Poster no. P238

Can artificial intelligence reduce racial and ethnic disparities in Fabry disease diagnosis?

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Introduction

- Fabry disease is a rare, pan-ethnic, X-linked lysosomal disorder in which variants of the *GLA* gene lead to dysfunctional α-galactosidase A (α-Gal A) enzyme and progressive accumulation of glycolipids throughout multiple organ systems, including the kidneys.[1]
- Birth prevalence estimates of Fabry disease have ranged from 1:170,000 to 1:40,000[2] – although recent studies have found considerably higher prevalences of predicted-pathogenic (1:3225)[3] or likely-pathogenic (1:5573)[4] *GLA* variants, as defined by the respective authors.[3,4]
- Early diagnosis and timely treatment of Fabry disease are crucial to minimize irreversible damage to organs.[5]
- Fabry disease is potentially underdiagnosed in minority ethnic groups,[6] and experts note that delays in diagnosis are likely exacerbated by a complex interplay of financial, educational, cultural and societal factors that affect access to healthcare, including genetic testing.[7]

Conclusions

- An artificial intelligence (AI) model that used clinical data recorded in electronic health records (EHRs) to identify individuals with potentially undiagnosed Fabry disease yielded a cohort with higher proportions of Black and Hispanic individuals than were represented in a cohort of individuals with confirmed Fabry disease or in the overall healthcare system population.
- It seems unlikely that fewer healthcare system encounters is a major driver of these disparities, as individuals identified by the AI model had numerically more lifetime encounters, on average.
- If the AI model is successful in identifying individuals with undiagnosed Fabry disease such methods may:
  - Reduce delays in diagnosis and associated unnecessary healthcare system encounters
  - Aid in determining the true prevalence of Fabry disease via large-scale screening programs
  - Contribute toward overcoming existing biases within healthcare systems.

Background and methods

- The overall aim of the present observational study is to characterize the feasibility of using an AI model to identify potentially undiagnosed adults with Fabry disease from within a large healthcare system population,[8] so that those identified can be considered for diagnostic confirmation of Fabry disease
  - The AI model previously demonstrated strong performance in identifying individuals with a Fabry disease diagnosis, and in highlighting multisystemic phenotypic characteristics that were clinically validated by a group of experts in Fabry disease.[8]

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- Here, we report results from a *post hoc* analysis of demographic characteristics of adults from the Penn Medicine, University of Pennsylvania Health System (i) overall, (ii) with confirmed Fabry disease, and (iii) identified by the AI model, with the aim of highlighting potential inequities in diagnosis and treatment.
- Anonymized EHRs that met study inclusion criteria were classified retrospectively as shown in ①, below
  - The date of site activation (and data transfer date) was October 1, 2024, and dates of birth were randomly offset for deidentification.
- Descriptive statistics were calculated for age (on September 3, 2025, based on the randomly offset dates of birth) and for number of healthcare system encounters in each population/cohort and in subgroups by race, ethnicity, current sex (as reported in EHRs at data transfer date) and age group. No statistical testing was conducted
  - Ethnicity subgroups were derived based on the presence of “Hispanic” in the EHR race and/or ethnicity fields.

Results

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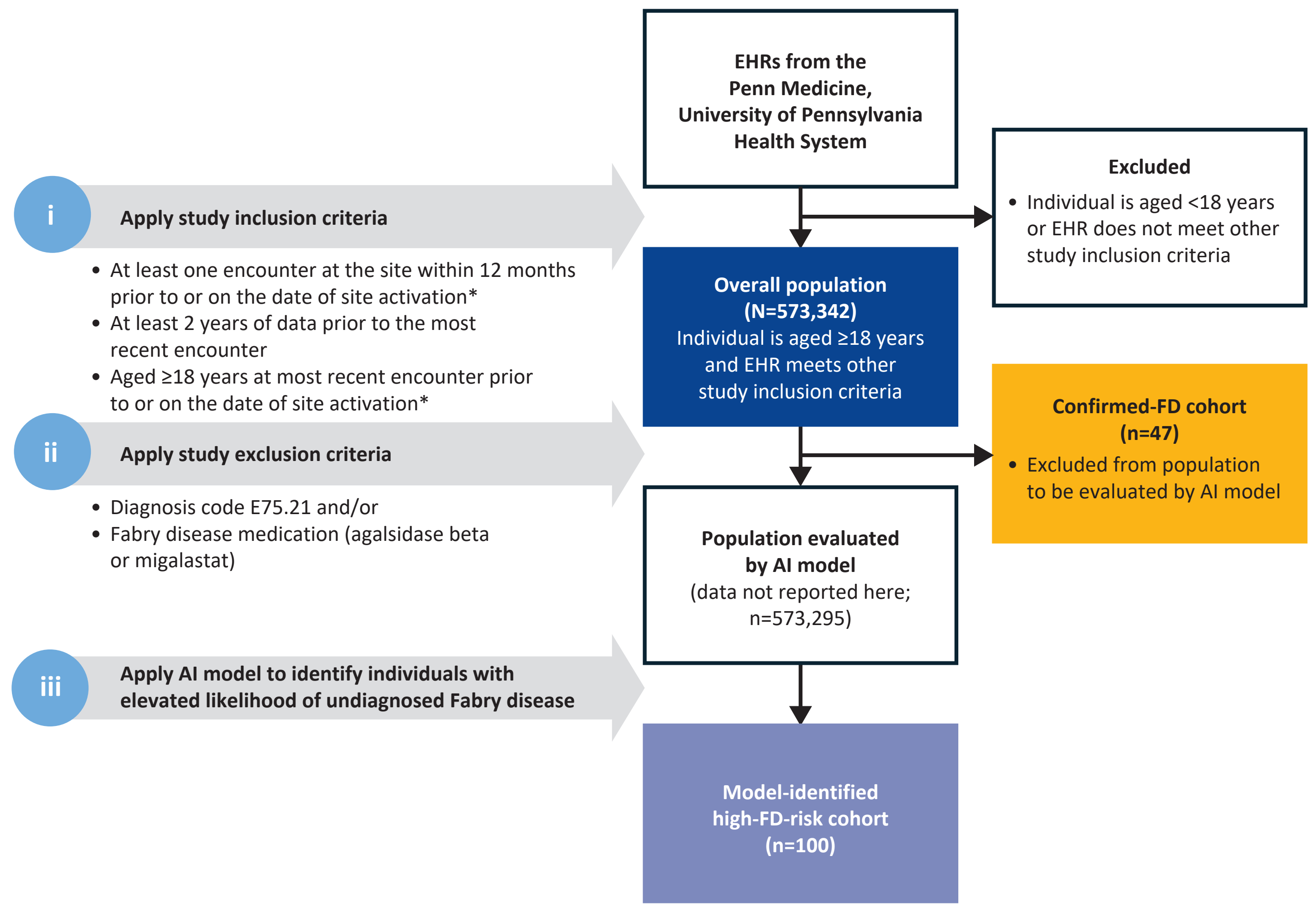
1 The AI model identified the 100 adults with the highest risk of undiagnosed Fabry disease in the overall population (N=573,342) after adults with confirmed Fabry disease (n=47) had been placed in their own cohort



EHRs from the Penn Medicine, University of Pennsylvania Health System

i **Apply study inclusion criteria**
- At least one encounter at the site within 12 months prior to or on the date of site activation*
- At least 2 years of data prior to the most recent encounter
- Aged ≥18 years at most recent encounter prior to or on the date of site activation*

Excluded
- Individual is aged <18 years or EHR does not meet other study inclusion criteria

Overall population (N=573,342) Individual is aged ≥18 years and EHR meets other study inclusion criteria

ii **Apply study exclusion criteria**
- Diagnosis code E75.21 and/or
- Fabry disease medication (agalsidase beta or migalastat)

Confirmed-FD cohort (n=47)
- Excluded from population to be evaluated by AI model

Population evaluated by AI model (data not reported here; n=573,295)

iii **Apply AI model to identify individuals with elevated likelihood of undiagnosed Fabry disease**

Model-identified high-FD-risk cohort (n=100)

We report *post hoc* demographic characteristics for the: **Overall population** **Confirmed-FD cohort** **High-FD-risk cohort**

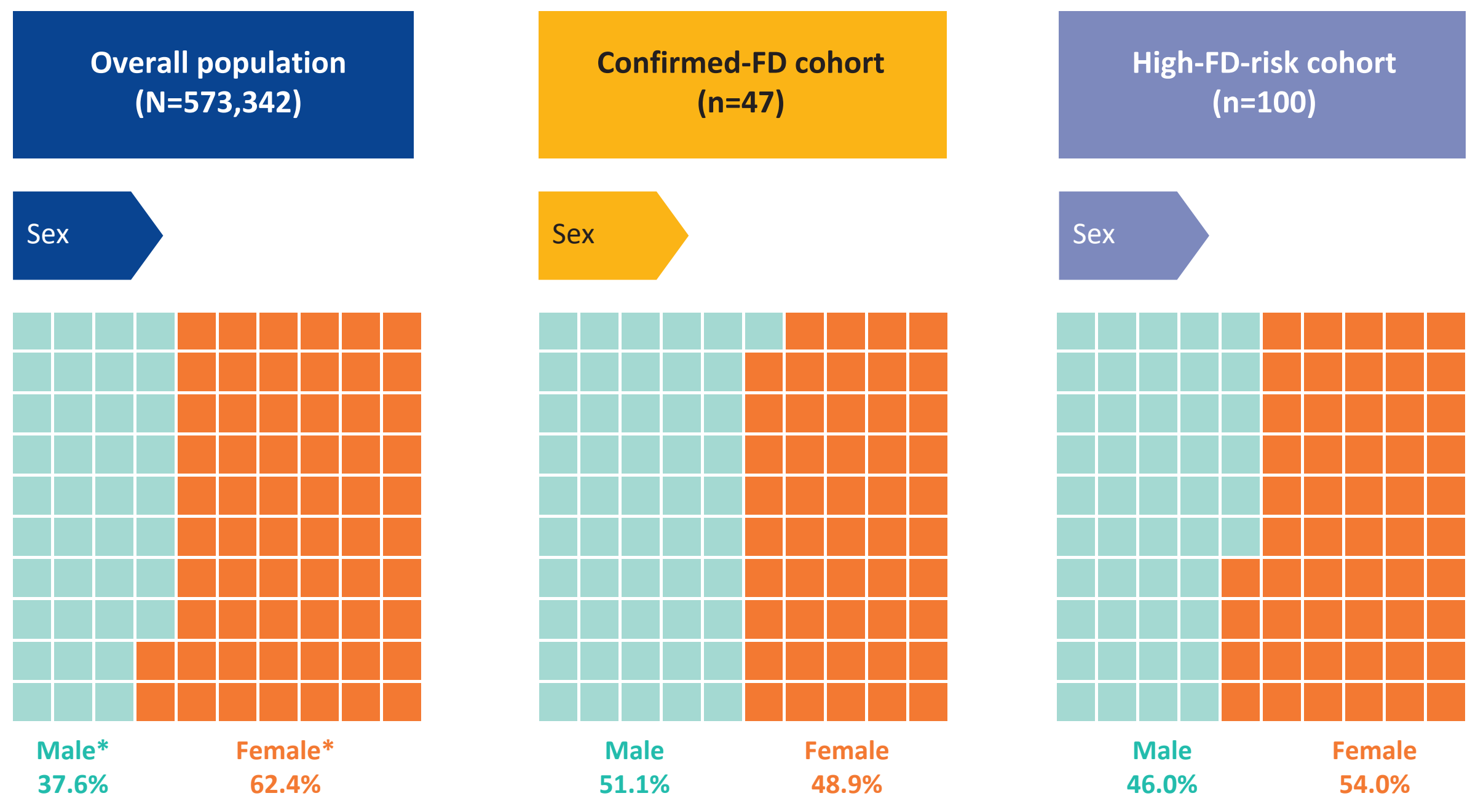
*Site: Penn Medicine, University of Pennsylvania Health System; date of site activation October 1, 2024.
Note: the following is a correction from the submitted abstract: population evaluated by AI model: n=573,295 (for 573,297).
FD, Fabry disease.

2 The model-identified high-FD-risk cohort included higher proportions of Black or African American individuals (30.0%) and Hispanic individuals (7.0%) than the overall population (18.3% and 4.4%) and confirmed-FD cohort (2.1% and 2.1%)

☐ One square represents ~1% of the population

*Included categories (per EHR nomenclature): American Indian or Alaskan Native (0.11% of overall population), East Indian (0.02%), HLB-Hispanic Latino/Black (0.03%), HLW-Hispanic Latino/White (0.15%), Native Hawaiian or Other Pacific Islander (0.11%). In addition, “Other” (per EHR nomenclature) comprised 3.41% of the overall population, 6.38% of the confirmed-FD cohort and 4.00% of the high-FD-risk cohort; †Included categories (per EHR nomenclature): blank entry (0.03% of overall population), patient declined (0.35% of overall population), unknown (3.42% of overall population, 2.13% of confirmed-FD cohort, 2.00% of high-FD-risk cohort); ‡Included categories: blank entry (0.41% of overall population).

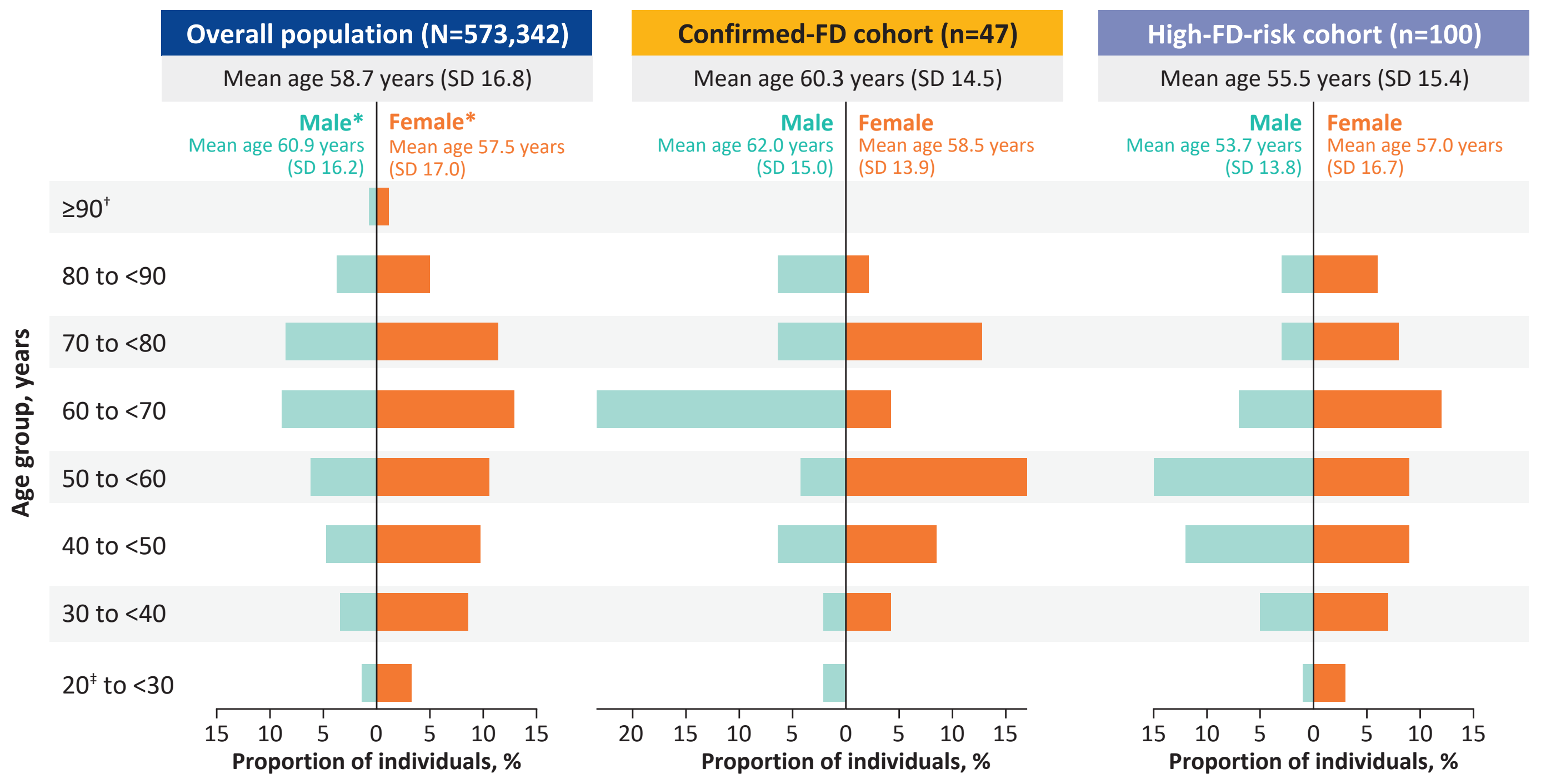
3 The proportion of females in the high-FD-risk cohort (54.0%) was lower than the two-thirds that would be expected for an X-linked Mendelian disease at a population level – especially given the a priori preponderance of females in the overall population (62.4%) – but was nevertheless higher than that in the confirmed-FD cohort (48.9%)



☐ One square represents ~1% of the population

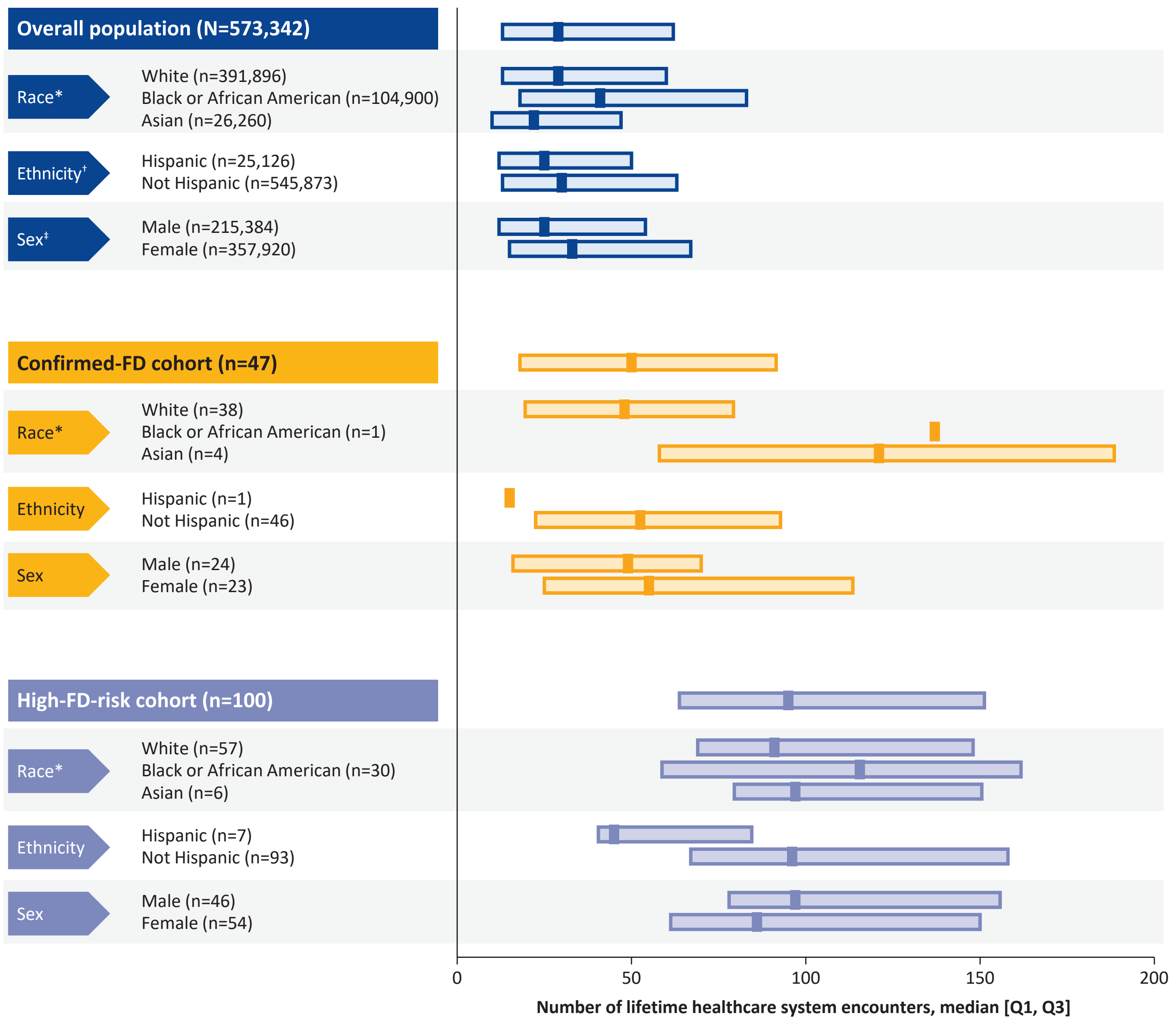
*The overall population also included 38 individuals (0.007%) whose EHRs recorded “X” (ie neither “M” nor “F”).

4 Individuals in the high-FD-risk cohort tended to be younger than those in the overall population or with confirmed Fabry disease; this was largely due to the males being younger (mean ages 53.7, 60.9 and 62.0 years, respectively)



*The overall population also included 38 individuals (0.007%) whose EHRs recorded “X” (ie neither “M” nor “F”) with mean age 36.6 years (SD 9.3); †Because of a deidentification-related cut-off, age was imputed to exactly 90 years for individuals ≥90 years of age; ‡No individuals were <20 years of age as calculated on September 3, 2025 using deidentification-related randomized dates of birth (see Background and methods).
SD, standard deviation.

5 Despite being younger on average, individuals in the high-FD-risk cohort had more lifetime healthcare system encounters (median 95) than those in the confirmed-FD cohort (50) or overall population (29), although the interquartile ranges were wide



*The three categories with the largest numbers of individuals in the high-FD-risk cohort are shown; †The overall population also included 2,343 individuals whose EHRs had blank entries and who had a median of 13 encounters (IQR 6, 29); ‡The overall population also included 38 individuals whose EHRs recorded “X” (ie neither “M” nor “F”) and who had a median of 24.5 encounters (IQR 11.25, 46.75).
IQR, interquartile range; Q, quartile.

Limitations

- It is not yet known which, if any, individuals identified by the AI model have Fabry disease; the overall aim of the ongoing present study is to characterize the feasibility of using the AI model to identify such individuals.
- Race and ethnicity were self-identified; moreover, the proportions of individuals reported as having Hispanic ethnicity may be underestimated due to data incompleteness.
- Individuals with Fabry disease recently referred to a specialist at Penn Medicine would not have met the inclusion criterion of ≥2 years of data prior to their most recent healthcare system encounter.

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