Epidemiology (Relevance to Screening) and the Natural Course of Fabry Disease

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Disclosure of Interests

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- Amicus Therapeutics
- Protalix Biotherapeutics
- Shire, Inc.

Classic Epidemiology (Based on Enzyme activity)

- The prevalence 1:17,000 to 1:117,000 in Caucasian males.
- 1:40,000 males and females
- 1:15,000 in Nova Scotia, Canada (founder effect, West et al 2002)
- About 350 missense mutations
- About 50% are relatively mild

Main reference: Human Gene Mutation Database at the Institute of Medical Genetics in Cardiff

http://www.hgmd.cf.ac.uk/ac/gene.php?gene=GLA

Newborn Screening for Fabry Disease

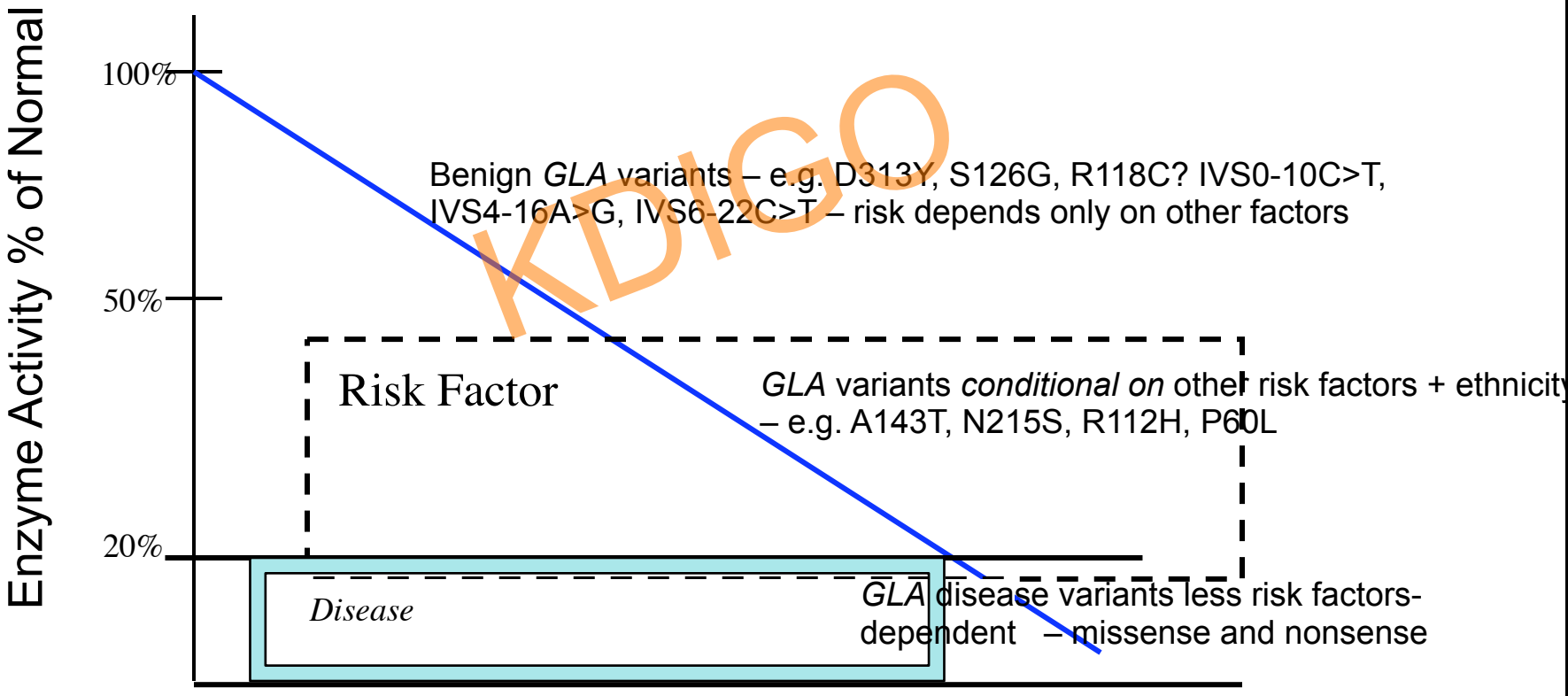
(DNA Sequencing-Based)

- (Spada et al 2006, Chien et al 2012) 1:4,600, with a 7:1 ratio of patients with the late-onset:classic phenotypes – *All pathogenic?*
- 1:7057 in Japan and 1:2996 in Taiwan
- Taiwan: 1:875 males and 1:399 females had the IVS4+919G→A mutation (Chien et al 2012) – 10% residual enzyme activity but not all are symptomatic

Is It Fabry Disease?

1. Residual enzyme activity ranges from 0% about 30% of mean normal value.
2. α–Galactosidase A deficiency is a genetic risk factor for a number of organ ailments (e.g. stroke, kidney and heart disease, small-fiber neuropathy)
3. Fabry complications are non-specific in nature – Difficulty to decide if a *GLA* variant is the cause
4. Newly identified *GLA* gene variants have higher residual enzyme activity. But are they clinically significant?

The Effect of Enzyme Activity



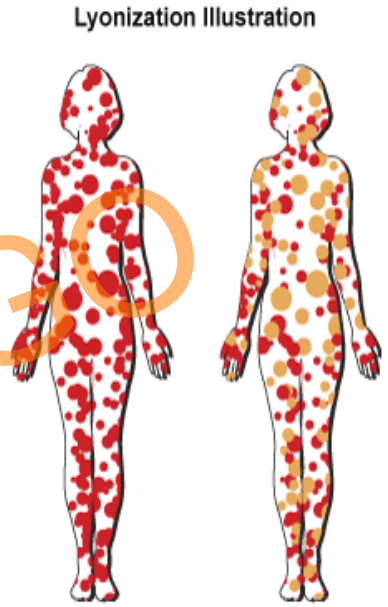
Is It Fabry Disease?

- Blood/urine Gb_3 or lyso-Gb_3 cannot be used as diagnostic tools

1. Can be normal in Fabry disease
2. Can be abnormal in non-Fabry heart disease
3. Can be increased in other LSD e.g. Gaucher (J. Aerts)

- Zebra bodies are non-specific (GM2, N-P, Silicon nephropathy) and may not be present
- Gb_3 in organ/tissue has to be elevated also IHC anti-Gb_3

TYPE	% of NORMAL White Blood Cells α-GAL*
Hemizygotes – classic forms (males)	Usually less than 1%
Milder Variants (male patients with symptoms limited to few organ systems)	≈5-30%
Heterozygotes (females)	Very low-100%
•α-GAL levels can vary considerably depending on the tissue or cell type assayed	



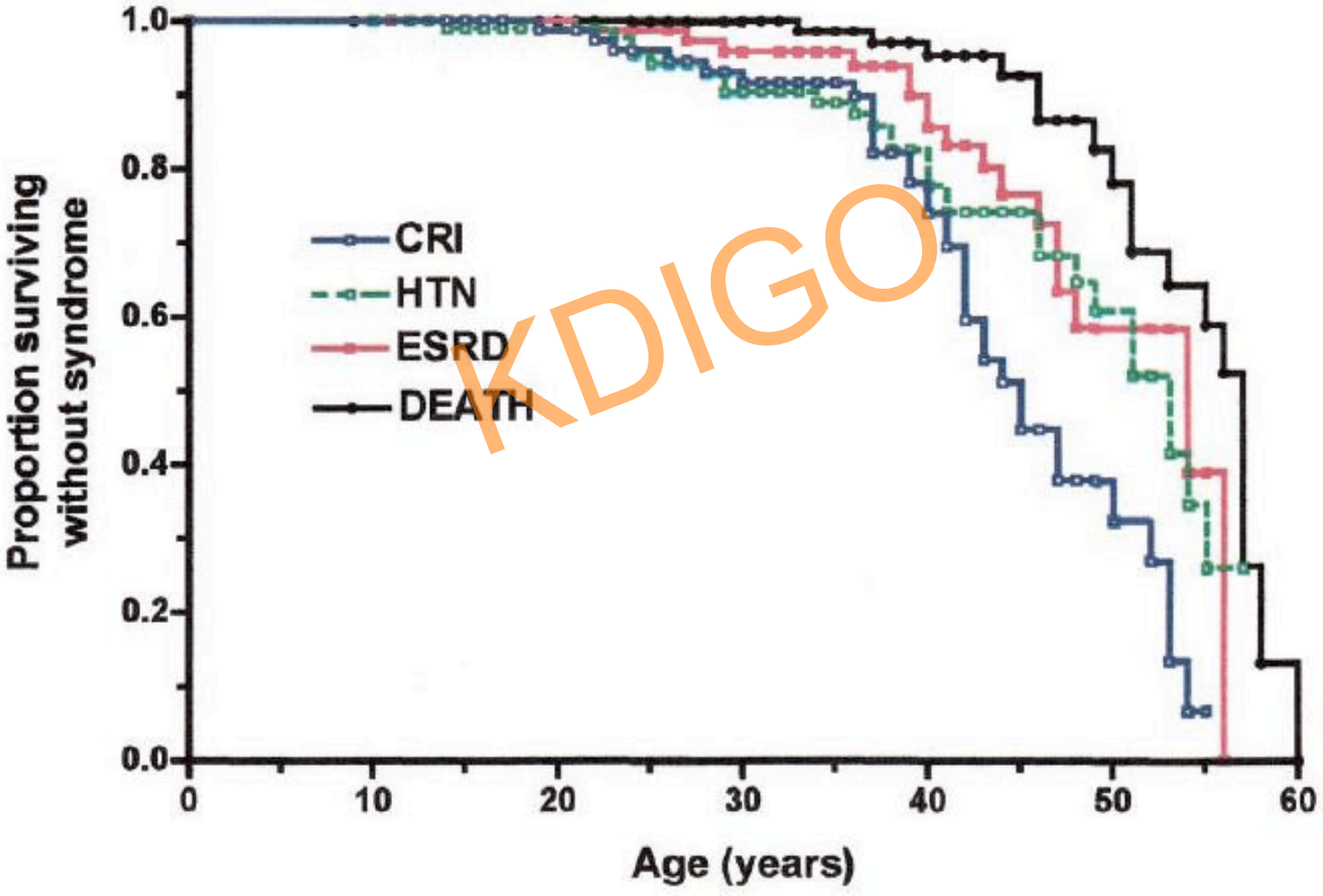
Normal (left), Mosaic (right)

2:1 female/ male ratio

Conclusions/recommendations

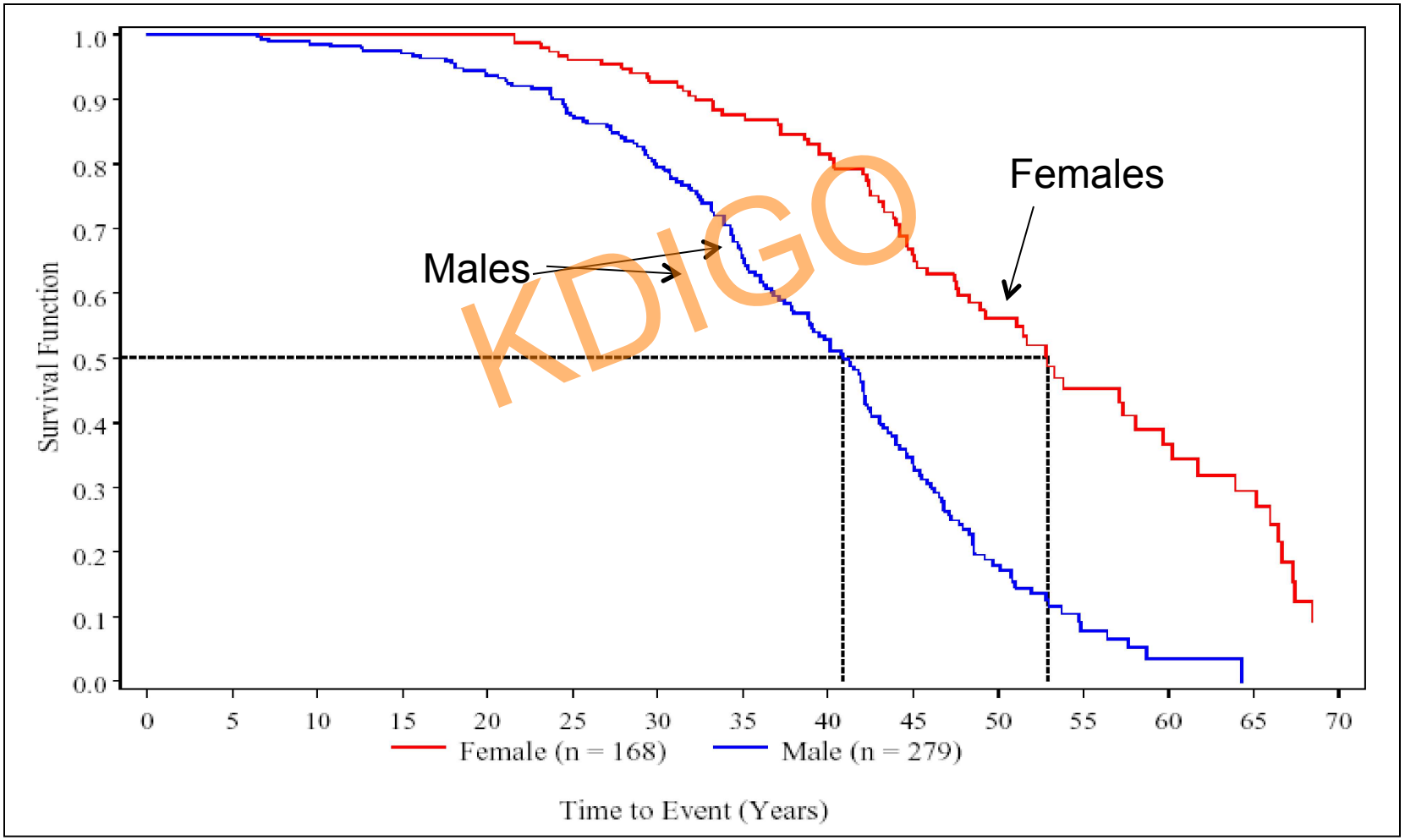
- The potential causality of *GLA* variants should depend ultimately on elevation of globotriaosylceramide with appropriate lipid profile in tissue extracts as determined by mass spectrometry.
- Even in accepted Fabry mutations, we do not know whether and how disease will be expressed
- Do we have treatment proven to meaningfully change the the natural history if initiated in childhood?

True Natural History: Probability of developing renal syndromes



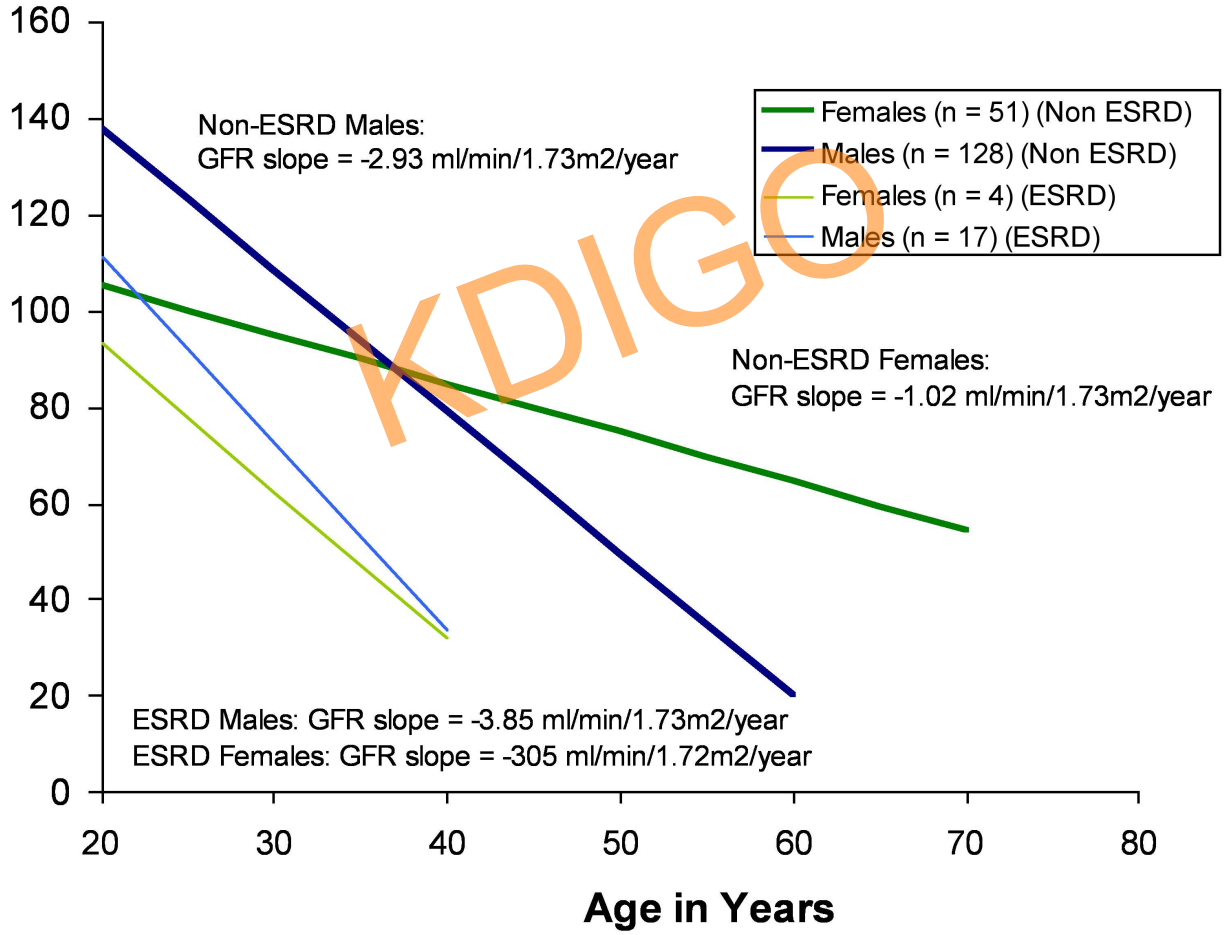
Branton et al. 2002

Kaplan-Meier estimates of time to first renal, cardiac, stroke, or death



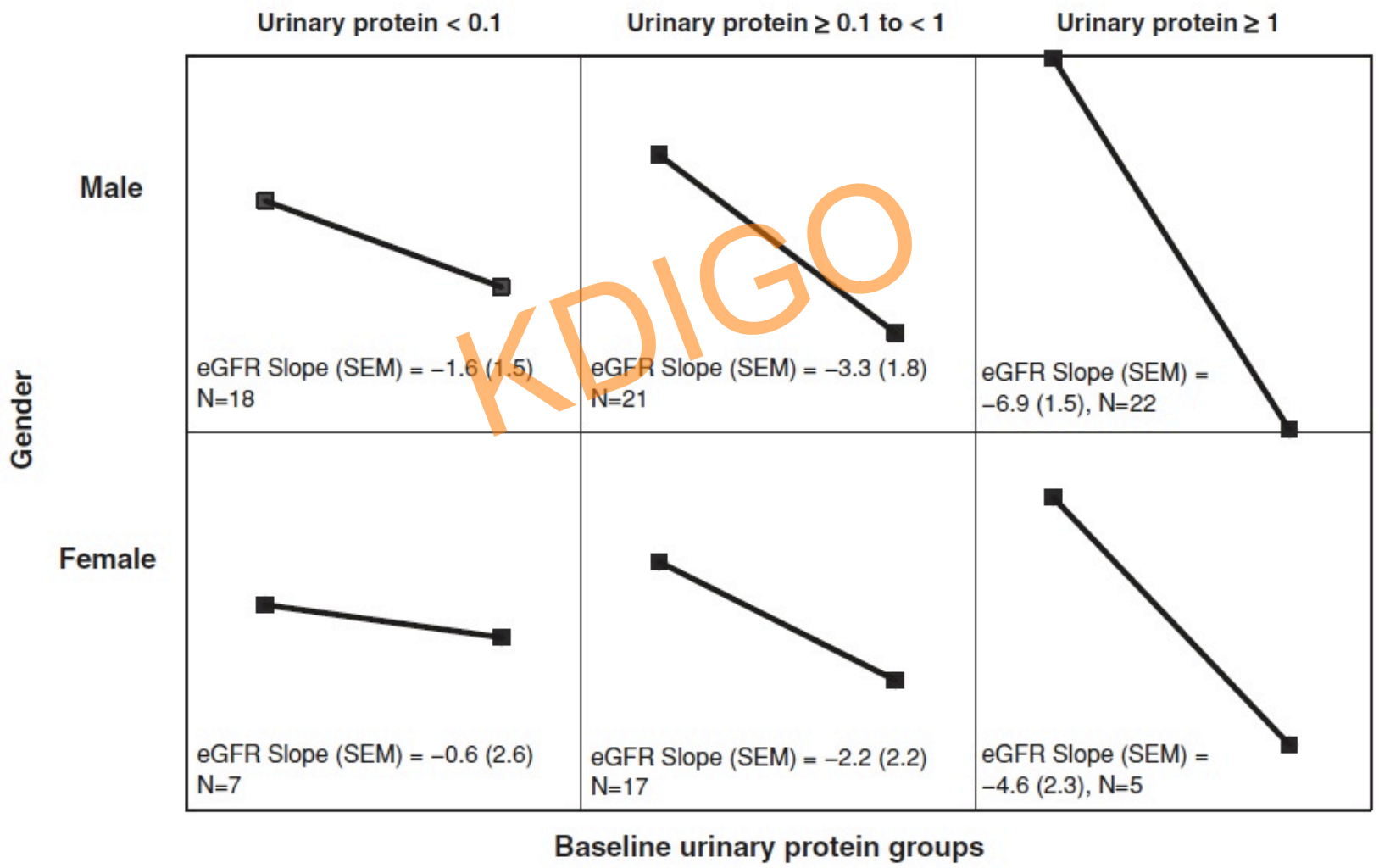
Schiffmann et al. NDT 2009

eGFR By Age For Male and Female Patients



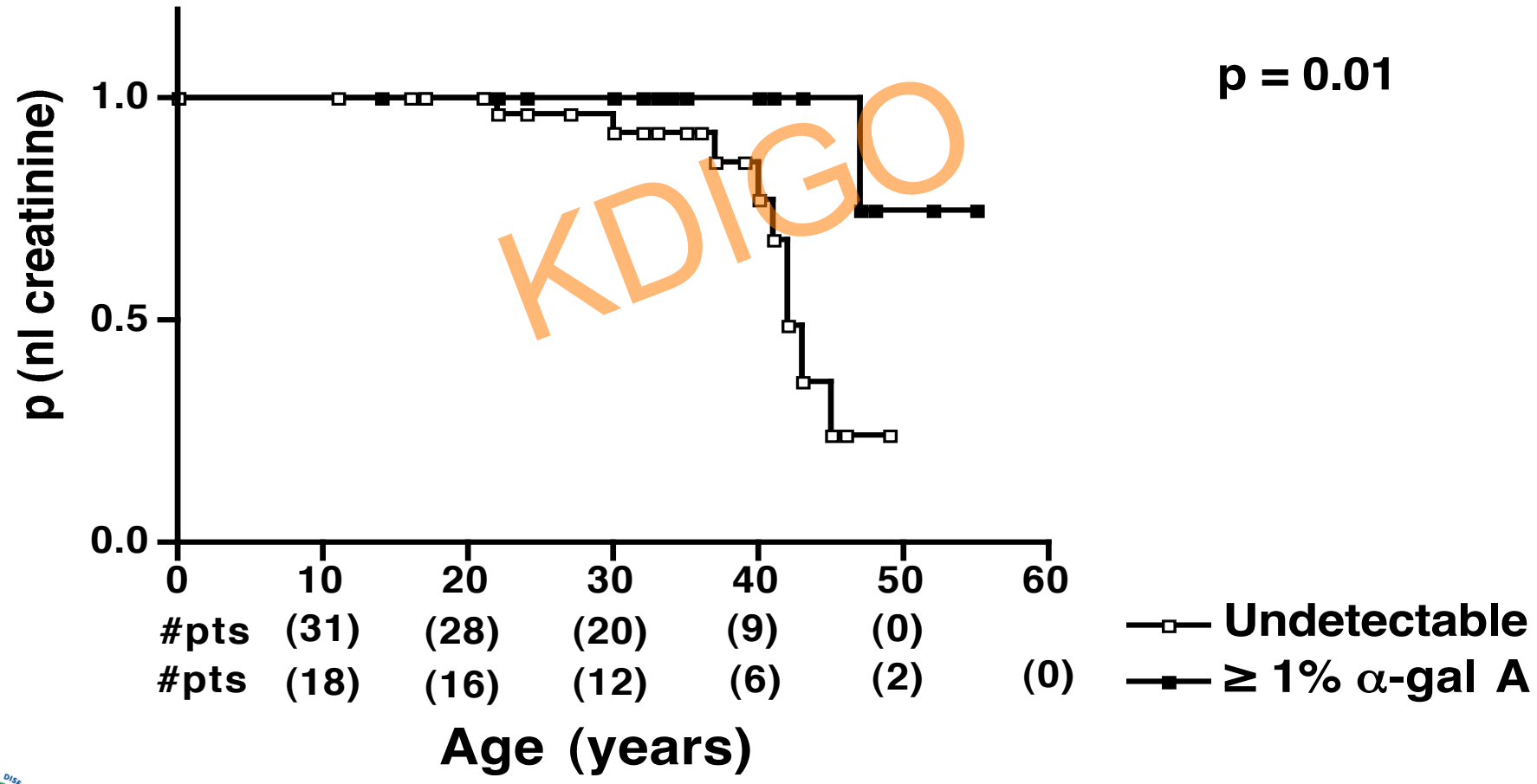
Schiffmann et al NDT 2009

Yearly Decline based on Estimated GFR Slopes (ml/min/1.73m^2 per year)



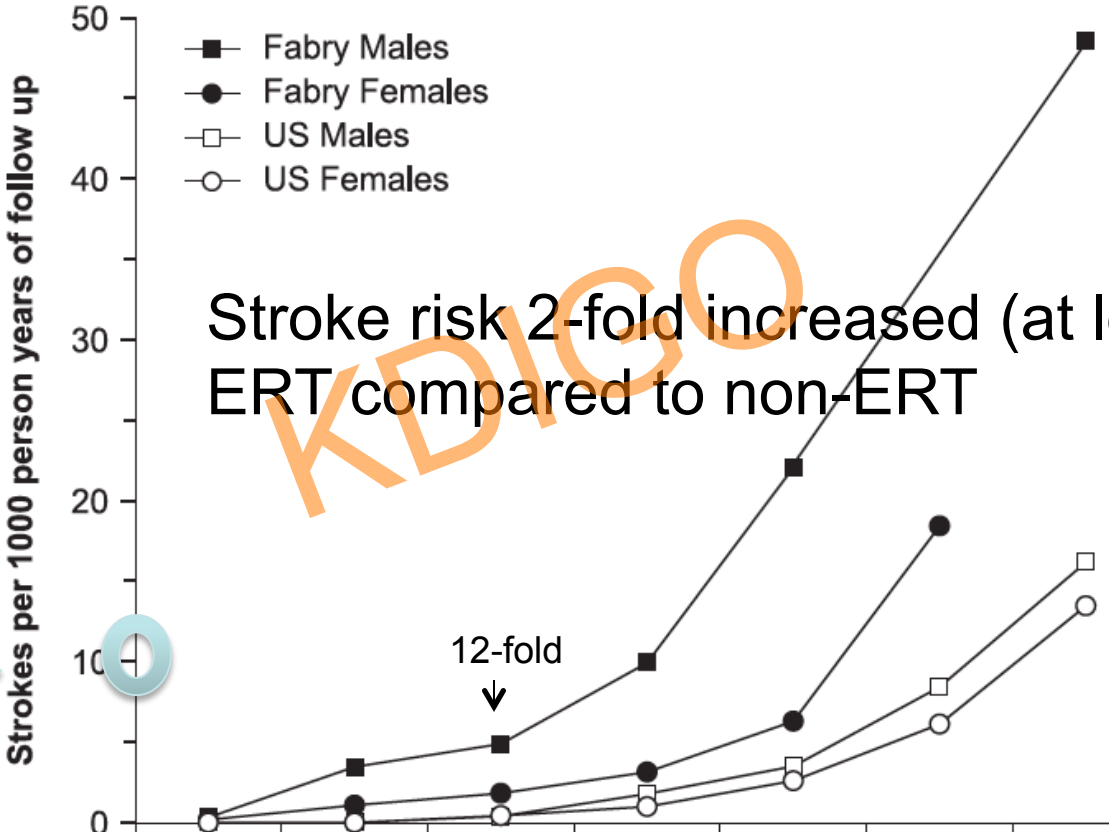
Schiffmann et al. NDT 2009

Onset of CRI by Residual α-gal A Activity



Branton et al. 2001, 2002

Incidence of Stroke in Fabry Disease (US Population)



Stroke risk 2-fold increased (at least) on ERT compared to non-ERT

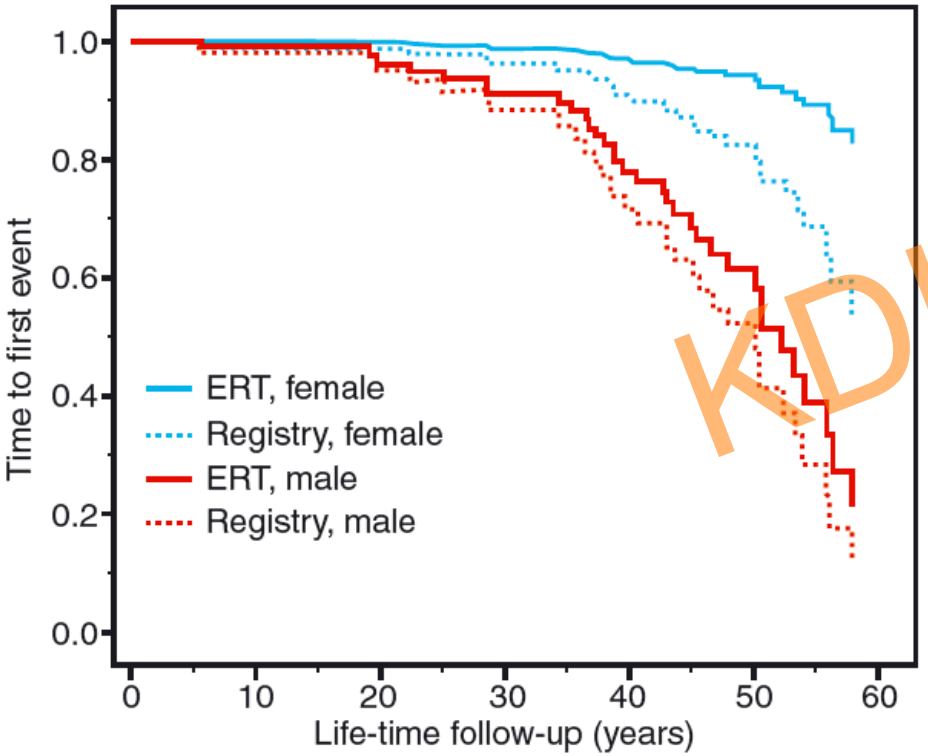
Germain et al 2015

	0 to < 25 yr	25 to < 35 yr	35 to < 45 yr	45 to < 55 yr	55 to < 65 yr	65 to < 75 yr	75 to <85 yr
Fabry Males	0.32	3.47	4.89	9.92	22.05	*	48.58
Fabry Females	0.18	1.09	1.83	3.14	6.30	18.43	#
US Males	0.00	0.00	0.40	1.79	3.50	8.43	16.17
US Females	0.00	0.00	0.44	0.99	2.60	6.12	13.46

Sims et al, Stroke, 2009

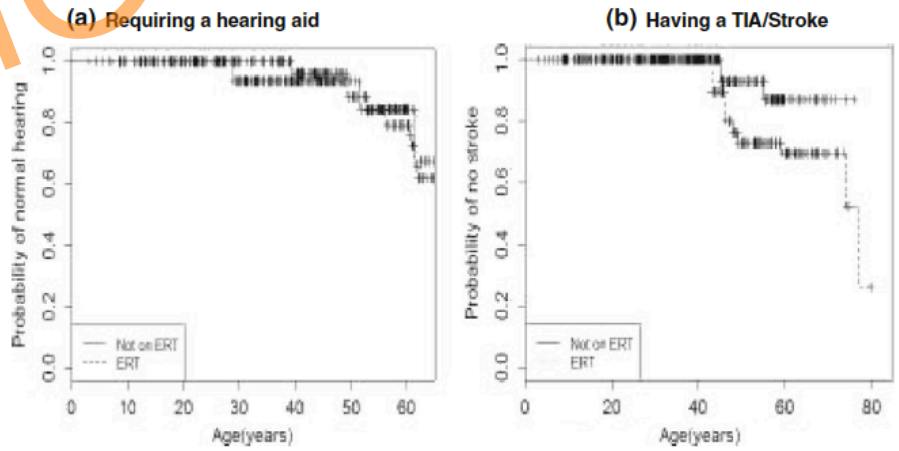
Effects of ERT on Events retrospective

Incidence of stroke, haemodialysis or death in 40 subjects treated with enzyme-replacement therapy (ERT) for a period of at least 5 years (ERT group)



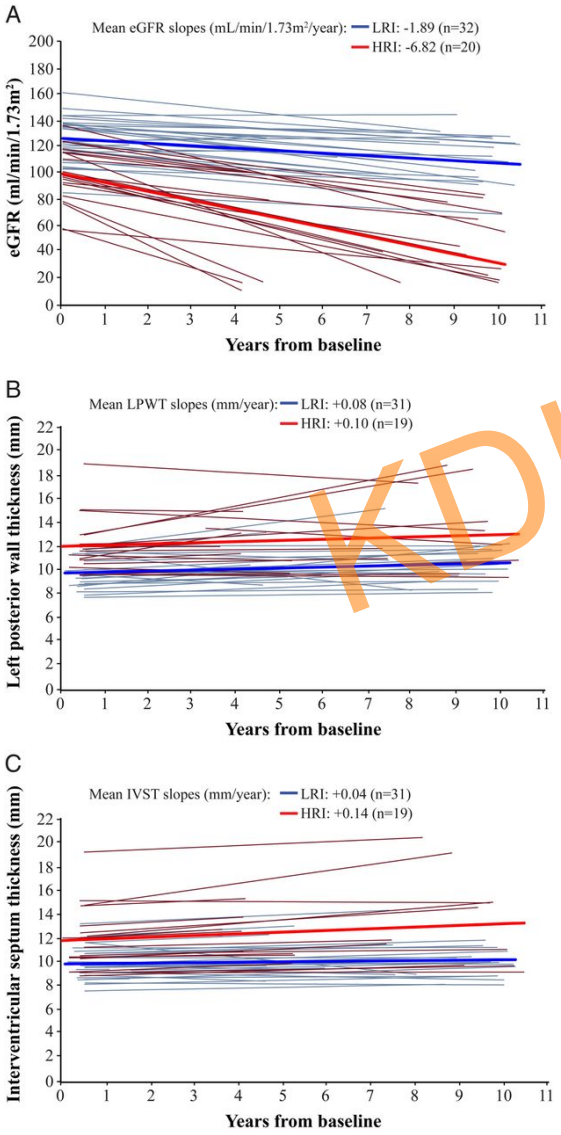
Weidemann et al J Int Med 2013

At recruitment 211 adults and seven children were on ERT (range of treatment duration, 0 to 9.7 and 0 to 4.2 years respectively).



Anderson et al JIMD 2014

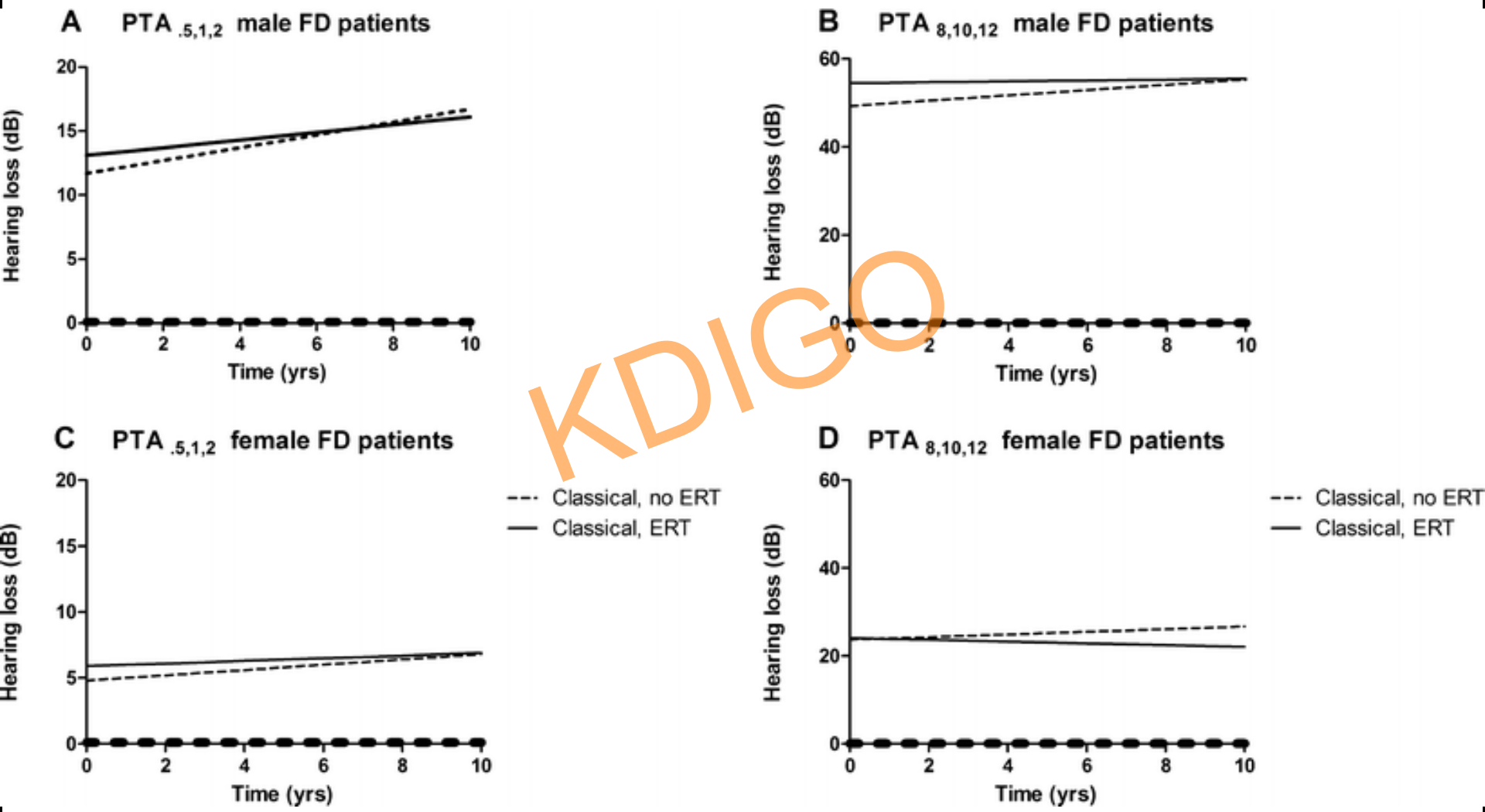
Estimated glomerular filtration rate (eGFR) slopes (A), left ventricular posterior wall thickness (LPWT) slopes (B), and interventricular septum thickness (IVST) slopes (C).



Patients with a UPCR ≤0.5 g/g and <50% sclerotic glomeruli were classified as low renal involvement (LRI);
Patients with UPCR >0.5 g/g or ≥50% sclerotic glomeruli at baseline were classified as high renal involvement (HRI)

Dominique P Germain et al. J Med Genet doi:10.1136/jmedgenet-2014-102797

Natural History of Hearing Loss in Fabry Disease



Suntjens et al 2015 JIMD

Conclusions

- **Screening for Fabry disease:** define which *GLA* variant is significant and what does it mean to diagnose Fabry patients pre-clinically
- **Natural history:** Organ/system specific may be the best approach

Thank You!