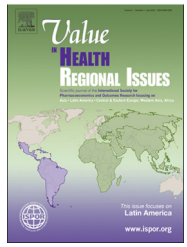
Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/vhri



Cost-Effectiveness Analysis of Diagnosis of Duchenne/Becker Muscular Dystrophy in Colombia

Sara C. Atehortúa, BEcon, MSc[1,2,], Luz H. Lugo, MD, MSc[3,4], Mateo Ceballos, BEcon[2], Esteban Orozco, BEcon[2], Paula A. Castro, BEcon[5], Juan C. Arango, MD, PhD[6], Heidi E. Mateus, MD, MSc[7]*

[1]*Departamento de Economía, Facultad de Ciencias Económicas, Universidad de Antioquia, Medellín, Colombia;* [2]*Grupo de Economía de la Salud, Facultad de Ciencias Económicas, Universidad de Antioquia, Medellín, Colombia;* [3]*Grupo de Rehabilitation en Salud, Facultad de Medicina, Universidad de Antioquia, Medellín, Colombia;* [4]*Clínica Las Américas, Medellín, Colombia;* [5]*Grupo de Epidemiología Clínica, Facultad de Medicina, Universidad de Antioquia, Medellín, Colombia;* [6]*Grupo de Biología y Clínica, Facultad de Medicina, Universidad de Antioquia, Medellín, Colombia;* [7]*Grupo GENIUROS, Escuela de Medicina y Ciencias de la Salud, Universidad del Rosario, Bogotá, Colombia*

A B S T R A C T

Objectives: To determine the cost-effectiveness ratio of different courses of action for the diagnosis of Duchenne or Becker muscular dystrophy in Colombia. **Methods:** The cost-effectiveness analysis was performed from the Colombian health system perspective. Decision trees were constructed, and different courses of action were compared considering the following tests: immunohistochemistry (IHC), Western blot (WB), multiplex polymerase chain reaction, multiplex ligation-dependent probe amplification (MLPA), and the complete sequencing of the dystrophin gene. The time horizon matched the duration of sample extraction and analysis. Transition probabilities were obtained from a systematic review. Costs were constructed with a type-case methodology using the consensus of experts and the valuation of resources from consulting laboratories and the 2001 Social Security Institute cost manual. Deterministic sensitivity and scenario analyses were performed with one or more unavailable alternatives. Costs were converted from Colombian pesos to US dollars using the 2014 exchange rate. **Results:** In the base case, WB was the dominant strategy, with a cost of US $419.07 and a sensitivity of 100%. This approach remains the dominant strategy down to a 98.2% sensitivity and while costs do not exceed US $837.38. If WB was not available, IHC had the best cost-effectiveness ratio, followed by MLPA and sequencing. **Conclusions:** WB is a cost-effective alternative for the diagnosis of patients suspected of having Duchenne or Becker muscular dystrophy in the Colombian health system. The IHC test is rated as the second-best detection method. If these tests are not available, MLPA followed by sequencing would be the most cost-effective alternative.

Keywords: Becker, cost-effectiveness analysis, Duchenne, economic evaluation, immunohistochemistry, MLPA, muscular dystrophy, PCR, sequencing, Western blot.

Introduction

Muscular dystrophy is a group of more than 30 genetic diseases that cause debilitation and progressive degeneration of the muscles, which leads to loss of the patient's functional capacity, decreased quality of life, and mortality at younger ages compared with the general population. Duchenne muscular dystrophy (DMD) and Becker muscular dystrophy (BMD) are the most common, affecting 1 out of every 3,500 births and 1 out of every 20,000 births, respectively [1]. In Colombia, although the exact incidence of DMD is not known, a genetic study found 933 cases of DMD for the 1996 to 2000 period, 962 cases for the 2006 to –2010 period, and an estimated 1030 cases for the 2012 to 2025 period [2]. DMD would be responsible for 51.8 years of life potentially lost over the life expectancy of the patient [2].

Other hereditary diseases that affect the muscles, the nerves, or the neuromuscular junction can produce symptoms that are very similar to those seen in muscular dystrophy, but they are caused by different genetic defects. The fact that these symptoms are shared between multiple neuromuscular diseases and the prevalence of sporadic cases in families not previously affected by dystrophy make a quick and timely diagnosis difficult for patients.

For the diagnosis of DMD or BMD, there are histological tests based on the analysis of surgically obtained muscular biopsy tissue. These tests include tissue staining using antibodies marked by immunohistochemistry (IHC) and the quantification of proteins using techniques such as Western blot (WB) [3,4]. Molecular testing techniques are also available, such as polymerase chain reaction (PCR), which amplifies multiple exons (known

Conflicts of interest: The authors have indicated that they have no conflicts of interest with regard to the content of this article.

* *Address correspondence to:* Sara C. Atehortúa, Departamento de Economía, Facultad de Ciencias Económicas, Universidad de Antioquia, Calle 67, 53-108, Oficina 13-114, Medellín 050010, Colombia.

E-mail: sara.atehortua@udea.edu.co.

2212-1099$36.00 – see front matter © 2018 Published by Elsevier Inc. on behalf of International Society for Pharmacoeconomics and Outcomes Research (ISPOR).

https://doi.org/10.1016/j.vhri.2017.10.003

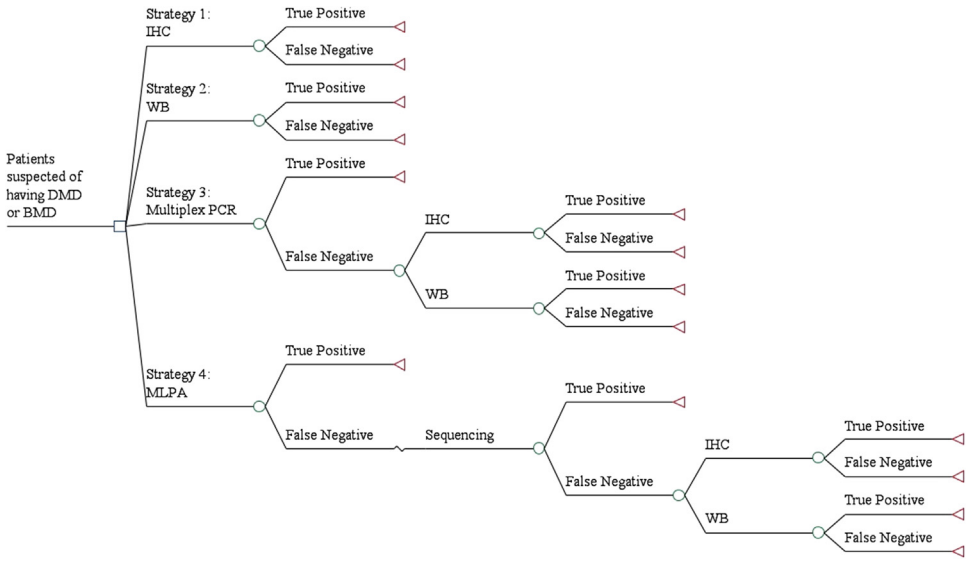


Fig. 1 – Decision model for diagnostic strategies. BMD, Becker muscular dystrophy; DMD, Duchenne muscular dystrophy; IHC, immunohistochemistry; MLPA, multiplex ligation-dependent probe amplification; PCR, polymerase chain reaction; WB, Western blot.

as multiplex PCR), multiplex ligation-dependent probe amplification (MLPA), and the complete sequencing of the dystrophin gene [5–8].

Molecular tests, on the basis of the analysis of DNA extracted from peripheral blood, can be performed without muscular biopsy, which means that an invasive and unpleasant procedure for patients can be avoided. These tests, however, cannot detect mutations in all cases, which makes it necessary to perform biopsies in cases in which the molecular test results are inconclusive [1,3,9].

There are currently no reported economic studies to determine the most cost-effective diagnostic strategy in patients with DMD or BMD. In Colombia, the most used techniques are multiplex PCR and MLPA, although they are not highly sensitive, and to a lesser extent, IHC. WB is not commonly used for diagnosis. This study attempts to determine the most efficient strategy for diagnosing DMD or BMD from the perspective of the health system.

Methods

A cost-effectiveness analysis was conducted from a health services perspective, which considered direct medical costs. The population of interest included patients with suspected DMD or BMD on the basis of electromyography suggestive with signs of instability membrane, a high value of creatine phosphokinase (10306.7 ± 6658.5), and clinical signs and symptoms [10]. We excluded patients with a family history of dystrophies for which the mutation had already been studied, patients with a diagnosis of carriers, and prenatal patients being treated.

The diagnostic techniques considered were IHC, which includes the staining analysis and the open muscular biopsy from which the tissue necessary for performing the tests is extracted; WB, which includes quantification of proteins from the tissue extracted in the biopsy; multiplex PCR, the 32-exon test that was considered because it is the only test for which there is local evidence; MLPA, covering the 79 exons of the dystrophin gene; and complete gene sequencing, including the standard method. The tests known as next-generation sequencing were not considered [11,12] because at the time of the study, they were not available in the country.

The molecular tests are not invasive and the sample extraction and analysis are relatively simple compared with those of the IHC and WB techniques. Nevertheless, the IHC and WB methods continue to be the criterion standard in the studies identified in the literature, for which they are considered as confirmatory tests. Thus, for a patient for whom a molecular test was performed, it is recommended that their diagnosis be confirmed using the IHC or WB when the result is negative. Complete gene sequencing is always considered after MLPA when this result is negative.

For these reasons, two decision trees are constructed in which true-positive and false- negative diagnoses are presented. True negatives and false positives were not included because, in the studies identified, all tests have a high enough precision to determine the absence of the disease [13–16].

The first tree (Fig. 1) includes different stepwise courses of action following the decision algorithms from the literature [17–19] and using WB and IHC as confirmatory methods in cases in which the genetic test results are negative. In this model, strategies 1 and 2 make reference to the use of IHC and WB, respectively, as initial tests without having used a molecular test first. Strategy 3 consists of the initial use of multiplex PCR, and in cases in which this test produces a negative result, WB or IHC is used to confirm the disease. Finally, strategy 4 considers MLPA as the initial test followed by sequencing if the result is negative, and if both molecular test results are negative, WB or IHC is used to confirm the disease.

In the second tree (Fig. 2), each diagnostic technique is individually compared without considering confirmatory tests, with the aim of observing their cost effectiveness independently, and when one or more than one test is not available. From here on, when reference is made to *strategy*, this term will be understood as the courses of action that include the confirmatory tests from Figure 1, whereas references to one specific *technique* will refer to only the diagnostic test from Figure 2. Models were constructed using TreeAge Pro 2009® software (TreeAge Software, Inc., Williamstown, MA).

A time horizon of less than 1 year was established. In general, it is expected that the period spanning from the sample collection to the analysis of results does not surpass 1 month. For these reasons, the long term was not modeled and a discount rate was