What we don't know about Fabry yet?

Alberto Ortiz

Jiménez Díaz Foundation and Autonomous University of Madrid
Madrid, Spain

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Plan de Recuperación, Transformación y Resiliencia

PREVENTCKD

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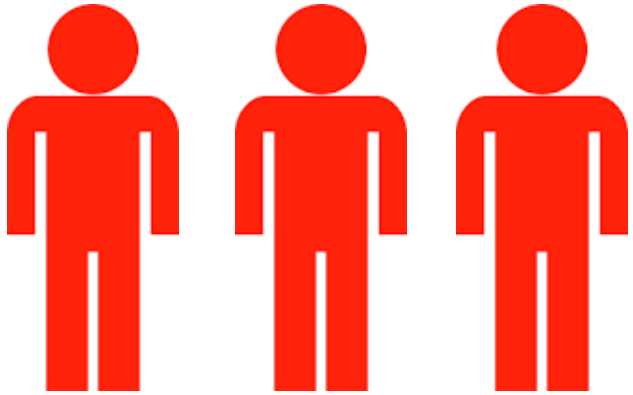
Disclosures

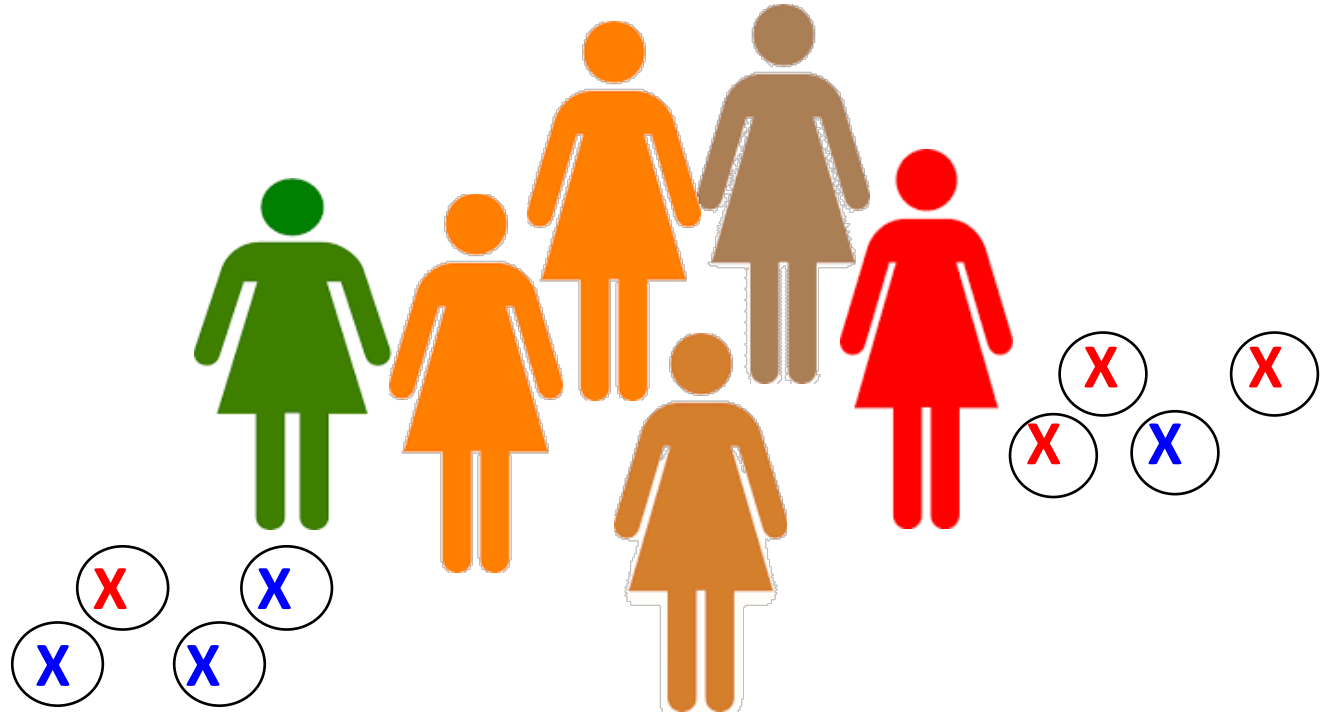
Consultant: Sanofi Genzyme, Chiesi, Freeline

Speaker fees: Sanofi Genzyme, Chiesi, Shire, Amicus

- **Who** and **when** to treat?
- How to accelerate the clearance of glycolipid deposits?
- Is it only glycolipid deposits?
- How to address anti-drug antibodies?

X-linked α-Gal A deficiency





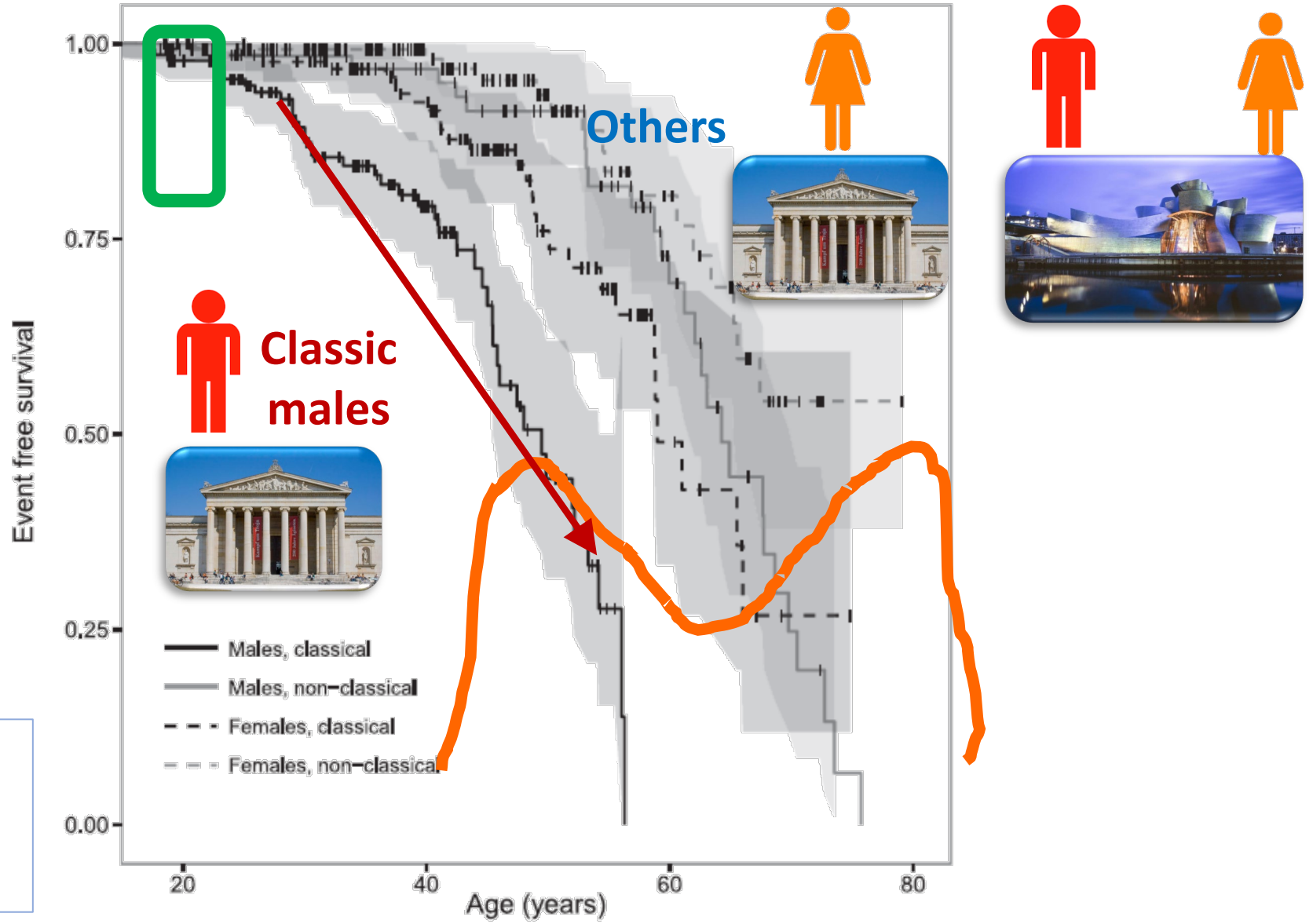
Glyptothek in Munich

Guggenheim Museum Bilbao

α-Gal A, alpha-galactosidase A.

Natural history severe event-free survival: classic males vs other Fabry patients

Natural history



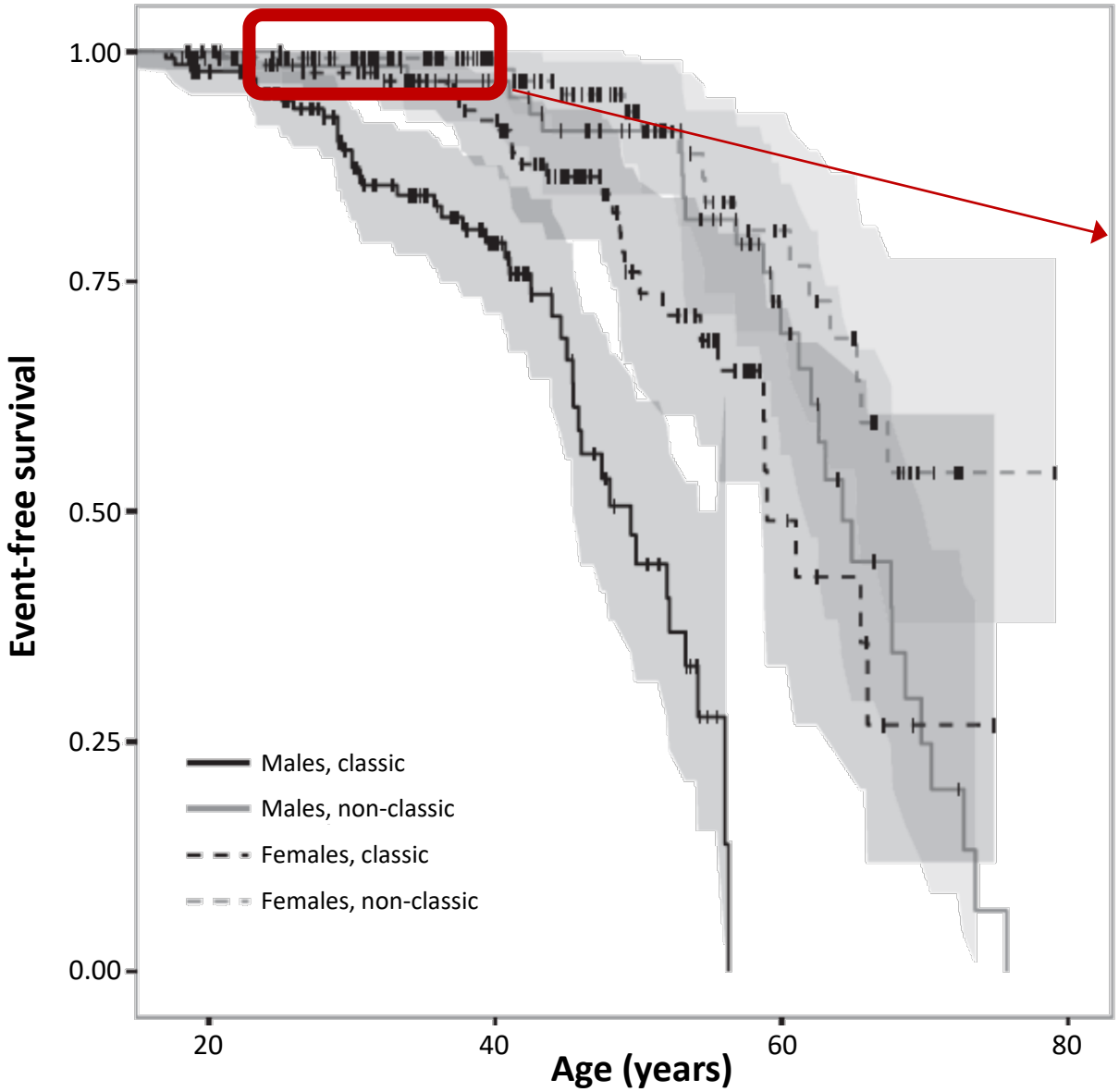
Retrospective assessment of event-free survival from birth to the first clinical visit (before ERT) in 499 adult patients (mean age 43 years old; 41% men; 57% with the classic phenotype) from three international centers of excellence

ERT, enzyme replacement therapy.

Arends M, et al. J Am Soc Nephrol 2017;28:1631-41.

Natural history severe event-free survival: classic males vs other Fabry patients

Natural history



Retrospective assessment of event-free survival from birth to the first clinical visit (before ERT) in 499 adult patients (mean age 43 years; 41% men; 57% classic phenotype) from 3 international centers of excellence

The so-far-so-good window

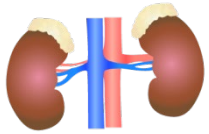
ERT, enzyme replacement therapy.

Arends M, et al. J Am Soc Nephrol. 2017;28:1631-41.

Treatment decisions: who and when?

Microalbuminuria

The European Fabry Working Group Consensus Document





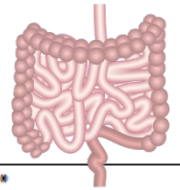


Table 3 Consensus criteria for initiation of ERT

	No signs or symptoms	Renal*	Cardiac*	CNS*	Pain*	GI*
Classical FD, males	if ≥ 16 years of age (Class IIB)	- microalbuminuria† (Class I) - proteinuria† (Class I) - renal insufficiency (GFR 60–90)# (Class I) - renal insufficiency (GFR 45–60)# (Class IIB)	- cardiac hypertrophy (MWT > 12 mm) without (or only minimal signs of) fibrosis (Class I) - signs of cardiac rhythm disturbances$ (Class I)	- WMLs (Class IIB) - TIA/stroke (Class IIA) - hearing loss, corrected for age (Class IIB)	- neuropathic pain (Class IIA) - neuropathic pain even if completely controlled (not interfering with daily activities) with pain medication (Class IIB)	GI symptoms (Class IIA if < 16 years of age, Class IIB if > 16 years of age)
Non-classical FD, males		- microalbuminuria† (Class I) - proteinuria† (Class I) - renal insufficiency (GFR 60–90)# (Class IIA) - renal insufficiency (GFR 45–60)# (Class IIB)	- cardiac hypertrophy (MWT > 12 mm) without (or only minimal signs of) fibrosis (Class I) - signs of cardiac rhythm disturbances$ (Class I)	- WMLs (Class IIB) - TIA/stroke (Class IIA) - hearing loss, corrected for age (Class IIB)	- neuropathic pain (Class IIA) - neuropathic pain even if completely controlled (not interfering with daily activities) with pain medication (Class IIB)	GI symptoms (Class IIA if < 16 years of age, Class IIB if > 16 years of age)
Classical FD, females		- microalbuminuria† (Class IIB) - proteinuria† (Class IIB) - renal insufficiency (GFR 60–90)# (Class IIA) - renal insufficiency (GFR 45–60)# (Class IIB)	- cardiac hypertrophy (MWT > 12 mm) without (or only minimal signs of) fibrosis (Class I) - signs of cardiac rhythm disturbances$ (Class I)	- WMLs (Class IIB) - TIA/stroke (Class IIA) - hearing loss, corrected for age (Class IIB)	- neuropathic pain (Class IIA) - neuropathic pain even if completely controlled (not interfering with daily activities) with pain medication (Class IIB)	GI symptoms (Class IIA if < 16 years of age, Class IIB if > 16 years of age)
Non-classical FD, females		- microalbuminuria† (Class IIB) - proteinuria† (Class IIB) - renal insufficiency (GFR 60–90)# (Class IIB) - renal insufficiency (GFR 45–60)# (Class IIB)	- cardiac hypertrophy (MWT > 12 mm) without (or only minimal signs of) fibrosis (Class I) - signs of cardiac rhythm disturbances$ (Class I)	- WMLs (Class IIB) - TIA/stroke (Class IIA) - hearing loss, corrected for age (Class IIB)	- neuropathic pain (Class IIA) - neuropathic pain even if completely controlled (not interfering with daily activities) with pain medication (Class IIB)	GI symptoms (Class IIA if < 16 years of age, Class IIB if > 16 years of age)

*consistent with FD and not fully explained by other pathology; †according to international guidelines of kidney disease, KDIGO criteria; #in ml/min/1.73 m^2 corrected for age (>40 years: −1 ml/min/1.73 m^2/year); $sinus bradycardia, AF, repolarization disorders; ERT = enzyme replacement therapy; GFR = glomerular filtration rate; MWT = maximal wall thickness; CNS = central nervous system; WMLs = white matter lesions; TIA = transient ischemic attack; GI = gastrointestinal.

Biegstraaten M et al. *Orphanet J Rare Dis* 2015;10:36

What we see depends mainly on **what we look for**
— John Lubbock

Albuminuria

(Not dipstick proteinuria)

We wait until women or late onset patients are sick to try to restore health

What is Chronic Kidney Disease?

Criteria for CKD (**either** of the following present for **>3 months**)

1. Markers of **kidney damage** (one or m

- **Albuminuria** (**>30 mg**/g creatinine) A cat
- Urine sediment abnormalities
- Electrolyte and other abnormalities due
- **Abnormalities detected by histology**
- **Structural abnormalities detected by im**
- History of kidney transplantation

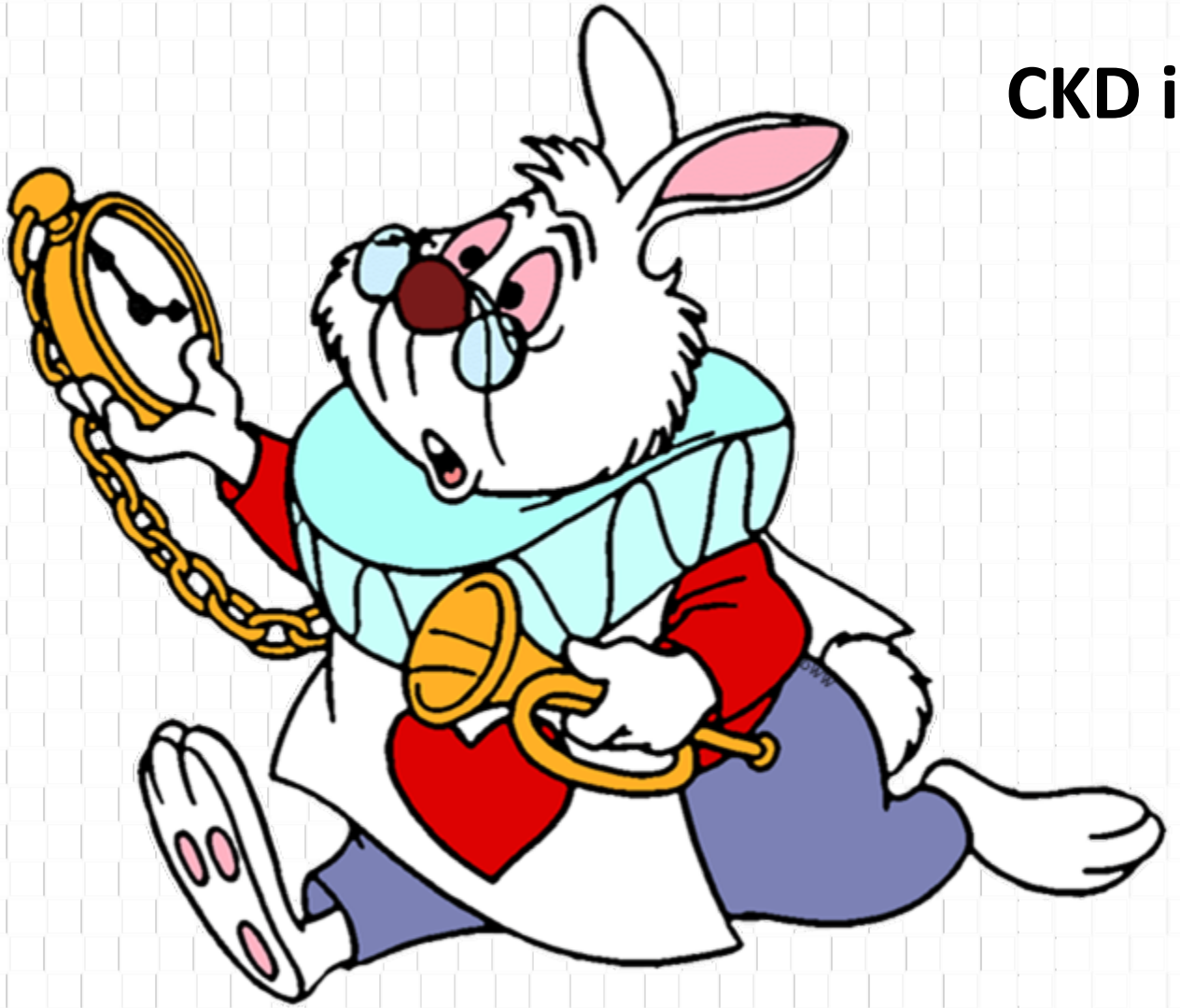
or

2. Decreased GFR: GFR **<60 ml/min**/1.73 m^2 (GFR categories G3a–G5)

Despite
normal renal function
(GFR), you may still
have **CKD**

KDIGO CKD 2012. Kidney Int 2013. CKD, chronic kidney disease; GFR, glomerular filtration rate.

Issue 2: the white rabbit issue



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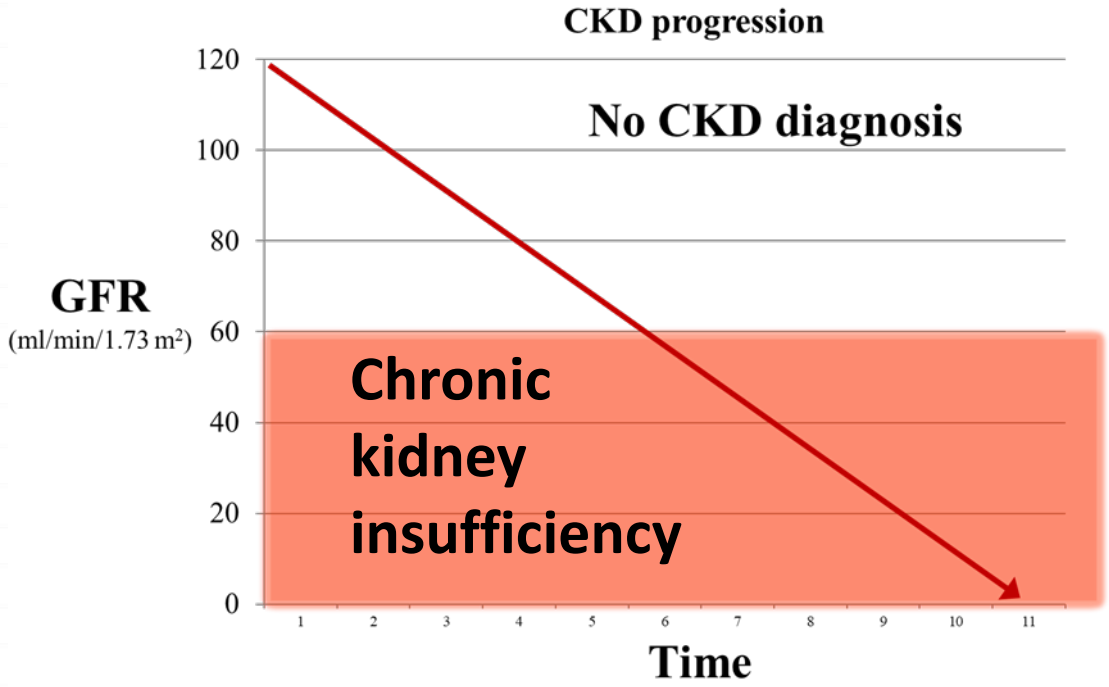
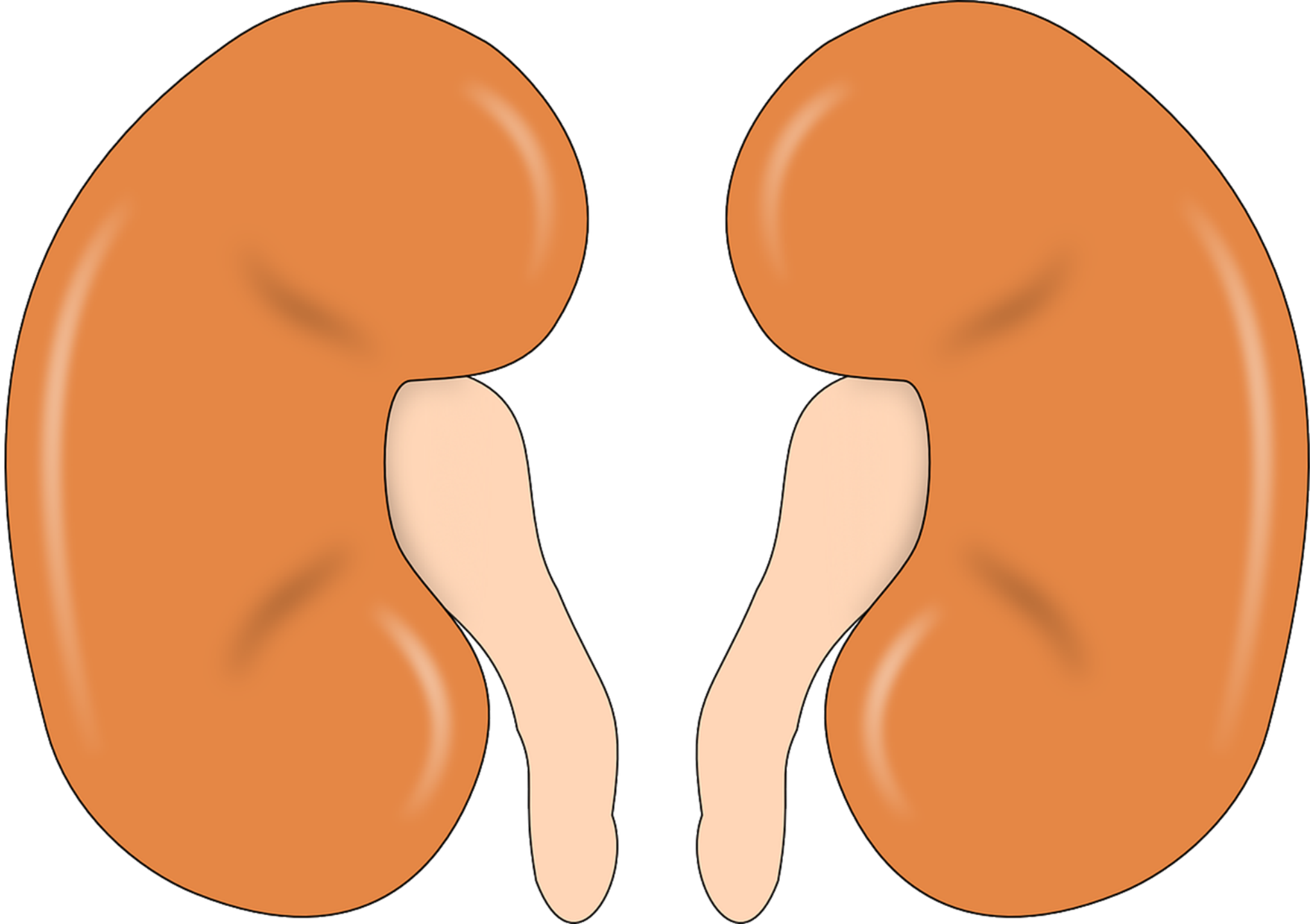
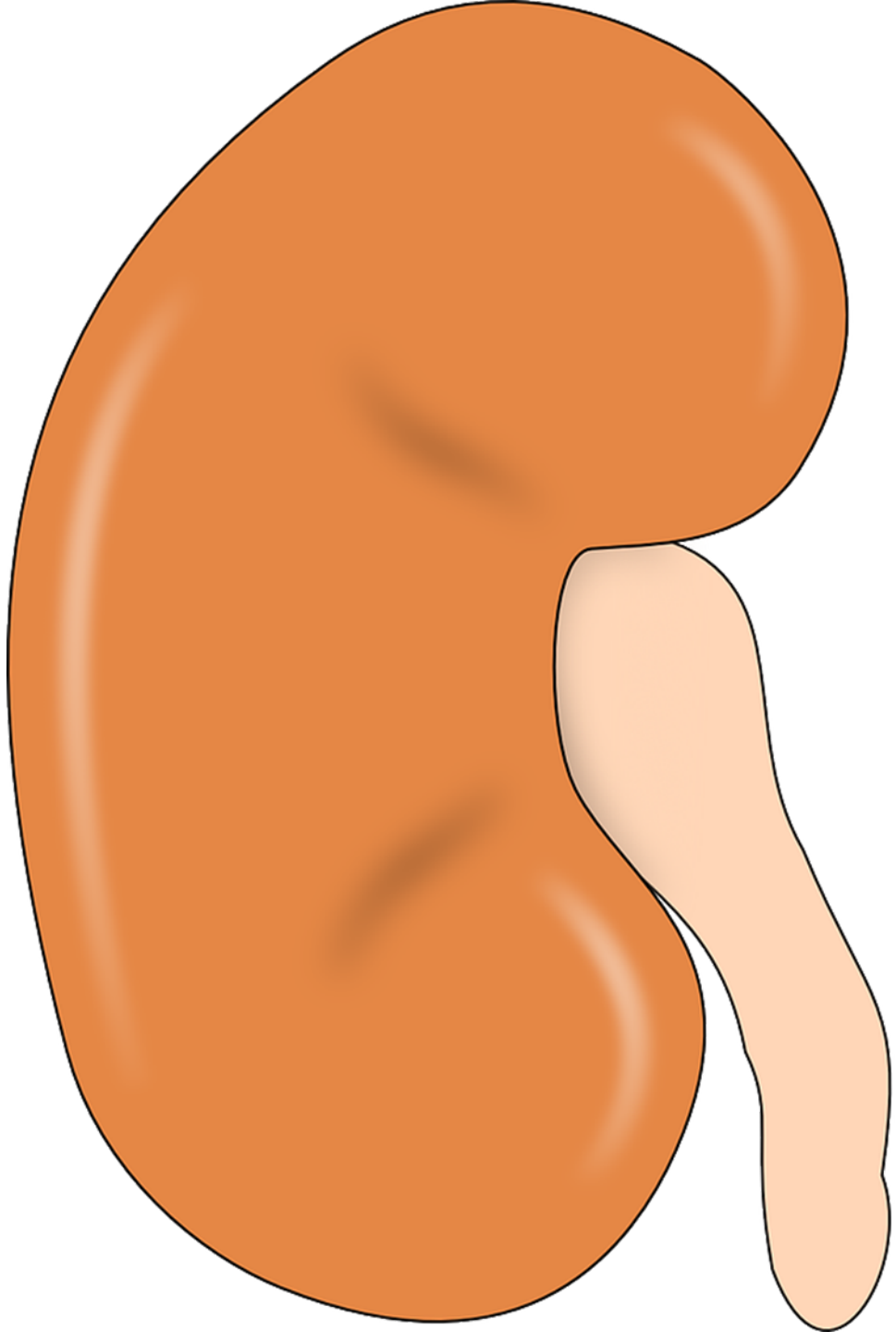
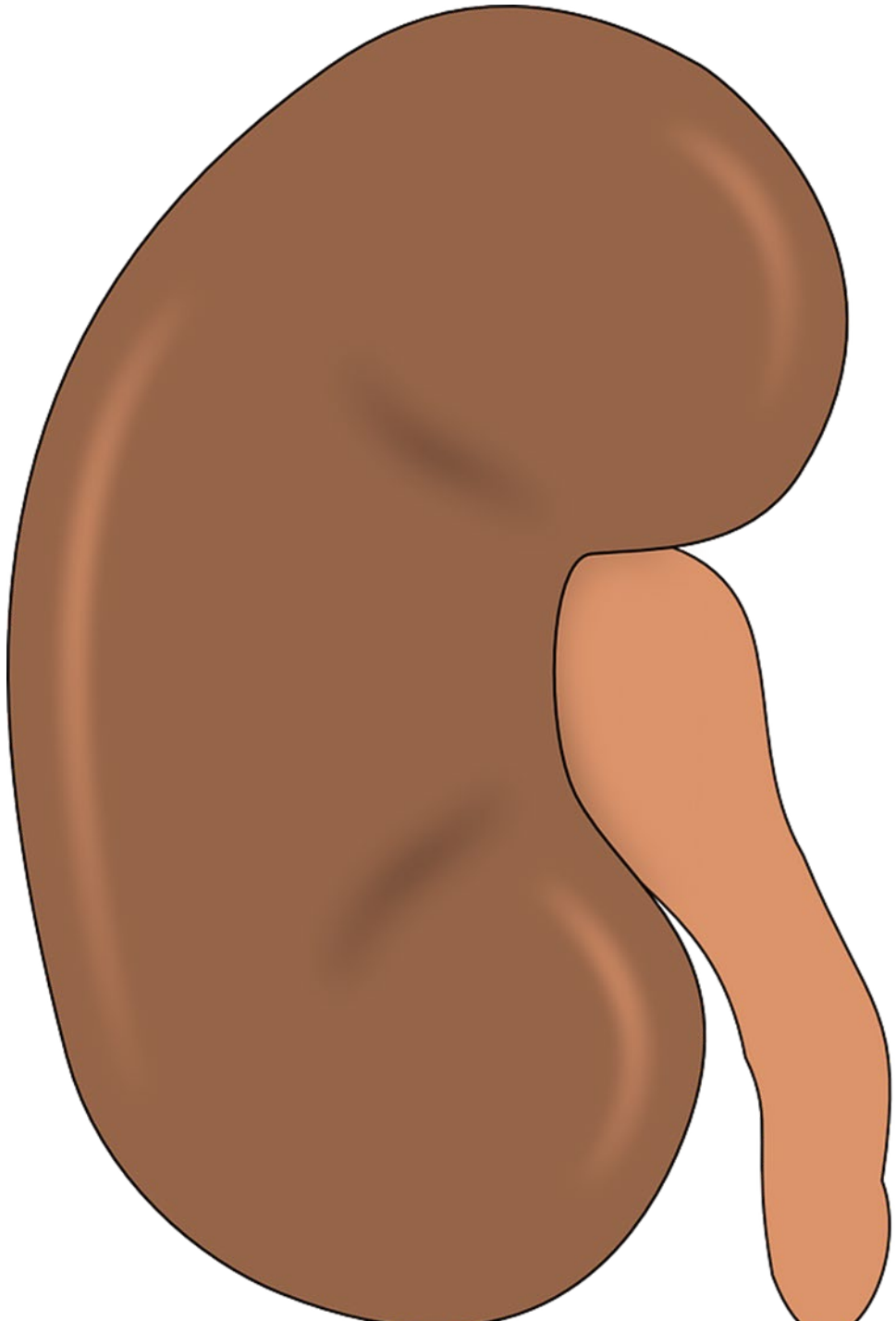
CKD is diagnosed late



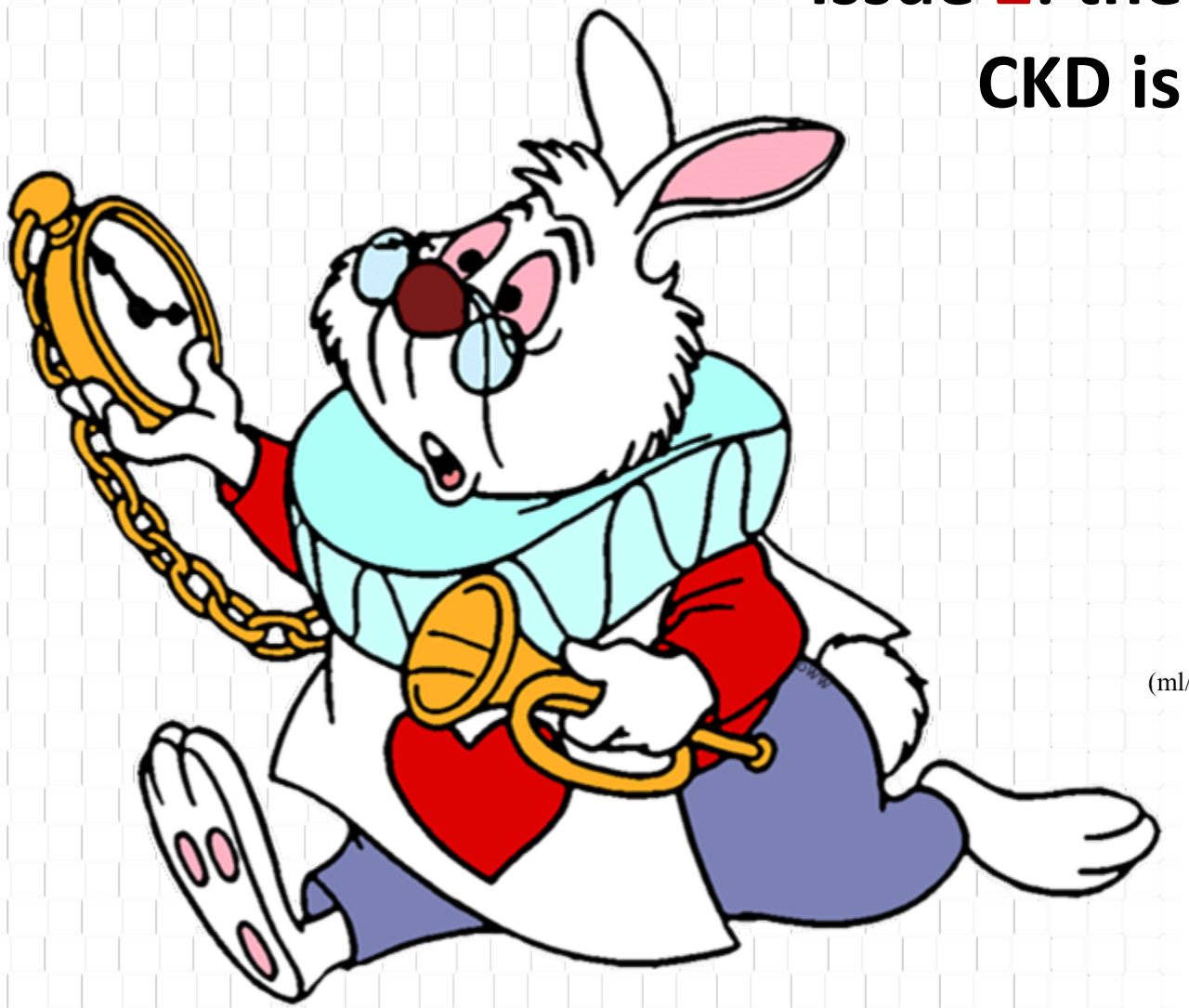






Issue 2: the white rabbit issue

CKD is diagnosed late



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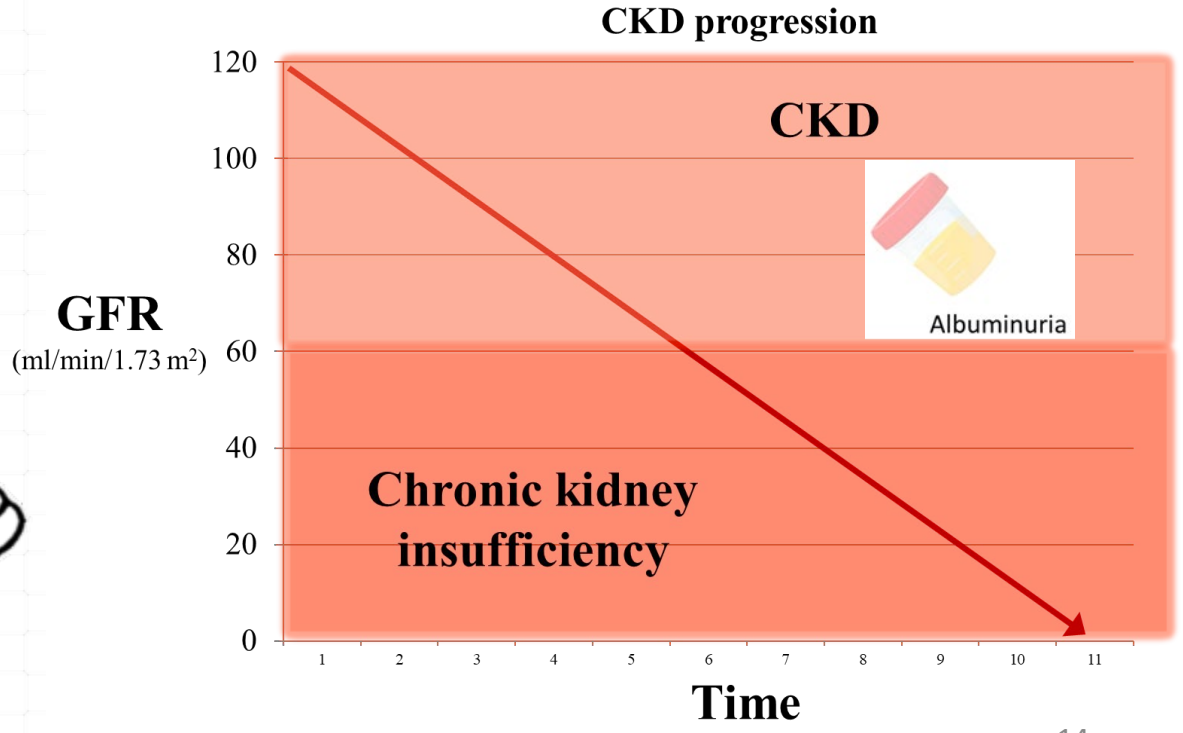


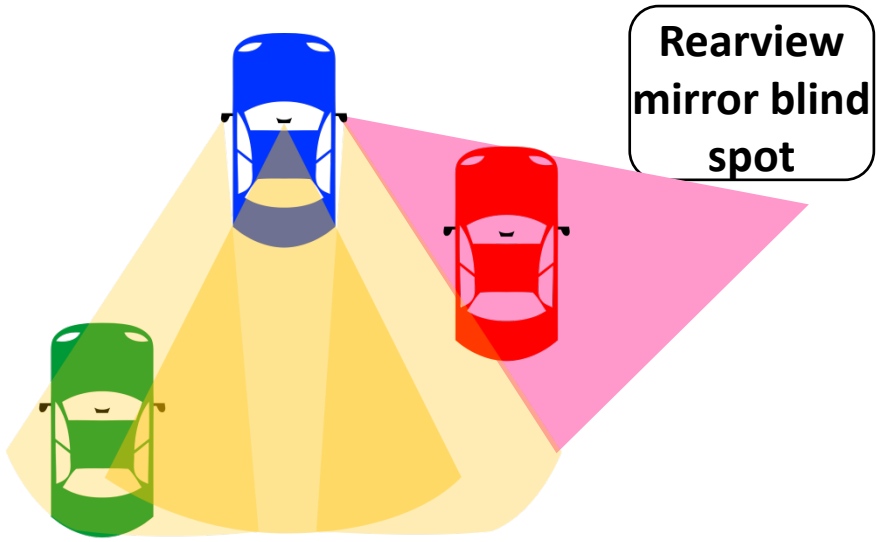
Issue 3: the blind spot issue

Clinical Kidney Journal, 2017, 188–191

doi: 10.1093/ckj/sfx023
Editorial Comment

EDITORIAL COMMENT

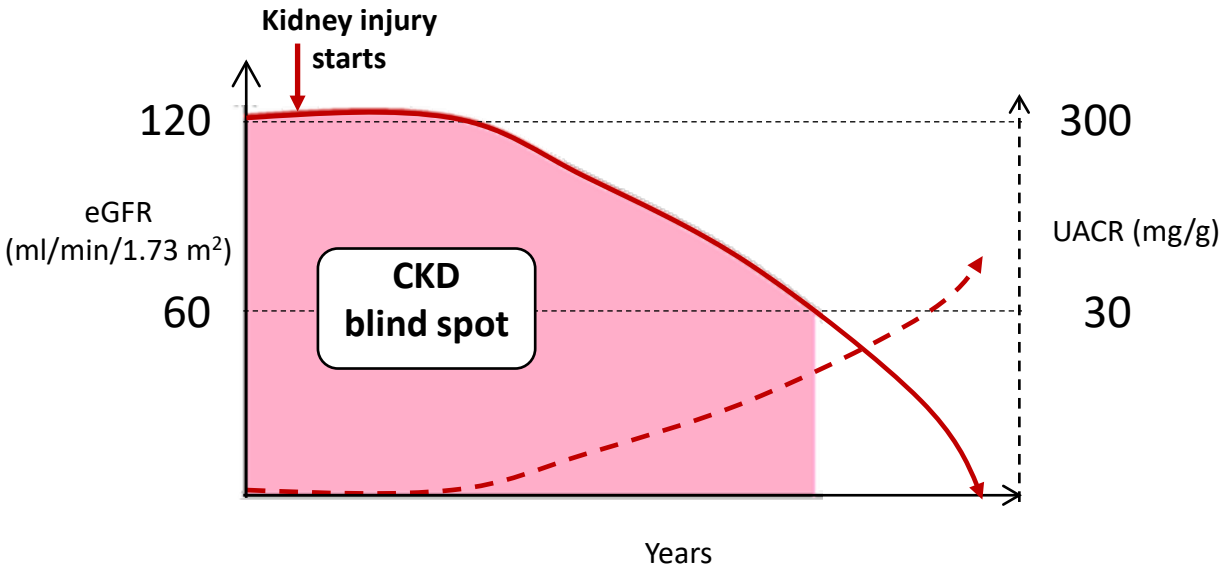
Clinical proteomics in kidney disease as an exponential technology: heading towards the disruptive phase



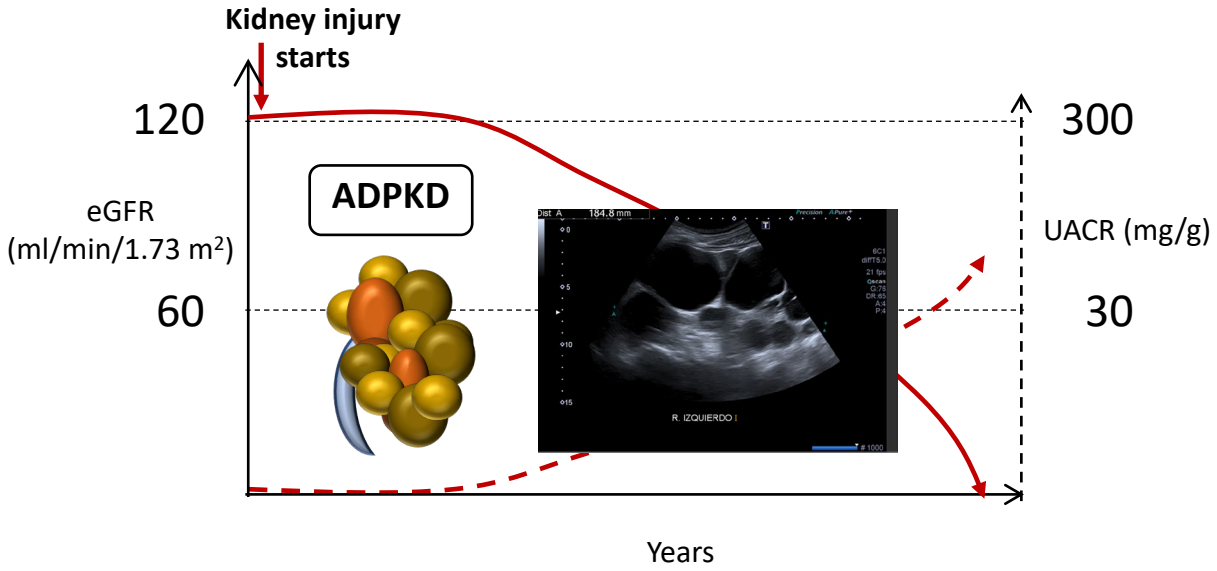
Sanchez-Niño et al. CKJ 2017, 188-191

The blind spot in CKD

CKD blind spot: the patient has CKD, but we are unable to diagnose it



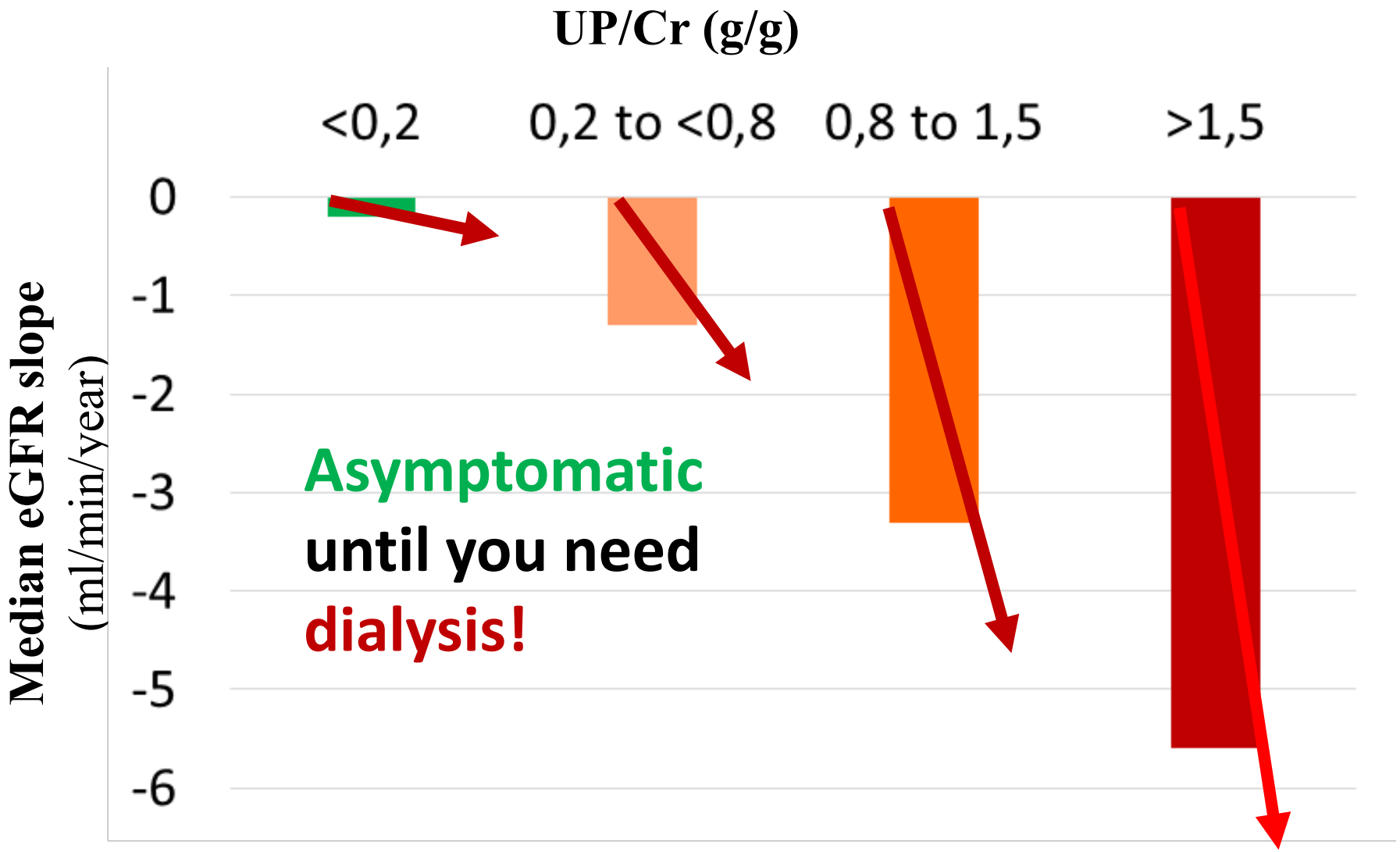
Proof of concept



Either we develop **new tools to diagnose CKD earlier** or **use current and new tools to identify people at high risk** of developing CKD

Sanchez-Niño et al. CKJ 2017,10:188-191

Proteinuria is a major **risk factor** for **CKD progression** in Fabry



Natural history data from 121 men not on ERT (Fabry Registry)

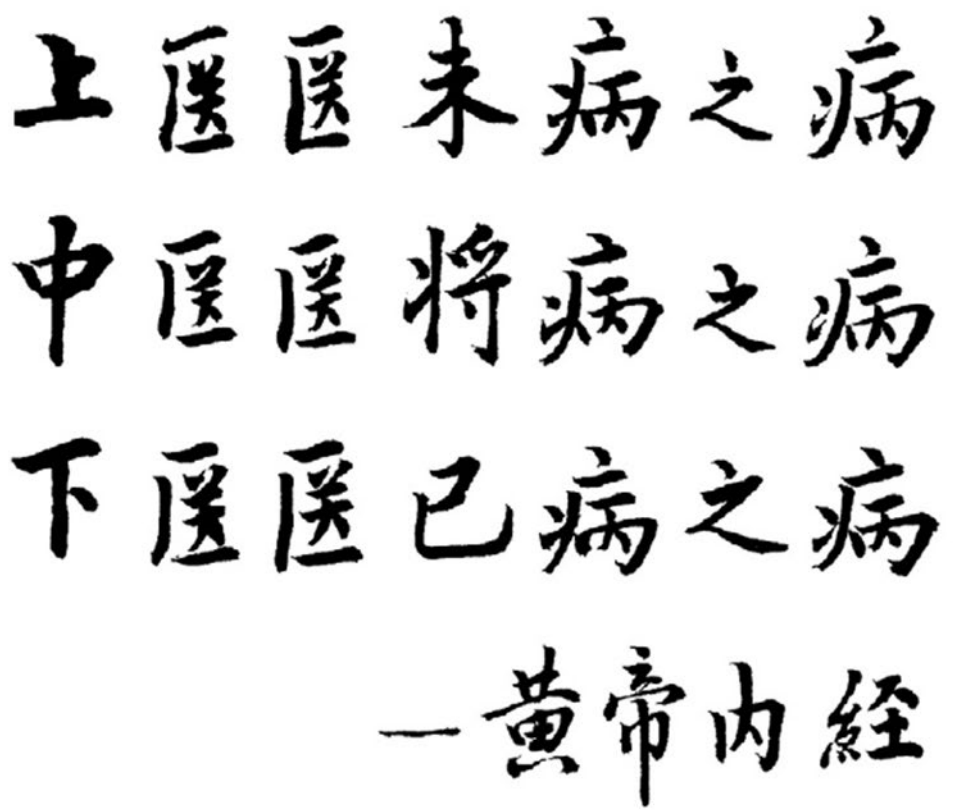
CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ERT, enzyme replacement therapy; UP/Cr, urinary protein:creatinine ratio

Wanner et al. CJASN 2010 Dec;5(12):2220-8

We do not know

How to **predict** what **women** with pathogenic GLA gene variants **will develop Fabry disease** in order to PREVENT disease development

168 BCE



The superior doctor prevents diseases;

the mediocre doctor attends to impending diseases;

the inferior doctor treats full-blown diseases.

-- *Huang Di Neijin*

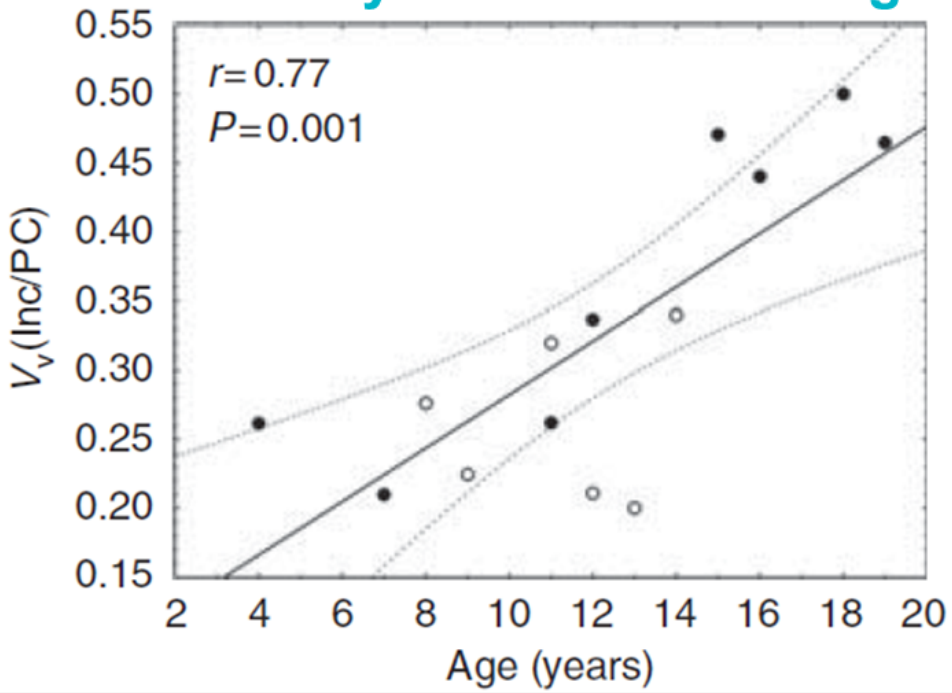
Fig. 1. A quotation from Huang Di Neijin or the Yellow Emperor's Canon of Internal Medicine. Chinese calligraphy (top) by Madame Ge Qiyun, wife of Han Xu, Chinese Ambassador to the United States, with English translation (bottom).

- Who and when to treat?
- How to **accelerate the clearance** of glycolipid deposits?
- Is it only glycolipid deposits?
- How to address anti-drug antibodies?

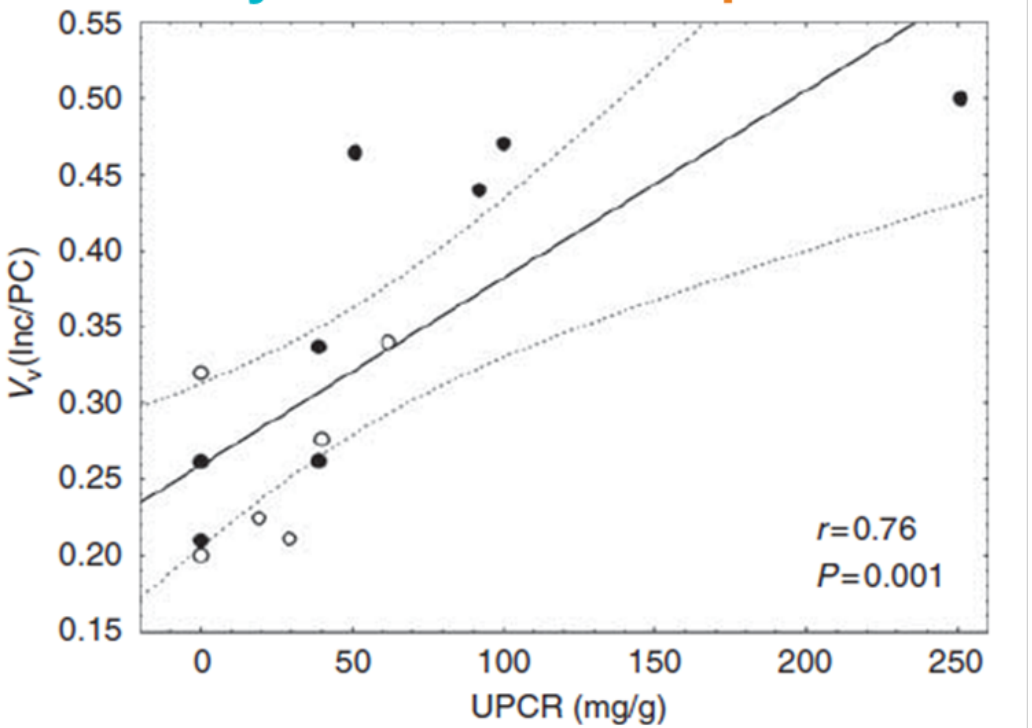
Progressive podocyte injury and globotriaosylceramide (GL-3) accumulation in young patients with Fabry disease

Behzad Najafian [1], Einar Svarstad [2], Leif Bostad [3], Marie-Claire Gubler [4], Camilla Tøndel [5], Chester Whitley [6], Michael Mauer [7]

Podocyte inclusions vs age



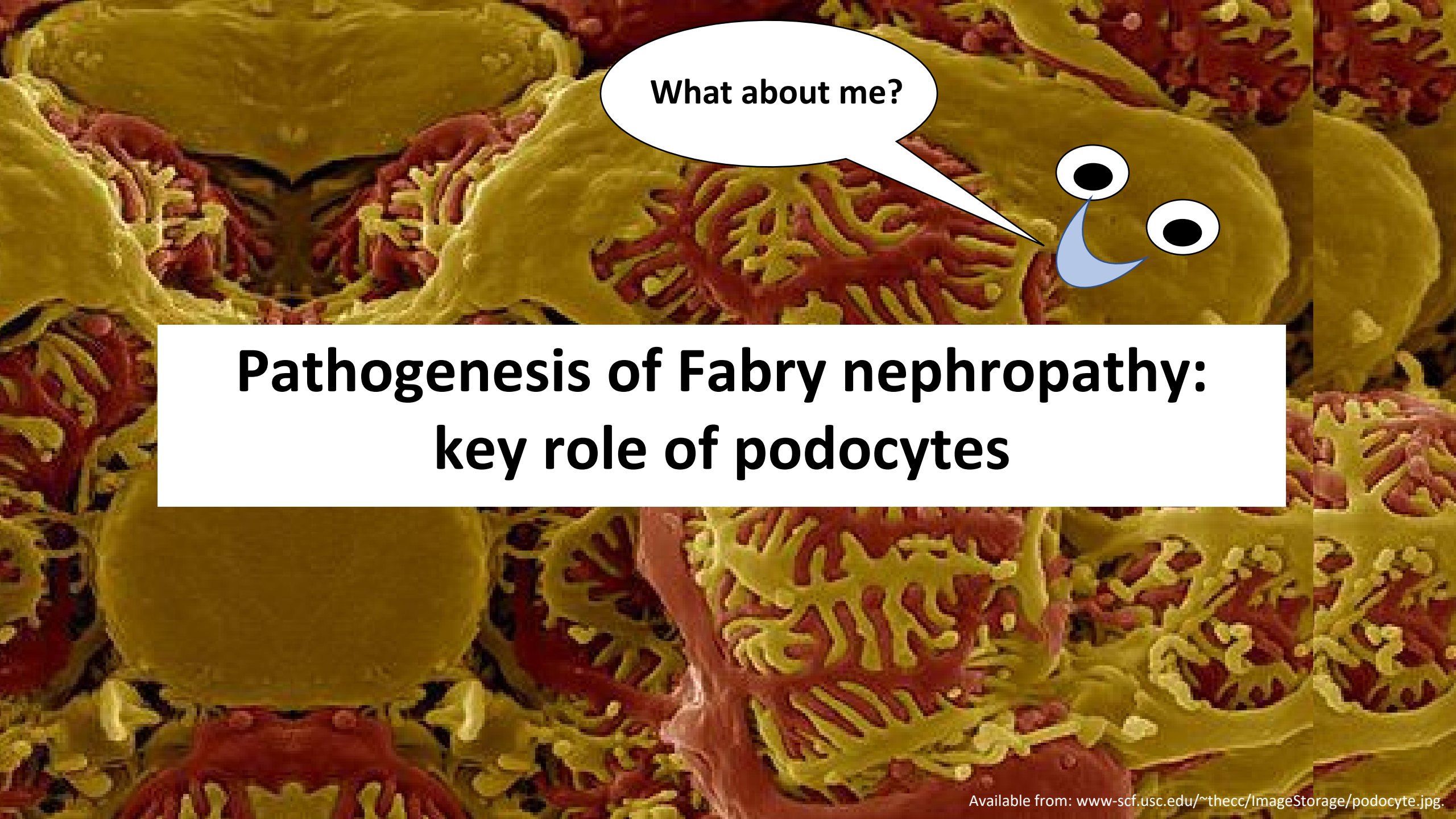
Podocyte inclusions vs proteinuria



Relationship between age and podocyte (Vv(Inc/PC)), and endotheli
cell (Vv(Inc/Endo)) GL-3 fractional volume of inclusions per cytoplas

Segmental foot process effacement was present in all glomeruli

Kidney Int. 2011 Mar;79(6):663-670. doi: 10.1038/ki.2010.484.



Pathogenesis of Fabry nephropathy: key role of podocytes

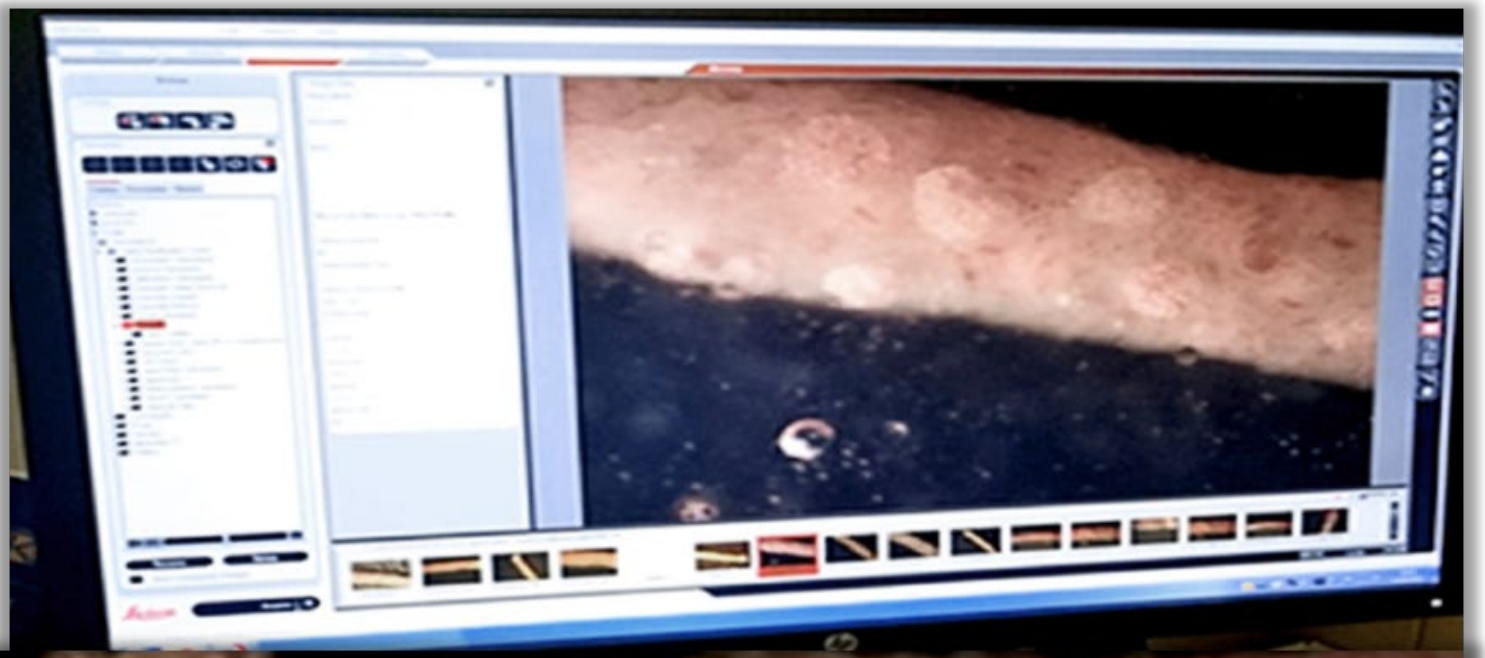
Available from: www-scf.usc.edu/~thecc/ImageStorage/podocyte.jpg.

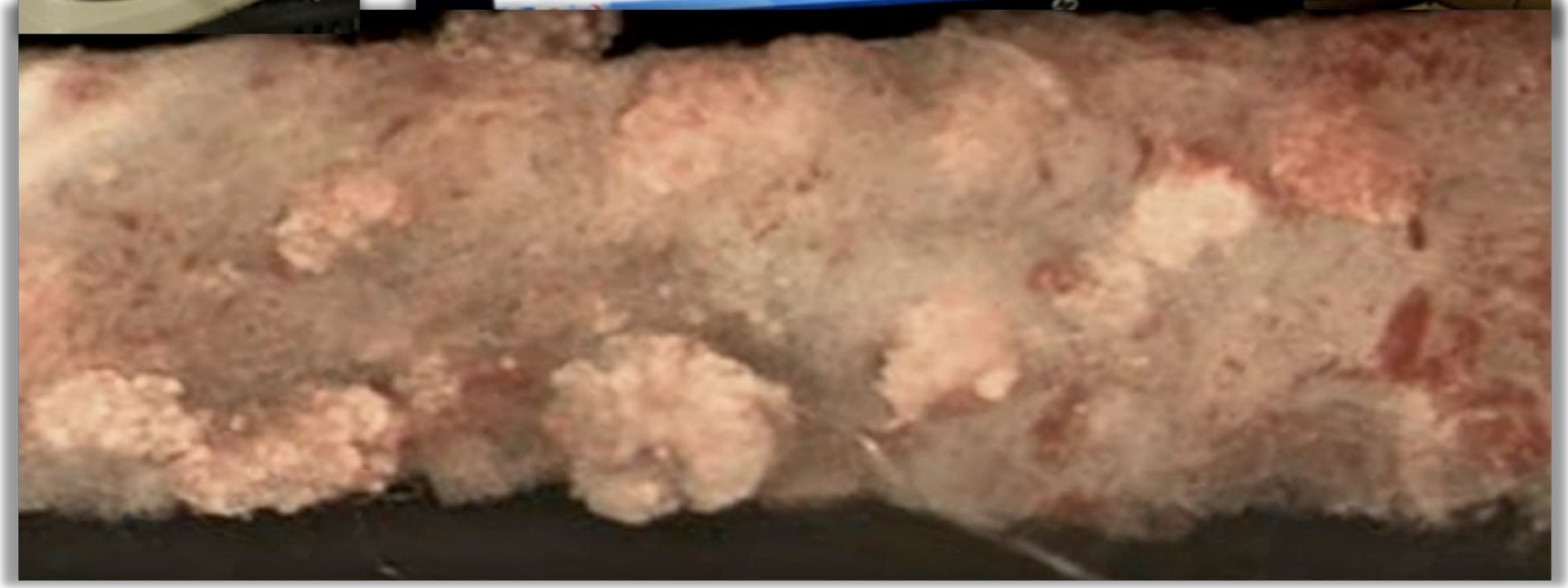
https://upload.wikimedia.org/wikipedia/commons/4/46/Sea_anemone_on_the_Oregon_Coast_%283222020816%29.jpg

This is not what it seems!!!!

Podocyte farewell ceremony by cell biology scientist

Fabry podocytes are fuuuuull of glycolipids



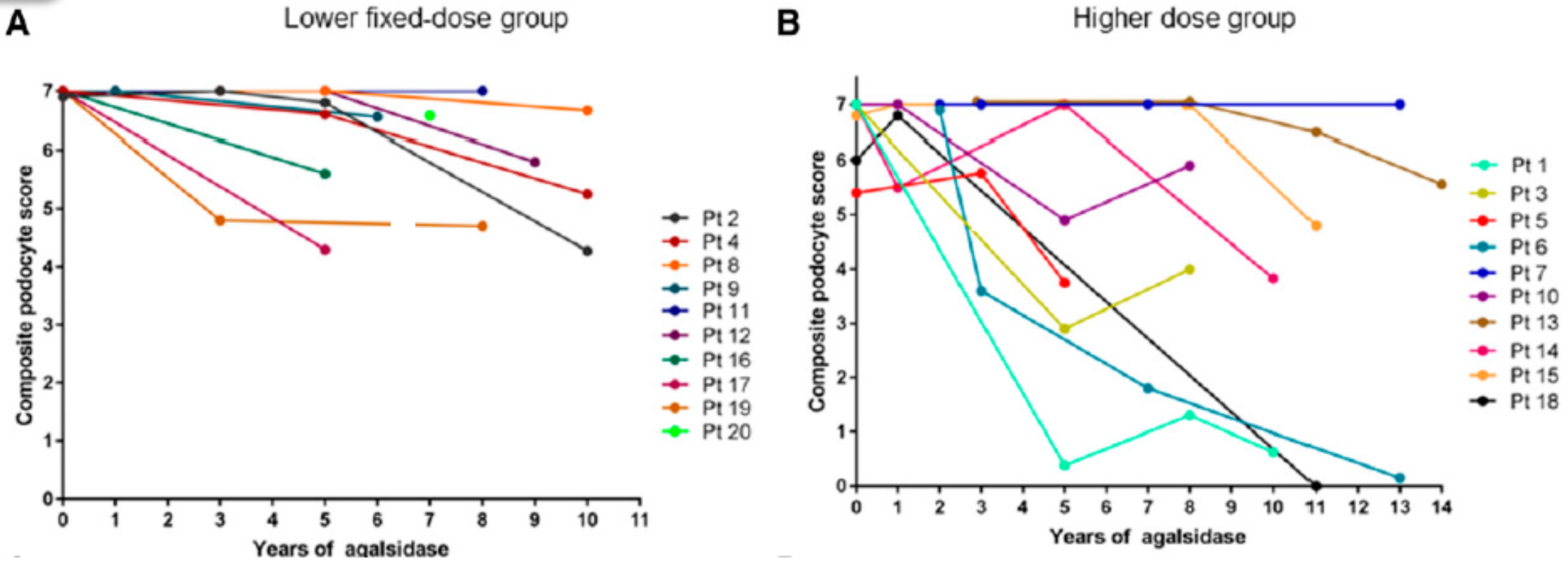


Svarstad E et al. *Nephron*. 2018;138(1):13-21.

It takes years to clear glycolipid deposits from podocytes

Endothelium cleared in all

Lower fixed-dose group



Gb3, globotriaosylceramide.

Skrunes R, et al. Clin J Am Soc Nephrol. 2017;12:1470-9.

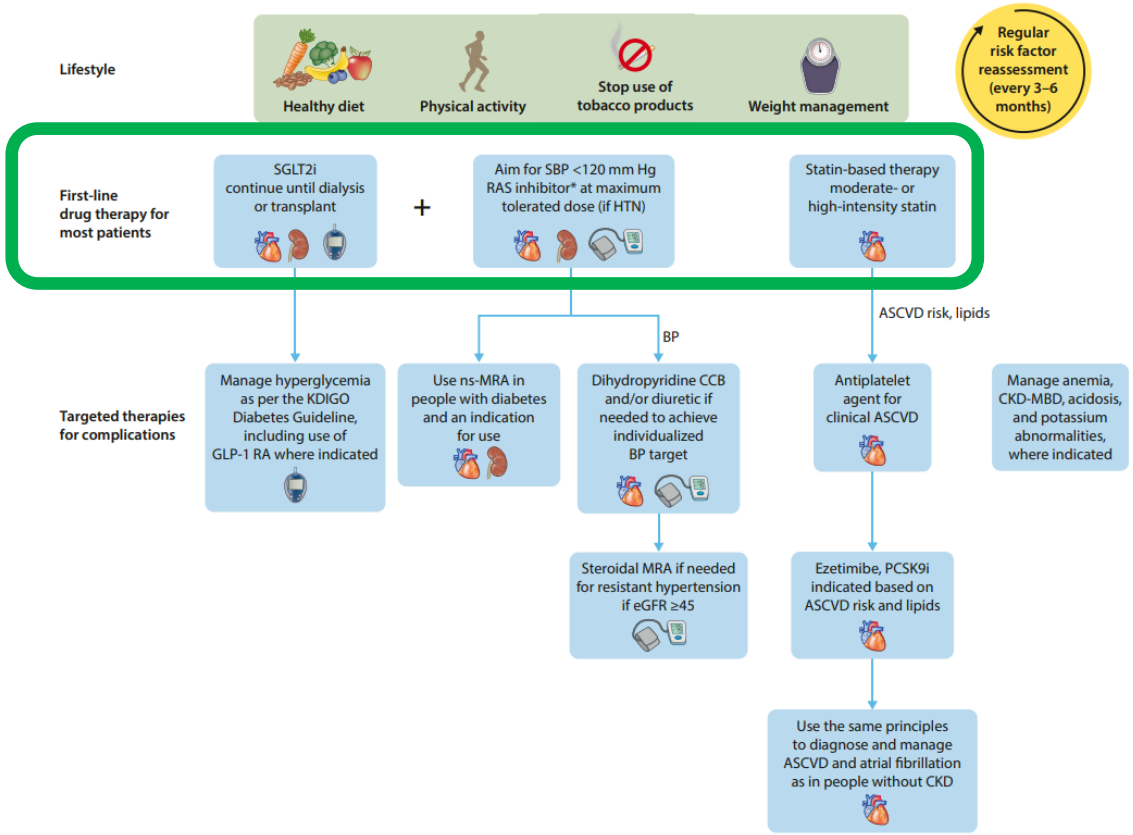
Early initiation of enzyme replacement therapy in classical Fabry disease normalizes biomarkers in clinically asymptomatic pediatric patients

Amy Kritzer[a], Aishwarya Siddharth[a], Kate Leestma[a], Olaf Bodamer[a,b,*]

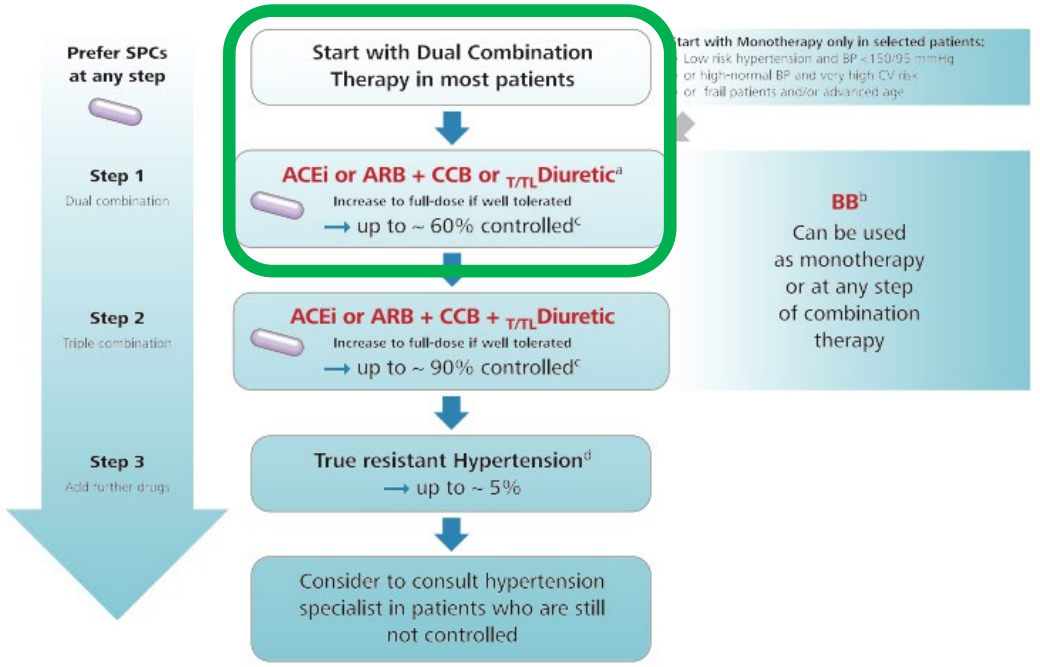
- classical FD male
- Plasma lyso Gb3 level **52.2** ng/mL (normal < 5 ng/mL).
- intravenous ERT with algalsidase-beta at 1 mg/kg q2weeks at **3 years and 6 months** of age.
- Lyso Gb3 levels **normalized after 10 months** of ERT to below the level of quantification (< 5 ng/mL).

- classical FD male
- Plasma lyso Gb3 level **35** ng/mL (normal < 5 ng/mL).
- intravenous ERT with agalsidase-beta at 1 mg/kg q2weeks at **5 years and 3 months** of age.
- Lyso Gb3 levels **normalized after 8 months** of ERT to below the level of quantification (< 5 ng/mL).

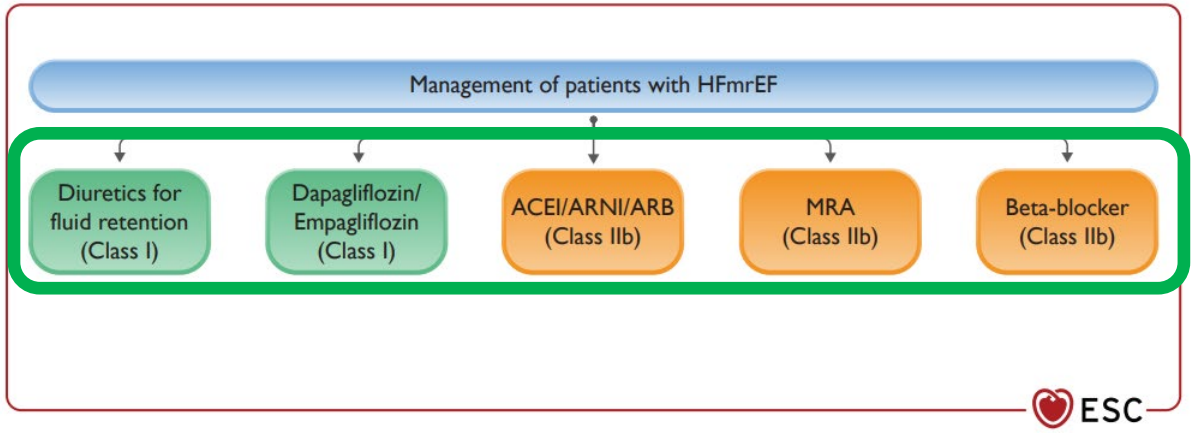
KDIGO 2024 treatment of CKD



ESH 2023 treatment of hypertension



ESC 2023 treatment of heart failure



Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *Kidney Int*. 2024;105(4S):S117-S314

Authors/Task Force Members:, McDonagh TA, Metra M, et al. 2023 Focused Update of the 2021 ESC Guidelines for the diagnosis and treatme of acute and chronic heart failure: Developed by the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) With the special contribution of the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail. 2024;26(1):5-17. doi:10.1002/ejhf.3024

Mancia G, Kreutz R, Brunström M, et al. 2023 ESH Guidelines for the management of arterial hypertension The Task Force for the manageme of arterial hypertension of the European Society of Hypertension: Endorsed by the International Society of Hypertension (ISH) and the European Renal Association (ERA). J Hypertens. 2023;41(12):1874-2071. doi:10.1097/HJH.0000000000003480

GCS inhibitors

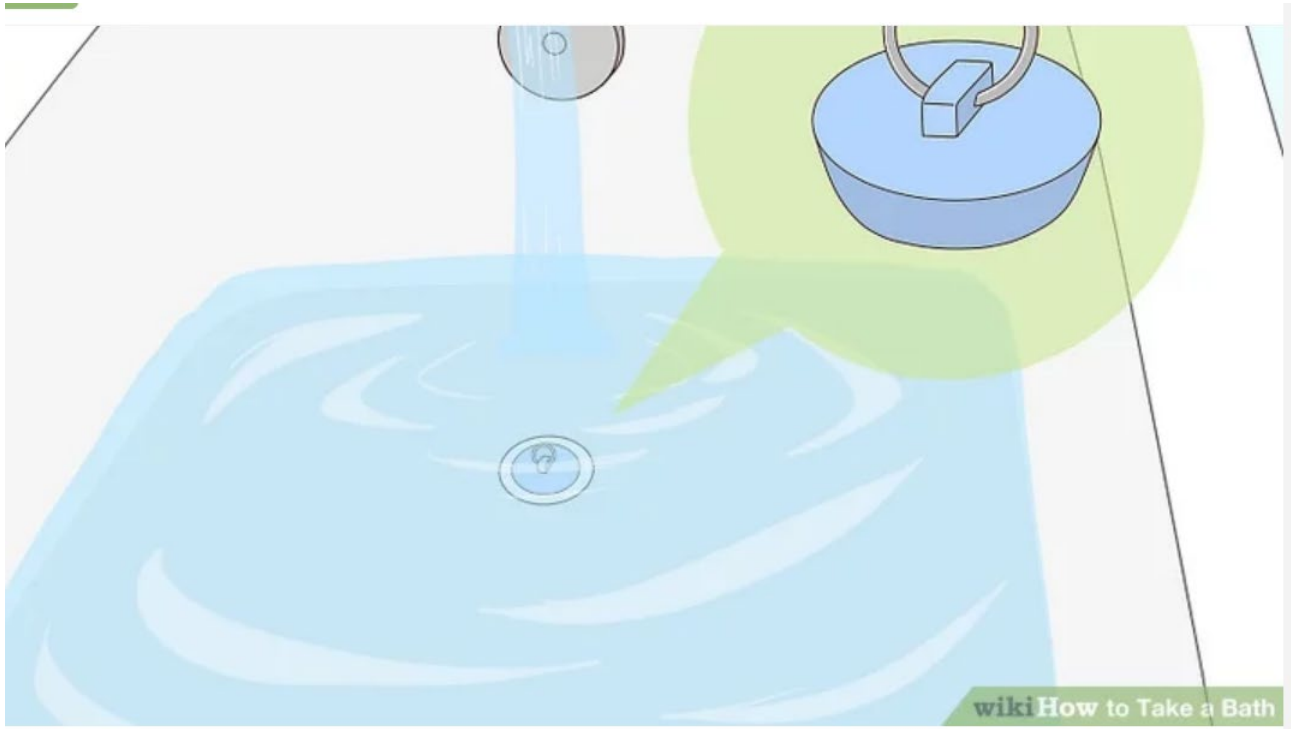
ERT

or

Chaperone

or

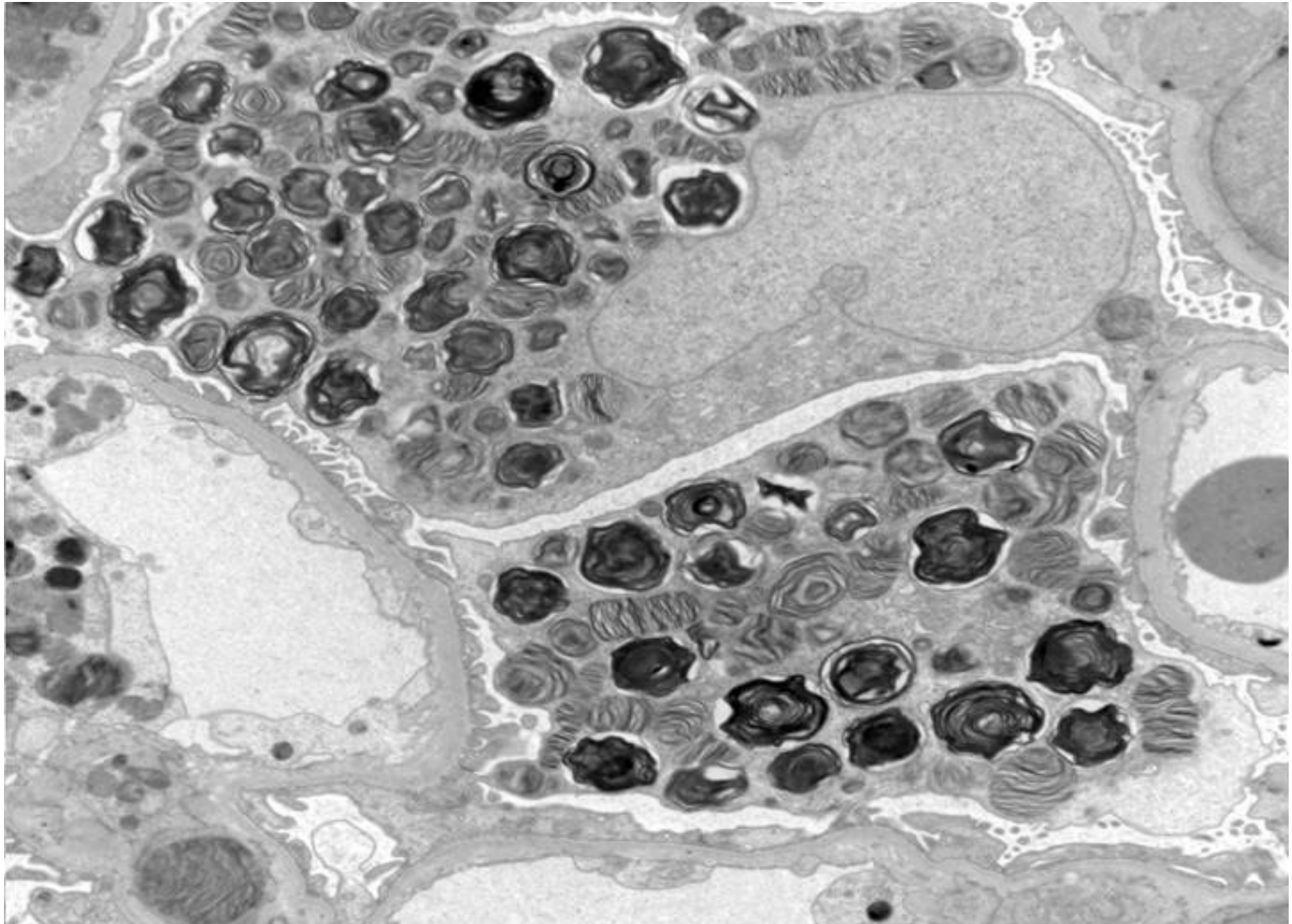
Gene therapy



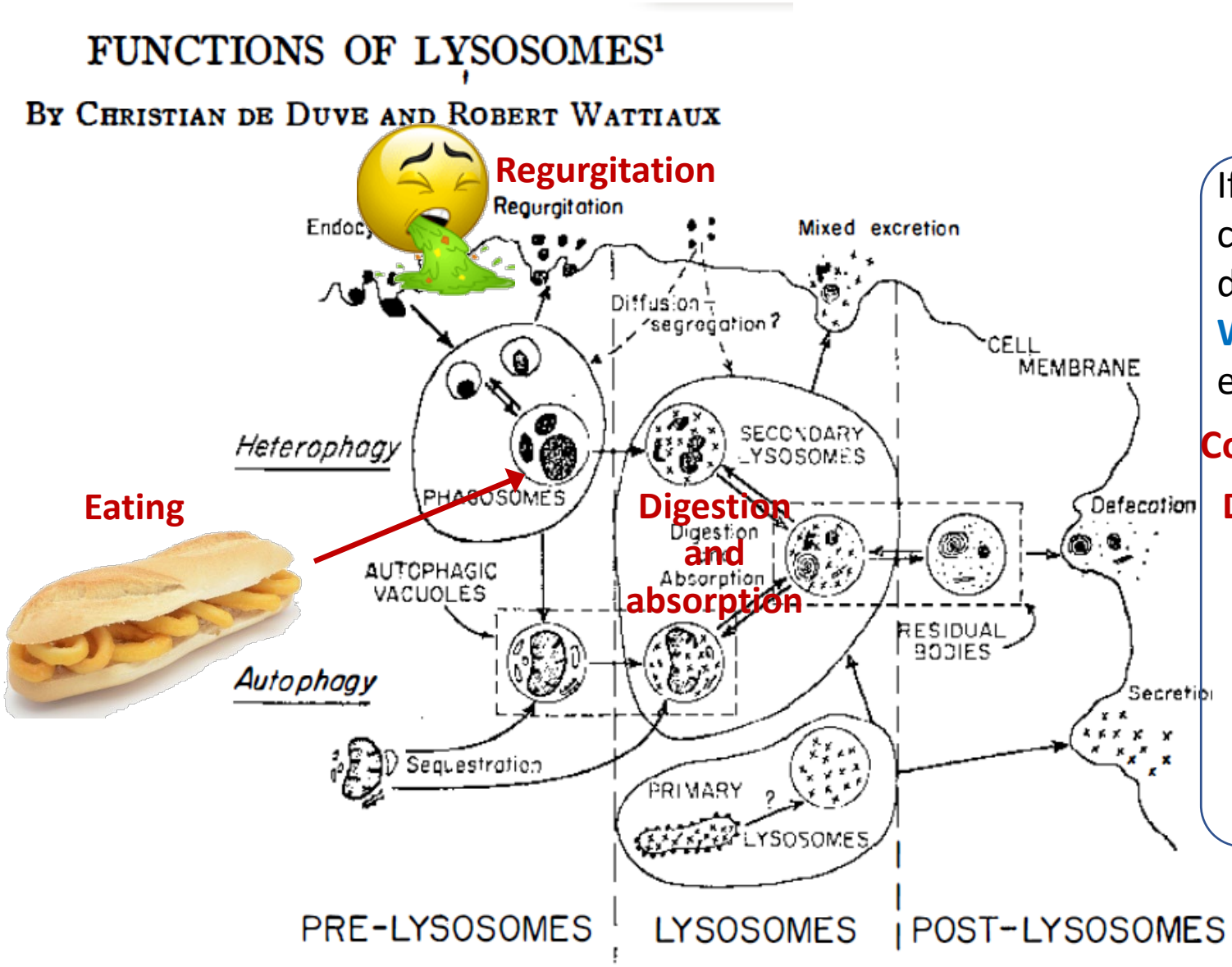
Why not combine both initially for rapid debulking

Plus subsequent maintenance with one agent not combine both initially for rapid debulking?

- Who and when to treat?
- How to accelerate the clearance of glycolipid deposits?
- **Is it only glycolipid deposits?**
- How to address anti-drug antibodies?



The lysosome according to De Duve



If lysosomes can defecate?

Why do LSDs exist?

Constipation?

Defecation

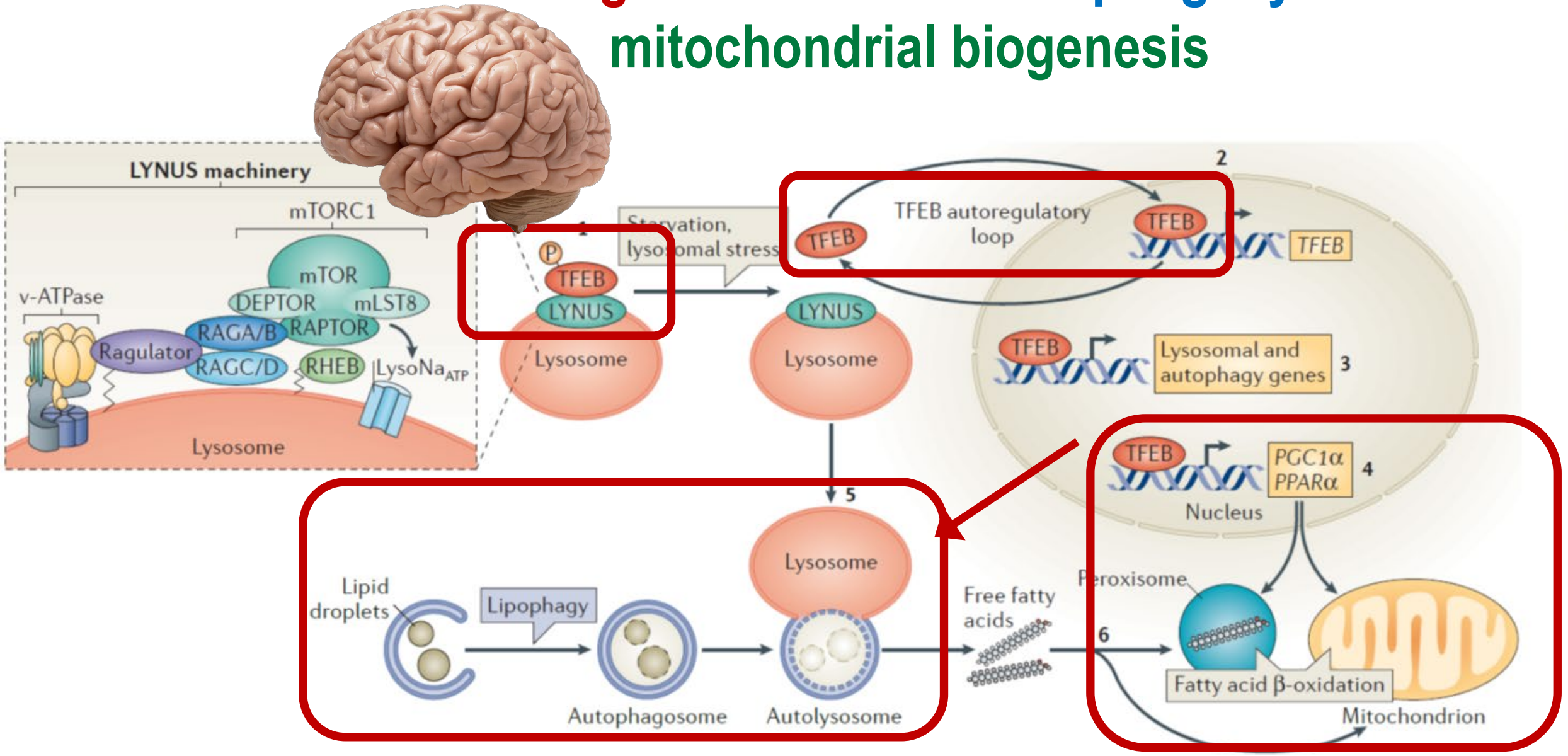
Day
After day
After day
…….

https://es.m.wikipedia.org/wiki/Archivo:Baby_eating_baby_food.jpg

De Duve et al. Annu Rev Physiol 1966

Is there an additional lysosomal dysfunction?

Starvation sensing and control of autophagocytosis and mitochondrial biogenesis



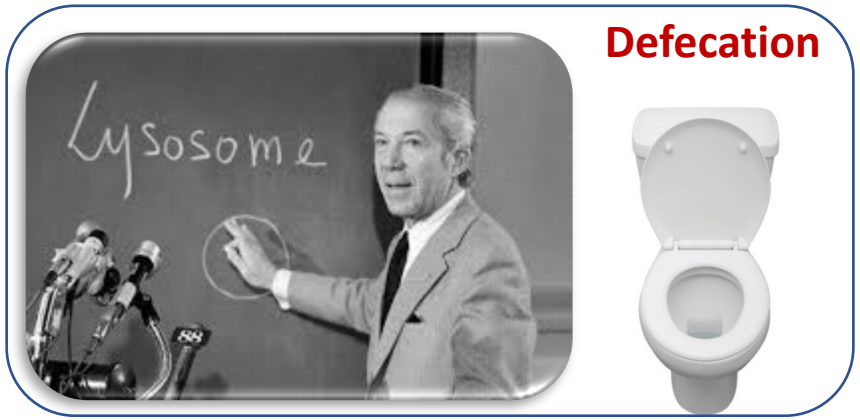
Settembre et al. Nat Rev Mol Cell Biol 2013;14(5):283-96

TFEB

a promoter of **autophagy,**

and of lysosomal **exocytosis**:

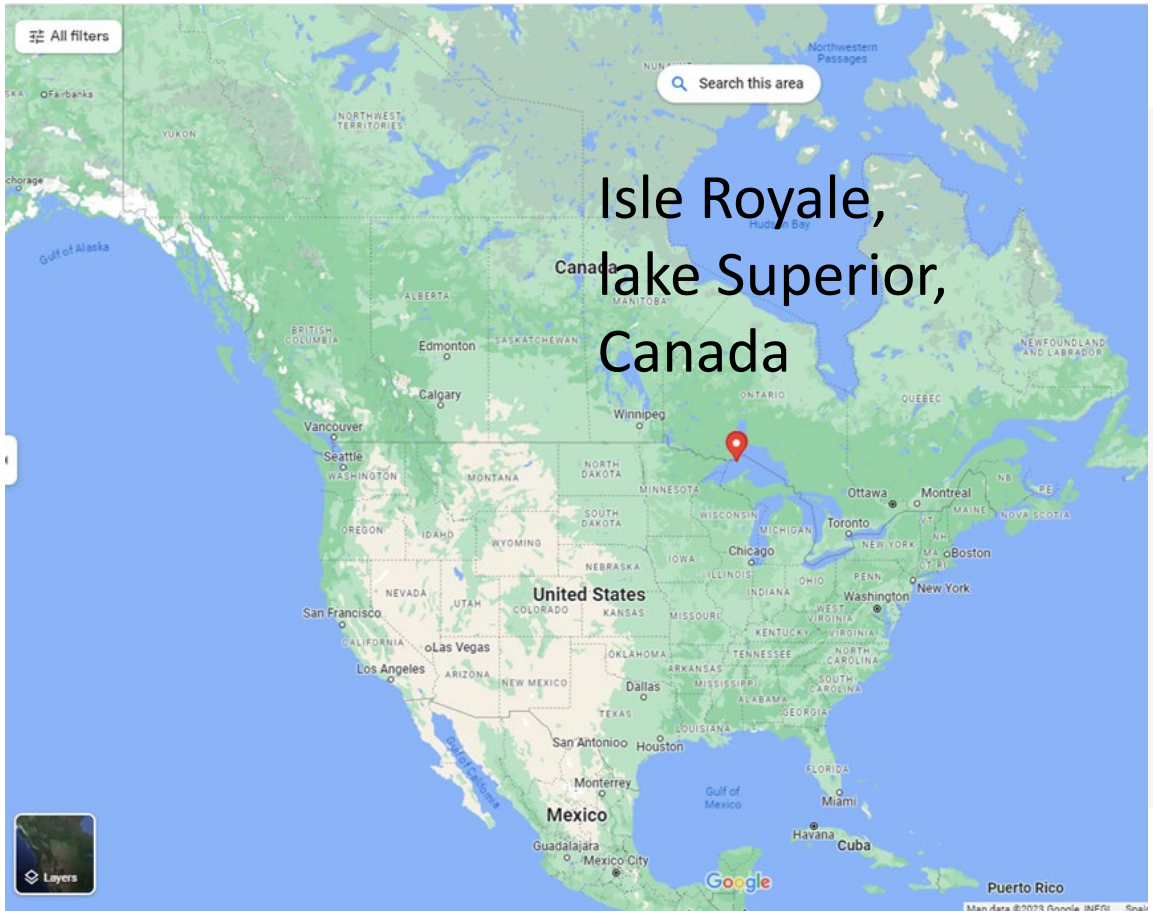
Lysosomes secrete their contents through a **Ca2+**-dependent, **TFEB**-regulated process.



Kaushik S, Cuervo AM. The coming of age of chaperone-mediated autophagy. *Nat Rev Mol Cell Biol*. 2018;19(6):365-381.

The 9 Hallmarks of Aging

López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G. The hallmarks of aging. *Cell*. 2013;153(6):1194-1217



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https://www.nicepng.com/ourpic/u2a9o0i1q8e6e6t4_wolf-png-clip-art-wolf-png/
https://www.google.com/maps/search/Isle+Royale/@48.0060536,-109.8237903,4z
https://www.nbcnews.com/science/wolf-population-moose-research-predator-prey-isle-royale-rcna24485

https://gestionrenove.es/SGP_Renove/

Enhancement of the **autophagic—lysosomal pathway** is an important determinant of the **anti-ageing** effect of …….

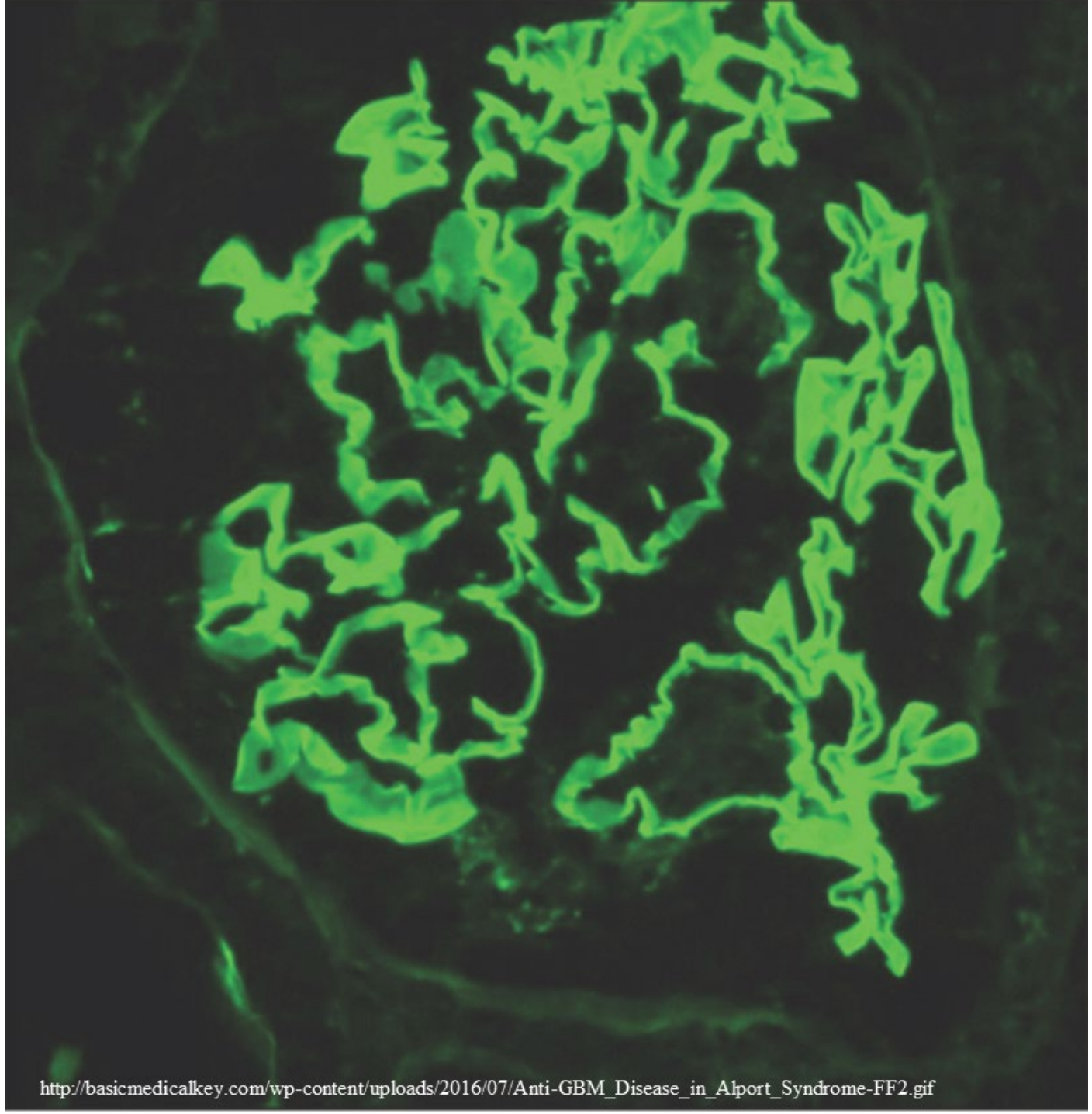
……..**caloric restriction**!!

Settembre et al. Nat Rev Mol Cell Biol 2013;14(5):283-96

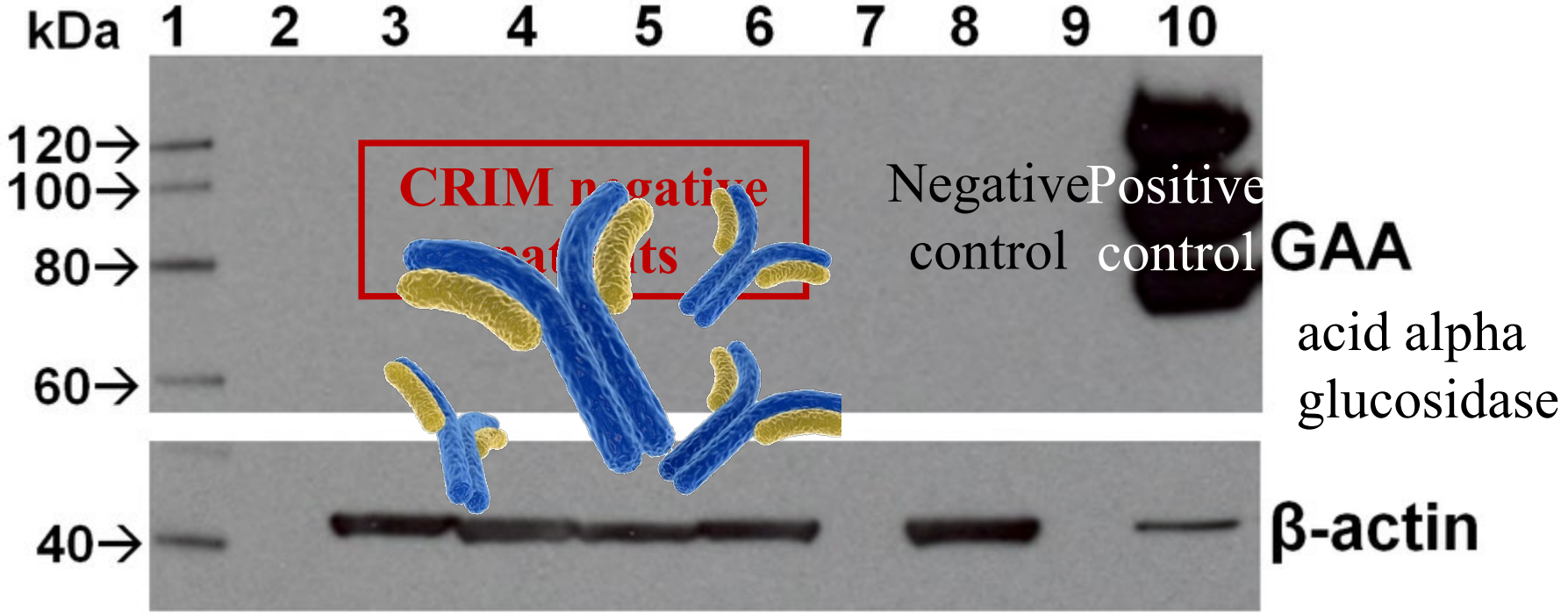
- Who and when to treat?
- How to accelerate the clearance of glycolipid deposits?
- Is it only glycolipid deposits?
- How to address **anti-drug antibodies**?

Anti-GBM antibodies in Alport patient receiving a kidney graft

Alport patients **lack** certain **GBM** components (type IV collagen)



Cross-reactive immunologic material (**CRIM**) in infantile Pompe



Banugaria SG, et al. PLoS One. 2013;8(6):e67052

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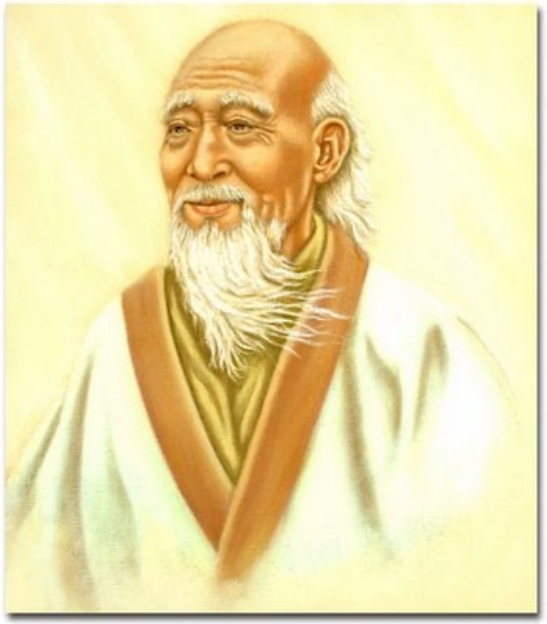
Dose-Dependent Effect of Enzyme Replacement Therapy on Neutralizing Antidrug Antibody Titers and Clinical Outcome in Patients with Fabry Disease

Malte Lenders,[1] Leon Paul Neußer,[1] Michael Rudnicki,[2] Peter Nordbeck,[3] Sima Canaan-Kühl,[4] Albina Nowak,[5] Markus Cybulla,[6] Boris Schmitz,[7] Jan Lukas,[8] Christoph Wanner,[3] Stefan-Martin Brand,[7] and Eva Brand[1]

Lenders M, *et al. J Am Soc Nephrol.* 2018;29(12):2879–89.

Anticipate the difficult by
managing the easy
— Lao Tse



Should we prevent the development of antibodies?

If so, how?

By providing a short immune suppression regimen to induce tolerance?

- **Who** and **when** to treat?
- How to **accelerate the clearance** of glycolipid deposits?
- Is it **only** glycolipid **deposits**??
- How to address **anti-drug antibodies**?

How to make therapy more **user-friendly** and **less costly**