Long-Term Survival, Quality-Adjusted Life-Years, and Economic Burden in Limb-Girdle Muscular Dystrophy Type 2I/R9: A Health Outcomes Model

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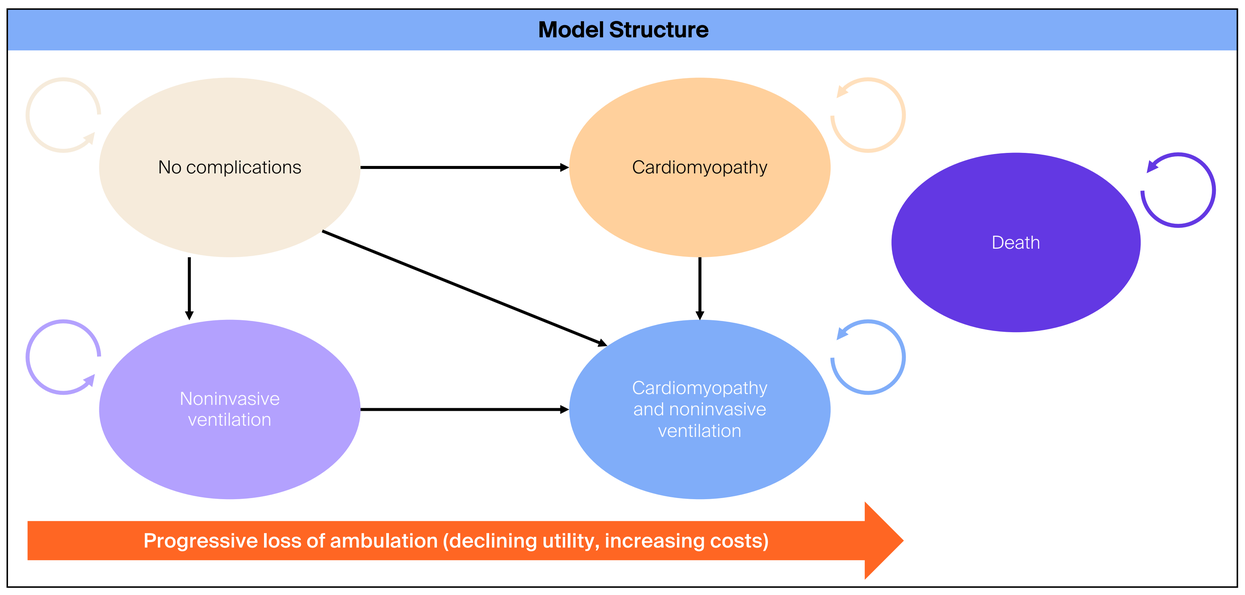
OBJECTIVE

- To develop a limb-girdle muscular dystrophy type 2I/R9 (LGMD2I/R9) health outcomes model to assess relationships between complications and mortality, and to estimate life expectancy and medical costs
- To assess health outcomes by *FKRP* genotype subgroup (c.826>A homozygous vs other)

BACKGROUND

- LGMD2I/R9 is a rare, progressive, and irreversible neuromuscular disorder caused by autosomal recessive *FKRP* variants leading to impaired α-dystroglycan glycosylation[1,2]
- LGMD2I/R9 is characterized by progressive muscle weakness and loss of ambulation, frequently accompanied by cardiomyopathy and respiratory decline[2]
- These complications contribute to substantial clinical burden and functional impairment and are expected to adversely affect survival, HRQoL, healthcare resource utilization, and costs[1,3]
- Long-term data for LGMD2I/R9 are limited, and the impact of disease complications on life expectancy remains poorly defined

METHODS



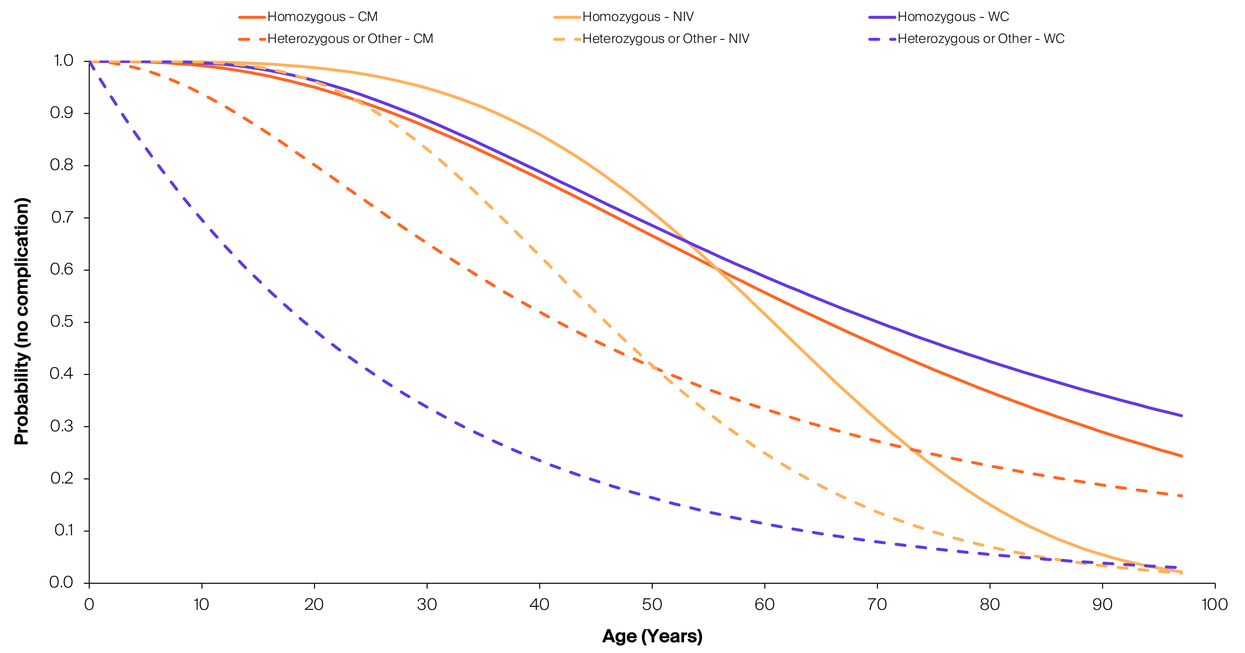
Model overview and population

- Markov state-transition model
- Lifetime horizon; 1-year cycle length
- US payer perspective
- Individuals living with LGMD2I/R9: subgroups by genotype
  - Stratified by *FKRP* genotype (c.826C>A homozygous vs other)

Model structure and clinical inputs

- Health states include no complications, cardiomyopathy (CM), noninvasive ventilation (NIV), CM + NIV, and death
- Risks of loss of ambulation, CM, and NIV estimated from LGMD2I/R9 cohort data using parametric survival models[4] (**Figure 1**)
- Mortality modeled using published HRs for CM (2.0–10.5)[5-7] and NIV (1.0–1.6); ranges reflect uncertainty[8]

Figure 1. Parametric survival functions for complication risk by genotype



Outcomes and costs

- Life expectancy (LY)
- QALY (utilities from EQ-5D in other LGMD subtypes: 2E/R4, 2D/R3, 2C/R5)
- Lifetime direct medical costs (ICD-10-CM G71.038 LGMD population)
  - Costs include inpatient, emergency department, outpatient, and pharmacy
- Costs and utility values were varied by ambulatory status

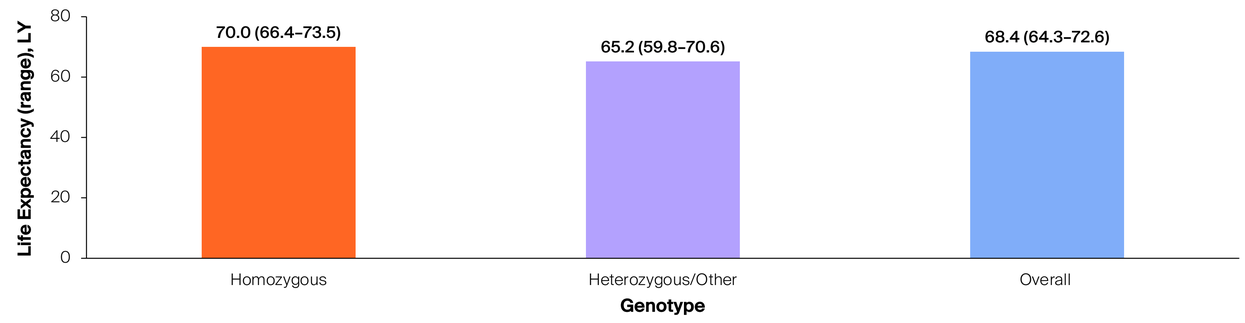
Analyses

- Base-case analysis
- Deterministic one-way sensitivity analysis
- Scenario analyses (EQ-5D vs EQ-VAS utilities,[9] cost sources)
  - EQ-5D: General population preferences
  - EQ-VAS: Patient-reported current health status

RESULTS

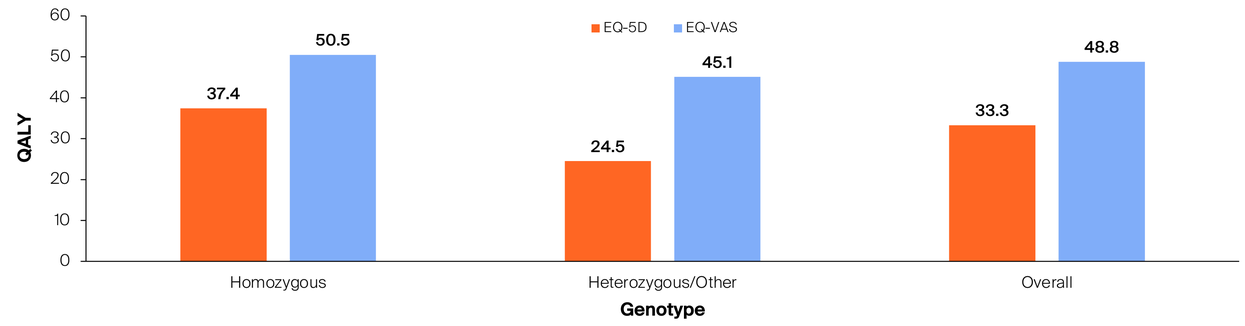
- In the base case analysis, modeled LY for individuals living with LGMD2I/R9 were estimated at 64.3 to 72.6 years depending on genotype, corresponding to an estimated 6- to 14-year reduction compared with the US general population average of 78.4 years (**Figure 2**)

Figure 2. Total life expectancy by genotype (base-case)



- Total QALY were higher using EQ-VAS vs EQ-5D across all genotypes (overall: 48.8 vs 33.3) (**Figure 3**)

Figure 3. Total QALY by utility source



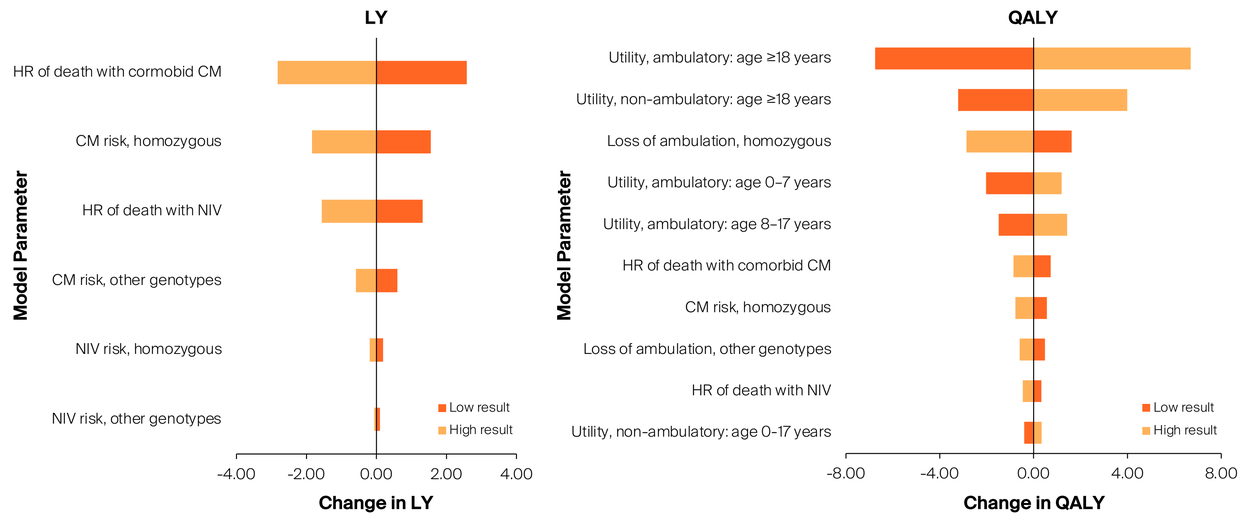
- Lifetime direct medical costs were substantial, with total per-person costs ranging from $2.81 to $3.25 million, with the highest costs observed among individuals with heterozygous/other *FKRP* variants due to earlier loss of ambulation (**Table 1**)

Table 1. Total lifetime direct medical costs by genotype (base case)

	Costs (range)		
Genotype	**Ambulatory**	**Non-ambulatory**	**Total**
Homozygous	$1,974,332 ($1,911,000–$2,038,000)	$877,669 ($771,000–$984,000)	**$2,852,001 ($2,682,000–$3,022,000)**
Heterozygous or Other	$876,358 ($856,000–$897,000)	$2,473,260 ($2,179,000–$2,767,000)	**$3,349,618 ($3,035,000–$3,664,000)**
Overall (weighted average)	$1,621,540 ($1,572,000–$1,671,000)	$1,390,351 ($1,223,000–$1,557,000)	**$3,011,891 ($2,795,000–$3,229,000)**

- In one-way sensitivity analysis, total life expectancy was most sensitive to cardiomyopathy-related mortality (change up to 5.4 LY), whereas total quality-adjusted life expectancy was most sensitive to adult ambulatory utility values (change up to 13.5 QALY) (**Figure 4**)

Figure 4. One-way sensitivity analysis



CONCLUSIONS

- LGMD2I/R9 is associated with substantial reductions in both LY and QALY, with outcomes and lifetime burden varying by genotype
- Reduced life expectancy is driven primarily by cardiomyopathy-related mortality, while loss of ambulation is the primary driver of reduced QALY
- LGMD2I/R9 is associated with a high lifetime medical cost burden, with higher costs projected among individuals with compound heterozygous or other *FKRP* genotypes due to earlier loss of ambulation
- Results align with patterns observed in other muscular dystrophies, supporting model assumptions and highlighting the relative disease burden of LGMD2I/R9

LIMITATIONS

- Results may not fully capture real-world disease heterogeneity, as they depend on structural assumptions and parameter inputs

STRENGTHS

- A structured lifetime health-state model allowed synthesis of multiple data sources to estimate long-term survival, QALY, and costs in the absence of comprehensive longitudinal data

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ABBREVIATIONS: CM, cardiomyopathy; EQ-5D, EuroQol 5-Dimension questionnaire; EQ-VAS, EuroQol Visual Analogue Scale; HR, hazard ratio; HRQoL, health-related quality of life; LGMD, limb-girdle muscular dystrophy; LGMD2I/R9, limb-girdle muscular dystrophy type 2I/R9; LY, life-years; NIV, noninvasive ventilation; QALY, quality-adjusted life-years; US, United States; USD, United States dollars; wc, wheelchair

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DISCLOSURES: C Villa is a full-time employee of the Cincinnati Children's Hospital Medical Center. **L Sun, D Veenstra, and L Bloudek** are full-time employees of Curta, Inc. **K Bartley** is a full-time employee and shareholder of BridgeBio Pharma, Inc., and a shareholder of Roche. **A Talaga** is a full-time employee and shareholder of BridgeBio Pharma, Inc. **D Saadé, M Staron-Ehlinger, and K Mathews** are full-time employees of the University of Iowa Carver College of Medicine.

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