Dynamic Simulation Modelling for Familial Hypercholesterolemia in Singapore

Familial hypercholesterolemia (FH) is an inherited condition that is caused by mutations in genes that are involved in the processing of low-density lipoprotein (most commonly LDLR, PCSK9 and APOB) and has an autosomal dominant mode of inheritance (except for PCSK9 mutations) which means that 50% of each generation is affected. Local prevalence is 1:140.[1] FH therefore affects 25-50,000 Singaporeans.

Modeling Team
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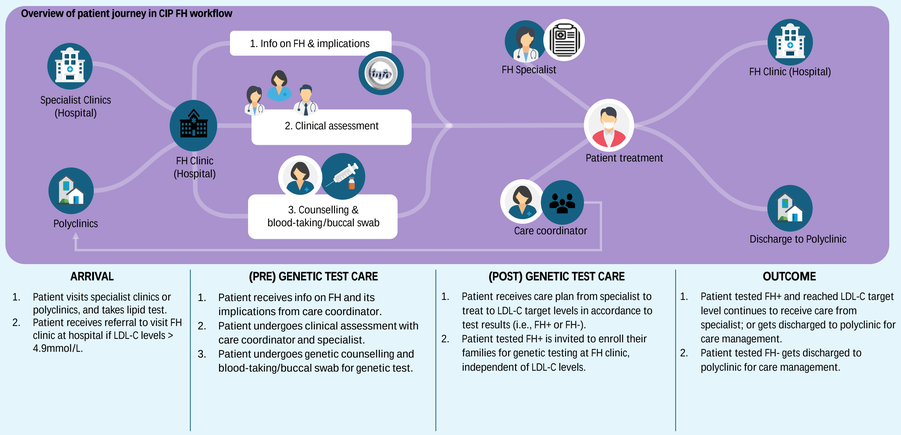
Compared to individuals without hypercholesterolemia, individuals with FH have a **20-fold higher risk of heart disease**, which often **occurs 10-15 years before it occurs in unaffected individuals**.

Given that the median age of first myocardial infarction in Singaporean men is 67, these events often occur when an individual is most economically productive. Thus, the **societal cost includes premature mortality and morbidity AND loss of productivity**.

This **excess risk is dramatically reduced by cholesterol lowering therapies which are considered cost effective** The **challenge for reducing the societal cost of FH lies in case identification** as most patients are undiagnosed and thus untreated until such time as they develop CVD.

Illustration of existing workflow



Problem statement

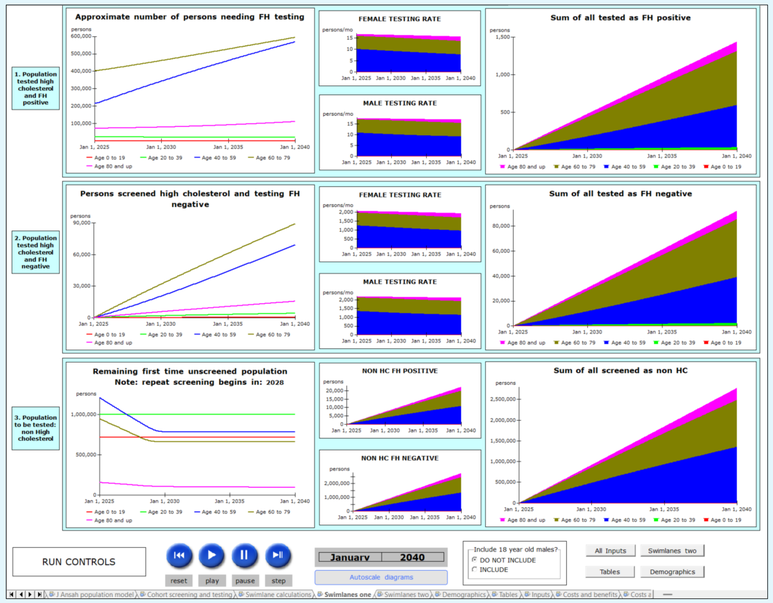
1. Understand the flow of persons through the cholesterol screening and genetic testing cycle.
2. Manage the cascade testing of relatives of those that are FH positive.
3. Test capacities of screening and testing, delays, and capacities in the system.
4. Understand the effects of age cohort and gender differences in the incidence of high cholesterol and FH
5. Estimate the costs and benefits of initiating screening (cholesterol) and testing (FH).
6. Hypothesize and test feedback on:
   a) Increases in the cholesterol screening rate as a function of the percent of individuals tested
   b) Increases in the demand for testing for other genetic disorders

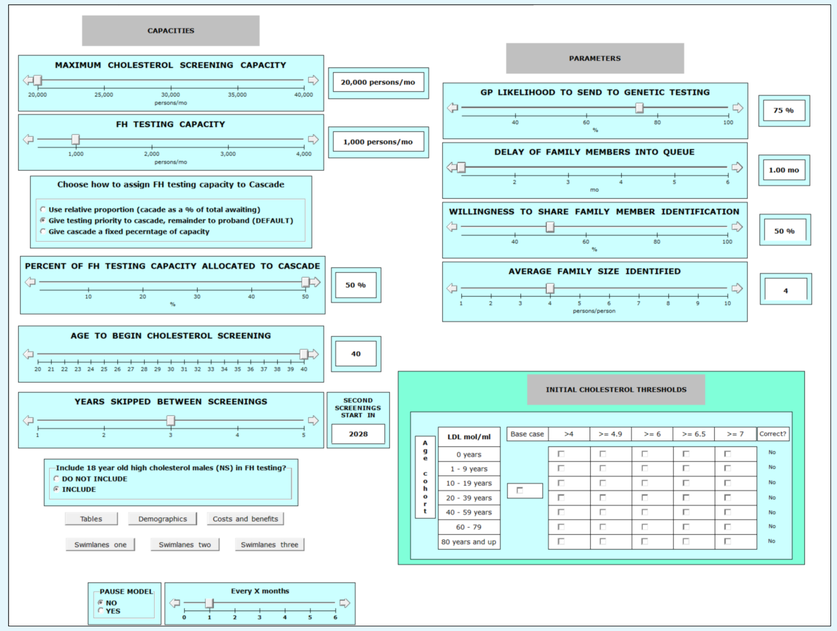
Important Insights:

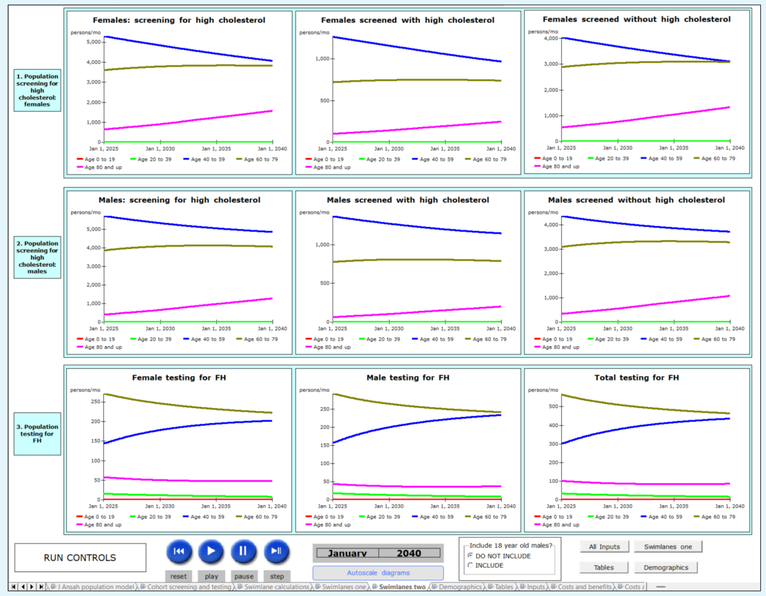
1. Testing demand is strongly influenced by awareness and perceived risk
2. Increasing HC screening capacity alone does not improve FH detection if FH genetic testing capacity remains limited.
3. Allocating limited genetic testing capacity such as prioritizing cascade testing over proband testing and adjusting the LDL referral threshold depending on the age, improves FH detection rate.

Phase 1 completed 10 March 2025 DYNAMICS first!
Group Model Building – 21 July 2024
Model has 4 cohorts for individuals
Phase 2 completed 30 June 2025 DETAIL next!
Oversight Group Review and discussion
Model has 202 age/gender cohorts and 6 incidence cohorts(cholesterol and FH)
Cholesterol and FH incidence differs by grouped age cohort and 5 LDL/FH levels

[1] Patrick Tan et al. (2022). Analysis of clinically relevant variants from ancestrally diverse Asian genomes. Nature Communications, https://doi.org/10.1038/s41467-022-34116-9.







CHALLENGES

- Maintaining material flow and material balance
- Chaining proband screening and FH testing to cascade (relatives) testing
- Maintaining the population aging chain
- Scope creep that comes with incremental understanding of the problem
- Presenting results from large arrayed sets of data
- Complex policy and sensitivity choices

The Cascade

Persons identified as relatives of those testing positive for FH and who are willing to cooperate by being tested for FH

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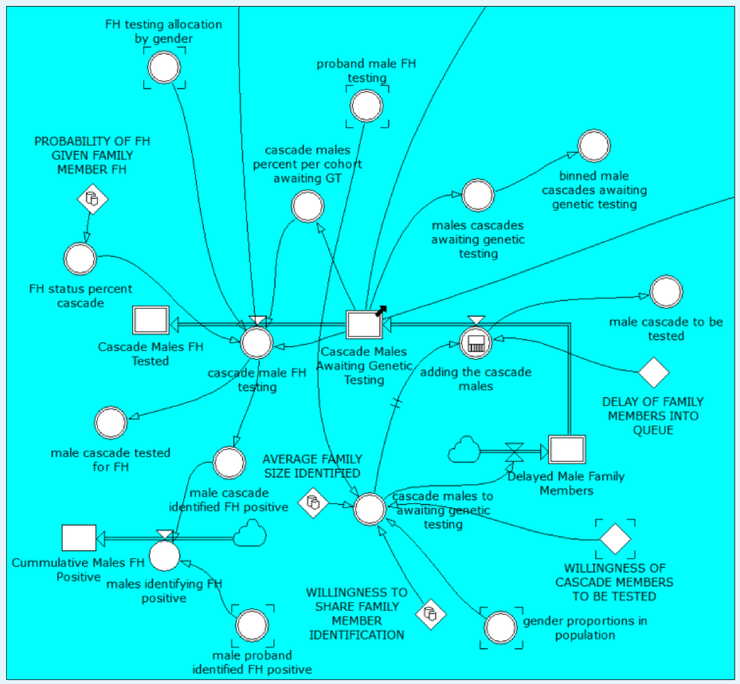

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