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HELLENIC SOCIETY OF NEPHROLOGY MEETING & SEMINAR

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Challenges in diagnosis and management of Fabry nephropathy

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Disclosures

- *Speaker's honoraria from Sanofi-Genzyme, Genesis Pharma (Cyprus) Ltd, Genesis Biopharma Romania, Takeda, AstraZeneca Pharma SRL*
- *Advisory board for Genesis Pharma (Cyprus) Ltd, Genesis Biopharma Romania, Fresenius Kabi Deutschland, Sanofi-Genzyme, Takeda, Alnylam Pharmaceutical.*

Fabry disease is a multisystemic disorder

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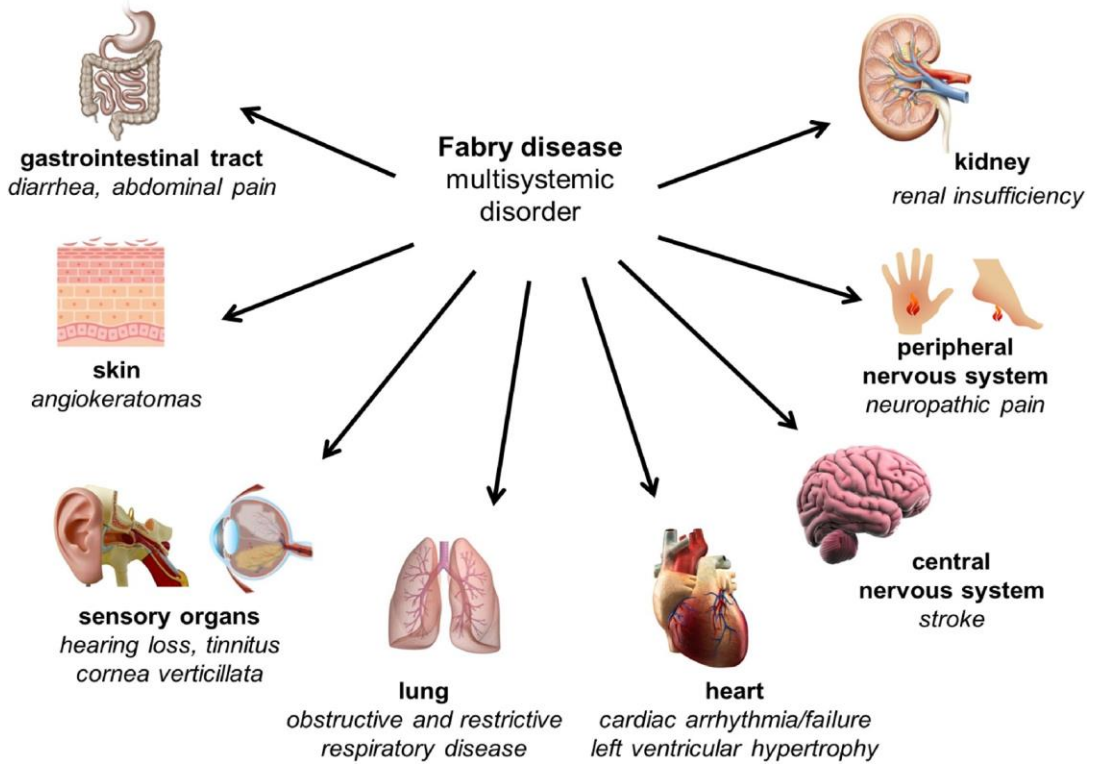
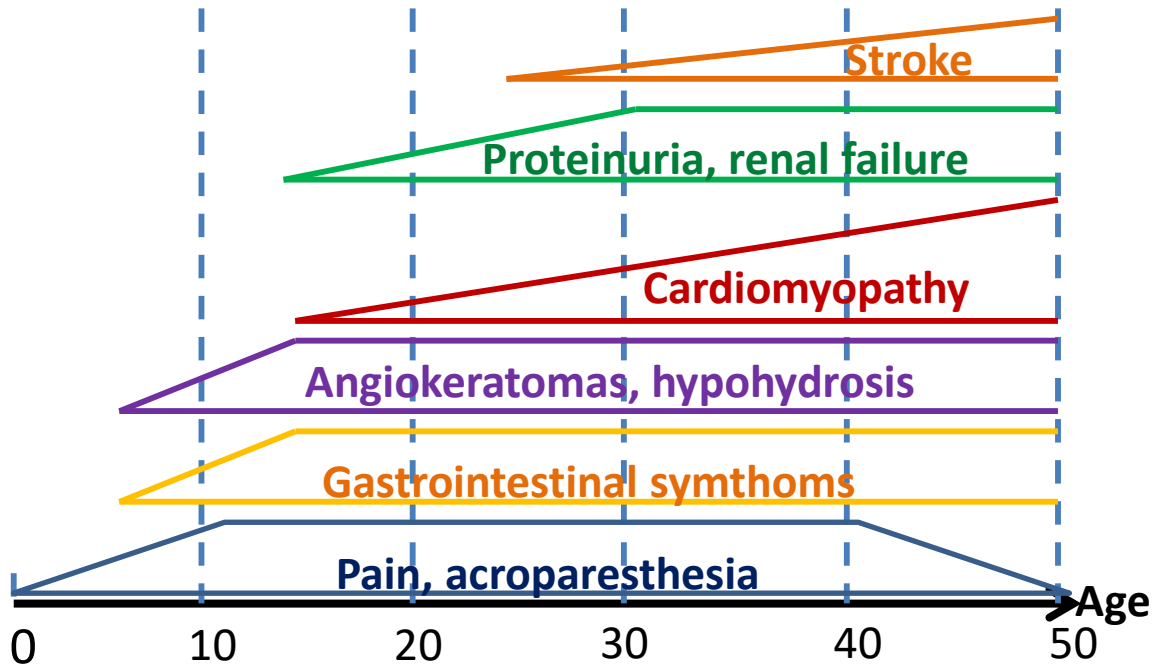
Fabry disease (FD) is an X-linked lysosomal storage disorder, caused by the deficiency of α-galactosidase A (α-Gal A), which leads to a progressive accumulation of the globotriaosylceramide (GL-3) and its derivatives, e.g., globotriaosylsphingosine (lyso-GL-3) in various tissues.



Malte Lenders and Eva Brands. Nephrol Dial Transplant 2021; 36: ii14-ii23

Timeline of Fabry Disease manifestations in hemizygous male patients*



**Adapted from Metha et al. Eur J Clin Invest 2004*

Kidney involvement in Fabry disease

Microalbuminuria and proteinuria [1,2]
Chronic kidney disease[3]
Decreased GFR and progressive kidney failure[1,3]
Podocyte foot process effacement[1]
Substrate accumulation in glomerular endothelial, mesangial, tubular and interstitial cells[1]
Glomerular sclerosis, tubular atrophy, and interstitial tissue damage (leading to kidney failure)[3]
Kidney biopsy demonstrating renal damage[1,2]

1. Germain DP. Orphanet J Rare Dis. 2010;5:30. 2. Mehta A, et al. QJM. 2010;103(9):641-659. 3. Eng CM, et al. Genet Med. 2006;8(9):539-548.

Challenges in diagnosis and management of Fabry disease

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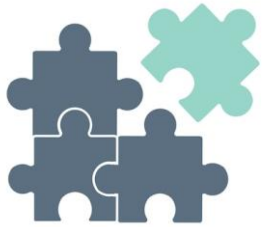
- Reduce the time to diagnosis
- Biomarkers of kidney involvement
- Tools to determine when to start the treatment
- Understanding the correlations between genotype and phenotype
- To establish the predictors of clinical response
- Improve treatment



Epidemiology of Fabry disease

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The prevalence of FD has been estimated between 1:40.000 and 1:170.000 individuals.

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

Newborn screenings

A recent newborn screening study from Italy revealed the overall incidence of 1:7879 newborns (1 in 4068 males), and pathogenic variants incidence 1:13.334 (1 in 6883 males).

Newborn Screening for Fabry Disease in Northeastern Italy: Results of Five Years of Experience

Vincenza Gragnaniello,[1,†] Alessandro P Burlina,[2,†] Giulia Polo,[1] Antonella Giuliani,[1] Leonardo Salviati,[3] Giovanni Duro,[4] Chiara Cazzorla,[1] Laura Rubert,[1] Evelina Maines,[5] Dominique P Germain,[6] and Alberto B Burlina[1,*]

Biomolecules. 2021 Jul; 11(7): 951

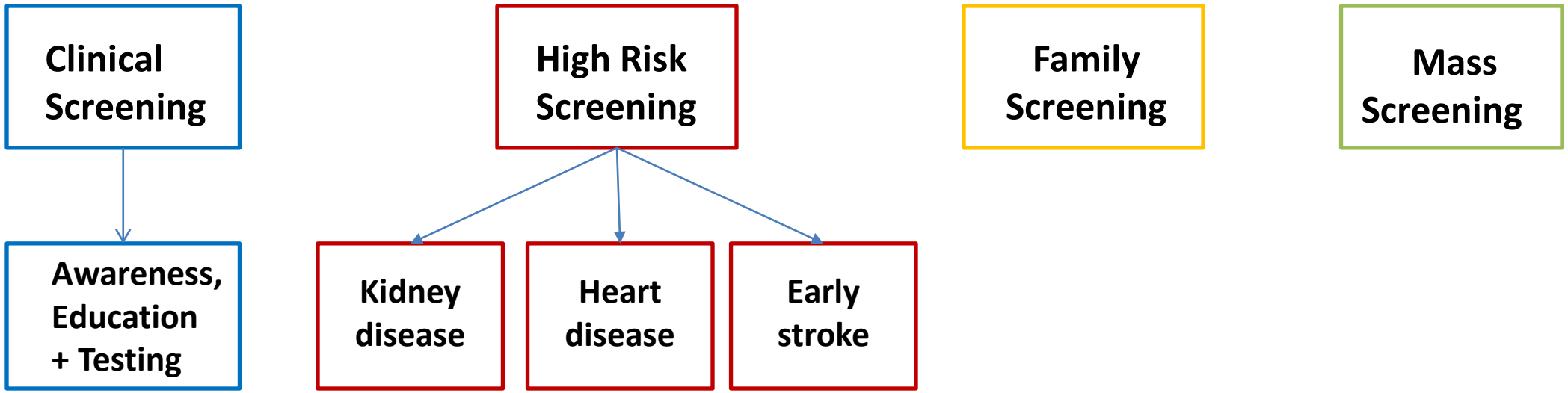
- *173,342 newborns (89,485 males) in 5.5 years*
- *α-galactosidase A activity and lyso-Gb_3 assays in DBS*

Prevalence of Fabry disease-causing variants in the UK Biobank

Mark Gilchrist ,[1] Francesco Casanova,[2] Jess S Tyrrell ,[2] Stuart Cannon ,[1] Andrew R Wood,[3] Nicole Fife,[1] Katherine Young ,[1] Richard A Oram,[4] Michael N Weedon[4] *J Med Genet 2023;60:391–396.*

The overall prevalence of Fabry disease causing variants in the UK Biobank is 1 in 5573 with the majority being those associated with a late-onset phenotype.

Types of screening for Fabry disease



Investigation of renal signs and symptoms could be key to prompt diagnosis and appropriate interventions for Fabry disease

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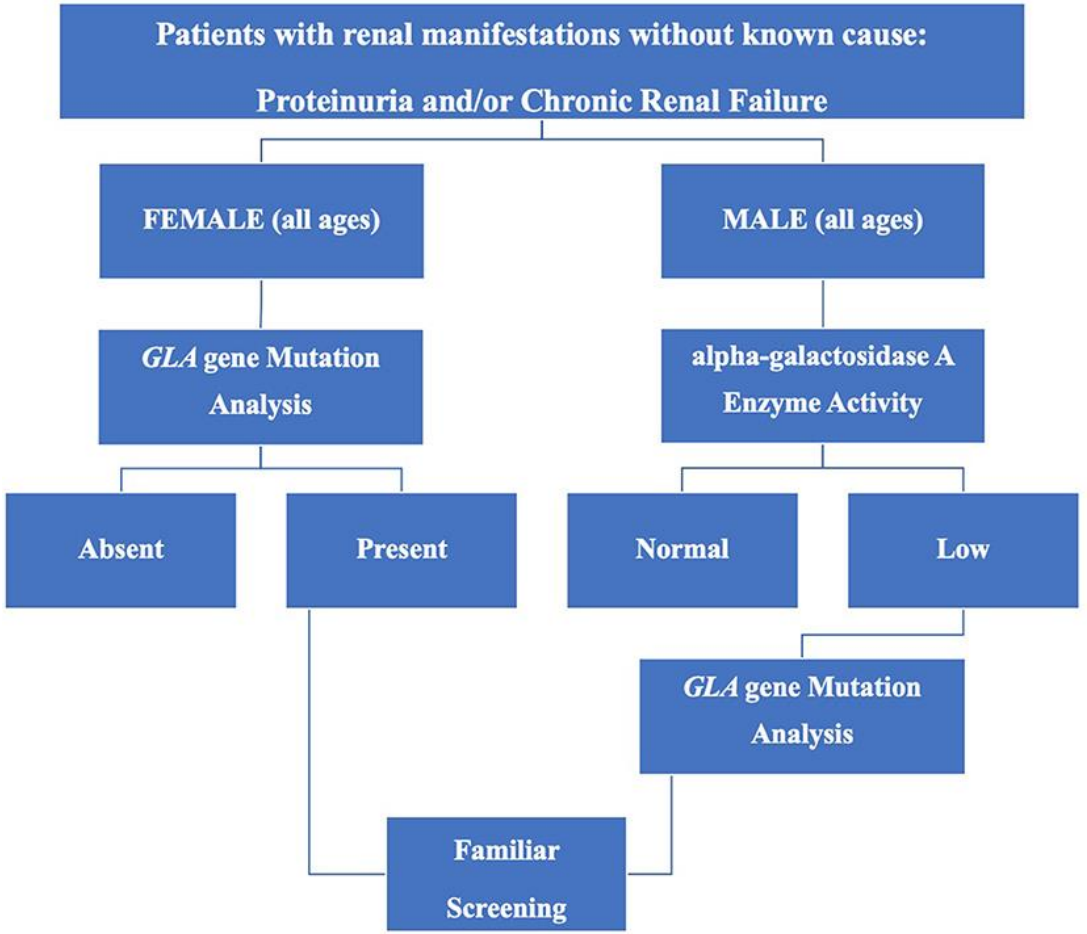
- **Red flags for Fabry nephropathy:[1]**
  - **Unexplained CKD, especially if presents proteinuria, without hypertension or mild hypertension in males < 50 year-old, and female, any age**
  - **Family history of nephropathy**
  - **Characteristic findings on kidney biopsy (zebra bodies)**

- **Non-renal red flags:**
  - Unexplained left ventricular hypertrophy
  - Stroke in young patient, neuropathic pain, impaired sweating
  - Angiokeratomas

Flow-chart for screening for FD in CKD patients[2]



1. ***Linthorst GE. Et al. J Med Genet, 2010***
2. ***Battaglia Y. et al. Front. Med., 2021***

Screening for Fabry disease

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High risk groups screening

Doheny et al reported prevalence of GLA variants in renal, cardiac and stroke clinics 1995-2017. Analysis included 63 studies and 51363 patients.

	Male	Female
Hemodialysis	0.21%	0.15%
Renal transplant	0.25%	0%
Cardiac	0.94%	0.9%
Stroke	0.13%	0.14%

Family screening
For an index case with FD approximately five family members are identified.

The efficacy of screening programs depends on careful selection of an appropriate patient with multi-organ morbidity and a positive family history.

Doheny et al. J Med Genet, 2018; Battaglia Y et al. Front Med, 2021, Vardarly Y et al. Ther Clin Risk Manag. 2020, Laney et al. J Genet Couns, 2013

Fundeni Expert Center for Rare Diseases of Reno-Urinary System

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Curr Health Sci J. 2019 Jul-Sep; 45(3): 272–277.
Published online 2019 Sep 30. doi: 10.12865/CHSJ.45.03.04
PMCID: PMC6993771
PMID: 32042454

Demographic and Clinical Characteristics of the Full 2015-2018 Cohort of Romanian Fabry Disease Patients

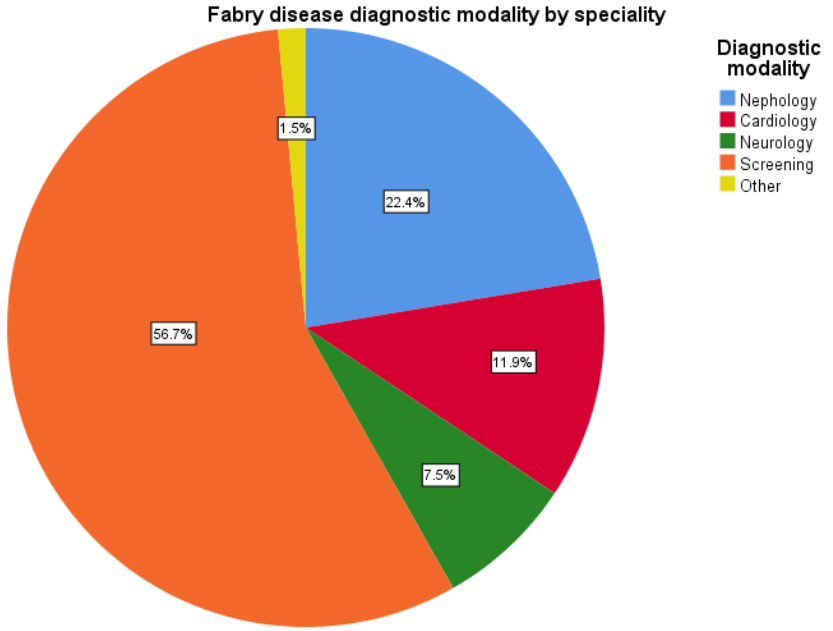
S MILITARU,[1,2] R ADAM,[2,3] G ISMAIL,[3,4] E RUSU,[3,4] A DULĂMEA,[3,4] and R JURCUT[2,3]

- ***Between 2015-2018, a cohort of 42 Romanian patients with FD***
- ***Underdiagnosed*** *- based on a prevalence of FD 1:100000 of approximately, in Romania should be about 200 patients diagnosed.*

Between **2015 – Sep 2023, in Fundeni Expert Center for Rare Diseases of Reno-Urinary System were evaluated 67 patients with Fabry Disease, 29 males and 38 females.**

15 index cases were diagnosed by nephrologists*:

- 5 patients were diagnosed by kidney biopsy,
- 10 patients by performing enzymatic and genetic test: 5 dialyzed patients, 1 patient with RTx, 3 with CKD 4, 1 patient CKD 3.



*Experience of Fundeni Expert Center for Rare Diseases of the Reno-Urinary System.

Key considerations for kidney biomarkers

Microalbuminuria is an early marker of Fabry nephropathy and a criterion for the diagnosis of CKD. Albuminuria should be expressed as a ratio to urinary creatinine or per 24 h.[1]

Albuminuria and eGFR slopes are current gold-standard biomarkers for monitoring FD-related nephropathy.

Loss of podocytes is an early marker of Fabry disease, likely preceding proteinuria and GFR decline, and is central to progression of Fabry nephropathy.[2,3] Podocyturia could potentially support the diagnosis of FD and guide treatment strategies.[4] The existing methods to assess podocyturia are not suitable for wide application in clinical settings.[5]

Use of cystatin-C provide a muscle-mass-independent criterion for early stage FD nephropathy and guide timely initiation of disease specific treatment.[4]

1. *D.P. Germain, G. Altarescu, et al. Mol Genet Metab 2022; 137: 49–614.*
2. *Trimarchi H, et al. J Nephrol. 2016;29(6):791-797.*
3. *Najafian B, et al. Kidney Int. 2011;79(6):663-670.*
4. *Burlina A, et al. Mol Genet Metab 2023; 139, 107585*
5. *B. Vujkovac et al. Clinical Kidney Journal, 2022*

Kidney biopsy – diagnostic biomarker for Fabry nephropathy

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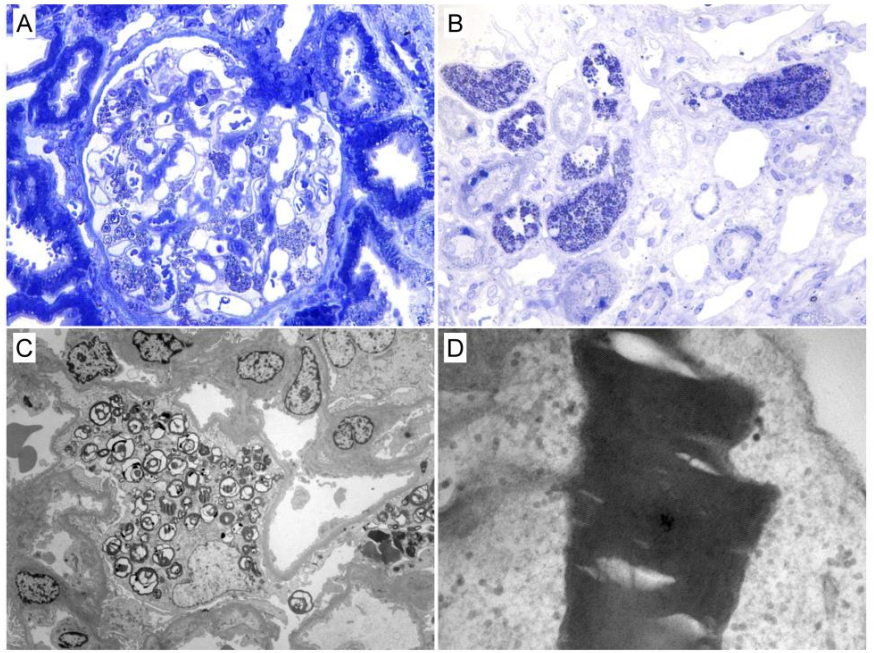
Indications for kidney biopsy (KB) in FD nephropathy[1,2]

- *To assess the degree of glomerulosclerosis and interstitial damage*
- *In patients with 30- to 300-mg/g albumin-to-creatinine ratio and normal kidney function, the biopsy can determine whether there are GL-3 deposits and quantify them.*
- *In women without evidence of FD nephropathy, the presence of significant renal deposits may serve as an indicator for the start of specific therapy.*
- *Exclusion of coexistent kidney disease*
- *Assessment of response to current therapy when a switch of therapy is being considered*



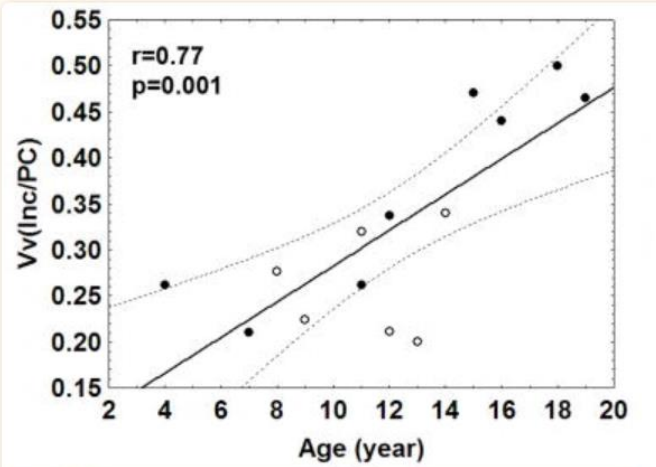
Kidney biopsy findings A: Light microscopy image of a semi-thin plastic section showing a glomerulus with many lamellar inclusion bodies in podocytes (toluidine blue stain, 200x); B: Light microscopy image of a semi-thin plastic section showing renal medulla with tubular epithelial cells and vascular smooth muscle cells having their cytoplasm filled with inclusion bodies (toluidine blue stain, 200x); C: Electron microscopy image showing electron dense, lamellate inclusions (typical "zebra bodies") in the cytoplasm of podocytes (5700x). D: Electron microscopy image showing the densely packed lamellate membranes contained into a lysosome (24000x). ***Rusu, E.E. et al. Biomedicines 2022, 10,1520. https://doi.org/10.3390/biomedicines10071520***

1. Germain DP, Altarescu G. et al. Mol. Genet. Metab 2022; 137: 49-61
2. Silva C.A.B. et al. , Can. J. Kidney Health Dis., 8 (2021)

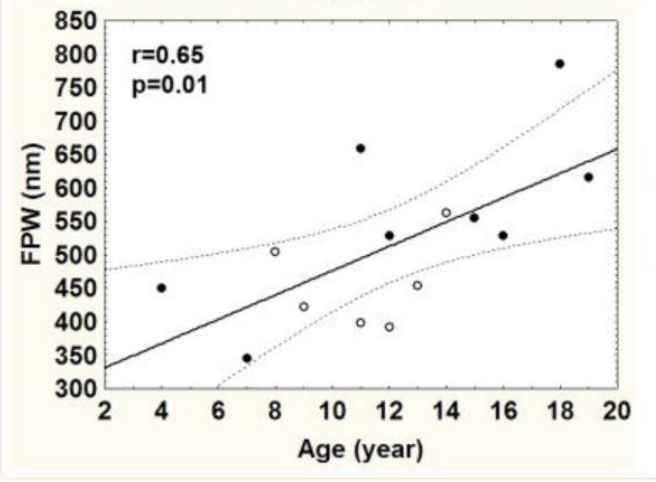
Renal histologic changes begin before microalbuminuria is present

- Renal biopsies from 14 (M/F=8/6) therapy naive Fabry patients (median age 12 years, range 4-19)
- Direct relationship between volume fraction of GL-3 per podocyte and foot process width (FPW), an indicator of podocyte injury
- Increase in foot process width (FPW), in normoalbuminuric young Fabry patients in the present study suggests that albuminuria/proteinuria is not sensitive enough to detect early kidney injury in Fabry nephropathy

Relationship between age and podocyte [Vv(Inc/PC)] GL-3 fractional volume of inclusions per cytoplasm.



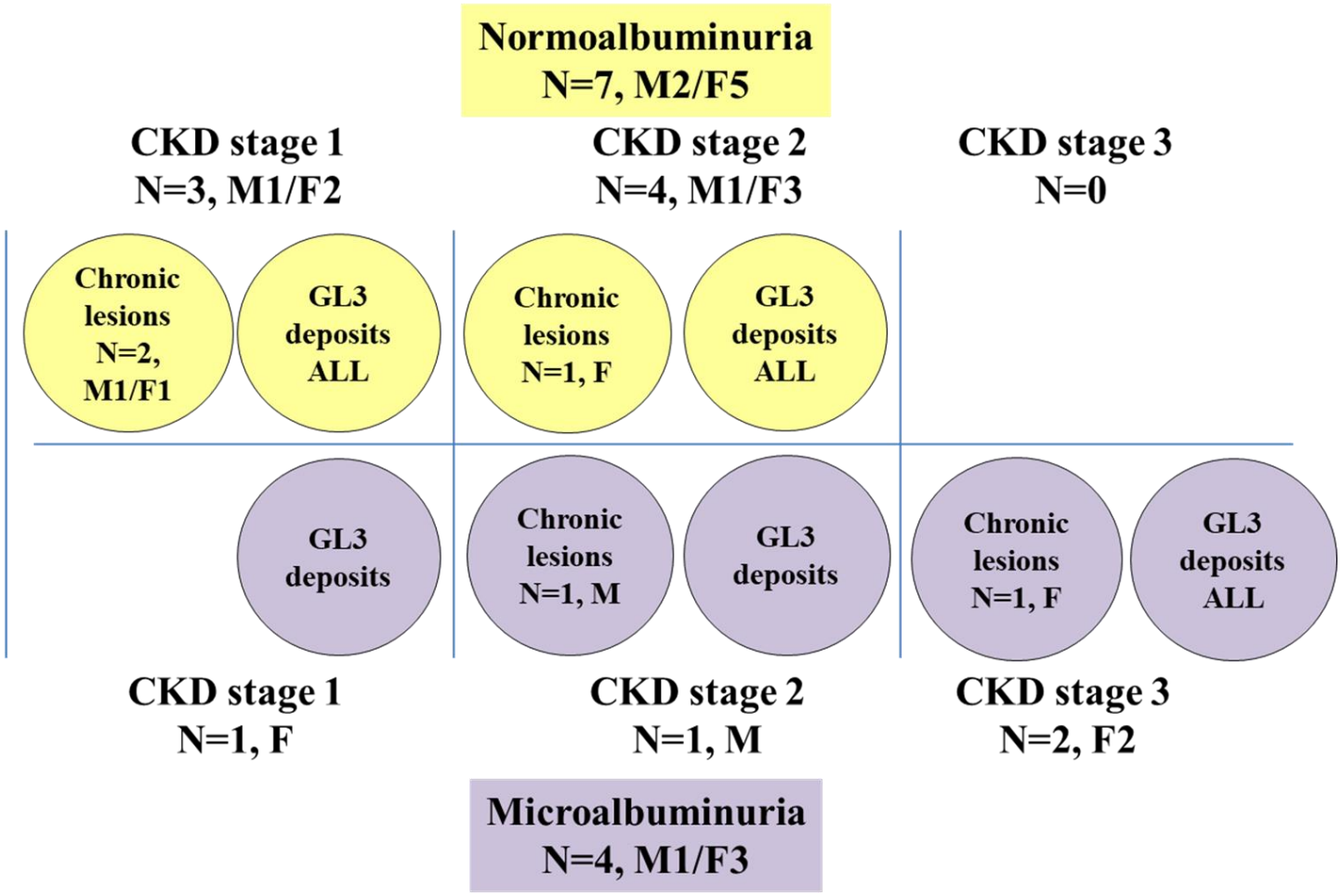
Relationship between age and foot process width (FPW) in Fabry patients.



Najafian B. et al. Kidney Int. 2011; 79(6): 663–670.

Renal histologic changes begin before microalbuminuria is present*

Rusu E et al. poster, The 3rd International Conference on Lysosomal Diseases, London 2023



- **11 patients who had normoalbuminuria or microalbuminuria (**without FD specific therapy) were evaluated by KB.
- **FD specific histological findings and nonspecific chronic lesions** were **observed even in normoalbuminuric patients**, demonstrating that albuminuria is not sufficiently sensitive biomarker to diagnose early kidney involvement in Fabry disease.
- These results indicate that evaluation by KB of FD patients can help to identify the early kidney injury, to establish the risk of progression, and can potentially be used to guide clinical decisions for FD specific therapy initiation.

**Experience of Fundeni Expert Center for Rare Diseases of the Reno-Urinary System.*

The PRoposing Early Disease Indicators for Clinical Tracking in Fabry Disease (PREDICT-FD)[1] - Renal indicators for disease progression

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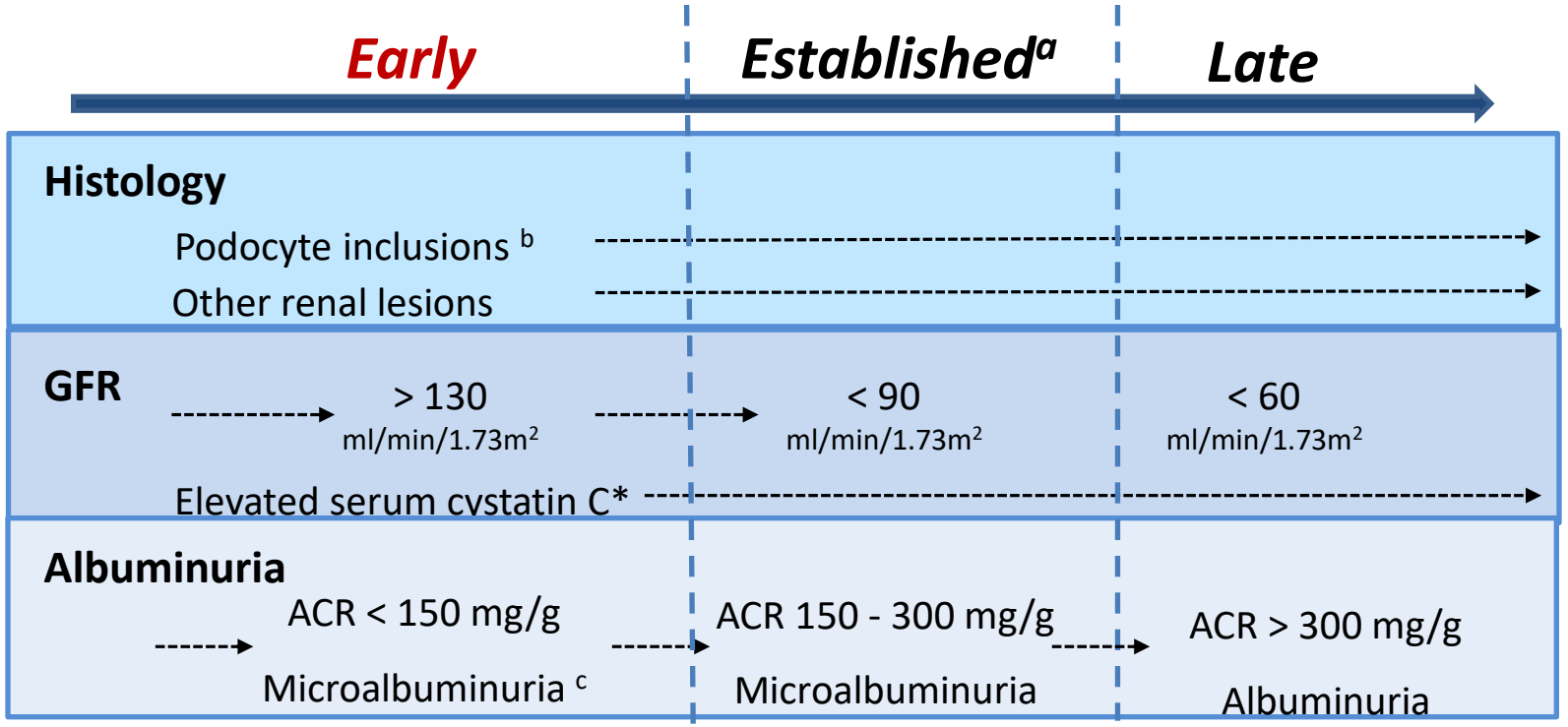
In the international PREDICT-FD expert consensus, the early indicators of clinical kidney damage included microalbuminuria, glomerular hyperfiltration and podocyte GL3 inclusions in the presence of other renal lesions, such as signs of glomerulosclerosis or vasculopathy, which may occur even in patients without microalbuminuria.



a = indicators that currently would be likely to trigger FD-specific treatment initiation.; b = in isolation, probably insufficient justification for FD-specific therapy initiation.
** indicator tested for, but not achieving consensus in round 3.*
*c = **Microalbuminuria could be a trigger for further investigations, such as confirmatory biopsy, and subsequent initiation of disease-specific treatment.***
ACR = Albumin : creatinine ratio

1 Hughes DA et al. BMJ Open 2020; 10:e035182

What are the indications for starting FD specific therapy?

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	Manifestations	Enzyme activity (in males)	Plasma lyso-GL
Classic Fabry disease	Early-onset and characteristic	Absent or deficient	High
Later-onset Fabry disease	Attenuated and non-specific	Residual	Moderately high

The European Fabry working group consensus document recommendations for enzyme replacement therapy[1]	
Classical FD males: 16 years or older, even if they have no symptoms or clinical signs of organ involvement	Class IIB recommendation
Classical FD males and females: as soon as there are early signs of FD organ involvement (kidney, heart, and/or CNS signs) and not fully explained by other pathology	Class I recommendation
Non-classical FD males: as soon as there are early signs of FD organ involvement (kidney, heart, and/or CNS signs and not fully explained by other pathology	Class I recommendation
Non-classical FD females: early clinical signs consistent with FD	Class IIB recommendation

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

Initiation of Fabry specific therapy in females: How early is early enough?

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- *Treatment recommendations suggest that females should start therapy only if incipient Fabry disease typical organ damage becomes apparent* [1]
- *Early treatment in females with a classical phenotype might be more effective before significant end-organ damage occurs* [2,3]
- *In an asymptomatic woman with a classic Fabry mutation, initiation of FD-specific treatment should be considered if there is laboratory, histologic, or imaging evidence of renal, cardiac, or central nervous system damage* [2]

1. Biegstraaten M et al. Orphanet J Rare Dis 2015; 10:36
2. Lenders M and Brand E. Nephrol Dial Transplant 2021; 36: ii14-ii23
3. Waldek and Feriozzi BMC Nephrology 2014; 15:72

Kidney biopsy findings from Fabry FEMALE patients

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Rusu E et al. Nephrol Dialysis Transplant, 37, Suppl. 3, 2022 https://doi.org/10.1093/ndt/gfac062.009

No	Age at KB	ERT duration (years)	eGFR (ml/min /1.73m)	Urine ACR (mg/g)	Proteinuria (g/24h)	Global sclerosis	Segmental sclerosis	Interstitial fibrosis	Arterial sclerosis	Podocyte GL3 deposits	Tubular GL3 deposits	Endothelial GL3 deposits
1	55	naive	61	819	1.8	+	+	+	+	+	+	+
2	61*	naive	85.3	20	0	-	-	+	+	+	+	+
3	35	naive	40	900	4.5	+	+	-	-	+	+	+
4	57*	2	88	150	0.2	-	+	+	-	+	+	+
5	49*	naive	104	100	0.2	-	-	+	-	+	+	+
6	50	naive	56	100	0.4	+	+	+	+	+	+	+
7	30*	naive	88	10	0.2	-	-	-	-	+	+	+
8	46*	naive	96	10	0.1	-	-	-	-	+	+	+
9	35*	naive	81	20	0.3	-	-	-	-	+	+	+
10	62	naive	53	10	0.1	-	-	-	+	+	+	-
11	63	naive	59	30	0.2	-	-	-	-	+	+	-

**Without renal criteria for initiation of enzyme replacement therapy, according to Romanian national protocol*

Kidney biopsy in females with Fabry Disease is an important tool to establish the indication to start Fabry therapy

Rusu E et al. Nephrol Dialysis Transplant, 37, Suppl. 3, 2022 https://doi.org/10.1093/ndt/gfac062.009

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- Considering Romanian national criteria for initiation of enzyme replacement therapy (eGFR < 80 ml/min/1.73m^2 and/or proteinuria > 300 mg/day), 6 patients with KB evaluation did not fulfill the renal criteria, but kidney biopsy showed FD specific lesions in all cases
  - *3 out of 6 patients presented criteria due to other organs involvement,*
  - *while 3 patients (mean age 37.7 years) did not fulfill any criteria for treatment initiation. These 3 patients were monitored at 6 months and 2 patients started FD-specific treatment after about 2 years.*

Our experience suggest that a revision of the Romanian national protocol is necessary, by adoption of early indicators of kidney involvement in order to promote earlier specific treatment in FD females.

Single center, cohort study evaluated the impact of Fabry nephropathy diagnosed by kidney biopsy on the management of patients and long-term outcomes

Rusu, E.E. et al. Biomedicines 2022, 10,1520. https://doi.org/10.3390/ biomedicines10071520

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Patient No.	Sex/ Age (yr)	ERT duration (mo)	eGFR (ml/min/ 1.73 m²)	UACR (mg/g)	Proteinuria (g/24h)	Global sclerosis	Segmental sclerosis	Glomerular Hyaline	Interstitial fibrosis	Tubular atrophy	Arterio-pathy	Podocyte GL3 deposits	Tubular GL3 deposits	Glomerular endothelial cell GL3 deposits
1	M/17	0	44.7	500	3.26	+	+	-	+	NA	+	+	+	+
2	M/10	0	87.5	10	0.08	-	-	-	-	-	-	+	+	+
3	M/41	0	45	100	1.37	-	-	-	+	NA	+	+	+	+
4	M/26	0	89	345	0.3	-	-	-	-	-	-	+	+	+
5	M/44	0	29	600	3.5	-	+	+	+	+	+	+	+	+
6	M/39	0	67	80	0.15	+	+	+	+	+	-	+	+	+
7	M/29	0	120	10	0.2	-	+	-	-	-	-	+	+	+
8	F/50	0	56	100	0.4	+	+	-	+	+	+	+	+	+
9	F/55	0	61	819	1.8	+	+	+	+	+	+	+	+	+
10	F/49	0	104.2	100	0.2	-	-	-	-	+	-	+	+	+
11	F/46	0	96	10	0.1	-	-	-	-	-	-	+	+	+
12	F/30	0	88	10	0.2	-	-	-	-	-	-	+	+	+
13	F/35	0	81	20	0.3	-	-	-	-	-	-	+	+	+
14	F/63	0	59	30	0.22	-	-	-	-	NA	-	+	+	-
15	F/35	0	40	900	4.5	+	+	-	-	-	+	+	+	+
16	F/61	0	85.3	20	ND	-	-	-	+	NA	+	+	+	+
17*	M/43	12	111	300	1.17	-	+	-	+	+	+	+	+	+
18*	M/32	144	120	20	ND	-	-	-	-	-	-	+	+	+
19*	M/58	72	102	10	0.2	-	+	-	+	+	-	+	+	+
20*	M/37	120	98	500	2.2	+	+	-	+	+	-	+	+	+
21*	F/57	27	88	150	0.2	-	+	+	-	-	-	+	+	+

**Previously enzyme replacement therapy treated patients; Plus (+) sign represent the presence and minus (-) sign represent the absence; M - male, F - female; NA - not applicable; GL3 - globotrioasylceramide*

The impact of kidney biopsy for Fabry nephropathy evaluation on patients' management and long-term outcomes: experience of a single center

Rusu, E.E. et al. Biomedicines 2022, 10,1520. https://doi.org/10.3390/ biomedicines10071520

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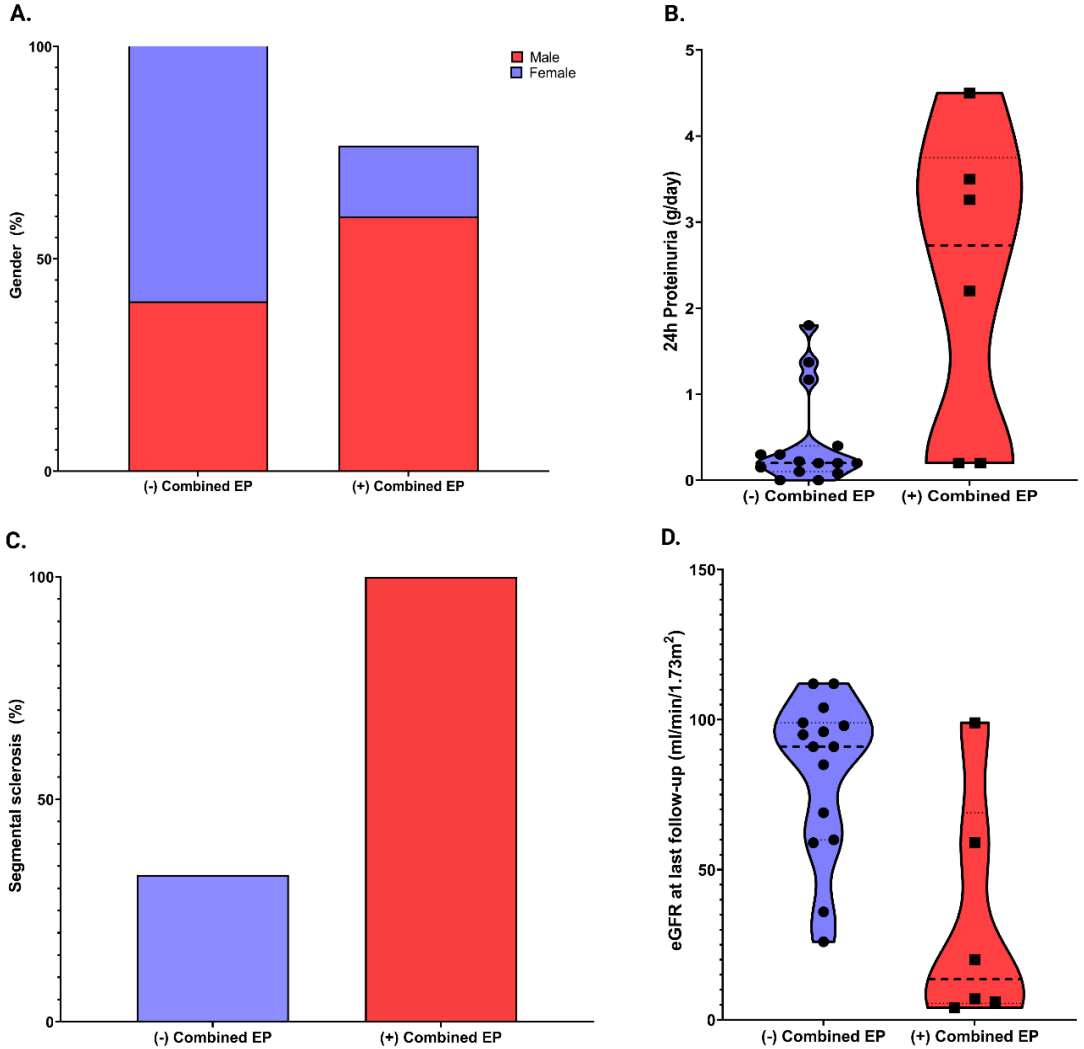

The mean follow-up period was 47.7 ± 19.1 months and a mandatory condition for monitoring for at least 12 months.

Variables associated with combined endpoint (*50% decrease of eGFR from baseline, reaching end-stage kidney disease and mortality*):

A. Gender (p=0.06)

B. Baseline 24h proteinuria (p = 0.02)

C. Segmental sclerosis (p = 0.009)

D. eGFR at last follow-up (p=0.003).

Changes in eGFR and proteinuria in individual patients under Agalsidase beta

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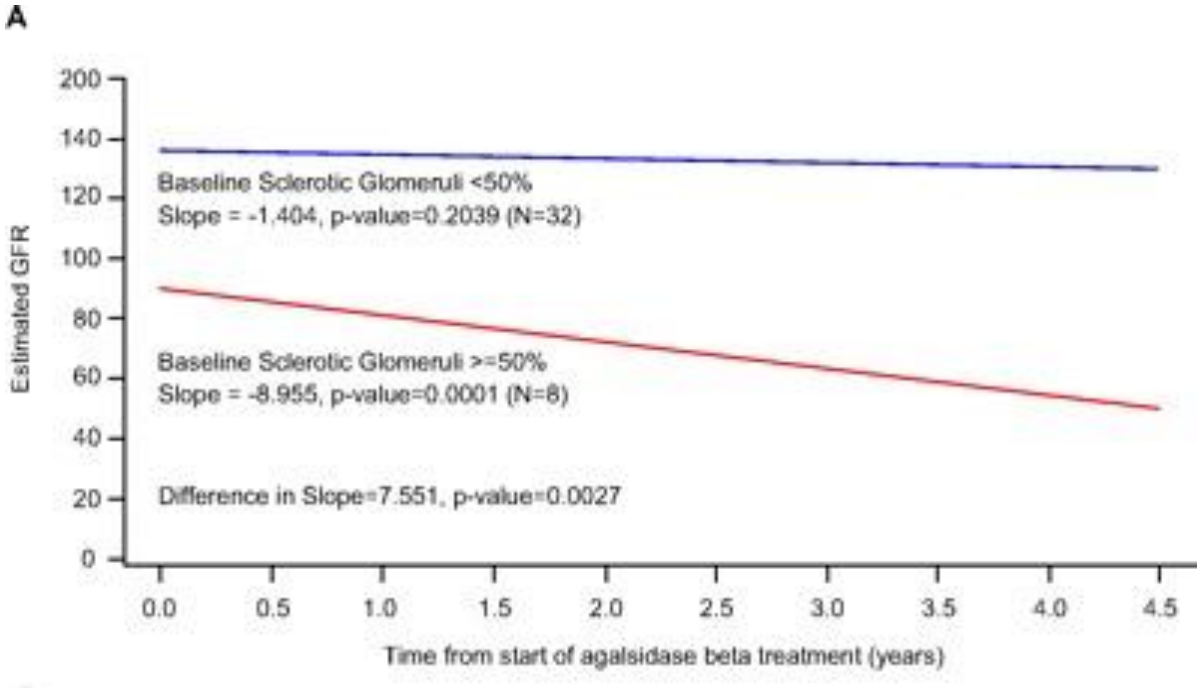

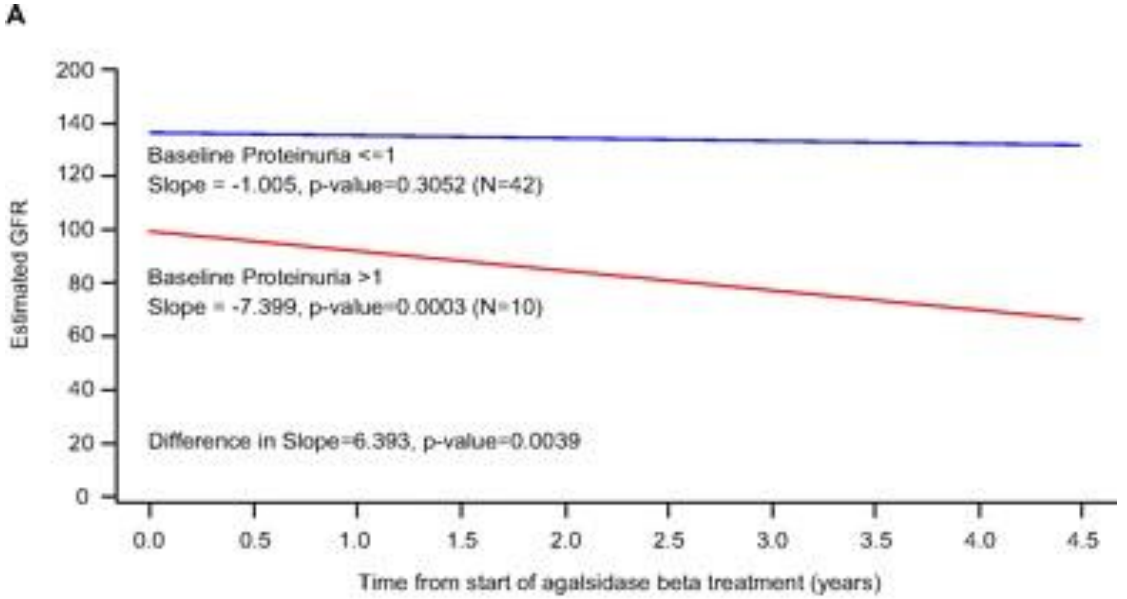

Subgroup analyses of patients in the "as treated" population show that those with **pre-treatment glomerulosclerosis (≥50% sclerotic glomeruli) and high (>1 g/24 h) baseline proteinuria is associated with higher rate of eGFR decline and increased probability of renal events.**

Germain, D.P. et al. Sustained, Long-Term Renal Stabilization After 54 Months of Agalsidase Beta Therapy in Patients with Fabry Disease. J Am Soc Nephrol 2007; 18(5):1547-1557.

Systems analyses of the Fabry kidney transcriptome and its response to enzyme replacement therapy identified and cross-validated enzyme replacement therapy-resistant targets amenable to drug repurposing

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Delaleu N, Marti HP, Strauss P, Sekulic M, Osman T, Tøndel C, Skrunes R, Leh S, Svarstad E, Nowak A, Gaspert A, ***Rusu E****, Kwee I, Rinaldi A, Flatberg A, Eikrem O*

Kidney International, Volume 104 Issue 4 Pages 803-819 (October **2023**)

Systems analyses of the Fabry kidney transcriptome and its response to enzyme replacement therapy identified and cross-validated enzyme replacement therapy-resistant targets amenable to drug repurposing

kidney INTERNATIONAL

ISN INTERNATIONAL SOCIETY OF NEPHROLOGY

Cohorts

Detection cohort:
- ERT-naïve
- 5 years of ERT
- 10 years of ERT

Validation cohort:
- ERT- naïve and ERT < 6 months
- ERT > 12 months

Normal controls

Methods

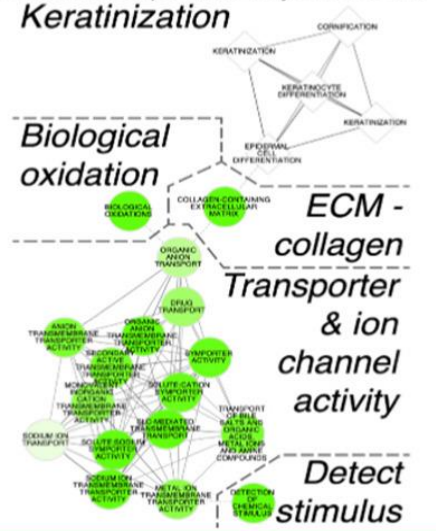
Laser capture microdissection from FFPE kidney biopsies:
- Glomeruli
- Proximal tubuli
- Distal tubuli
- Arteries

RNA extraction and RNAseq

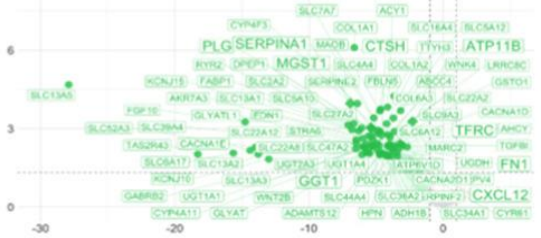
Mapping transcriptional landscapes over time within controlled, machine-readable and curated networks

Candidate – drug interactome

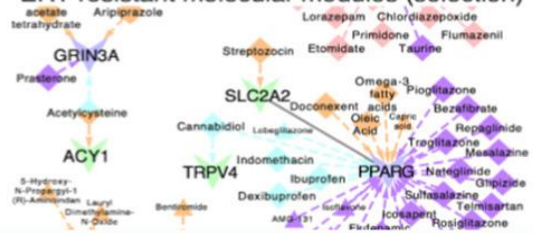
Cross-validated glomerular transcriptional landscape after 10 years of ERT



Genes underlying molecular modules resistant to modulation via ERT (selection)



Drug interactions with targets identified from ERT-resistant molecular modules (selection)



Delaleu et al. 2023

CONCLUSION

Investigation of ERT's long-term impact on Fabry nephropathy via transcriptomics of serial biopsies provides an analytical framework identifying features resistant to ERT that may potentially represent novel drug-targets.

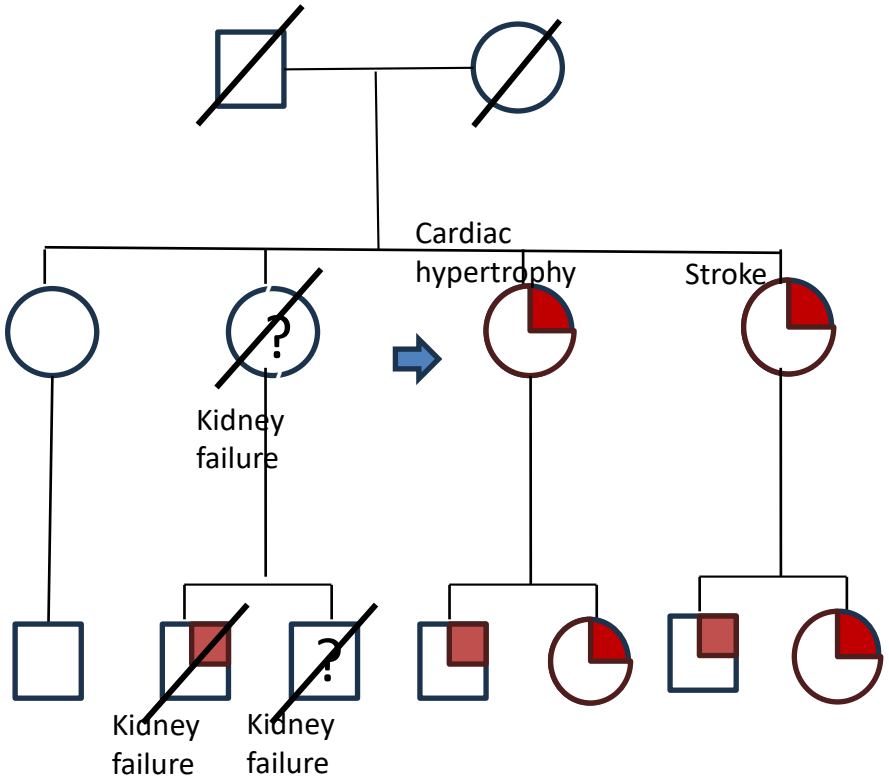
Transcriptome has potential to be an adjuvant tool for elucidating the variability of phenotypes in the same family

Molecular Genetics and Metabolism
Volume 138, Issue 2, February 2023, 106998

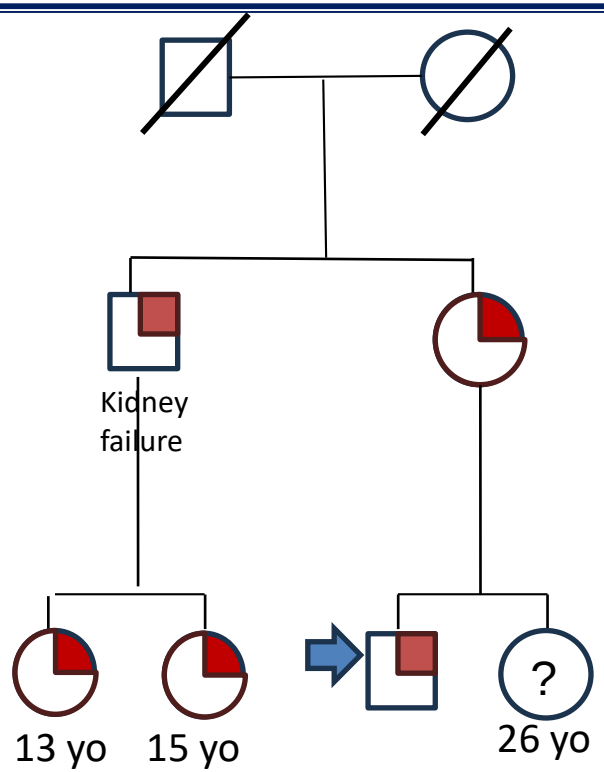
Whole blood transcriptomic profiling in the interpretation of variable phenotype presentation in Fabry disease

Gheona Altarescu [a], Omer Murik [a], Ruxandra Jurcut [b], Elena E. Rusu [c], Adriana Mursa [d], Tzvia Mann [a], Yifat Eldar-Yedidia [e], David A. Zeevi [a]

"Conclusion: We show here that the expression profiles of FD patients are distinguished from healthy controls for a subset of over 100 genes, some of which are associated with the biological and clinical manifestations of FD. We propose to use transcriptomic profiling in order to gain a better understanding of the biological consequences of FD and in order to improve the interpretation of variable phenotypes in Fabry disease patients bearing the same GLA gene genotype.



Pedigree of the first family evaluated in "Fundeni" Center



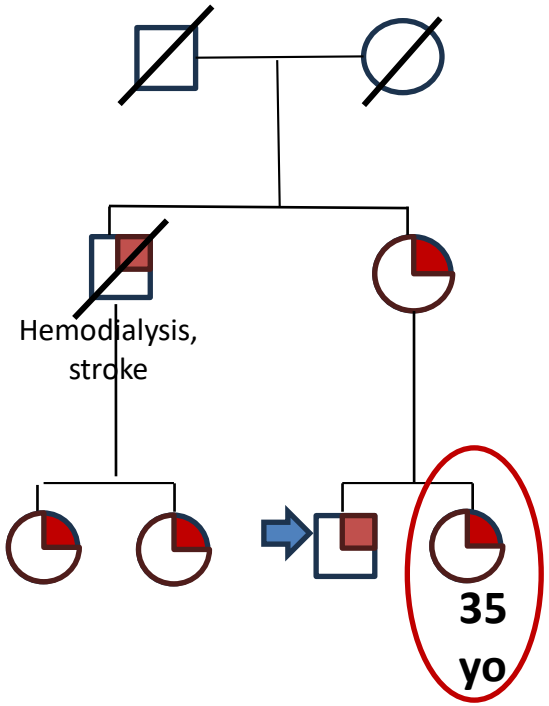
Heterozygous female with FD

Male with FD

2006 Screening by enzymatic tests, (genetic test not available)	Index case	Male, age 25: acroparesthesias, angiokeratomas, impaired sweating, cardiac hypertrophy, proteinuria =1.8 g/24h, eGFR=98ml/min/1.73m^2 - α-Gal A enzyme activity = 0.01 µmol/L/h - ERT (Agalsidase beta) treatment started in 2007.
	Family screening by enzymatic test	I-1 – uncle, age 44: acroparesthesias, angiokeratomas, impaired sweating, CKD stage 4, cardiac hypertrophy, stroke, α-Gal A enzyme activity = 0.009 µmol/L/h, ERT treatment started in 2007 I-2 – mother, age 46: acroparesthesias, depression, impaired sweating, α-Gal A enzyme activity = 0.3 µmol/L/h II-1 – age 13, carrier, negative phenotype, not tested II-2 – age 15, carrier, negative phenotype, not tested **II-3 – sister, age 26, normal activity of α-Gal A (not exclude Fabry disease), microalbuminuria, normal neurological and cardiac assessment. Monitoring was recommended.**

**Represents a FD family evaluated in Fundeni Nephrology Clinic*

Case report – 35 yo female with Fabry disease*



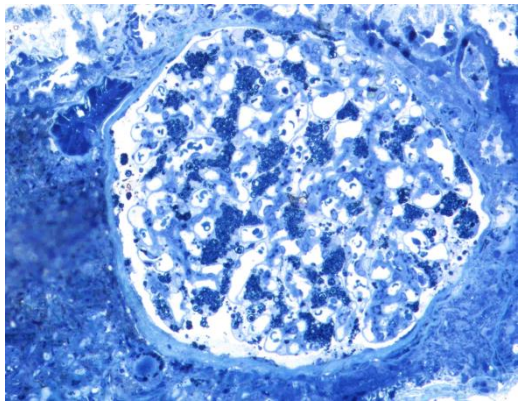
Heterozygous female with FD

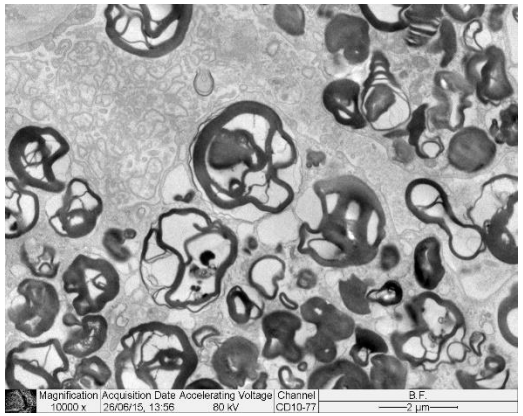
Male with FD

2006-2015	• **lost nephrology follow-up** • **2014 - hypertension**
2015, 35 yo	• **genetic test: pathogenic mutation c.486 G>A**

Clinical assessment (2015)	
Kidney	- hypertension, CKD stage G3bA3 (eGFR=40 ml/min/1.73 m^2, proteinuria 4.5 g/day) - Kidney biopsy: 30% global glomerular sclerosis, numerous GL-3 deposits in podocytes, tubes, and arterioles. Another etiology for CKD was excluded.
Cardiac	- normal ECG and echocardiography, without arrythmia
Cerebrovascular	- Normal MRI
Dermatological	- upper limbs fingers angiokeratoma
Ophthalmological	- Cornea verticillata

2015	• **Started ERT**
2022	• **ESKD, Jan 2022 started hemodialysis, Sep 2022 RTx. ERT therapy was continued.**

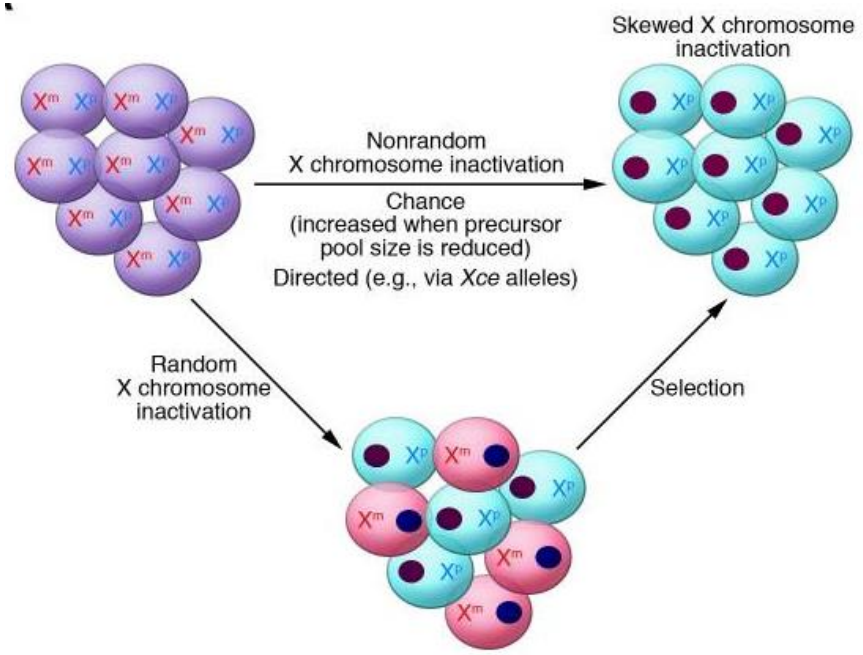




**Represents a FD patient evaluated in Fundeni Nephrology Expert Center*

X Chromosome Inactivation

- **X chromosomes inactivation** (XCI) involves a random choice to silence either maternal or paternal X chromosome early in mammalian female development.
- Therefore, females are generally mosaics, having a mixture of cells with one or the other paternal X active. The most females the number of cells with either X being active is roughly equal. However, **skewing of X chromosome inactivation** is observed in a percentage of women.
- Thus, women can vary from asymptomatic, mildly symptomatic, to severely symptomatic but with a later onset of symptoms.



Minks J et al. J Clin Invest. 2008 Jan 2; 118(1): 20–23.
Maier EM et. Acta Paediatr Suppl. 2006;95(451):30-8.
Echevarria L et al. Clin Genet. 2016;89(1):44-54.

Multidisciplinary approach

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- *Pathogenicity of mutation*
- *Enzyme activity level*
- *Personal medical history*
- *Family history, pedigree, family screening*
- *Sign & symptoms*
- *Questionnaires (SF36, Pain-Q, FD-PRO)*

- *Organ manifestations*
- *Biological evaluation*
- *Biomarkers: Lyso-GL3*

"Fundeni" Expert Center for Rare Diseases of Reno-Urinary System:
- Clinic of Nephrology
- Clinic of Pediatric Nephrology
- Renal Transplant

The Expert Center for Rare Genetic Cardiovascular Diseases

Clinic of Neurology

Radiology and Medical Imaging

Nephrological evaluation:

- *eGFR, UACR, 24h proteinuria, Cystatin-C, 25-OH Vit D*
- *Echo, ABPM, Guided Kidney Biopsy*

Cardiac:

- *echo, ECG, ECG Holter, LE-MRI*
- *Biomarkers: BNP, NTproBNP, troponin*

Neurological, cerebral evaluation:

- *Sudotest, EMG, Brain-MRI*

- *Others target organ involvement*

National protocol for Fabry disease treatment and Fundeni Nephrology Clinic Protocol

"Fundeni" Expert Center for Rare Diseases of Reno-Urinary System

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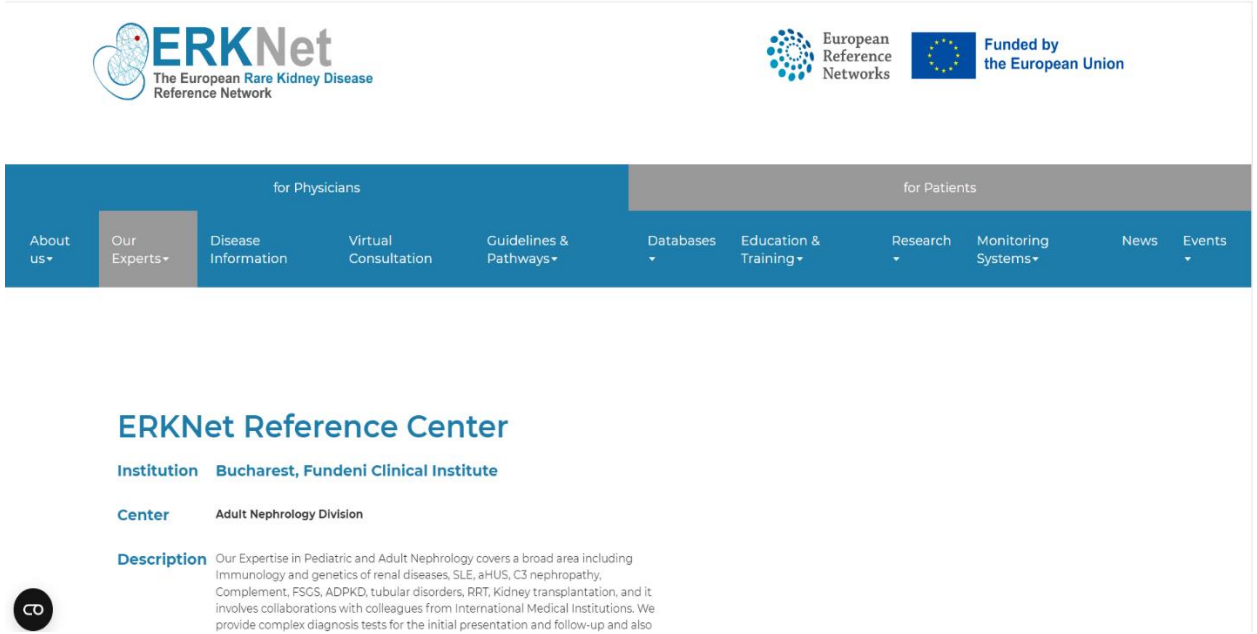
2006 – Romanian Association for the Study of Hereditary Kidney Diseases

2016 – Expert Center for Rare Diseases of Reno-Urinary System

2021 – full member of the European Rare Kidney Disease Reference Network (ERKNet)

www.nephroered.ro, www.erknet.org



Experience of "Fundeni" Expert Center for Rare Diseases of Reno-Urinary System

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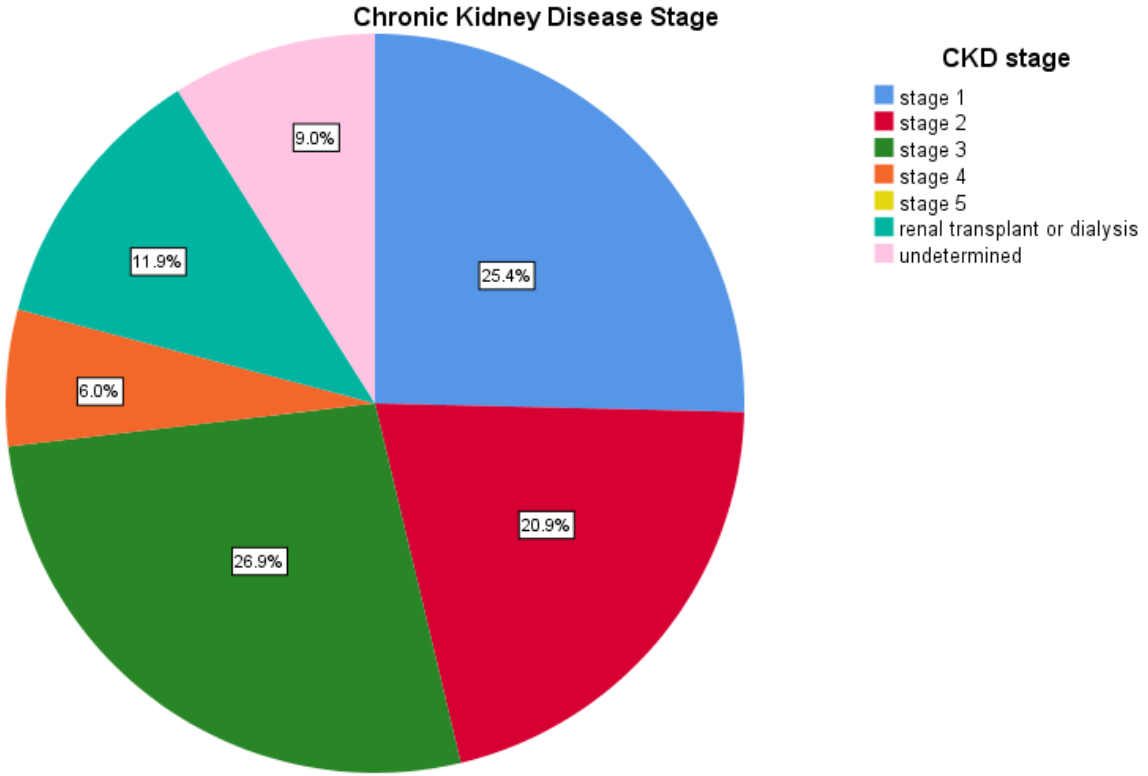
Between 2015 – Sep 2023, in our center were evaluated 67 patients with Fabry Disease:

- **29 males and 38 females**
- **Mean age: 40.6 ± 16.3 (3-75) years**
- **No of adult: 62**
- **No of children: 5**
- **No of families: 27**



Experience of "Fundeni" Expert Center for Rare Diseases of Reno-Urinary System

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Baseline characteristics of Fabry adult patients

		Male (n= 27)	Female (n=35)
General features and cardiovascular risk factors*	Mean age at baseline, years	39	46
	Mean age of diagnosis	35	44
	Mean age at symptoms	20	33
	Hypertension	11	13
	Dyslipidemia	10	13
	Diabetes	0	2
	Smoking	11	15

**The cohort of patients evaluated in Fundeni Expert Center for Rare Diseases of the Reno-Urinary System.*

Experience of "Fundeni" Expert Center for Rare Diseases of Reno-Urinary System

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Kidney symptoms		Male* (n= 24)	Female* (n=31)
CKD stage at baseline	Subclinic/no CKD	0	3
	G1	7	10
	G2	3	9
	G3a	5	9
	G3b	2	2
	G4	3	1
	G5/Dialysis	2	1
	Kidney transplant	5	0
Proteinuria level	Without albuminuria	4	14
	Microalbuminuria	8	9
	Proteinuria	12	8
Kidney biopsy	26 adult patients	11	15

**Patients evaluated in Fundeni Expert Center for Rare Diseases of the Reno-Urinary System.*

Experience of "Fundeni" Expert Center for Rare Diseases of Reno-Urinary System

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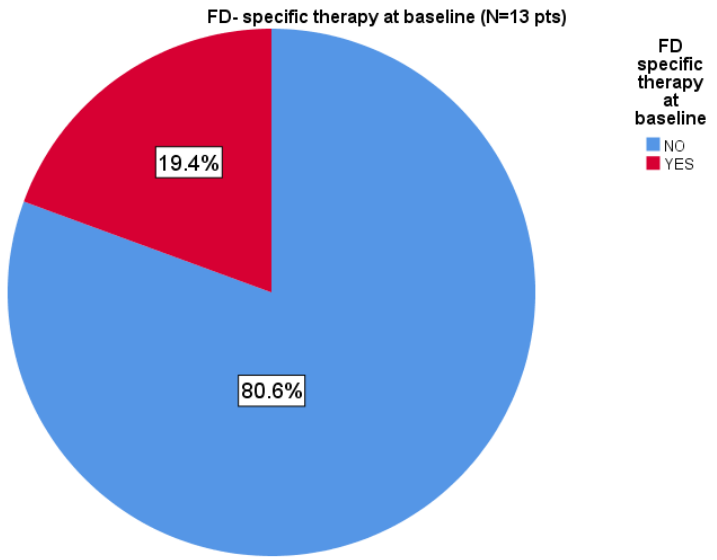
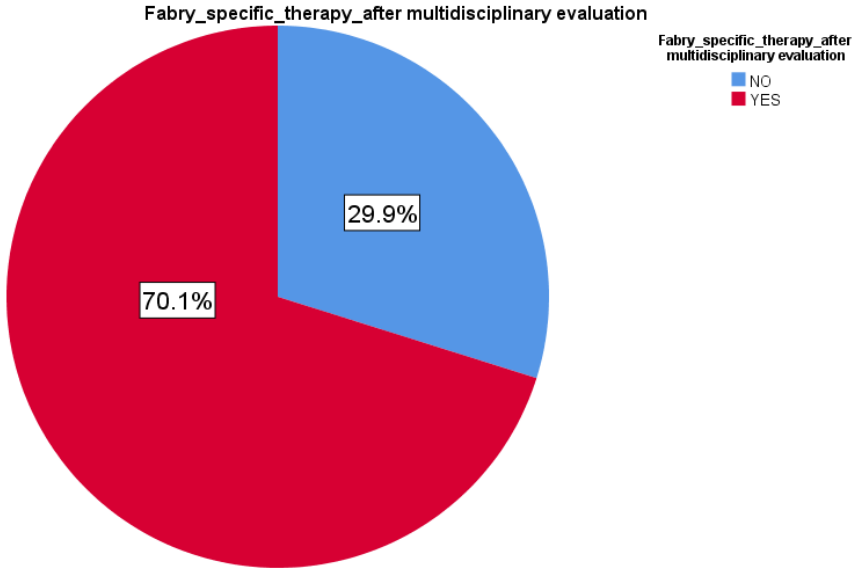
FD-specific therapy at baseline = 13 pts



FD-specific therapy after multidisciplinary evaluation = 48 pts



26 patients with kidney biopsy in our cohort of patients

**The cohort of patients evaluated in Fundeni Expert Center for Rare Diseases of the Reno-Urinary System.*

Experience of "Fundeni" Expert Center for Rare Diseases of Reno-Urinary System

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		Male (n=27)	Female (n=35)
Fabry features in adult patients at baseline*	Hypertrophic cardiomyopathy, n (%)	22 (81.5)	13 (37.1)
	Pacemaker, n (%)	2 (7.4)	6 (17.1)
	Acroparesthesias, n (%)	26 (96.3)	29 (82.8)
	Stroke, n (%)	2 (7.4)	5 (14.3)
	TIA, n (%)	2 (7.4)	0
	Hypohydrosis, n (%)	20 (74)	12 (34.3)
	Angiokeratomas, n (%)	21 (77.7)	9 (25.7)
	ENT involvement, n (%)	9 (33.3)	8 (22.8)
	Cornea verticillata, n (%)	18 (66.6)	14 (40)
	α-GLA activity, nmol/h/mg, median	0.57	1.36
	Lyso-GL3 at baseline, ng/ml	60.06	6.34

**The cohort of patients evaluated in Fundeni Expert Center for Rare Diseases of the Reno-Urinary System.*

Treatment of Fabry nephropathy

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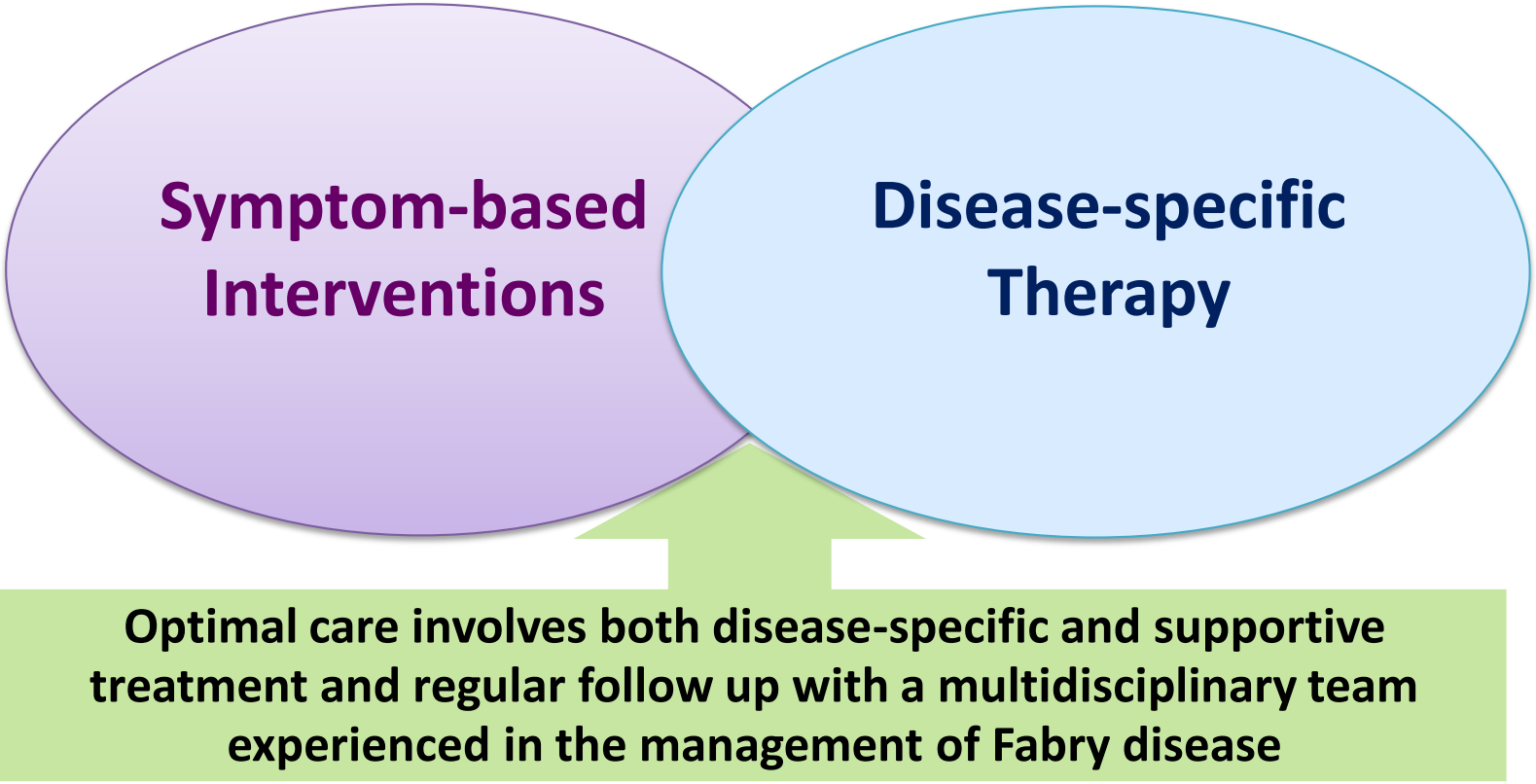
The following therapeutic goals should be aimed:

- reduction of complaints
- delaying/preventing the progression of organ manifestations
- improvement of quality of life
- improvement/ normalization of life expectancy



Lenders M and Brand E. Nephrol Dial Transplant 2021; 36: ii14-ii23

Therapeutic renal goals for patients with Fabry disease

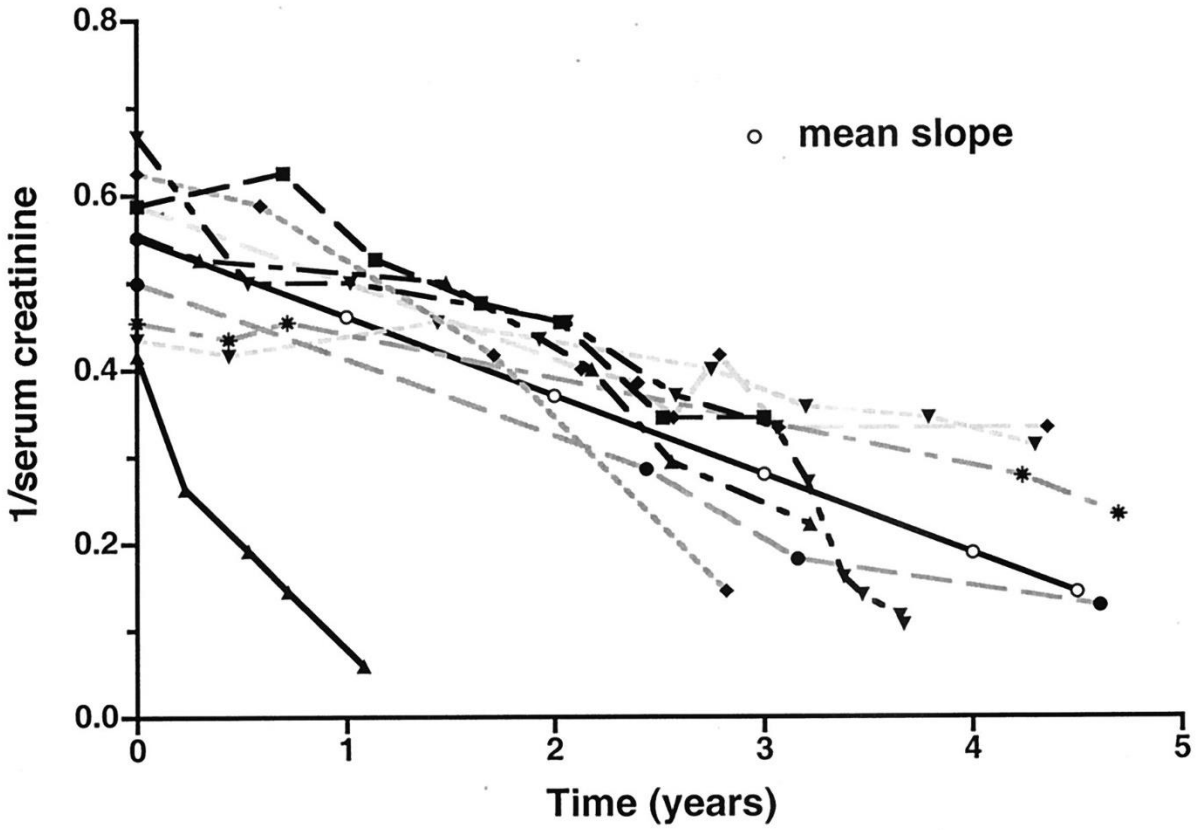
Patient subgroup	Therapeutic goals
Mild kidney involvement, **eGFR at normal levels or hyperfiltration** (eGFR > 90 mL/min/1.73m^2)	• eGFR should be maintained in an age-appropriate normal range
Mild-to-moderate kidney function impairment, mild eGFR decreases (eGFR 60–90 mL/min/1.73m^2)	• Prevent progression of eGFR loss and stabilize eGFR level
Moderate-to-severe kidney function impairment, mild-to-moderate eGFR decreases (eGFR 45–59 mL/min/1.73m^2)	• Prevent progression of eGFR loss to delay/avoid ESKD
Moderate-to-severe eGFR decreases (eGFR 30–44 mL/min/1.73m^2)	Prevent progression of eGFR loss to delay/avoid ESKD
Severe eGFR decreases (eGFR 15–29 mL/min/1.73m^2)	Decrease the slope of eGFR as much as possible; delay the progression to ESKD
ESKD	• Provide optimal RRT by dialysis or RTx (first choice therapy), maintain ERT to avoid damage to heart, CNS • Suggest and encourage RTx before dialysis to prevent impact on other organs

Patient subgroup	Therapeutic goals
Mild-to-moderate kidney function impairment; albuminuria levels: <30 mg/g (< 3 mg/mmol)	• Normalize/stabilize albuminuria
Albuminuria levels: 30–300 mg/g (3–30 mg/mmol)	• Normalize/stabilize albuminuria
Albuminuria levels: >300 mg/g (> 30 mg/mmol)	• Reduce levels to <300 mg/g (<30 mg/mmol)
Moderate-to-severe kidney function impairment	Slow progression of albuminuria

Wanner C. et al. Molecular Genetics and Metabolism 2018; 189-203

Natural course of Fabry nephropathy

Mean GFR decline = 12,2 ml/min/year



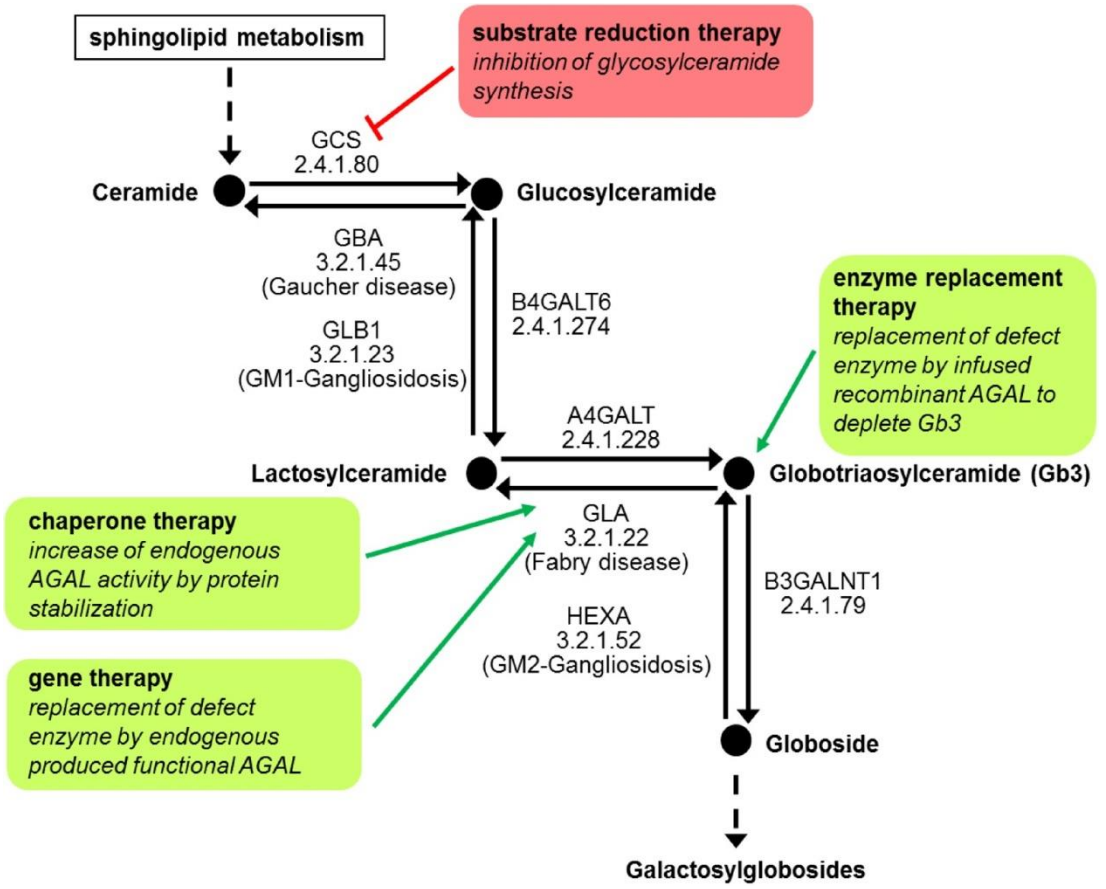
Branton M et al. JASN 2002;13:S139-S143

- **A loss of up to 1 ml/min/1.73m^2/year is considered normal.**
- **Stabilization of renal function is achieved if a patient has a GFR slope loss ≤ 1-3 ml/min/1.73m^2/year.**
- **Progression of renal disease is demonstrated by an annual decrease in GFR > 3 ml/min/1.73m^2.**
- **Rapid progression is considered when GFR decrease is > 5 ml/min/1.73m^2/year.**

KDIGO clinical practice guideline for the evaluation and management of CKD. Kidney Int 2013
Kantola IM. Nephrol Dial Transplant 2019

Fabry disease specific treatment

Drug Name		Mechanism of Action	Route of Administration
Enzyme replacement therapy	Agalsidase-beta	Recombinant α-GAL	iv., every 2 weeks
	Agalsidase-alpha	Recombinant α-GAL	iv., every 2 weeks
	New approved ERT - Pegunigalsidase alfa	Plant derived α-GAL	iv., every 2 weeks
Chaperone	Migalastat	Binds reversibly to the active site of the amenable mutant of α-GAL	Oral, every other day
Investigational drugs	Substrate reduction therapy: lucerastat, venglustat	Glucosylceramide synthase inhibitor	Oral, daily
	Gene therapy		



Malte Lenders and Eva Brands. Nephrol Dial Transplant 2021; 36: ii14-ii23
Umer M et al. Pharmaceuticals 2023, 16(2), 320

Supportive therapy for Fabry nephropathy

- **RAAS blocker (ACEI or ARB)**
- **General management of CKD** regarding anemia treatment, statin indication, and CKD-MBD prevention and management according to guidelines
- **SGLT2 inhibitors** might be of future interest due to the general cardiovascular and kidney protection in non-diabetic patients.

Malte Lenders and Eva Brands. Nephrol Dial Transplant 2021; 36: ii14-ii23
Battaglia Y et al. J Clin Med 2023

Experience of "Fundeni" Expert Center for Rare Diseases of Reno-Urinary System

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Since 2006 – Enzyme replacement therapy with Agalsidase beta has been started as a compassionate program

Since 2008 - Romanian National Program for Rare Diseases, which provides the source of funding of the treatment for rare diseases, including treatment with Agalsidase beta for Fabry disease

Since 2019 - Migalastat treatment has been approved in Romania

Since 2021 - Agalsidase alpha has been approved

Patients with Fabry disease *	Total N	Treated N (%)	Type of treatment		
	67	48 (71.6%)	Agalsidase beta	Migalastat	Agalsidase alfa
Males	27	26 (96.3%)	21	4	1
Females	35	21 (60%)	15	6	-
Children	5	1 (20%) (10 yo boy)	1	-	-

**The cohort of patients evaluated in Fundeni Expert Center for Rare Diseases of the Reno-Urinary System.*

Evolution of proteinuria for 19 patients treated with Fabry specific therapy during follow-up period*

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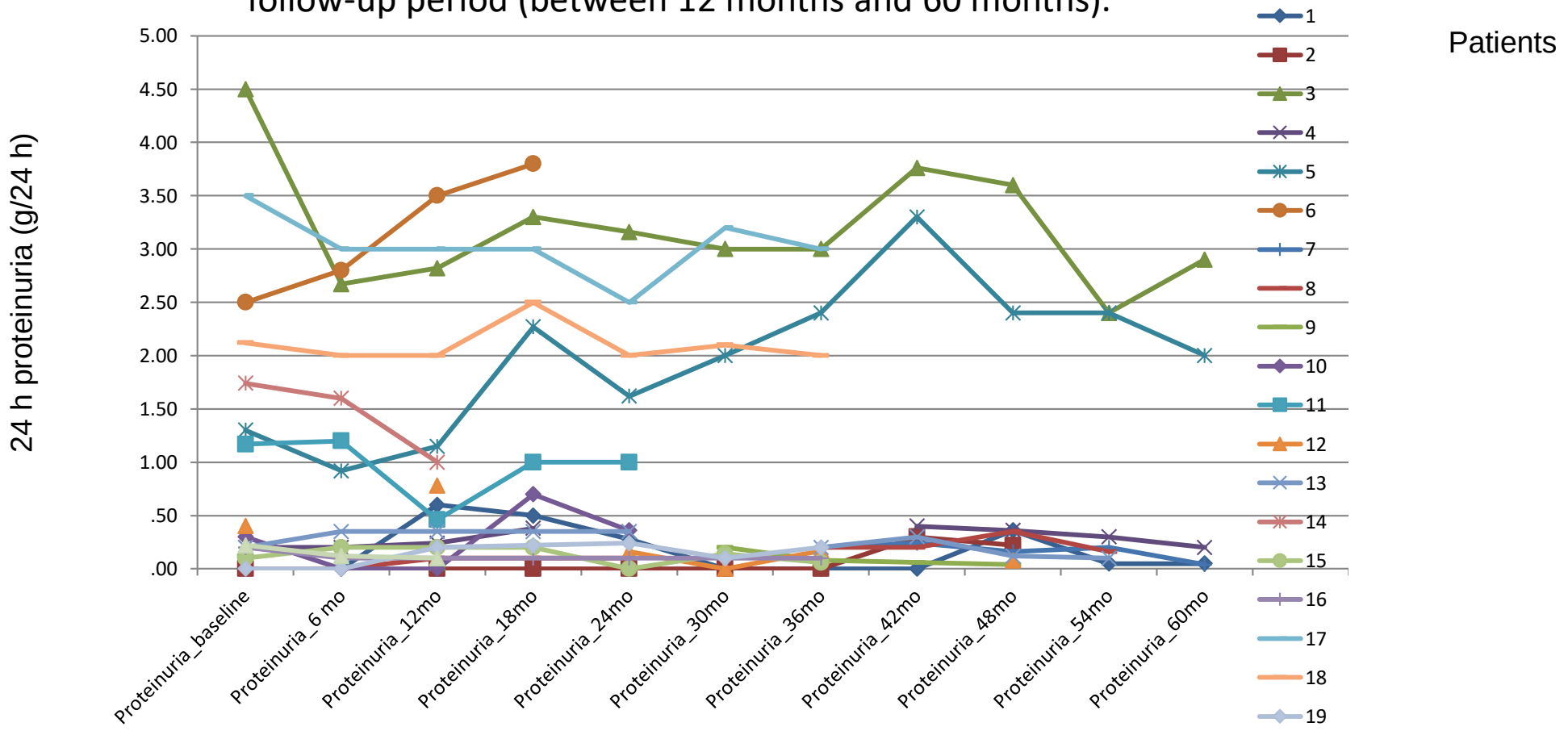
Evolution of proteinuria for 19 patients treated with Fabry specific therapy during follow-up period (between 12 months and 60 months).



*Experience of Fundeni Expert Center for Rare Diseases of the Reno-Urinary System.

Treatment effect on GFR slope can predict clinical benefit*

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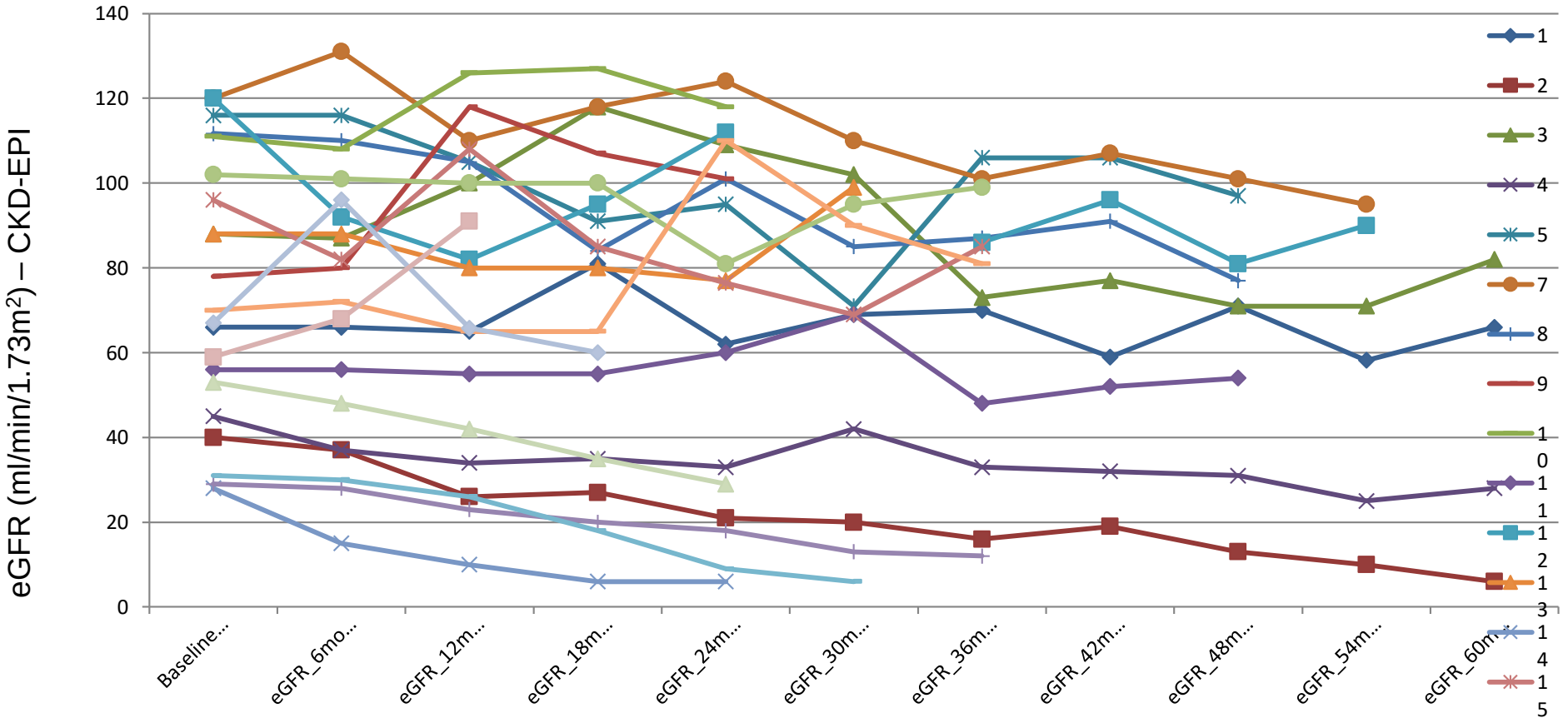
Evolution of eGFR for 22 patients treated with Fabry specific therapy during follow-up period (between 18 months and 60 months).



**Experience of Fundeni Expert Center for Rare Diseases of the Reno-Urinary System*

Long-term outcome of the "Fundeni" Expert Center cohort

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	Before the initiation of Fabry disease specific treatment	After the initiation of Fabry disease specific treatment
Cardiovascular event (Arrhythmia, congestive heart failure, myocardial infarction, significant cardiac procedure, complete heart block)	**3 (1M,2F)**	**6 (4M/2F)**
Age at cardiovascular event	53.4±8.2 (range 45-62)	
Cerebrovascular event (TIA, stroke)	**9 (4M/5F)**	**5 (4M/1F)**
Age at cerebrovascular event	45.3±12.1 (range 26-65)	
Renal event (reaching ESKD, dialysis or kidney transplant)	**7 (6M,1F)**	**4 (3M/1F)**
Age at renal event	37.27±14.8 (range 18-64)	
Death	**2 (1M/1F)**	**6 (5M/1F)**
Age at death	52.3± 11.7 (range 33-66)	

**Experience of Fundeni Expert Center for Rare Diseases of the Reno-Urinary System. Not published data.*

KEY TAKEAWAYS

- **Fabry disease is heterogeneous, with classical and non-classical presentations**
- **Screening and testing is important to identify new patients**
- **Kidney biopsies** increase **knowledge** about histological lesions and could be used for identifying **new treatment targets** in Fabry disease
- **Factors influencing GFR and GFR slope in FD patients are: age, gender, baseline CKD stage, baseline proteinuria, and the presence of glomerular sclerosis on kidney histology**
- **Updated recommendations underline the importance of early treatment initiation in both males and females,** and stress the importance of patient-specific care and a **multidisciplinary approach** to disease management.

Thank you!