A Population Genetics-Based Microsimulation Platform for Forecasting the Health and Economic Burden of Rare Genetic Diseases

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Objectives

- Develop a microsimulation model incorporating genetic disease risk using allele frequencies and penetrance.
- Enable accurate quantification and projection of the burden of rare genetic diseases.
- Quantify health and economic benefits of targeted rare genetic disease interventions.

Background

- Rare diseases, most of which are genetic in origin, are defined as a condition affecting fewer than 1 in 2,000 people, and collectively impact 4-7.6% of the global population.[1] Despite this, most key epidemiological measures remain poorly quantified.
- Incomplete data and underdiagnosis mask true prevalence; diagnostic delays obscure true incidence; and low prevalence limits visibility of patient journeys.
- These challenges create a critical evidence gap for policymakers, payers, and providers, limiting the ability to understand the current and future health and economic burden of rare diseases, and assess the impact and value of interventions.

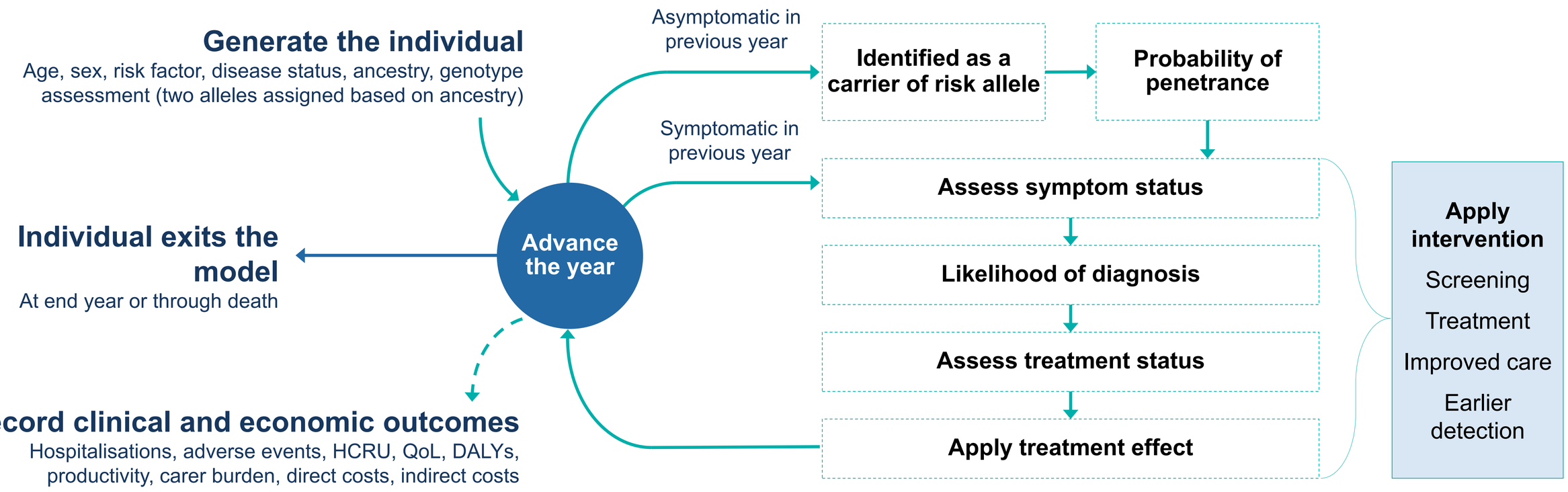
Methodology

- Microsimulation is a particularly valuable tool in the analysis of rare genetic diseases because it allows individual-level modelling based on population demographics, ancestry-linked genetic data, disease penetrance data, risk factors, comorbidities, and other relevant parameters.
- Integration of such datasets allows the model to overcome empirical data scarcity in other areas, e.g. national prevalence estimates.

1	Individuals are generated using national age, sex, and ancestry-stratified demographic data.
2	Genotypes are assigned based on allele frequencies by ancestry from large-scale genetic reference databases (e.g. gnomAD[2]).
3	The risk of disease onset is then modelled using penetrance estimates specific to genotype, age, and sex.
4	A dedicated inheritance module allows genotypes to be passed on through generations, modelling familial disease dynamics.
5	Patients' clinical burdens and costs associated with disease are calculated based on their health state in any given year.
6	Diagnosis and treatment are applied and may affect patient outcomes. Interventions may be modelled which alter these parameters.

- Crucially, the platform is modular by design, enabling flexible representation of key rare disease complexities, including diagnostic pathways, pharmacological treatments, disease progression, quality of life, survival, intervention effects, and other parameters.

Overview of the genetics-based microsimulation platform



Conclusions

- The model structure supports the quantification of disease burden, even where empirical evidence is limited.
- The structure is well-suited to the evaluation of long-term clinical and cost-effectiveness of treatments.
- This structure allows modelling of interventions such as improved diagnosis and novel pharmacological therapies.
- The model can be leveraged to generate evidence to raise awareness of disease burden and effective interventions, and inform payers, providers and policymakers to advance access to timely and effective treatment.

References: [1] Rare diseases in numbers, Orphanet Report Series (2026); [2] Chen S et al. Nature. 625, 92-100 (2024)

Abbreviations: gnomAD, Genome Aggregation Database; HCRU, Health Care Resource Use; QoL, Quality of Life; DALYs, Disability-Adjusted Life Years

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