Fabry in females

Understanding the need for improved diagnosis and management

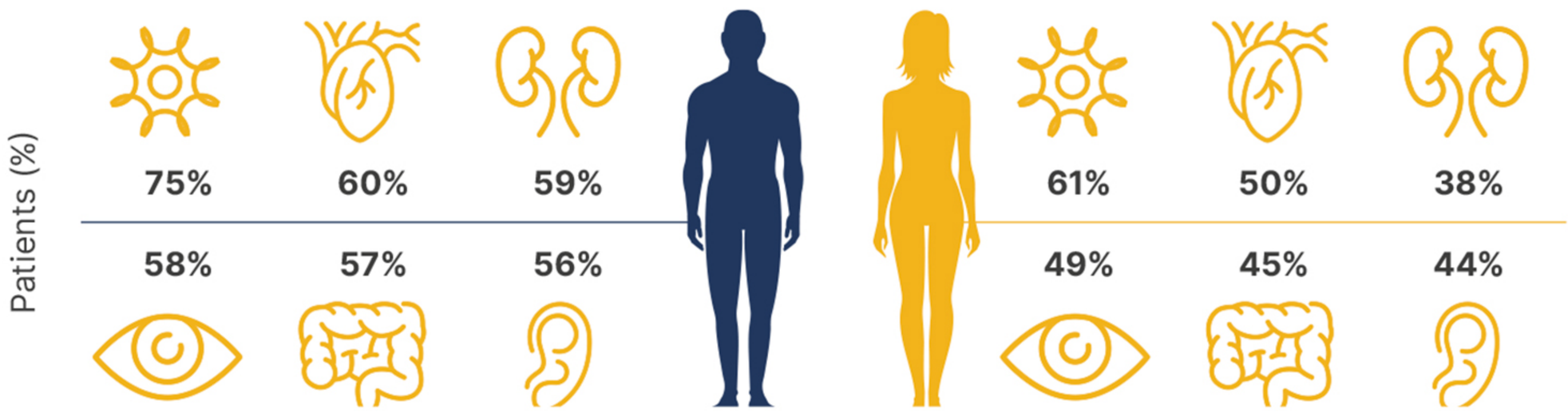
Fabry disease may cause significant symptoms, complications, and quality-of-life impairment in female patients

The course of Fabry disease in females is exceptionally variable

- Once considered only “carriers” of Fabry disease, females are now known to have disease courses ranging from mild to severe, with symptoms similar to those seen in males[1]
- Most are symptomatic, with a high percentage developing complications in vital organs[1]
- Reasons for variability include:
  - The lack of genotype-phenotype correlation, even within families[2,3]
  - The effects of X-chromosome inactivation, including the potential for skewed expression of the mutant *GLA* allele[4]

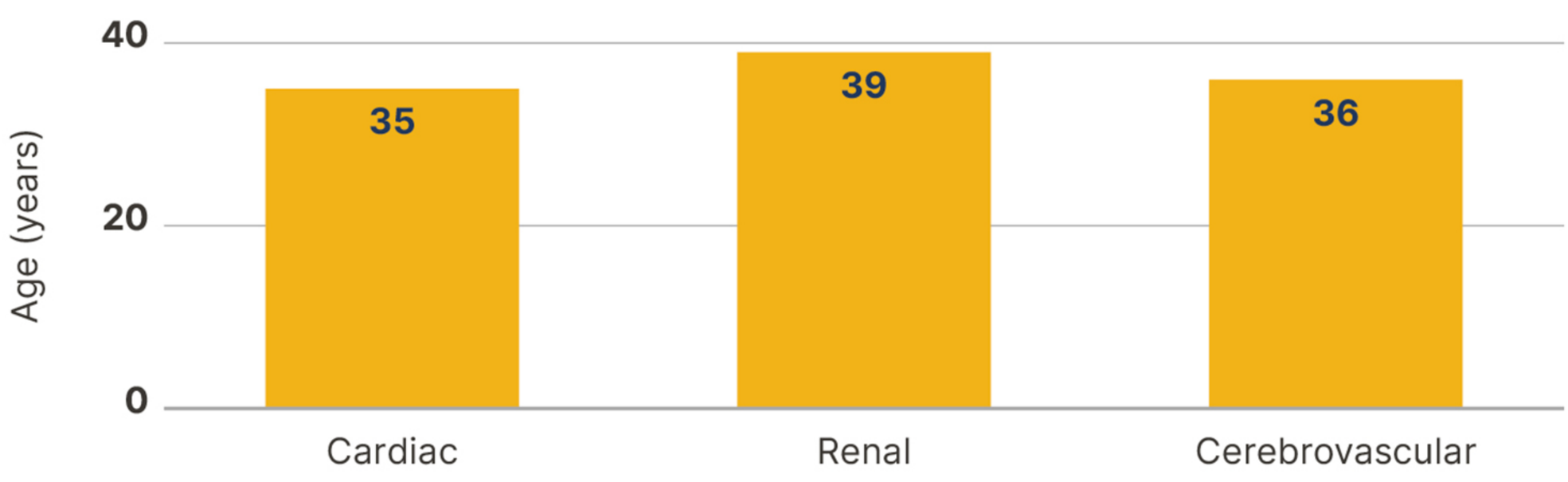
The majority of females with Fabry disease have symptoms in multiple organ systems[5]

Organ systems most frequently involved in untreated males (n=699) and females (n=754) with Fabry disease[5]



Major organ involvement in females often begins in the 30s[5]

Mean age at onset of organ involvement in females (n=754)[5]



“Females should be followed clinically and evaluated comprehensively to monitor for disease burden and progression.” — *Wilcox WR, et al, 2008*[6]

Fabry disease may have profound psychosocial impacts on females[9-11]

Females with Fabry disease may experience more than physical symptoms

Pain

The most common symptom in females at presentation is neurologic pain at a mean age of 14.2 years.[6] Pain was most often described as burning[7] and was comparable in intensity, location, and frequency between males and females.[8]

Depression

Depression is frequent and underreported in Fabry disease.[1] In a study, about a third of women living with Fabry disease described feelings of depression, anxiety, fatigue, and frustration.[9]

Impact on childbearing

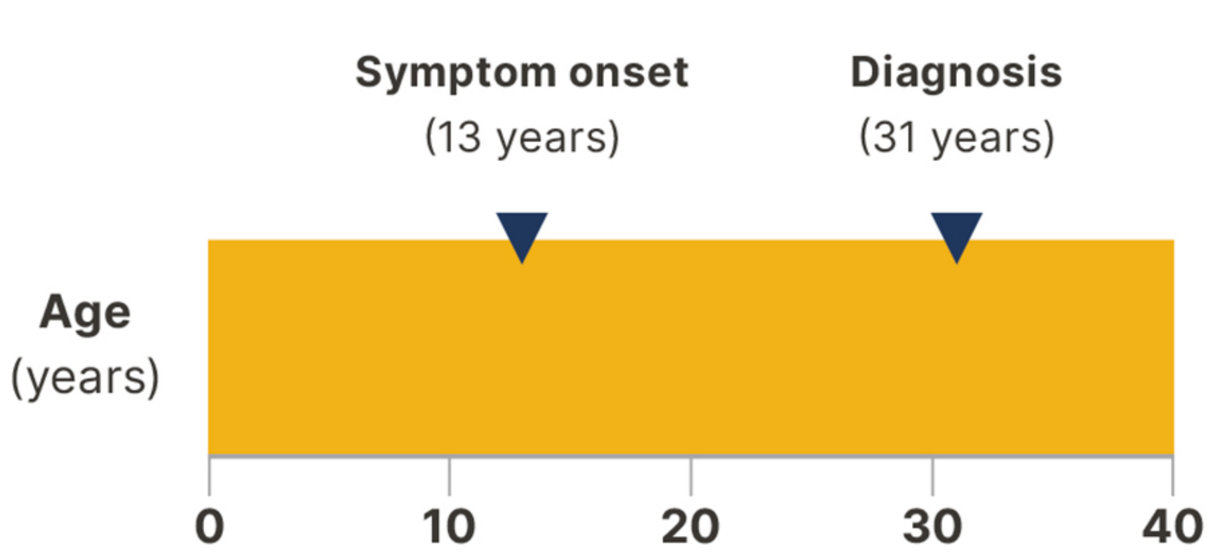
Women often report having negative feelings about passing Fabry disease on to their children.[10] In one study, almost half of women of childbearing age reported being against bearing more children because of the disease.[9]

Health-related quality of life (HRQoL)

HRQoL scores in females with Fabry disease were significantly diminished relative to healthy controls in all eight measured domains and more similar to those in females with multiple sclerosis and rheumatoid arthritis.[11]

Diagnosis of Fabry disease in females may be delayed by a decade or more — even with a family history of Fabry disease[6]

Median age at symptom onset and diagnosis in female patients[6]



84% of females in the study had a family history of Fabry disease[6]

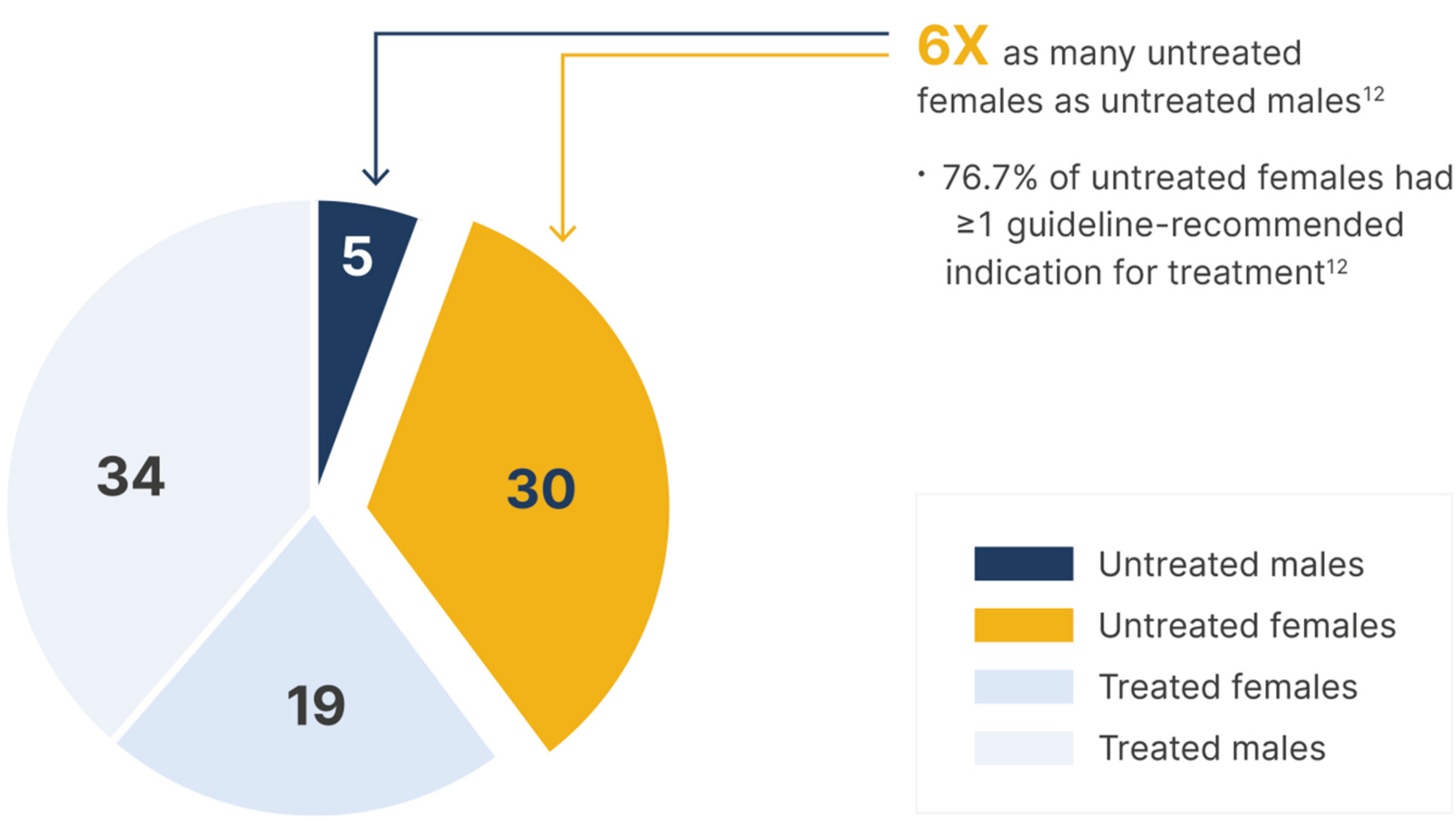
Age at diagnosis was available for 1018 of 1077 total female patients in the study, of whom 581 had data on age of symptom onset. Family history data are a percentage of total female patients in the study (906/1077).[6]

Females with Fabry disease may be undertreated

Females with Fabry disease may be undertreated relative to males despite having indications for Fabry-specific treatment[12]

- In a cohort of untreated Spanish females with Fabry disease[13]:
  - 20/29 (69.0%) considered themselves asymptomatic, even though
  - 22/32 (68.8%) had ≥1 Fabry disease symptom reported by their physicians

Treatment status of 88 male and female Spanish patients with Fabry disease[12]



6X as many untreated females as untreated males[12]

- 76.7% of untreated females had ≥1 guideline-recommended indication for treatment[12]

Data from a retrospective analysis of patients from 28 Spanish centres enrolled in a registry study.[12]

- In a retrospective study of 261 adult female patients with genetically confirmed Fabry disease from six centres in Germany, 34% of patients were untreated despite having an indication for Fabry-specific treatment[14]
  - 37 patients with VUS and polymorphisms were excluded from the analysis[14]
- Females with Fabry disease may be disadvantaged as a result of disease rarity, devalued status as "carriers," and gender[15]

"These observations urge the need for a more stringent implementation of the new European FD guidelines for females across centres and reevaluation of untreated females." — *Lenders M, et al, 2016*[14]

FD, Fabry disease; VUS, variant of unknown significance.

Strategies for improved diagnosis and management of females with Fabry disease

Prompt diagnosis is essential[15]

- The majority of people with Fabry disease are female, based on genetic inheritance[16]
- Diagnosis of females requires genetic testing, as testing by enzyme activity is inconclusive[1,17,18]

Fabry-specific treatment is recommended for all females with disease-related symptoms or evidence of organ involvement[19,20]

- Older age at treatment initiation and having a severe event before treatment initiation were independent risk factors for future severe events in females with Fabry disease[21]

Recommendations for initiation of Fabry disease-specific treatment in females[19]

Patient Population	Recommendation
Symptomatic female with classic mutation	Specified signs/symptoms suggesting major organ involvement warrant initiation of treatment
Asymptomatic female with classic mutation	Treatment should be considered if there is laboratory, histological, or imaging evidence of injury to the kidney, heart, or CNS Treatment should also be considered if a skewed X chromosome inactivation pattern with predominant expression of the mutant *GLA* allele with or without very low α-Gal A activity has been demonstrated in the presence of signs and symptoms of disease
Male or female patient with late-onset mutation or *GLA* VUS	Treatment should be considered and is appropriate if there is laboratory, histological, or imaging evidence of injury to the kidney, heart, or CNS attributable to Fabry disease even in the absence of typical Fabry symptoms The advice of an expert in genetics and management of Fabry disease should be sought for interpretation of the pathogenicity of any VUS

α-Gal A, alpha-galactosidase A; CNS, central nervous system.

Treatment recommendations shown above are for enzyme replacement therapy (ERT).[19] At the time of publication, there was insufficient experience to make recommendations concerning other therapy.[19]

- Treatment may be initiated in males and females as soon as there are persistent signs or symptoms, even in a single organ system[20]*

The clinical hetereogeneity of Fabry disease mandates an individualised approach to patient care that reflects the patient's gender along with other personal, disease, and family characteristics[19]

*At the time of publication, the only available treatment was ERT, and treatment recommendations made were for ERT.[20]

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