Novel Partnership to address the diagnostic odyssey in Paroxysmal Nocturnal Hemoglobinuria (PNH)

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[1]Mendelian

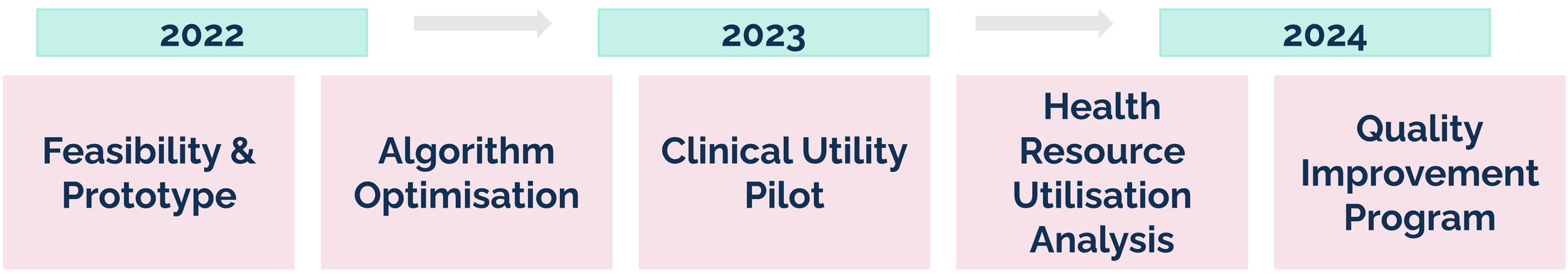
Background

Mendelian, a London-based health tech company, aims to reduce diagnostic delays in rare diseases using data and technology. MendelScan, a Class 1 Medical Device, analyzes structured Electronic Health Record (EHR) data to identify symptom clusters suggesting undiagnosed rare diseases. The output is delivered to clinicians for review, along with supporting literature and recommended follow-up actions.

Paroxysmal Nocturnal Hemoglobinuria (PNH), a rare (Prevalence 38.1/million) blood disorder, presents with variable symptoms [1]. As with many rare diseases patients face pronounced diagnostic delays, with a median delay from 5 to 10 months; however, delays exceeding 5 years are not uncommon, with one study reporting that this occurs in 25% of PNH cases [2]. Untreated, PNH can lead to serious outcomes, including thrombosis related death. Treatments are available, and clinical trials are ongoing in the UK [1].

An industry partnership began in 2022 to address the diagnostic odyssey in PNH through the application of novel "Case Finding" technology that combines machine learning with clinical expertise. The partnership aims to develop and evidence a "Case Finding" approach that can be deployed at scale to the benefit of patients, clinicians, and health services.

Stages of Partnership



Feasibility & Prototype (2022):

- A detailed analysis of the disease and diagnostic pathway, including insight from Highly Specialised Services, was conducted, informing a PNH case finding algorithm

Algorithm Optimisation (2023):

- Two paths were explored to evolve the PNH case finding algorithm - one including more complex clinical logic and one using Machine Learning (ML)
  - **Complex Clinical Logic Model Results:**
    - The algorithm had:
      - **Sensitivity of 34.95%** (95% CI 28.12 - 42.27)
      - **Specificity of 99.9771%** (95% CI 99.98 - 99.98)
      - **Positive predictive value (PPV) of 5.49%** (95% CI 4.47 - 6.73)*
    - 72% of PNH cases would be flagged before their coded diagnosis, and 57% more than a year before this diagnosis
    - The median flag time of all cases was 14 months before diagnosis
    - When looking only at cases flagged before diagnosis, the median flag time was 46 months before diagnosis
  - **ML Model Results:**
    - 60.4% of cases classified as positive by the final model were PNH patients (positive predictive value) [3]
    - The algorithm had:
      - **Sensitivity of 27%** (95% CI 15.0-39.0)
      - **Specificity of 99.9%** (95% CI 99.9-99.9)
      - **Adjusted PPV of 19.59%** (95% CI 7.63-41.81)

- While the sensitivity may appear low, this is in order to optimise other performance metrics. The priority in rare disease case finding approaches is to maximise the Specificity and PPV, this:
  - Ensures flagged potential patients are more likely to have the condition
  - Reduces false positives
  - Focuses resources on individuals who would benefit most from further diagnostic evaluation

*When adjusted for disease prevalence according to literature [4]

Clinical Utility Pilot (2023/2024):

- The prototype algorithm was deployed via the MendelScan platform in **371,016 primary care EHRs** from participating practices
  - **Results:**
    - The algorithm flagged 31 records out of the total population
      - 12 were excluded on review by a Mendelian clinician (Including 1 already diagnosed with PNH)
    - 19 reports were sent to GPs
      - Feedback was received on 17 of them
      - 9 were referred for PNH testing
      - Nil positive tests so far, the study is ongoing

Health Resource Utilisation Analysis (2024):

- The impact of deploying the ML model in a population on diagnosis trends and Health Service resource use was modelled
  - **Results:**
    - Significant potential to improve patient outcomes. Due to the rarity of the disease, the impact on resource utilisation is marginal to positive
    - The most significant impact is the potential to avoid complex clotting events which may result in hospital or ICU admissions

Quality Improvement Program (2024):

- A quality improvement program was developed in partnership with Optimum Patient Care enabling case finding and supported clinical follow up in a population of **6 million**
  - **Results:**
    - Early results suggest that the algorithm can successfully identify patients who are appropriate for PNH screening
    - Operational challenges remain to this type of initiative in Primary Care in the NHS

Discussion

- **This partnership is enabling tangible progress towards a scalable solution that benefits patients, clinicians, and the health system by bringing together deep disease expertise with innovative technology.**
- **Achieving the overall goals of the partnership faces obstacles such as the quality and availability of EHR data, limited channels and incentives to implement novel technology.**
- **Future work will focus on evidence generation and continued collaboration with the NHS.**

References

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Acknowledgements: This study is in part based on data from the Optimum Patient Care Research Database (www.opcrd.co.uk) obtained under a limited licence from Optimum Patient Care Limited. We acknowledge the practices and individuals that contribute their de-identified data to the Optimum Patient Care Research Database.

Funding: This project was funded by Alexion, AstraZeneca Rare Disease

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