Background

• The diagnosis of Fabry disease (FD), a rare, progressive, X-linked lysosomal storage disorder,\(^1,2\) presents a significant challenge to non-FD specialists owing to the wide variability in age, severity, and clinical presentation, and significant overlap of symptoms with other disorders.\(^3,4\)

• Misdiagnoses or delayed diagnoses lead to unnecessary tests, inappropriate treatment and patient anxiety, and can result in irreversible organ damage.\(^3,4\)

• Early and appropriate treatment, most frequently with enzyme replacement therapy, the standard of care,\(^5\) can reduce and prevent the development of irreversible disease complications.\(^4,6-10\)

Objective

• The primary objective of the study is to develop a predictive model for accurately identifying potential patients with FD on the basis of real-world clinical data from hospitals of the MIRACUM (Medical Informatics in Research and Care in University Medicine) Consortium within the BMBF (Bundesministerium für Bildung und Forschung/Federal Ministry of Education and Research) Medical Informatics Initiative (MII) using natural language processing.
Methods

Study design
• The study, which will take place in 2 parts, is a multicentre, national, retrospective observational database analysis (part A) and a prospective diagnostic study (part B) (Figure 1).

Figure 1. Overview of the study design

- In Part A, an algorithm model for the identification of FD will be developed and applied to the electronic health records database from participating centres to identify potential patients with FD
- The study will utilise ~500,000 de-identified electronic health records from 2 university hospitals that are part of the MIRACUM consortium

- In Part B, patients identified as potentially having FD will be confirmed by genetic testing
- To be included in part B, patients identified as having a high likelihood of FD will be required to provide written informed consent and, in the opinion of the investigator, be capable of understanding and complying with the protocol requirements

• The study will be conducted in accordance with the protocol, the guidelines of the Declaration of Helsinki, Good Pharmacoepidemiology Practices (GPP) and local regulations.
• The protocol will be submitted to ethics committees of the participating centres for approval.

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Methods

Data sources
- Medical records of inpatients or outpatients of any age who have attended the participating hospitals over the previous 10 years will be assessed retrospectively.

Data extraction
- Medical records, including discharge letters, billing data and laboratory parameters from the previous 10 years, will be evaluated.
- Data will be extracted on demographic parameters; department of inpatient or outpatient treatment; dates of inpatient admission and discharge; morbidities and comorbidities; and disease phenotypes (signs and symptoms and functional test results), using defined and standardized processes.
- The commercial software ‘Health Discovery’ from Averbis will be used as text mining software.

FD profile
- Signs and symptoms and functional test results will be based on an FD profile created from public datasets, published literature and medical expert review, and will include all known symptoms and phenotypes and their relative frequencies.
Methods

**Part A: Development of the predictive algorithm**
- Multilevel likelihood ratios will be used to develop a predictive algorithm for FD.
- The likelihood ratio of each feature will be calculated as the probability of a patient with FD to present with this feature divided by the probability of a patient who does not have FD to present with the feature.
- A disease score will be calculated for each patient record from the likelihood ratios of all the features present. This score will be used to rank patients by their risk of having FD.
- The positive predictive value will be calculated at different cut-off values (e.g., top 10, 20, 50, 100, 200) for approximately 200 patients with the highest disease scores.
- Patients with high scores and an existing diagnosis of FD will be identified as true positives (control patients); those with no existing diagnosis of FD will be identified as potential FD patients and be reviewed for inclusion in part B of the study.
- Patients with the lowest disease scores will be evaluated to confirm the number of true negatives and identify any false negatives (i.e., patients with an existing diagnosis of FD).

**Part B: Confirmatory genetic testing of potential patients with FD**
- Patients with the highest disease scores identified in Part A who had no existing diagnosis of FD and provided informed consent will undergo confirmatory genetic testing for FD.
- Results of FD diagnostic tests will be tabulated and mutations detected by genetic analyses will be presented using descriptive statistics only. Missing values will not be replaced by any method of imputation.

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Discussion

• The detection of potential patients with FD by using an algorithm, independent of physicians’ ability to recognize signs and symptoms, is expected to help reduce delays to diagnosis and allow for timely initiation of appropriate therapy.
• The large sample size in part A, along with detailed medical records, are expected to result in a predictive model with the best possible accuracy, given the rarity of the disease.
• The resulting model will also improve our understanding of FD based on the relative importance of the features of FD.
• External validation of the best model is planned, to provide an unbiased estimate of the model’s accuracy in different patient cohorts.

References

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