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[Cost-benefit Analysis]

[Scenario]

Familial Cardiomyopathies(Hypertrophic, Dilated, Restrictive, Arrythmogenic Right Ventricle Dysplasia, Spongiform or Non-Compaction…) and Channelopathies (diseases due to ionic cannel mutations including Long and Short QT Syndrome, Brugada Syndrome, Polymorphic Catecholergic Ventricular Tachycardia, Primary Conduction Disorder, …) include most causes for Sudden Death (SD) in young individuals which are also important factors for SD in older patients. These diseases share a genetic origin (mutations in the inherited material) and they are transmitted with some probability from parents to children, thus being considered familial diseases.

All these conditions are difficult to predict due to their heterogeneous clinical presentation and evolution. They are genetically caused familial illnesses and genetics has already proved very useful in diagnosis, prognosis and therapeutical orientation for patients with these diseases. Genetic diagnosis poses important problems both in its execution and in the interpretation and communication of the results[1-32].

[Scale of the problem]

Estimated prevalence of these diseases:

The prevalence of these illnesses varies between 1/500 and <1/10.000 (MCH) in channelopathies.

- Hypertrophic Cardiomyopathy: 1/500 in the general population, this being a disease with great genetic and clinical heterogenicity, with multiple variants, all of them infrequent (more than 600 different mutations in more than 15 genes associated with the condition). Nowadays, between 5 and 15% carries an implantable defibrillator[8-12].
- Familial Dilated Cardiomyopathy (genetically caused): 1/2.000 – 3.000. More than 200 described mutations in at least 30 different genes. 40-50% family related[13-21].
- Restrictive Cardiomyopathy: <1/5.000. Very high morbimortality, evidence of a genetic base (>10 identified mutations)[1-3,7].
- Arrythmogenic Right Ventricle Dysplasia: 1/2.500 – 3.000. With > 100 mutations in > 5 different genes, with differences in the prognosis. Important morbimortality in young adults (sportsmen)[7,23-26].

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- Non – Compaction Cardiomyopathy: 1/5.000 – 10.000. > 50 mutations in > 10 different genes[1-3,7].
- Brugada Syndrome: 1/200 – 2.000. > 100 different mutations in several genes. High mortality in young adults[3, 4, 7, 27-29].
- Long QT Syndrome: 1/5.000. > 400 identified mutations in > 7 different genes. High mortality rate in children and teenagers[3, 4, 7, 31, 32].
- Short QT Syndrome: < 1/10.000. > 10 identified mutations in several genes. Very high mortality[3, 4, 7].
- Polymorphic Catecholergic Ventricular Tachycardia: < 1/10.000. Multiple mutations identified in one gene. Very high mortality.

[Benefits of genetic diagnosis]

1- Identification of the specific cause of the disease in patients with an established clinical diagnosis:

It allows for a more adjusted prognosis and it optimizes prevention and treatment strategies. It prevents inadequate defibrillator implants in relatives.

Examples:

a- Presence of mutations associated with a high risk of sudden death in young patients. If sudden death is averted these patients have, in many instances, good functional capacity and normal life expectancy. Defibrillator implant has a very high cost – benefit rate in these cases. For example, mutations in the lamin A/C gene in patients with Dilated Cardiomyopathy are associated with 50% of sudden deaths, something that can occur with normal function. The R719Q mutation in MYH7 is associated with the high incidence of sudden death in youngsters. This adequate risk stratification is only possible through early genetic diagnosis of the patient.

b- Identification of double mutations. Between 6 and 10% of patients with Hypertrophic Cardiomyopathy has more than one mutation. These patients face a higher risk and this should be taken into account when monitoring them. When sudden death happens in a patient with more than one mutation assessment of family members has to seriously take into account this fact (risk is much lower in relatives with just one mutation). Genetic diagnosis can prevent inadequate defibrillator implants in these cases. Considering a 6% rate of double mutations and an average of 4 screened relatives, there will be an estimated savings of approximately 2 to 5 defibrillators per 100 diagnosed index cases. The average cost of one diagnosis is 1.500€. With an estimated cost of 50.000€ per defibrillator (including parts, hospital, etc.) genetic diagnosis of Hypertrophic Cardiomyopathy, Dysplasia and Long QT Syndrome would practically pay off that investment with the associated benefit of identifying double mutants.

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2- <u>Confirmation of clinical and differential diagnosis in difficult cases:</u>

Genetic diagnosis might be the only way of solving cases with a complicated differential diagnosis; for example, differentiating between an athlete's heart and Hypertrophic Cardiomyopathy, Dilated Cardiomyopathy or Arrythmogenic Dysplasia. The cost – benefit ratio of a genetic study is higher than the one form periodical repetition of other diagnostic tests. Early identification of a cardiopathy that might result in sudden death has a very high cost – benefit ratio. (Cost – benefit in these cases is adequate when there is clinical suspicion the disease might exist, not in apparently healthy cases or in those with a normal base study).

3- <u>Preclinical or predictive diagnosis in relatives:</u>

When a patient is diagnosed with a familial cardiopathy it is essential to carry out a study of the family that includes, at least, those relatives in the first degree (parents, siblings and children) and if any of them is affected cascade screening should be performed.

The clinical study includes a medical appointment and different complementary test, always comprising an ECG and an Echocardiogram and many times requiring more complex and costly test (magnetic resonance, provocation test, etc.). **A negative "clinical" study of the relatives, mostly in the case of young people, does not exclude the possibility that they might develop the disease later on or that it might have a subclinical form. This requires periodical repetition of clinical studies (every year in youngsters). Because genetic information doesn't change for life, identifying the alteration that provokes the disease might happen before there are any symptoms and, besides that, genetic analysis is only necessary once during a patient's lifetime.**

When the genetic cause of the disease is identified in the index case, the genetic study of family members has a very high cost – benefit rate (the prize of each study in the same family is much lower than that of the index case). Besides, this prevents unnecessary monitoring of non – carriers and it can identify carriers with risk of sudden death that would otherwise go unnoticed (for example, in Long QT there might be a normal QT at rest and sudden death may happen after prescribing QT – prolonging drugs or in hydroelectrolitic unbalance situations).

Example of cost – benefit in relatives: Patient with Hypertrophic Cardiomyopathy who has 3 children between the ages of 12 and 16 with a normal clinical study.

> **Cost of the genetic study:** 1.500€. Percentage with a positive diagnosis: 60% of index cases. Average cost to obtain a positive study in a HCM index case: 2.500€. Cost of testing the 3 children in a positive case: 600€. Total cost of the study: 3.100€.
>
> **Cost of the clinical evaluation of family members without genetic diagnosis:** The estimated cost of a medical appointment with ECG and Echocardiogram: 150€. The 3 children must be tested every year until they are 30 and from then on every 3 – 5 years. Total: 15 checkups x 3 children x 150€ = 6.750€.
>
> **Savings per genetic study:** 3.500€ (not including other frequent test such as Holter, Ergometry, NMR, etc.).

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4- Diagnosis on the cause of one sudden death:

When sudden death happens in a patient with a familial cardiopathy, carrying out a previous genetic diagnosis is essential for the evaluation of the relatives. If no genetic study of the deceased has been done we are forced to carry out a complete familial study and a prolonged monitoring of the young relatives (children and siblings), and that is frequently the moment when a genetic study is considered. For example, if one family member suddenly dies with Long QT, the genetic study of 3 siblings and 2 children will cost, at least, 7.500€. If we had the genetic diagnosis of the index case (with an average cost of 2.500€, considering the percentage of negative studies), the cost for studying the family members would be 1.000€, thus saving 4.000€. But the most important thing in this case is the peace of mind the family members would get when there is consistent evidence of the lack of risk, or when early detection of those relatives who can suffer sudden death is possible.

[Other meaningful facts]

- Health in Code has a clinical team of expert cardiologists who individually advises the clinical team, establishing the guidelines for a more effective genetic diagnosis for each particular patient.
- Health in Code has a database with information about more than 14.000 individuals worldwide. This provides the clinical team with access to relevant information for their practice that otherwise would be impossible to get or very difficult to effectively analyze.
- Health in Code presently Works with 25 Spanish hospitals in the genetic diagnosis of patients with clinical suspicion of this type of diseases, thus both helping to improve the quality of the patient's care and giving the hospital and the clinical time a solid basis for their clinical approach.

[Summary]

- The prize of diagnostic services provided by Health in Code (an average of 1.000€ for index cases and 200€ for relatives), is similar to many other diagnostic tests normally used in today's medical practice.
- Health in Code provides a complete medial report that:
    - Lets the clinical team access worldwide information in a clear and easily understandable format that would otherwise be impossible to access;
    - Allows an adequate treatment and follow – up of both the patients and their families by correlating the biological cause of the disease with the prognosis and the risk of each case, thus minimizing the appearance of irreversible events;

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- Optimizes the implantation of preventive portable defibrillators, thus reducing the high cost these devices have for the healthcare system.
- Optimizes medical appointments by monitoring only those patients/relatives with a real high risk of developing the disease;
- Positions both the medical team and the hospital as a reference in the adequate handing of these types of pathologies.

- Health in Code provides personalized and continuous assessment to the clinical team that requests it.

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