From Scarcity to Strategy:

Generative AI for Rare Disease Model Conceptualization

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Introduction:

Health economic models (HEM) development in **rare diseases** is often challenging due to multiple factors such as limited patient populations, heterogeneous clinical manifestations, and scarce data on disease progression and outcomes. These issues can complicate model conceptualization and lead to high uncertainty in cost-effectiveness analyses.

This proof-of-concept (PoC) study demonstrates how a proprietary generative AI (Gen-AI) tool augmented with human feedback, guidelines and domain-specific knowledge can address these challenges by conceptualizing a HEM for a rare disease with significant data gaps.

Indication considered for PoC: Transthyretin amyloid polyneuropathy (ATTR-PN), a rare disease characterized by the accumulation of amyloid protein in nerve tissues.[1]

> This study demonstrates a practical human-in-the-loop agentic gen-AI approach, combining domain expert reasoning with gen-AI to conduct model conceptualization especially in rare diseases where data and guidance are often limited.

Methods

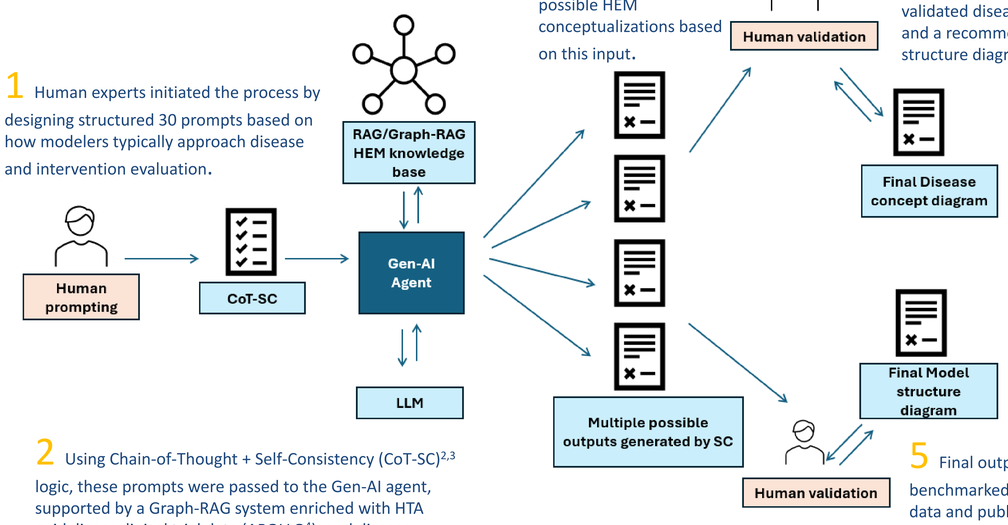
1 Human experts initiated the process by designing structured 30 prompts based on how modelers typically approach disease and intervention evaluation.

2 Using Chain-of-Thought + Self-Consistency (CoT-SC)[2,3] logic, these prompts were passed to the Gen-AI agent, supported by a Graph-RAG system enriched with HTA guidelines, clinical trial data (APOLLO[4]), and disease-specific insights but not existing models, to avoid bias.

3 The Gen-AI Agent generated multiple possible HEM conceptualizations based on this input.

4 These were filtered and validated by human experts, resulting in two core outputs: a validated disease concept diagram and a recommended model structure diagram

5 Final outputs were benchmarked against real-world data and published models to ensure robustness and applicability.



Results

The LLM's initial recommendation for natural history was further refined using the human-in-loop approach. Initial recommendation was promising and closely aligned with what human experts might have generated through comprehensive manual conceptualization. **Figure 1** presented recommended natural history.

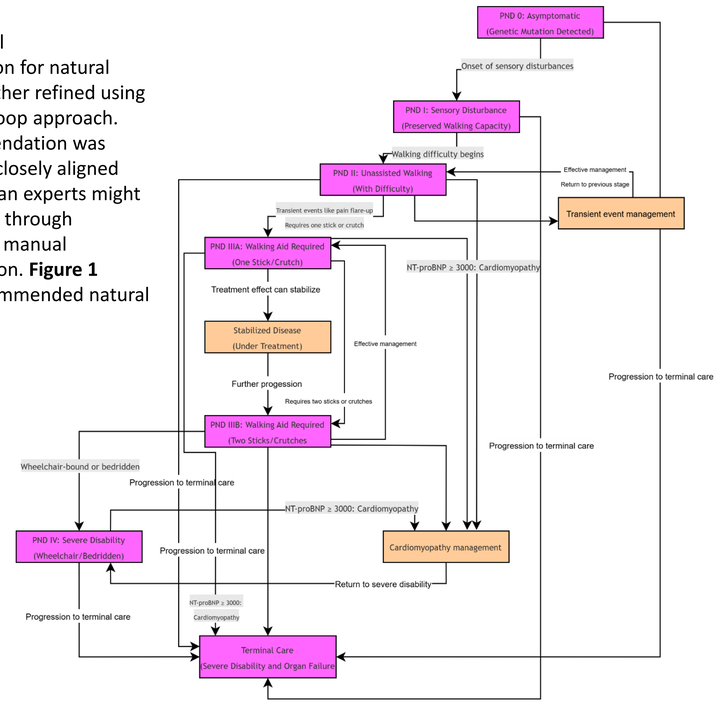


Figure 1: Disease concept diagram generated by the HITL approach of Gen-AI for ATTR-PN

For the model structure, LLM suggested a semi-Markov model suitable for capturing the complex, non-linear progression of ATTR-PN. Recommended health states are presented in **Figure 2.**

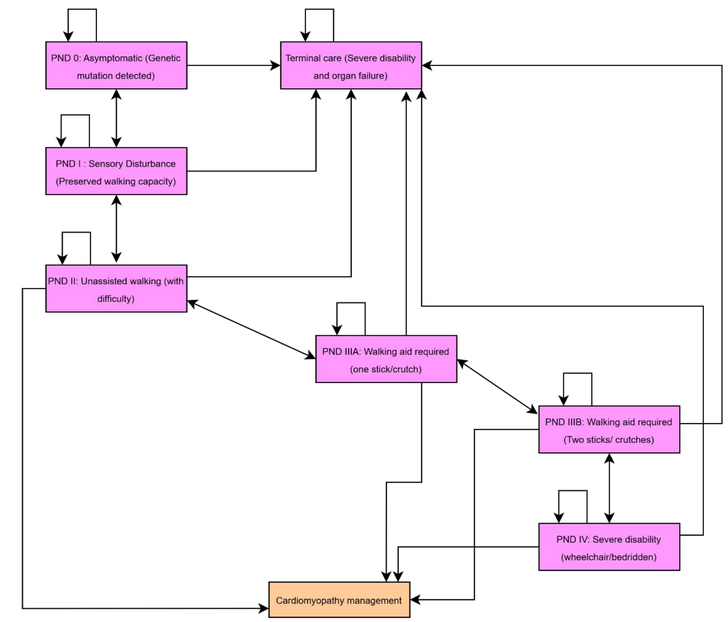


Figure 2: Recommended semi-Markov model structure generated by the HITL approach of Gen-AI for ATTR-PN

Discussion

- **Hybrid intelligence framework**: We present the first unified framework combining HITL, CoT-SC reasoning, and Graph-RAG for Gen-AI driven HEM conceptualization achieving near-final outputs in hours instead of months.
- **Human Role**: Expert-designed prompts and contextual inputs (PICO, guidelines) structured the AI's reasoning path, while expert review anchored outputs in methodological and clinical credibility.
- **Limitations:** Outputs are proof-of-concept; advanced reasoning requires compute and code literacy, and deeper clinical validation is needed before decision-use.
- **Future Work**: Next steps include layering advanced ToT/GoT [5,6] logic, developing no-code interfaces for health economists, and embedding real-time data streams (e.g., EHRs) for dynamic model generation.

References:

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