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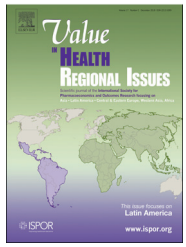

ECONOMIC EVALUATION

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

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ABSTRACT

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

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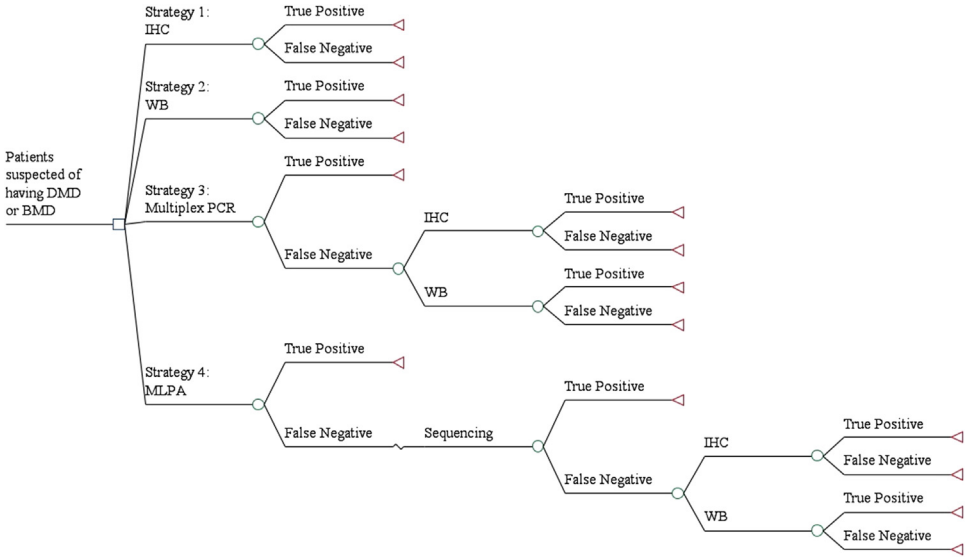

Fig. 1 – Decision model for diagnostic strategies. BMD, Becker muscular dystrophy; DMD, Duchenne muscular dystrophy; IHC, immunohistochemistry; MLPA, multiplex ligation-dependent probe amplification; PCR, polymerase chain reaction; WB, Western blot.

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 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

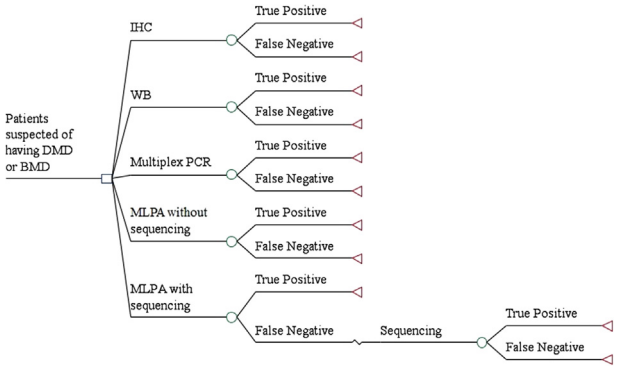

Fig. 2 – Decision model for separate techniques. BMD, Becker muscular dystrophy; DMD, Duchenne muscular dystrophy; IHC, immunohistochemistry; MLPA, multiplex ligation-dependent probe amplification; PCR, polymerase chain reaction; WB, Western blot.

not used. Because no clinical evidence was found to establish a link between the diagnostic tests and a final outcome related to morbidity or mortality, the health outcome was defined as the percentage of correct diagnostics.

To estimate the model transition probabilities, a systematic review of the clinical literature was performed in 2013 in the MEDLINE, Embase, Lilacs, and Bireme databases and was based on the information reported on the Clinical Trials Web page. Medical Subject Headings and free terms associated with the population and the diagnostic strategies analyzed were used in both English and Spanish. General search protocols were developed, and no language, study type, or publication date restrictions were applied.

A total of 443 potentially relevant studies were identified after removing duplicates. On reviewing of titles and abstracts, 355 of these studies were excluded because they did not analyze the patient population or diagnostic alternatives considered, used animal models, or were narrative reviews, case reports, descriptions of techniques, expert consensus reports, or letters to the editor. The remaining 88 articles were reviewed in full text, from which 49 were excluded for the aforementioned reasons. A total of 39 articles were included.

None of the studies identified in the search addressed the operative characteristics of the diagnostic tests. They were all case series aimed at studying the frequency of the presence or absence of the disease in patients suspected. They were also highly heterogeneous in terms of population characteristics, sample selection criteria, and the number of exons analyzed (for multiplex PCR). Many of the molecular test studies focused on the type of mutation found and did not differentiate between patients with DMD and those with BMD, implying that it was impossible to perform an analysis for each dystrophy separately.

Because of the high heterogeneity of the evidence, methodological weaknesses of the study and low compatibility with other studies were considered as additional exclusion criteria. Factors such as sample size (10 patients or more), clear and standardized patient classifications, the inexistence of a relative or family member in the sample, and the use of comparisons as complete as possible (not just clinical criteria as a standard) were considered inclusion criteria. Using these criteria, 23 studies were chosen to calculate the sensibility and specificity of the alternatives [8,13–34], which are presented in Table 1. The true positive and false negative were considered as the clinical inputs in the two proposed models.

The few studies that incorporated controls in the analysis included healthy patients or patients with other types of dystrophinopathies [13–16]. These studies reported negative results of disease in all the controls, which implies that the tests have a specificity of 100%.

Only one study presented conditional probabilities for IHC when multiplex PCR result was negative [14] or when the result from MLPA followed by sequencing was negative [16]. Nevertheless, these data were not considered for the analysis because of the small sample size and the way in which patients were considered to be eligible for IHC after molecular tests. Thus, the data for WB and IHC after a negative result from any of the molecular tests were assumed to be the same (Table 1).

The only study in Colombia that analyzed the frequency of deletions with multiplex PCR for 32 exons [8,20] found 32% within and outside of hot spots for patients with DMD or BMD, a finding that is similar to others reported in Latin American. Despite the fact that this research has limitations related to lack of a criterion standard and the possible inclusion of other types of dystrophies, it was used for the base case because it was the only evidence available on a local level. The frequency of international studies was used in the sensitivity analysis.

In addition, we determined the percentage of patients for whom the disease was confirmed with IHC or with WB when the molecular test results were negative. No studies were found that quantified the frequency of use; thus, it was assumed to be 50% and was modified in the sensitivity analysis.

For estimation of costs, a search of national institutional databases was initially conducted and no useful related information was found. Therefore, estimates were requested directly from the six laboratories in the country. For WB, a quote from a not-for-profit laboratory associated with a university research group was received (the only laboratory where it was available). Information for IHC was obtained from a not-for-profit private foundation laboratory. Information on the price of multiplex PCR was received from a private laboratory (this did not correspond to the 32-exon test because it is not available on the market), and the average prices of MLPA and complete gene sequencing were obtained from the quotes sent by three private laboratories. The average prices of these diagnostic tests are presented in Table 2.

Table 1 – Diagnostic performance of the alternatives used in the models.

Diagnostic test	True positive	False negative	Sensitivity	Specificity	Reference
WB	1	0	1	1	[14,20,29]
IHC	0.995	0.995	0.995	1	[13–15,20,27,29,31]
Multiplex PCR (base case)	0.3226	0.6774	0.3226	–	[8,19]
Multiplex PCR (international studies)	0.5966	0.4034	0.5966	1	[13,21,24,28,30]
MLPA	0.6844	0.3156	0.6844	1	[12,22,23,25,26,28,32,33]
Sequencing	0.9091	0.0909	0.9091	–	[23,25,32]

IHC, immunohistochemistry; MLPA, multiplex ligation-dependent probe amplification; PCR, polymerase chain reaction; WB, Western blot.

Table 2 – Average costs of the diagnostic tests.

Test	Average price (US $)	Inputs (sample and reading) (US $)	Total cost (US $)
Multiplex PCR	174.96	8.50	183.46
WB	327.93	91.14	419.07
IHC	889.70	91.14	980.85
MLPA	918.96	8.50	927.46
Complete gene sequencing	3737.93	8.50	3746.42

IHC, immunohistochemistry; MLPA, multiplex ligation-dependent probe amplification; PCR, polymerase chain reaction; WB, Western blot.

Subsequently, other resources were identified to perform the tests. In the case of multiplex PCR, MLPA, and sequencing, only a sample of blood was needed. For the application of IHC and WB, the 2001 Social Security Institute Manual was consulted to establish the cost of muscular biopsy testing. The presurgical and preanesthesia appointments (required for children), the actual muscular biopsy, and an appointment after the surgery with a specialized physician for the analysis of results were considered. All values obtained from this manual were adjusted with an additional 30%, as suggested by the Colombian methodological guide for economical evaluations [35].

With respect to the decision rule, in the scenario in which a strategy or a technique offers the greatest number of cases correctly diagnosed at the lowest price (a dominant), we concluded that it has the better cost-effectiveness ratio. Nevertheless, in the scenario in which the strategy or technique with the greatest number of cases correctly diagnosed does not have the lowest price (not dominant), the incremental cost-effectiveness ratio (ICER), comparing each alternative to the less costly (common baseline), was used as a method for determining the most cost-effective strategy.

All values in Colombian pesos were converted to US dollars using an average exchange rate representative of the 2014 market (US $1 = Col$ 2000.44).

Finally, to incorporate uncertainty in the models, one-way deterministic analysis was performed. The first modified the cost of the WB test, the frequency of WB or IHC use as a disease confirmatory test, and the probability of finding a positive result with multiplex PCR and MLPA. The second was constructed for modifying probabilities of identifying mutations and costs of the MLPA and sequencing tests. It was not possible to perform a probabilistic sensitivity analysis, because the construction of probability distributions with few sources of information is not adequate.

Results

In the base case, for the analysis of courses of action presented in Figure 1, strategy 2 is found to be dominant. This approach is the most sensitive course of action for detecting the disease (100%), followed by strategy 4 (99.99%). Similarly, in terms of costs, strategy 2 has the lowest expected cost, followed by strategy 3 (Table 3).

WB reports a sensitivity of 100% in the international literature, but it could be lower in Colombia because of issues with the technique, the lack of standardization, and the training of the medical personnel involved in taking samples. The sensitivity analysis shows that when the sensitivity of WB is less than 98.2%, strategy 3 achieves the best cost-effectiveness ratio (see Supplemental Materials found at https://doi.org/10.1016/j.vhri.2017.10.003), overcoming strategy 2. Although multiplex PCR has a very low sensitivity (32.26%), the high sensitivities of the WB and IHC confirmatory tests make it possible that the expected effectiveness of strategy 3 is higher.

When modifying the cost of the WB technique, it is observed that strategy 2 is dominant as long as the price is lower than US $837.38. Once the price is higher than this value, strategy 3 would have the best cost-effectiveness ratio. The same strategy becomes cost-effective if the sensitivity of the multiplex PCR is greater than 70%, a value that is higher than the reported average of 59.66% from international studies. Finally, modifying the frequency of use of the WB and IHC techniques as confirmatory tests does not affect the dominance of strategy 2, even when considering extreme values of 0% and 100% (see Supplemental Materials found at https://doi.org/10.1016/j.vhri.2017.10.003).

In the analysis presented in Figure 2 in which the techniques are considered separately, the ICER for WB compared with that of multiplex PCR was calculated to be US $347.82 per correct diagnosis. For the cases when WB is not available, the technique with the best cost-effectiveness ratio is IHC, with an ICER compared with that of multiplex PCR of US $1185.88 per correct diagnosis. Multiplex PCR as a *technique* has the worst effectiveness. When considering the scenario in which WB and IHC are not available, MLPA and sequencing have the best cost-effectiveness ratio, with an ICER compared with that of multiplex PCR of US $2969.54 per correct diagnosis (Table 3).

When conducting the sensitivity analysis without considering WB, for IHC to no longer have the best cost-effectiveness ratio, its price would have to be greater than US $2160.00. Once this value was exceeded, the most cost-effective technique is MLPA followed by sequencing. Finally, for the multiplex PCR to have the best cost-effectiveness ratio, its sensitivity should be greater than 97%, a value much higher than those reported for Colombia (32%) and from the international literature (59.66%) (see Supplemental Materials found at https://doi.org/10.1016/j.vhri.2017.10.003).

Conclusions

The results of this study suggest that WB is a cost-effective strategy for diagnosing DMD or BMD. As an alternative, in cases in which WB is not available, the strategy with the best cost-effectiveness ratio is IHC. There could, however, be situations in which the implementation of these tests is not possible because of the patient refusing to undergo an invasive surgical procedure, or the lack of infrastructure and/or medical personnel trained in the extraction, treatment, and management of the samples necessary to adequately perform the tests. In these situations, the MLPA technique, followed by sequencing in negative cases, is the most cost-effective strategy, over multiplex PCR or MLPA alone.

This economic analysis attempted to incorporate all the evidence available regarding a subject around which little clinical and economical evidence exists. To the authors' knowledge, no economic evaluation exists in the published literature that concerns the histological and molecular diagnosis of DMD or BMD.

The primary limitations of our study are related with the difficulty in finding high-quality data. First, the analysis was

Table 3 – Cost-effectiveness results.

Alternative	Costs (US $)	Incremental cost (US $)	Effectiveness	Incremental effectiveness	Cost per correct diagnosis (US $)	ICER (US $)
			Strategies			
Strategy 2: WB	419.07		100.00%		419.07	
Strategy 3: Multiplex PCR	657.61	238.54	99.83%	−0.17%	658.73	Dominated
Strategy 1: IHC	980.85	561.78	99.50%	−0.50%	985.78	Dominated
Strategy 4: MLPA	2129.91	1710.84	99.99%	−0.01%	2130.07	Dominated
			Techniques			
Multiplex PCR	183.46		32.30%		568.69	
WB	419.07	235.61	100.00%	67.74%	419.07	347.82
MLPA	927.46	744	68.40%	36.18%	1355.14	2056.38 Dominated
IHC	980.85	797.39	99.50%	67.24%	985.78	1185.88 Dominated
MLPA + sequencing	2109.83	1926.37	97.10%	64.87%	2172.15	2969.54 Dominated

ICER, incremental cost-effectiveness ratio; IHC, immunohistochemistry; MLPA, multiplex ligation-dependent probe amplification; PCR, polymerase chain reaction; WB, Western blot.

limited to an intermediate outcome because clinical data did not allow us to use a final health outcome, more relevant for the patient and the decision maker.

Second, it was not possible to include measures related to quality of life and patient preferences because of the lack of relevant data and the difficulty in finding a significant sample of patients. Because WB and IHC are invasive, patients and their families could have less of a preference for them, but patients could also report a preference for these because they are confirmatory tests that avoid uncertainty about their condition. In fact, it is difficult to quantify positive and negative indirect effects that may be relevant when evaluating genetic diagnostic tests. The literature indicates that genetic diagnosis can generate negative psychological consequences for the patient and their family (i.e., fear of discrimination, anxiety, rage, and isolation). Nevertheless, they can also present positive psychological effects related to the reduction of uncertainty [36–38].

Third, possible adverse effects of the procedure and medications administered in surgery when the muscular biopsy was taken were not considered. For example, general anesthesia always presents risks for the patient; nevertheless, no studies exist that identify whether patients with DMD or BMD can have significant adverse effects beyond the general population. Skin biopsy is a method still in the experimental phase but promises great benefits for patients because it would allow WB or IHC to be performed as a noninvasive procedure [39].

Fourth, because there are a few laboratories in the Colombian market, they have a considerable market power to set prices. Even more, they can discriminate and set different prices for different types of insurers or patients. In our analysis we cannot consider these usual particularities in a market in which there are few suppliers.

Because the analysis was performed from the Colombian health system perspective, indirect costs were not taken into account. A priori, it would be expected that different factors related to the disease would involve a large amount of out-of-pocket costs for the patient and the patient's family [40–42]. For example, if more techniques are practiced on the patient or if the patient has an incorrect or late diagnosis, he and his family would pay higher transport and out-of-pocket costs. The measurement of the indirect costs incurred in the diagnosis of DMD and BMD in Colombia is a focus of future research that would enrich the results found in this article.

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Supplemental Materials

Supplemental material accompanying this article can be found in the online version as a hyperlink at https://doi.org/10.1016/j.vhri.2017.10.003 or, if a hard copy of article, at www.valueinhealthjournal.com/issues (select volume, issue, and article).

REFERENCES

[1] Burgunder JM, Schöls L, Baets J, et al. EFNS guidelines for the molecular diagnosis of neurogenetic disorders: motoneuron, peripheral nerve and muscle disorders. Eur J Neurol 2011;18:207–17.
[2] Bernal J, Suárez F. La carga de la enfermedad genética en Colombia, 1996–2025. Univ Med 2008;49:16.
[3] Na SJ, Kim WJ, Kim SM, et al. Clinical, immunohistochemical, Western blot, and genetic analysis in dystrophinopathy. J Clin Neurosci 2013;20:1099–105.
[4] Paciello O, Papparella S. Histochemical and immunohistological approach to comparative neuromuscular diseases. Folia Histochem Cytobiol 2009;47:143–52.
[5] Itto AB, Hamzi K, Bellayou H, et al. Evolution of molecular diagnosis of Duchenne muscular dystrophy. J Mol Neurosci 2013;50:314–6.
[6] Lai PS, Tay JS, Low PS, et al. Deletion analysis of DMD/BMD children in Singapore using multiplex polymerase chain reaction (PCR) technique. J Trop Pediatr 1992;38:224–7.
[7] Yuge L, Hui L, Bingdi X. Detection of gene deletions in Chinese patients with Duchenne/Becker muscular dystrophy using CDNA probes and the polymerase chain reaction method. Life Sci 1999;65:863–9.
[8] Silva C, Fonseca D, Restrepo C, et al. Deleciones en el gen de la distrofina en 62 familias colombianas: correlación genotipo fenotipo para la distrofia muscular de Duchenne y Becker. Colomb Med 2004;35:7.
[9] Morandi L, Mora M, Confalonieri V, et al. Dystrophin characterization in BMD patients: correlation of abnormal protein with clinical phenotype. J Neurol Sci 1995;132:146–55.
[10] Ministerio de Salud y Protección Social. Guía de práctica clínica para la detección temprana, atención integral, seguimiento y rehabilitación de pacientes con diagnóstico de distrofia muscular. N°37. 1°Ed. Bogotá. 2013. Available from: http://gpc.minsalud.gov.co/guias/Documents/Distrofia%20Muscular/GPC-DM%2037%20para%20usuarios.pdf. [Accessed December 20, 2015].
[11] Lim BC, Lee S, Shin JY, et al. Genetic diagnosis of Duchenne and Becker muscular dystrophy using next-generation sequencing technology: comprehensive mutational search in a single platform. J Med Genet 2011;48:731–6.
[12] Vasli N, Böhm J, Le Gras S, et al. Next generation sequencing for molecular diagnosis of neuromuscular diseases. Acta Neuropathol 2012;124:273–83.
[13] Chen WJ, Lin QF, Zhang QJ, et al. Molecular analysis of the dystrophin gene in 407 Chinese patients with Duchenne/Becker muscular dystrophy by the combination of multiplex ligation-dependent probe amplification and Sanger sequencing. Clin Chim Acta 2013;423:35–8.
[14] Freund AA, Scola RH, Arndt RC, et al. Duchenne and Becker muscular dystrophy: a molecular and immunohistochemical approach. Arq Neuropsiquiatr 2007;65:73–6.
[15] Nicholson LV, Johnson MA, Gardner-Medwin D, et al. Heterogeneity of dystrophin expression in patients with Duchenne and Becker muscular dystrophy. Acta Neuropathol 1990;80:239–50.
[16] Wang Q, Yang X, Yan Y, et al. Duchenne or Becker muscular dystrophy: a clinical, genetic and immunohistochemical study in China. Neurol India 2011;59:797–802.
[17] Bushby K, Finkel R, Birnkrant DJ, et al. Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and pharmacological and psychosocial management. Lancet Neurol 2010;9:77–93.
[18] Abbs S, Tuffery-Giraud S, Bakker E, et al. Best practice guidelines on molecular diagnostics in Duchenne/Becker muscular dystrophies. Neuromuscul Disord 2010;20:422–7.
[19] Juan-Mateu J, Gallano P, Trujillo-Tiebas MJ, AEGH/CIBERER Group. Recommendations of good practices for the genetic diagnosis of Duchenne and Becker muscular dystrophies [in Spanish]. Med Clin (Barc) 2012;139:307–12.
[20] Fonseca D, Mateus H, Contreras N, et al. Análisis de deleciones en 15 exones situados dentro y fuera del hot spot mutacional del gen de la distrofina en pacientes con distrofia muscular de Duchenne. Rev Cienc Salud 2009;7:7.
[21] Bushby KM, Gardner-Medwin D, Nicholson LV, et al. The clinical, genetic and dystrophin characteristics of Becker muscular dystrophy, II: correlation of phenotype with genetic and protein abnormalities. J Neurol 1993;240:105–12.
[22] Dastur RS, Gaitonde PS, Khadilkar SV, Nadkarni JJ. Becker muscular dystrophy in Indian patients: analysis of dystrophin gene deletion patterns. Neurol India 2008;56:374–8.
[23] Hwa HL, Chang YY, Chen CH, et al. Multiplex ligation-dependent probe amplification identification of deletions and duplications of the Duchenne muscular dystrophy gene in Taiwanese subjects. J Formos Med Assoc 2007;106:339–46.
[24] Hwa HL, Chang YY, Huang CH, et al. Small mutations of the DMD gene in Taiwanese families. J Formos Med Assoc 2008;107:463–9.
[25] Janssen B, Hartmann C, Scholz V, et al. MLPA analysis for the detection of deletions, duplications and complex rearrangements in the dystrophin gene: potential and pitfalls. Neurogenetics 2005;6:29–35.
[26] Kohli S, Saxena R, Thomas E, et al. Gene changes in Duchenne muscular dystrophy: comparison of multiplex PCR and multiplex ligation-dependent probe amplification techniques. Neurol India 2010;58:852–6.
[27] Lai KK, Lo IF, Tong TM, et al. Detecting exon deletions and duplications of the DMD gene using multiplex ligation-dependent probe amplification (MLPA). Clin Biochem 2006;39:367–72.
[28] Muntoni F, Mateddu A, Cianchetti C, et al. Dystrophin analysis using a panel of anti-dystrophin antibodies in Duchenne and Becker muscular dystrophy. J Neurol Neurosurg Psychiatry 1993;56:26–31.
[29] Murugan S, Chandramohan A, Lakshmi BR. Use of multiplex ligation-dependent probe amplification (MLPA) for Duchenne muscular dystrophy (DMD) gene mutation analysis. Indian J Med Res 2010;132:303–11.
[30] Nicholson LV, Johnson MA, Bushby KM, et al. Integrated study of 100 patients with Xp21 linked muscular dystrophy using clinical, genetic, immunochemical, and histopathological data, part 1: trends across the clinical groups. J Med Genet 1993;30:728–36.
[31] Sura T, Eu-ahsunthornwattana J, Pingsuthiwong S, Busabaratana M. Sensitivity and frequencies of dystrophin gene mutations in Thai DMD/BMD patients as detected by multiplex PCR. Dis Markers 2008;25:115–21.
[32] Werneck LC, Scola RH, Maegawa GH, Werneck MC. Comparative analysis of PCR-deletion detection and immunohistochemistry in Brazilian Duchenne and Becker muscular dystrophy patients. Am J Med Genet 2001;103:115–20.
[33] Yang J, Li SY, Li YQ, et al. MLPA-based genotype-phenotype analysis in 1053 Chinese patients with DMD/BMD. BMC Med Genet 2013;14:29.
[34] Zeng F, Ren ZR, Huang SZ, et al. Array-MLPA: comprehensive detection of deletions and duplications and its application to DMD patients. Hum Mutat 2008;29:190–7.
[35] Ministerio de la Protección Social; Colciencias; Centro de Estudios e Investigación en Salud de la Fundación Santa Fe de Bogotá; Escuela de Salud Pública de la Universidad de Harvard. Guía Metodológica para el desarrollo de Guías de Atención Integral en el Sistema General de Seguridad Social en Salud Colombiano. Bogotá, Colombia, Ministerio de la ProtecciónSocial- Departamento administrativo de ciencia, tecnología e innovación-Colciencias- 2010.
[36] Assasi N, Schwartz L, Tarride JE, et al. Economic evaluations conducted for assessment of genetic testing technologies: a systematic review. Genet Test Mol. Biomarkers 2012;16:1322–35.
[37] Grosse SD, Wordsworth S, Payne K. Economic methods for valuing the outcomes of genetic testing: beyond cost-effectiveness analysis. Genet Med 2008;10:648–54.
[38] McAllister M, Payne K, Nicholls S, et al. Improving service evaluation in clinical genetics: identifying effects of genetic diseases on individuals and families. J Genet Couns 2007;16:71–83.
[39] Tanveer N, Sharma MC, Sarkar C, et al. Diagnostic utility of skin biopsy in dystrophinopathies. Clin Neurol Neurosurg 2009;111:496–502.
[40] Mushlin AI, Ruchlin HS, Callahan MA. Cost effectiveness of diagnostic tests. Lancet 2001;358:1353–5.
[41] Kemper AR, Wake MA. Duchenne muscular dystrophy: issues in expanding newborn screening. Curr Opin Pediatr 2007;19:700–4.
[42] Jarrett J, Mugford M. Genetic health technology and economic evaluation: a critical review. Appl Health Econ Health Policy 2006;5:27–35.