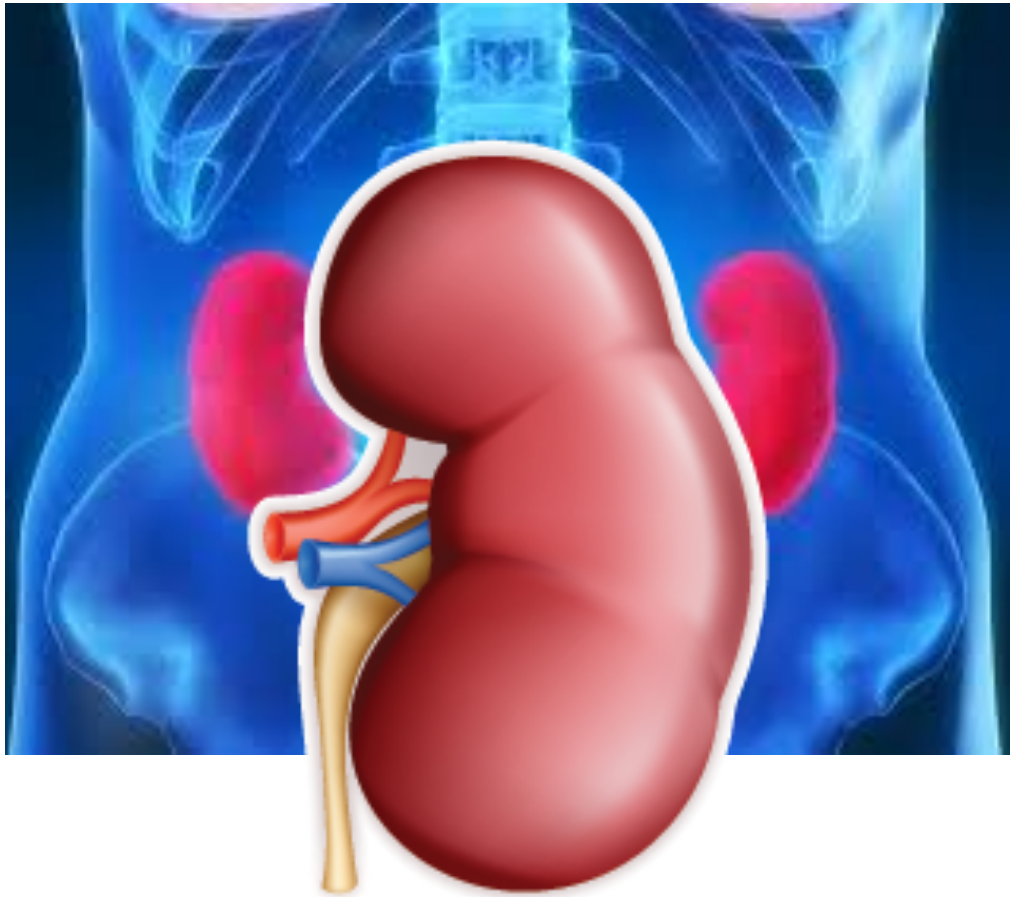
Trimarchi H et al. Creatinine- vs cystatin c-based equations compared with ^{99m}TcDTPA scyntigraphy to assess glomerular filtration rate in chronic kidney disease. *Journal of Nephrology 2012; 25 (6): 1003-1015*

RENAL FUNCTION

“Moderate” *

Stage 3

GFR 59-30 ml/min/1.73 m^2



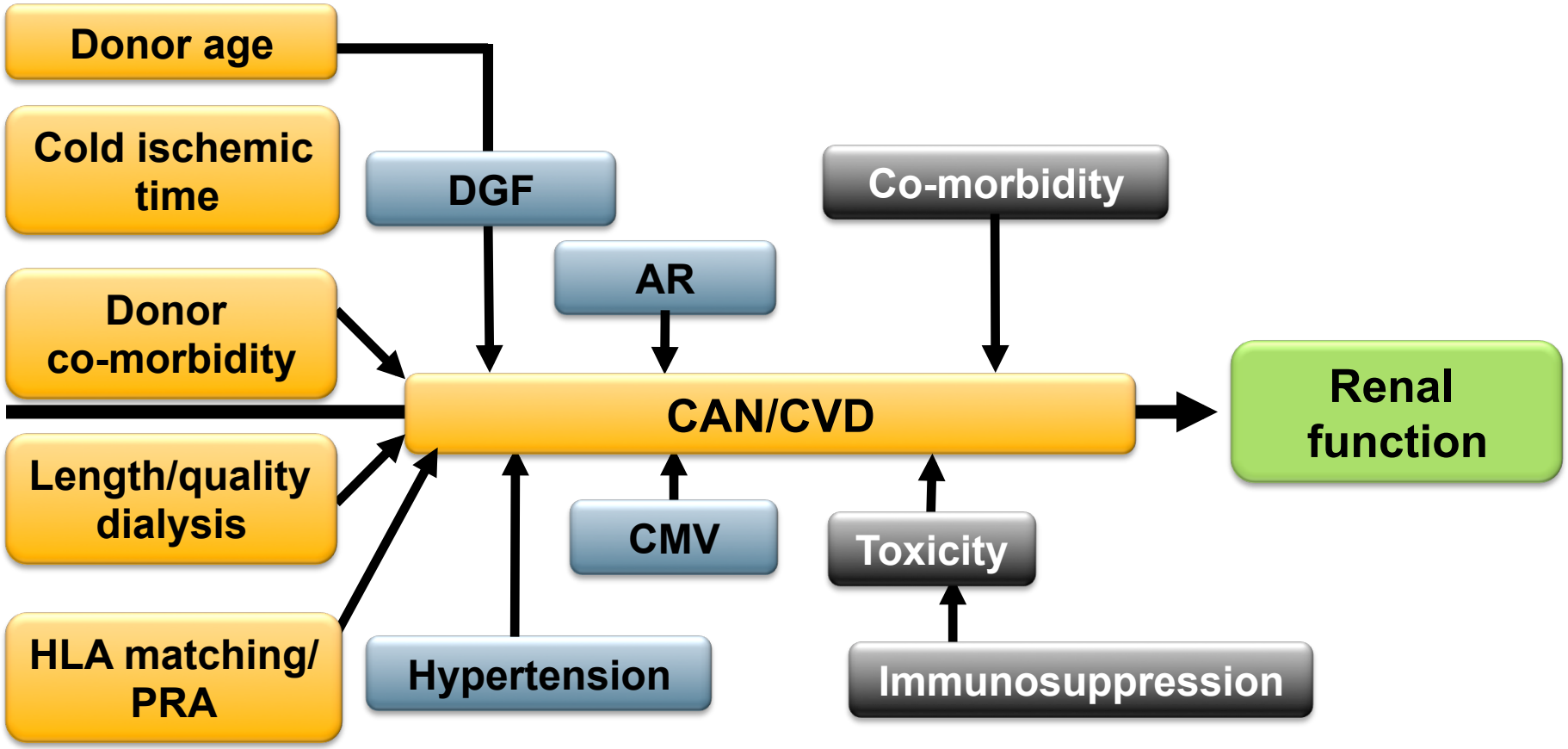
“Severe” *

Stage 4

GFR 29-15 ml/ min/1.73m^2

CKD

FACTORS THAT CAN DETERMINE GRAFT FUNCTION



AR, acute rejection; CAN, chronic allograft nephropathy; CMV, cytomegalovirus; CVD, cardiovascular disease; DGC, delayed graft function; HLA, human leukocyte antigen; PRA, panel reactive antibodies.

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RENAL FUNCTION

HYPERFILTRATION: Absolute increase in the GFR that occurs in response to an elevated protein load or other molecules with osmotic properties.

Bergström, J. et al. Acta Med. Scand. 1985:;217: 189–196

This GFR increase is mediated, at least initially, by elevated levels of local nitric oxide and kalikreins

Pecly, I. M et al Int. J. Clin. Pract. 2006; 60: 1198–1203

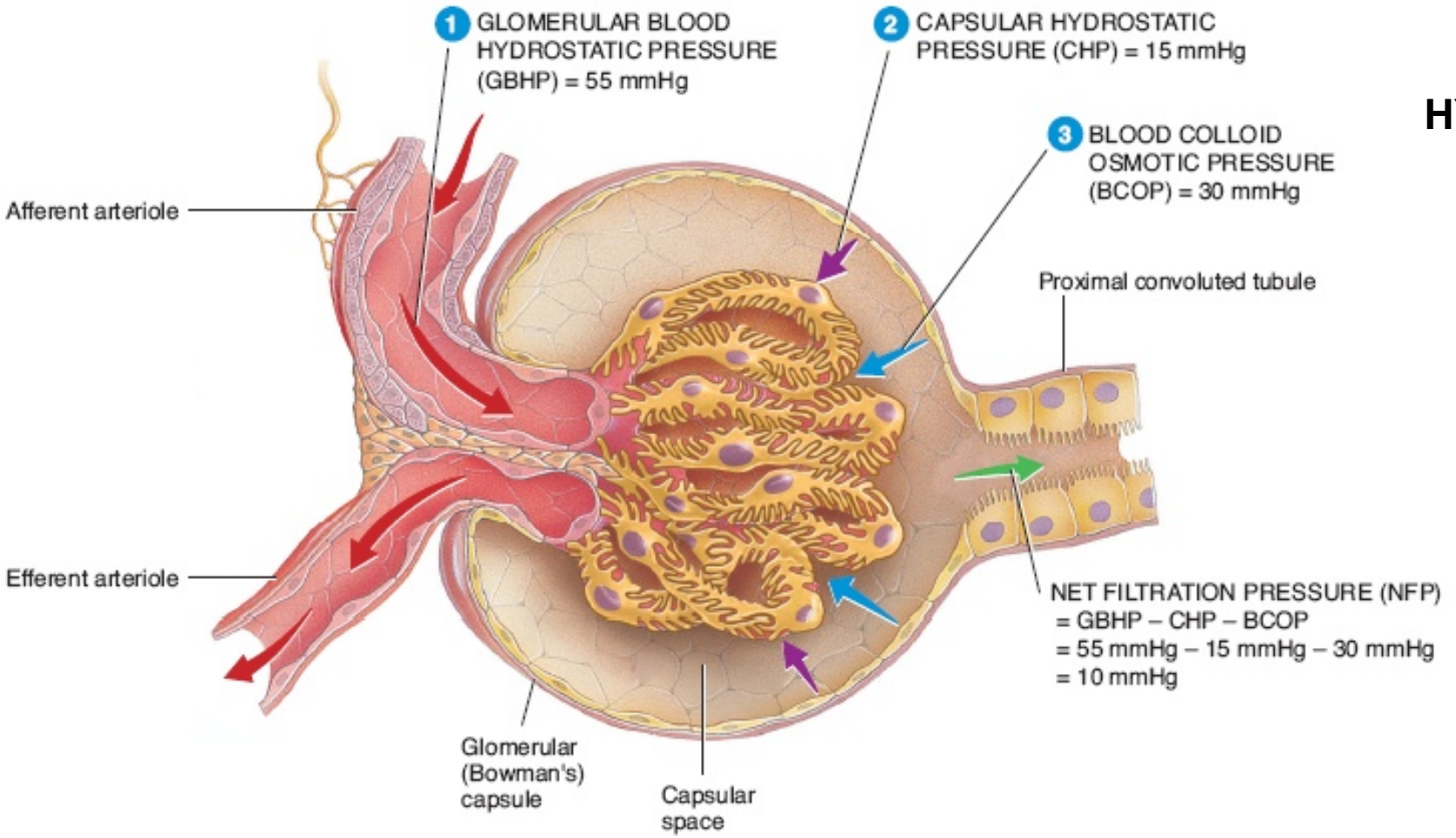
This capability to increase the GFR after a protein load is named **RENAL FUNCTIONAL RESERVE**.

The loss of this reserve combined with the subsequent hyperfiltration will directly contribute to the progression of CKD

Bosch, J. P. Am. J. Med. 1984;77: 873–879 (1984

Helal, I. et al. Nat. Rev. Nephrol. 2012; 8: 293–300

RENAL FUNCTION



GFR

RENAL PLASMA FLOW

HYDRAULIC PRESSURE GRADIENT ACROSS THE GBM

Kf

Helal, I. *et al. Nat. Rev. Nephrol. 2012; 8: 293–300*

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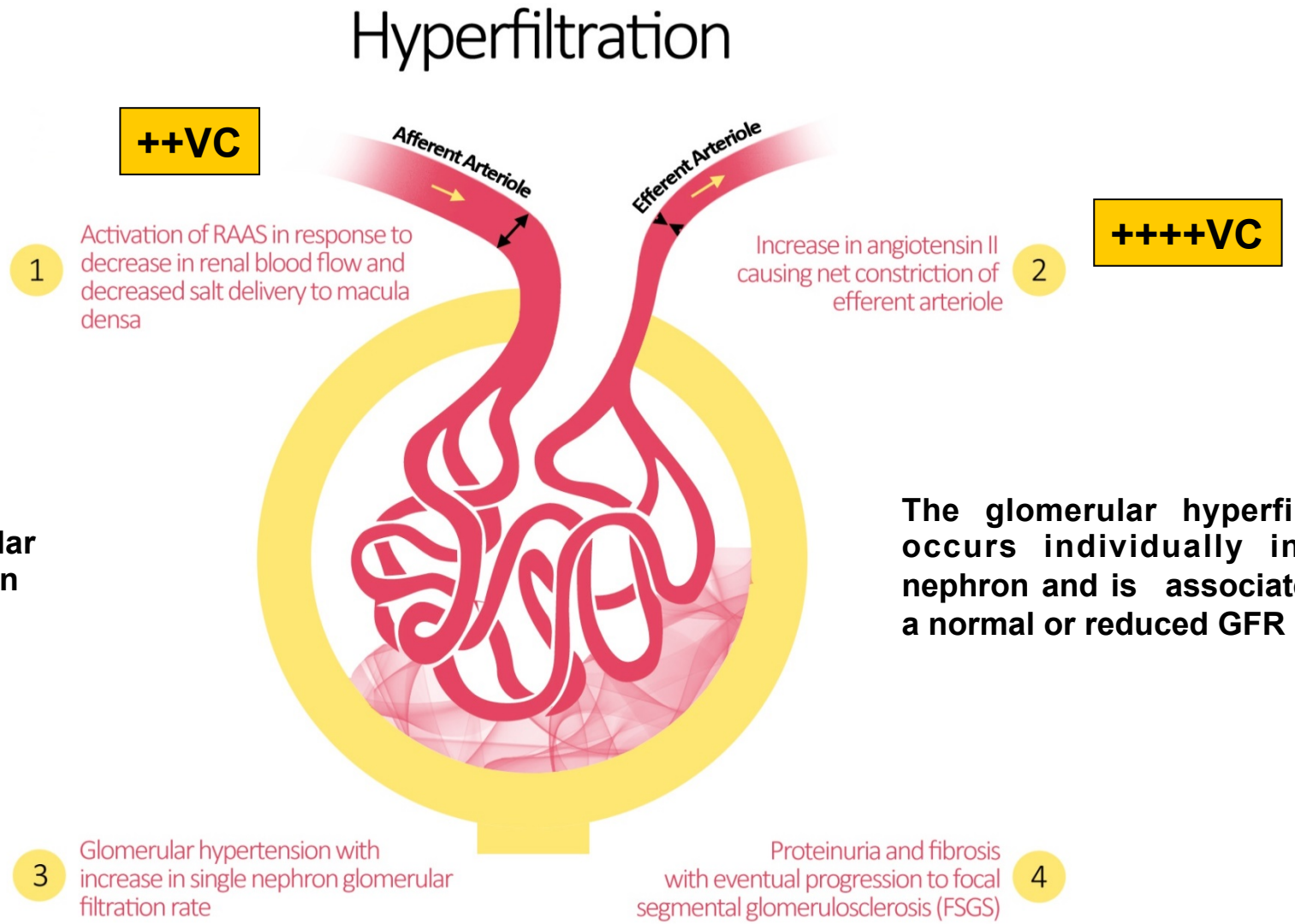
RENAL FUNCTION



Intraglomerular hypertension

The glomerular hyperfiltration occurs individually in each nephron and is associated with a normal or reduced GFR

Neuringer, J. R. et al J. Hypertens. Suppl. 1992; 10: S91–S97

Neuringer, J. R. et al Am. J. Kidney Dis. 1993;22: 98–104

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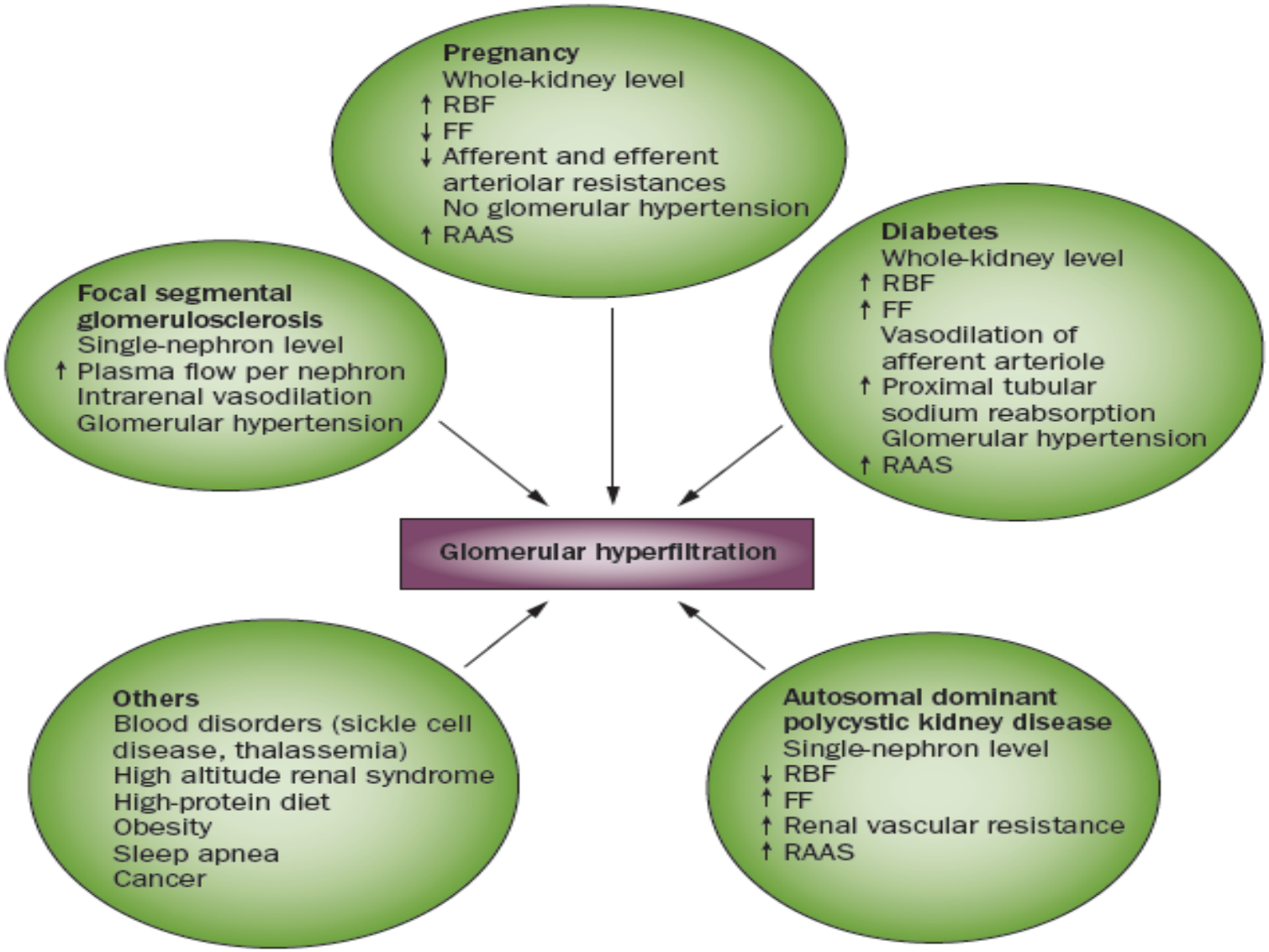
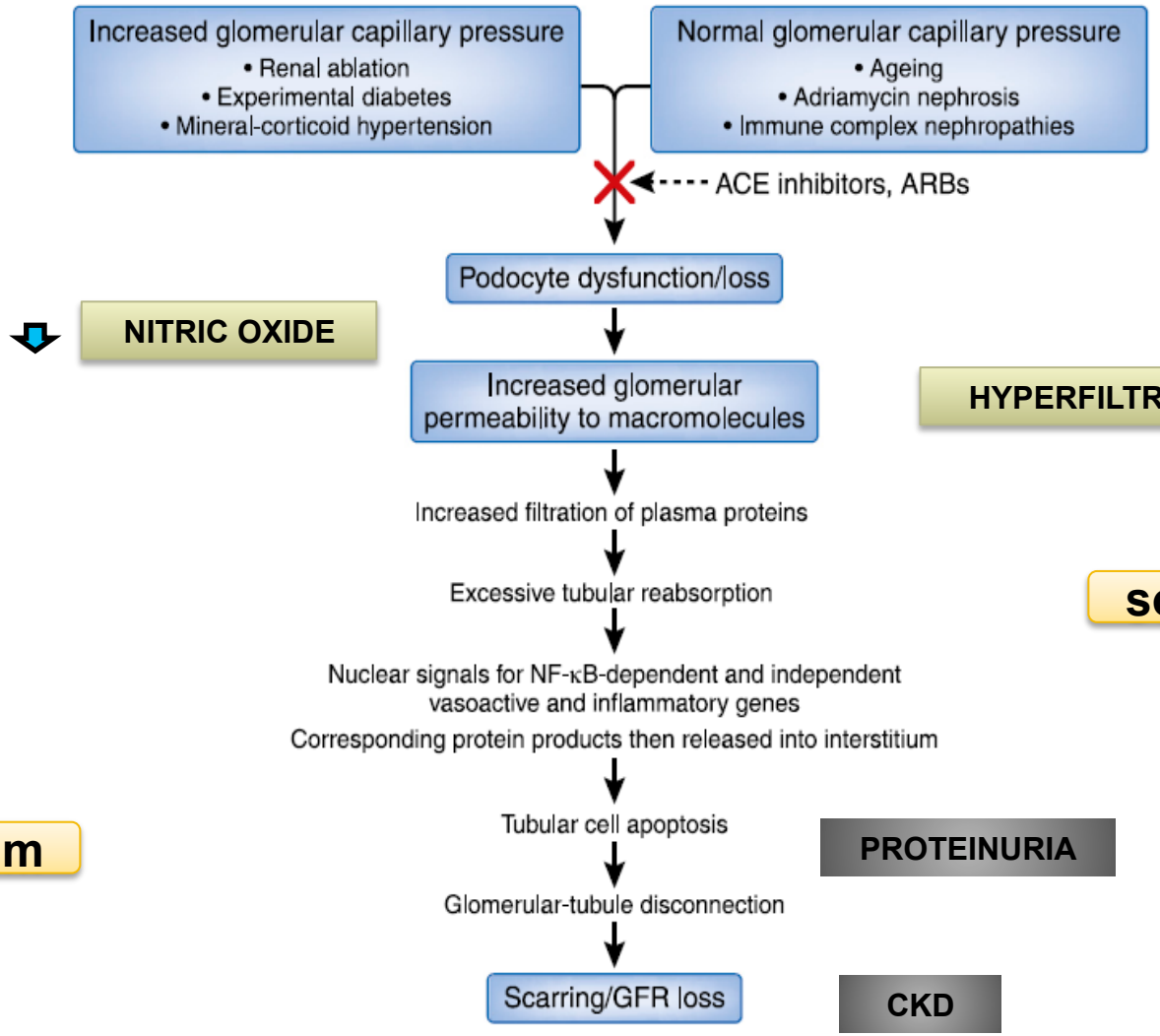


Helal, I. et al. Nat. Rev. Nephrol. 2012; 8: 293–300

NOVARTIS PHARMACEUTICALS

RENAL FUNCTION

sodium



INCREASE OF VASCULAR TONE

HYPERFILTRATION

ENDOTHELIAL RENAL DAMAGE

sodium

SYSTEMIC HYPERTENSIÓN

sodium

PROTEINURIA

CKD

Ruggenenti P, Cravedi P, Remuzzi G J Am Soc Nephrol 2012; 23: 1917–1928

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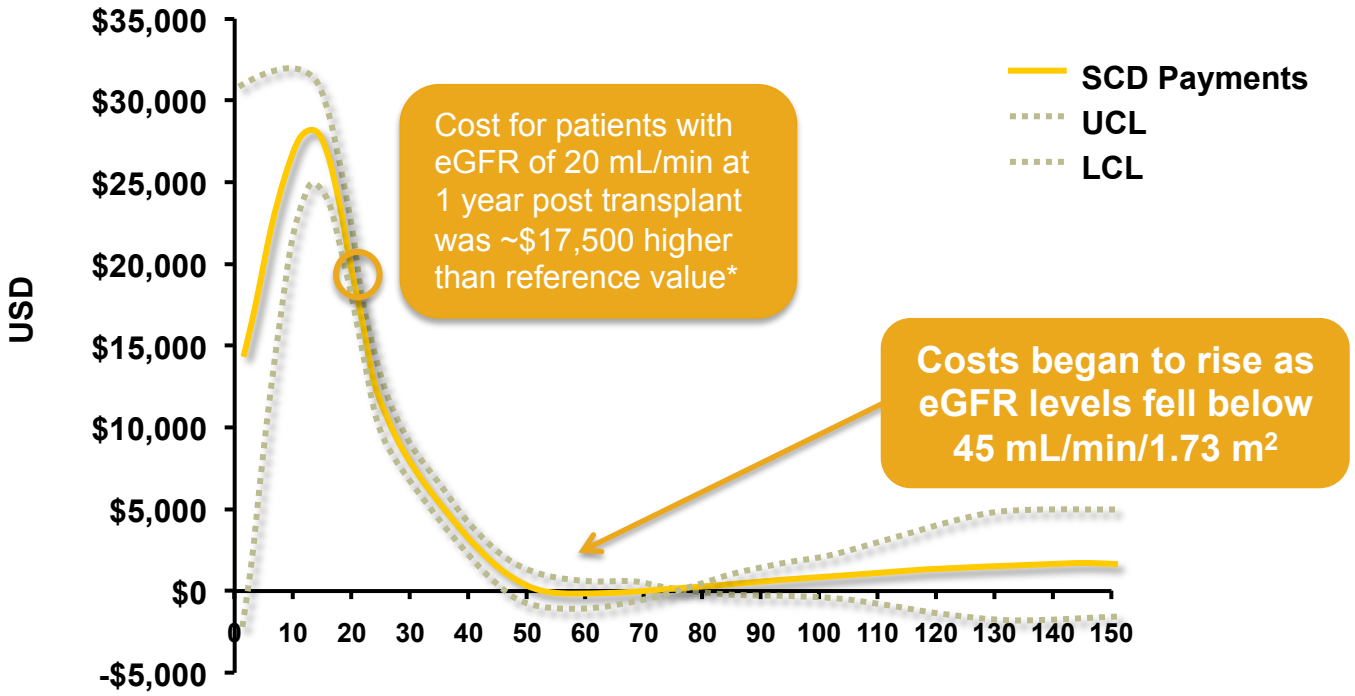
One-year post-transplant eGFR levels are associated with substantial healthcare cost

Cost relationship with eGFR*

***Second year Medicare payments according to eGFR status at 1 year post transplantation* (N=22,110 SCD recipients)**



*Compared to the reference of 75 mL/min/1.73 m^2

eGFR, estimated glomerular filtration rate; LCL, lower 95% confidence limit; SCD, standard criteria deceased; UCL, upper confidence limit; USD, United States dollars

Schnitzler MA et al. *J Med Econ.* 2013;16:75-84

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TAKING HOME MESSAGES

- More than 50% of renal transplant patients have a GFR lower than 60 mL/min at 1 year after transplantation
- Poor renal function following renal transplantation continues to prevent improvements in long-term outcomes for patients and grafts
- Poor renal function at 1 year has multiple consequences including increased CVD risk, graft failure and an increased risk of mortality
- CNIs are nephrotoxic agents, whose use should ideally be optimized post-transplantation
- Poor renal function has also negative consequences on economical costs

A “MUST” MESSAGE

GOAL IN KIDNEY TRANSPLANTATION:

TO PRESERVE KIDNEY FUNCTION

A TRANSPLANTED KIDNEY IS GENERALLY A HYPERFILTRATING KIDNEY WITH CKD STAGE 3 OR 4

Beagle Channel, Ushuaia Argentina