COST-EFFECTIVENESS ANALYSIS OF GENETIC TESTING OF FIRST-DEGREE RELATIVES AT RISK OF SUDDEN CARDIAC DEATH DUE TO GENE-RELATED CARDIOPATHIES IN SPAIN: PRELIMINARY RESULTS

Fernández I[1], García-Pavía P[1], Ripoll T[2], Boldeanu A[3], Gracia A[3], Ramírez de Arellano A[3], Paz S[4] Lizán L[4], Salas E[5]

[1]Unidad de Miocardiopatías, Servicio de Cardiología, Hospital Universitario Puerta de Hierro, Madrid, Spain; [2]Unidad de Cardiopatías Familiares y Genéticas, Servicio Cardiología, Hospital Son Llàtzer, Palma de Mallorca, Spain; [3]Ferrer Grupo, Barcelona, Spain; [4]Outcomes'10, Castellón, Spain.; Gendiag , [5]Barcelona, Spain.

BACKGROUND

- Family members of patients with established inherited cardiopathies may be carriers of the causative mutation and be at risk of sudden cardiac death (SCD)[1]
- Genetic testing could prevent SCD in asymptomatic first-degree relatives of patients with established inherited cardiopathies[2].

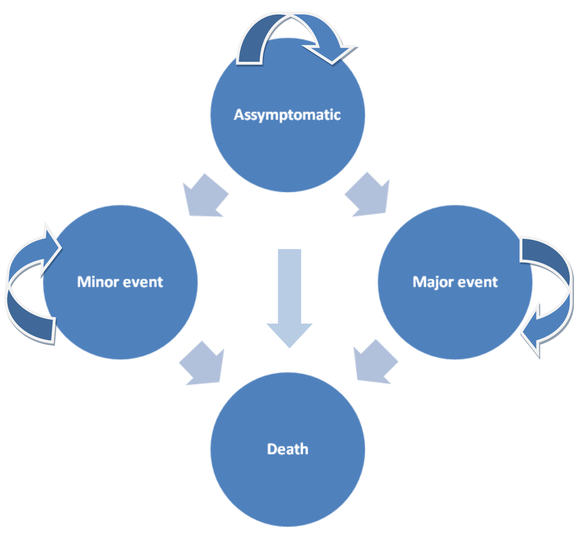
OBJECTIVES

- The objective is to estimate the cost-effectiveness of conducting genetic testing in first-degree relatives of patients with: 1. **Hypertrophic Cardiomyopathy** (HCM); 2. **Arrhythmogenic Right Ventricular Cardiomyopathy** (ARVC); 3. **Long-QT Syndrome** (LQTS); 4. **Brugada Syndrome** (BrS); 5. **Catecholaminergic Polymorphic Ventricular Tachycardia** (CPVT) in Spain.

METHODS

- A Markov model was developed to determine the **cost per life-year gained (LYG**) and **per symptom-free years (SFY**) gained of conducting genetic testing in first-degree relatives at risk of SCD due to gene-related cardiopathies compared to real clinical practice (with no genetic testing).
- The target population was defined as **hypothetical cohorts of 1,000 patients** (a cohort per cardiopathy) **followed over their lifetime**.
- Four health states were defined as follows: 1. Asymptomatic; 2. Minor events (palpitations, dizziness, fatigue, chest pain, dyspnea) 3. Major events (syncope, aborted SCD); and 4. Death (figure 1)
- The analysis was conducted from the **Spanish National Health System** (NHS) perspective. Only direct costs were taken into account. Future costs and effects were discounted at a 3% rate per year. All costs referred to €,2012.

Figure 1: Markov model



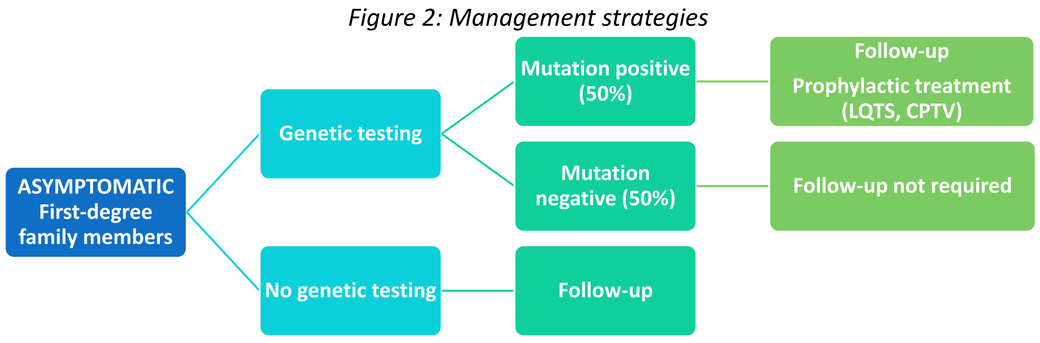
- It was assumed that **patients would enter the model at age 18 years as asymptomatic individuals**, and every year, they could either remain in their current health state or move to a different one.
- Probabilities of transitions among health states (base case scenario) are summarized in Table 1. It was conceived that pharmacological treatment and Implantable Cardioverter Desfibrilator (ICD) would reduce the probabilities of minor and major events, respectively. Data were derived from relevant trials and registries, and complemented the experts' opinion in case of insufficient data.

Table 1: Transition probabilities of Markov model

Probability	HCM	ARVC	LQTS	BrS	CPTV
Annual probability of minor event	1.50%	6.25%	5.00%	0.10%	1.00%
Annual probability of major event	1.00%	11.00%	0.80%	0.50%	4.12%
Annual probability of SCD in patients with minor event or asymptomatic	1.00%	1.67%	0.50%	0.50%	3.13%
Annual probability of SCD in patients with major event	5.30%	9.00%	8.50%	4.80%	8.50%
Probabilities reduction due to pharmacologic al treatment	74.00%	50.00%	57.50%	50.00%	55.00%
Probabilities reduction due to ICD	90.00%	90.00%	90.00%	95.00%	90.00%

- It was also assumed that **asymptomatic patients with negative mutations did not require follow-up** while those with positive mutations would require it. Although those with LQTS or CPVT would receive prophylactic treatment. All patients with no genetic testing would require follow-up (Figure 2).

Figure 2: Management strategies



- Patients with minor events required follow-up and pharmacological treatment. In case of major events an ICD was also used.
- Table 2 describes the probabilities of identifying gene-related cardiopathies with clinical screening alone; of identifying a mutation within an index case; and the prevalence of mutations in first-degree family members.

Table 2: Probabilities (%) of identifying patients at risk of SCD

Data	HCM	ARVC	LQTS	BrS	CPTV
Probability of identifying cardiopathy with clinical screening	70%	50%	60%	20%	40%
Probability of identifying mutation in the index case	65%	60%	78%	25%	65%
Prevalence of mutation in family members of index case with diagnosis	50%	50%	50%	50%	50%

- The corresponding use of resources for diagnosis, follow-up and treatment were estimated. Costs were calculated by multiplying the number of resource items consumed (expert opinion) by the unit costs (local databases) of resources. The costs data inputted to the model is presented in Table 3.

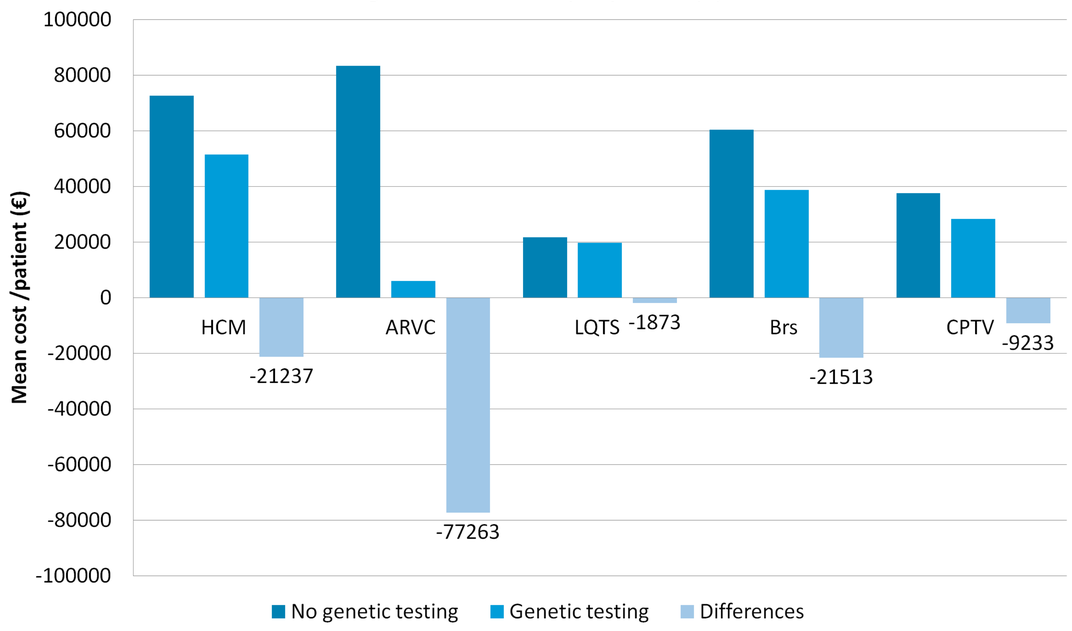
Table 3: Annual cost per patient (€)

Annual cost per patient	HCM (€)	ARVC (€)	LQTS (€)	BrS (€)	CPTV (€)
Diagnosis	279	646	496	568	470
Follow-up symptomatic patients (major and minor)	306.9	537.1	496.3	849.1	470.4
Follow-up asymptomatic patients	219.8	515.7	496.3	849.1	470.4
Treatment major symptoms	21,055.1	17,201.6	14,940.0	23,677.2	14,940.0
Treatment minor symptoms	4,188.9	793.9	85.8	0.0	85.8
Treatment asymptomatic patients with positive mutation (LQTS. TVPC)	0.0	0.0	85.8	0.0	42.9

RESULTS

- The **mean cost per patient** when the genetic test was conducted compared to usual practice was € 51,374 vs. € 72,611 for HCM, € 58,454 vs. € 80,337 for ARVC, € 20,575 vs. € 21,659 for LQTS, € 38,005 vs. € 60,307 for BrS, and 28,286 vs. € 37,519 for CPTV, respectively. Figure 3 illustrates the mean cost per patient for both comparators and the **difference in costs for each gene-related cardiophaty**.

Figure 3: Mean cost per patient (€)



- **For LQTS and CPTV, genetic testing implied 0.96 and 0.04 SFY increase, and 0.01 and 0,04 LYG, respectively, per patient compared to clinical practice**. These variables remained unchanged for HCM, ARVC and BrS.
- **Genetic testing was more effective and less costly** (superior) **for LQTS and CPTV**.
- **For HCM, ARVC and BrS it was almost equally effective and less costly** (dominant) than usual practice (Table 4):

Table 4: Incremental cost-effectiveness ratio (ICER)

Cardiopathy	ICER (€/SFY)	ICER(€/LYG)
HCM	Dominant	Dominant
ARVC	Dominant	Dominant
LQTS	**-1,941 (Superior)**	**-149,965 (Superior)**
Brs	Dominant	Dominant
CPTV	**-260,888 (Superior)**	**-125,385 (Superior)**

- **Probabilistic sensitivity analyses confirmed the consistency of results**. Scatter plot diagrams for LQTS (Figure 4) and CPTV (Figure 5) show that genetic testing could provide better clinical results at lower costs than current clinical practice with no genetic testing.

Figure 4: Scatter plot diagram for LQTS

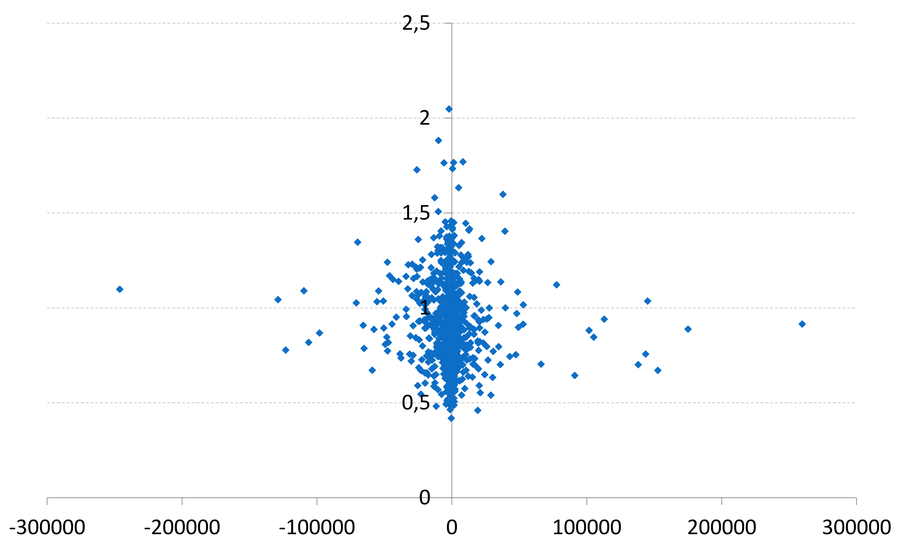
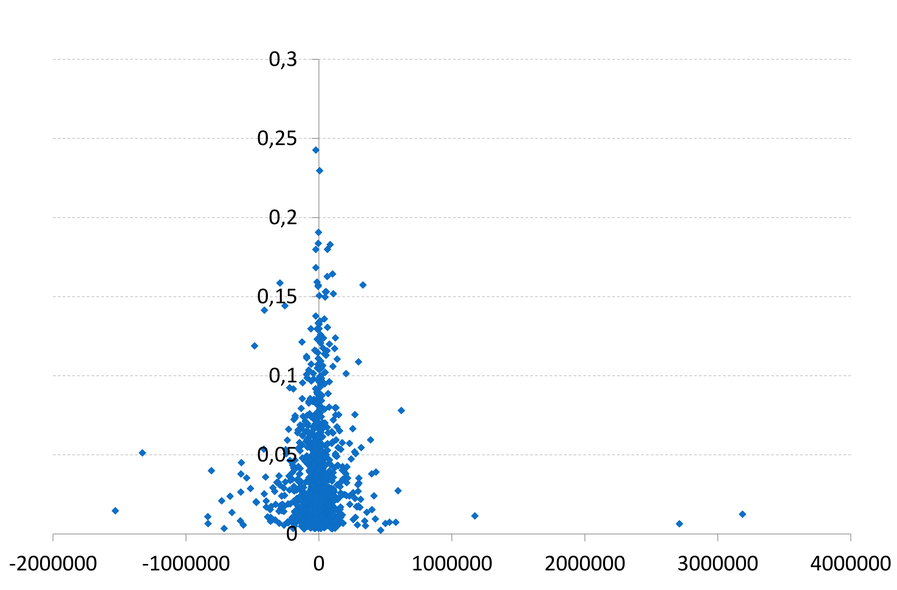


Figure 5: Scatter plot diagram for CPTV



CONCLUSIONS

- **Compared to current practice only with clinical screening, genetic testing in first-degree relatives at risk of SCD is superior cost-effective for CPTV and LQTS in Spain. For HCM, ARVC and BrS genetic testing is dominant (similar in effectiveness but less costly) due to the population in whom unnecessary follow up is averted.**

REFERENCES

1. Ackerman et al. Heart rhythm 2011;8:1308-1339.
2. ACC/AHA/ESC. Europace 2006;8:746-837.