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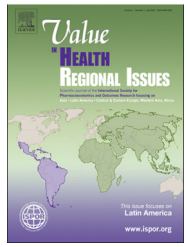

Cost-Effectiveness of the Quantification of Enzymatic Activity in Leukocytes in Comparison to Its Nonrealization for a Rare Disease in Latin America: The Case of Mucopolysaccharidosis Type II in Colombia

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ABSTRACT

Background: Mucopolysaccharidosis (MPS) type II is produced by a deficiency of iduronate-2-sulfatase (I2S). The quantification of the enzyme activity in leukocytes is used as diagnostic confirmation of MPS. **Objective:** To determinate the cost-effectiveness of the measurement of I2S enzyme activity in leukocytes compared with not carrying out the enzyme activity measurement for diagnostic confirmation of MPS II from the perspective of the Colombian health system. **Methods:** A cost-effectiveness analysis was conducted on the basis of a decision tree model. The measure of effectiveness was the correct diagnosis of cases of MPS II. The costs of I2S enzymatic quantification in leukocytes, consultation with a geneticist and with other specialists, and costs of diagnostic procedures were included. The time horizon was less than 1 year. A probabilistic sensitivity analysis was performed using Monte-Carlo simulation with 10,000 iterations. **Results:** The incremental cost was –US $43,145 with an incremental effectiveness of 42 cases. The probabilistic sensitivity analysis confirms the results of basal data, in which the quantification of I2S enzyme activity was less costly and more effective than the alternative. **Conclusions:** The quantification of I2S enzymatic activity is a dominant technology for the diagnostic confirmation of MPS II, compared with not making the quantification, from the perspective of the Colombian health system.

Keywords: cost-effectiveness, Hunter syndrome, iduronate-2-sulfatase, mucopolysaccharidosis.

Introduction

Mucopolysaccharidosis (MPS) is a set of disorders of the lysosomal storage produced as a result of a deficiency of the enzymes necessary for the degradation of glycosaminoglycans (GAG). The accumulation of GAG produces changes in different body systems.

MPS type II or Hunter syndrome is caused by the deficiency of iduronate-2-sulfatase (I2S), which leads to deposits of heparan and dermatan sulfate. The incidence of this type of MPS is one of the most frequent, estimated at 1 in 140,000 to 156,000 live births in Europe [1]. In the United States, the incidence is estimated at 1 in 250,000 live births [2]. The incidence in Latin America oscillates between 0.69 and 1.19 cases in 100,000 live births [3].

In Colombia, the reported frequency of MPS II is 0.45 cases per 1000 live births [4], with 4 cases reported during the period 1987 to 2008 [5]. According to the Colombian Fund for High Cost Illnesses, there are actually 46 known cases of MPS (Fondo Colombiano de Enfermedades de Alto Costo, personal communication, October 2014).

Given the systematic involvement of the illness, early diagnosis is necessary as a means to establish therapeutic plans for the minimization of the illness impact on the personal and social functioning of the patient. Nevertheless, the diagnosis may be delayed given the epidemiological behavior of the illness, the physician's unfamiliarity with this condition, and the presence of only slight clinical manifestations in some patients.

Diagnosis includes the examination of clinical factors, biochemical parameters, and molecular characteristics. Faced with a suspicion of MPS, the concentration of GAG in urine should be measured as a first test. If elevated, the determination and quantification of its amount should be carried out with a view to guiding the request for enzymatic quantification. Given that

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the concentration of GAG may show a high proportion of false negatives, it is always recommendable to carry out the enzymatic measurement [1,6,7]. At present, the metabolic confirmation of the condition is made by the quantification of enzymatic activity in leukocytes, fibroblasts, or plasma.

MPS has an important impact on the health and quality of life of the patient. Because of its chronic and multisystemic character, considerable costs are generated for the health system and society in general. In the United Kingdom, the average annual cost per patient with MPS financed by the health service (hospital and other services) is £7,600 for children and £11,900 for adults [8].

Published information on costs related to this illness in Colombia could not be found. Nevertheless, it is desirable to have the tools available for decision making in the health sector, such as the economic evaluations in the Colombian context. Therefore, the objective of this study was to determinate the cost-effectiveness ratio in the quantification of I2S enzyme activity in leukocytes as compared with not making the quantification, from the perspective of the Colombian health system.

Methods

This article was developed following the Consolidated Health Economic Evaluation Reporting Standards and the CHEERS Checklist.

Population Studied

The population studied consisted of male patients of any age with clinical indications of MPS II of whatever severity. Only male patients were chosen because the illness is X-chromosome–linked. No subgroup analysis by age or by other characteristics was carried out because it appeared that no clinical characteristics or aspects related to particular diagnostic tests affected costs or outcomes.

Selection of Alternatives

The intervention was the quantification of I2S enzymatic activity in leukocytes in the Colombian health system. The comparison was the nonrealization of the quantification of enzymatic activity. In this case, given the necessity of making a diagnosis in a setting in which it was not possible to make a quantification, the diagnostic strategy most reported in the literature, and validated by clinical experts, consists in specialist consultations, diagnostic imaging, laboratory tests, and the quantification of GAG in urine.

Time Horizon and Discount Rate

The time horizon was less than 1 year, which is the period in which differences in outcomes are expected, associated with the use of quantification of I2S enzyme activity in leukocytes to confirm diagnosis of MPS type II. For this time horizon, adjustments for discount rate are not applied.

Perspective

Following methodological recommendations for the realization of economic evaluation studies in the Colombian agency for health technology assessment (in Spanish: Instituto de evaluación tecnológica en salud, IETS) [9], the perspective of the Colombian health system was selected.

Effectiveness

The effectiveness is measured as the number of cases diagnosed correctly, that is, the sum of the *true positives* and the *true negatives*. Despite being an intermediate outcome, dealing with an economic evaluation of diagnostic tests, the principal reason for this is to provide information for the making of clinical decisions. Quality-adjusted life-year could not be quantified because of the absence of data in the literature.

Table 1 – Number of correctly diagnosed cases of MPS II for both alternatives evaluated in a hypothetical cohort of 100 patients with suspected MPS II for a pretest probability of 70%[*].

Parameter	Intervention (quantification of I2S enzymatic activity)	The comparison (no quantification of I2S enzymatic activity)
True positive	70	32
False negative	0	38
False positive	0	6
True negative	30	24
Number of correctly diagnosed cases (true positive + true negative)	100	56

I2S, iduronate-2-sulfatase; MPS II, mucopolysaccharidosis type II.
[*] Source: Consultation with clinical experts.

For the measurement of this outcome, in accordance with the recommendations in the methodology guide, the clinical group was asked to provide estimations and ranges of sensitivity and specificity for each of the diagnostic alternatives because of the absence of this information derived from studies of diagnostic validity. The pretest probability is considered as the proportion of patients with reduced enzymatic activity given the presence of an MPS II phenotype. For this case, the experts considered this probability to be 70%. Given that the quantification of enzyme activity in leukocytes is the criterion standard method that defines the illness, a sensitivity and specificity of 100% is attributed to it. Information regarding sensitivity and specificity related to the physical examination, diagnostic imaging, and GAG in urine was absent from the literature. Therefore, 17 clinical geneticists were questioned by means of an electronic questionnaire.

The number of cases correctly diagnosed for each alternative are presented in Table 1.

Costs: Identification, Measurement, and Valuing

Because this study is from the perspective of the Colombian health system, only the direct resources of the health system were taken into account.

For the identification of the resources associated to the technologies, information was initially sought in the MPS diagnostic guides [1,10], and this information was later validated by the clinical geneticists by means of a virtual questionnaire, with the objective of appraising the use of these resources in the habitual clinical practice in the Colombian context.

The questions related to resources were principally orientated to the group that did not carry out the test of enzyme activity, that is, to which clinical specialists are patients with clinical suspicion of MPS referred and what diagnostic procedures are carried out. In accordance with this information and that from the literature, the costs related to the present technology are those of medical consultations, nonconfirmatory diagnostic procedures, and the test for GAG in urine.

For the new technology, costs of the quantification of enzyme activity (US $192.06), the consultation with a geneticist, and the enzymatic quantification of a second arylsulfatase (arylsulfatase B, US $74.18) are considered.

Once the resources are identified, a quantity is assigned to each. It is assumed that these resources for diagnostic procedures are available just once. The number of clinical specialists that a patient with suspicion of MPS visits for diagnostic purposes was obtained from a MPS diagnosis study carried out in Brazil, with a total of 113 patients [11]. In this study, a patient suspected of having MPS consulted on average 4.7 clinical specialists before a diagnosis was made. The number of specialists consulted varied from 1 to 11 specialties.

The quantity of procedures was obtained from the virtual questionnaire. The geneticists were asked which procedures they ordered for diagnosis. Because there was a wide variety of answers, one quantity was considered for the base case and two scenarios (minimum and maximum) for the sensitivity analysis.

The total value of each resource is equal to the quantity multiplied by the unit value. The total value of the procedures corresponds to the sum of the total values for each resource.

It is assumed that with the new technology, the patient needs to go to the clinical geneticist twice, once for the test and once for the interpretation of the results.

Costs were expressed in US dollars. The conversion to Colombian pesos (COP) used the exchange rate of COP$2386 = US $1 consulted in the Central Bank of Colombia on January 27, 2015.

Decision Model

Because of the short term, with no recurring event and with no interaction between individuals, the decision model considered most appropriate for the technology to be evaluated and the outcomes was that of a decision tree. This model was approved by all interested parties. The software used was TreeAge Pro 2013® (TreeAge Software, Inc., USA).

The decision model is presented in Figure 1. The following assumptions were made:

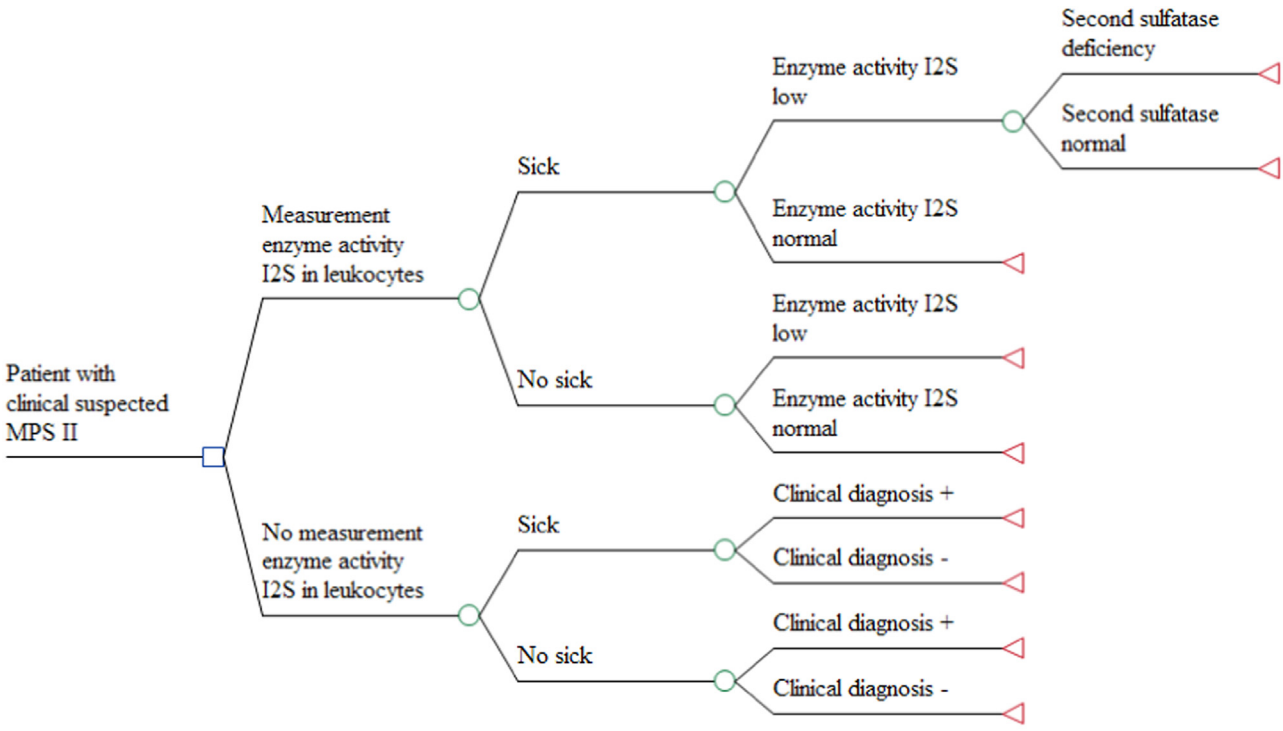
1. The cost of consultation with a general practitioner is not considered because the definitive diagnosis is made by a medical geneticist with diagnostic support from other specialist areas such as neurology and pneumology. In the case in which a patient requires a consultation with a general practitioner, it would not be for diagnostic purposes but for referral to other specialist opinions. In this case, the cost would be the same for both interventions.
2. There are no complications arising from the procedure for neither of the options evaluated.
3. All patients carry out all the diagnostic procedures requested.
4. The technique for the enzyme quantification is the same for all patients.
5. All samples are in adequate conditions to be processed.
6. The sensitivity and specificity data for the quantification of the enzyme activity in leukocytes are 100%, and it is assumed that they will not vary.
7. The probability of finding a reduction in a second arylsulfatase is 1% according to reports of clinical experts.

The number of correctly diagnosed cases for each repetition was obtained as follows:

$$\text{True positive} = [P(\text{patient/clinical suspicion of MPS II}) \times \text{test sensitivity}] \times 100$$

$$\text{True negative} = [1 - P(\text{patient/clinical suspicion of MPS II}) \times \text{test specificity}] \times 100$$

where P stands for conditional probability. Because the work was done with a hypothetical cohort, techniques for censored, biased,



I2S: iduronate-2-sulfatase

Fig. 1 – Structure of the decision tree of the evaluated alternatives in patients with suspected MPS II. I2S, iduronate-2-sulfatase; MPS II, mucopolysaccharidosis type II.

Table 2 – Distribution parameters for each of the variables subjected to sensitivity analysis using second-order Monte-Carlo simulation.

Variable	Distribution	Value base case	Parameters of the distribution	Source
Probability of disease in patients with clinical suspicion of MPS II	Triangular	0.7	Min. = 0.3 Likeliest = 0.7 Max. = 1	Experts consultation
Sensitivity of nonrealization of the quantification of enzymatic activity in leukocytes	Triangular	0.45	Min. = 0.05 Likeliest = 0.45 Max. = 0.9	Experts consultation
Specificity of nonrealization of the quantification of enzymatic activity in leukocytes	Triangular	0.8	Min. = 0.67 Likeliest = 0.80 Max. = 0.95	Experts consultation
Number of consultations with medical specialties	Poisson	4.7	Lambda = 4.7	[9]
Clinical specialist consultation cost (US $)	Gamma	13.63	Alpha = 377.47 Lambda = 27.76	ISS fees 2001 (+30%)
Medical procedures cost* (US $)	Triangular	656.33	Min. = 341.16 Likeliest = 656.33 Max. = 1019.68	ISS fees 2001 (+30%)
GAG in urine cost (US $)	Gamma	54.79	Alpha = 20.51 Lambda = 0.37	Health care institutions/ clinical laboratories

CT, computed tomography; GAG, glycosaminoglycans; ISS, Institute for Social Security; Max., maximum; Min., minimum; MPS II, mucopolysaccharidosis type II; MRI, magnetic resonance imaging.

* Medical procedures for the realization of no quantification of enzymatic activity in leukocytes included the following costs: head x-ray, cervical spine x-ray, chest x-ray, fingers x-ray, cranial CT, cranial MRI, chest MRI, saturometry, oxygen saturation, sleep study, electrocardiogram, echocardiogram, nerve conduction velocity study, electromyography, lumbar puncture with pressure measurement in cerebrospinal fluid, bone mapping, audiometry, and impedance.

or missing data were not used. For this same reason, there was no pooling of data. Because a decision tree was being used, midcycle corrections were not made.

Because subgroups of patients were not established, no evaluation of heterogeneity was performed.

Sensitivity Analysis

The second-order Monte-Carlo simulation was used to carry out a probabilistic sensitivity analysis with 10,000 iterations. The variables subjected to sensitivity analysis, the probability distribution used, and the parameters are described in Table 2. To evaluate efficiency, the criterion used was the willingness to pay (WTP), which was between 1 and 3 times the gross domestic product per capita for 2014, which was equivalent to a WTP between US $6,000 and US $18,000.

Results

Table 3 presents the deterministic and probabilistic values of the cost-effectiveness ratio. The quantification of the I2S enzymatic activity is 2.3 times less costly than the alternative (not to quantify enzymatic activity). Furthermore, it is more effective given a correct diagnosis of 100 patients from the hypothetical cohort. In this sense, quantifying the enzyme activity is a dominant alternative and is less than 1 time the gross domestic product per capita. For each additional correctly diagnosed case by the quantification of enzyme I2S activity in leukocytes, there is a saving of US $43,145, compared with not making the quantification of the enzyme activity, from the point of view of the Colombian health system. Figure 2 shows the results of the Monte-Carlo simulation. It can be seen that all the points of no quantification of enzyme activity are above the cost of the enzyme activity quantification and the quantification is less effective. The acceptability curve is given in Figure 3 and shows that all the iterations were cost-effective in favor of the quantification of enzyme activity for a WTP value ranging between US $6,000 and US $18,000.

Discussion

The results obtained in this evaluation demonstrate that the quantification of the activity of enzyme I2S in leukocytes for the diagnostic confirmation of MPS II is more effective and less costly for the Colombian payer than a strategy that involves different interconsultations, diagnostic procedures, and the quantification of GAG in urine. Unfortunately, studies similar to this one have not been carried out in Colombia to enable a comparison of results.

Although a valid outcome, the use of the number of cases correctly diagnosed has its limitations. The two alternatives supply additional information beyond that of a mere diagnostic confirmation. In this order of ideas, it is important to mention that the quantification of enzyme activity not only gives a diagnostic certainty necessary for the eventual prescription of therapy for enzyme replacement but also strongly supports the necessity for molecular diagnosis in search of mutations. The principal limiting factor is that no additional information is supplied regarding the complications of the illness. This information could be available from a strategy of nonquantification on the basis of the detection of complications through several interconsultations, laboratory tests, and imaging, including the detection of GAG in urine.

The principal limitation of measuring GAG in urine is the possibility of false positives and negatives in the diagnosis, which would have significant repercussions for the patient and the family as well as for the health system if replacement therapy is initiated for a patient not having the conditions.

Table 3 – ICER of the evaluated alternatives in a hypothetical cohort of 100 patients with clinical suspicion of MPS II.

Alternatives	Costs (US $)	Incremental cost (US $)	No. of correctly diagnosed cases	Incremental no. of correctly diagnosed cases	ICER
Deterministic results					
No quantification of enzymatic activity in leukocytes	71,129		58		
Quantification of enzymatic activity in leukocytes	27,983	−43,145	100	42	Dominant
Results of probabilistic sensitivity analysis using second-order Monte-Carlo simulation of the evaluated alternatives in a hypothetical cohort of 100 patients with clinical suspicion of MPS II					
No quantification of enzymatic activity in leukocytes, mean ± SD	71,128 ± 13,479		57.79 ± 13.06		
Quantification of enzymatic activity in leukocytes, mean ± SD	27,983 ± 70.24	−43,145	100 ± 0.0	42.21	Dominant

ICER, incremental cost-effectiveness ratio; MPS II, mucopolysaccharidosis type II.

Nevertheless, the nonquantification strategy described earlier provides valuable information about the presence and severity of complications in different body systems, which is necessary knowledge for the commencement of therapy in these patients. The need to reduce diagnostic uncertainty in the case of nonquantification of enzyme activity is the factor that results in a significant cost increase. It could be said that the introduction of enzyme replacement therapy and the carrying out of more molecular tests for counseling purposes have led to an improvement in diagnostic certainty, which is a requirement for eventual prescription and action.

It could be argued that another strategy of nonquantification could be merely the medical evaluation by a geneticist and the request for GAG in urine. Although this alternative was considered initially by the evaluating group, various factors were responsible for its exclusion. The first was that the measurement

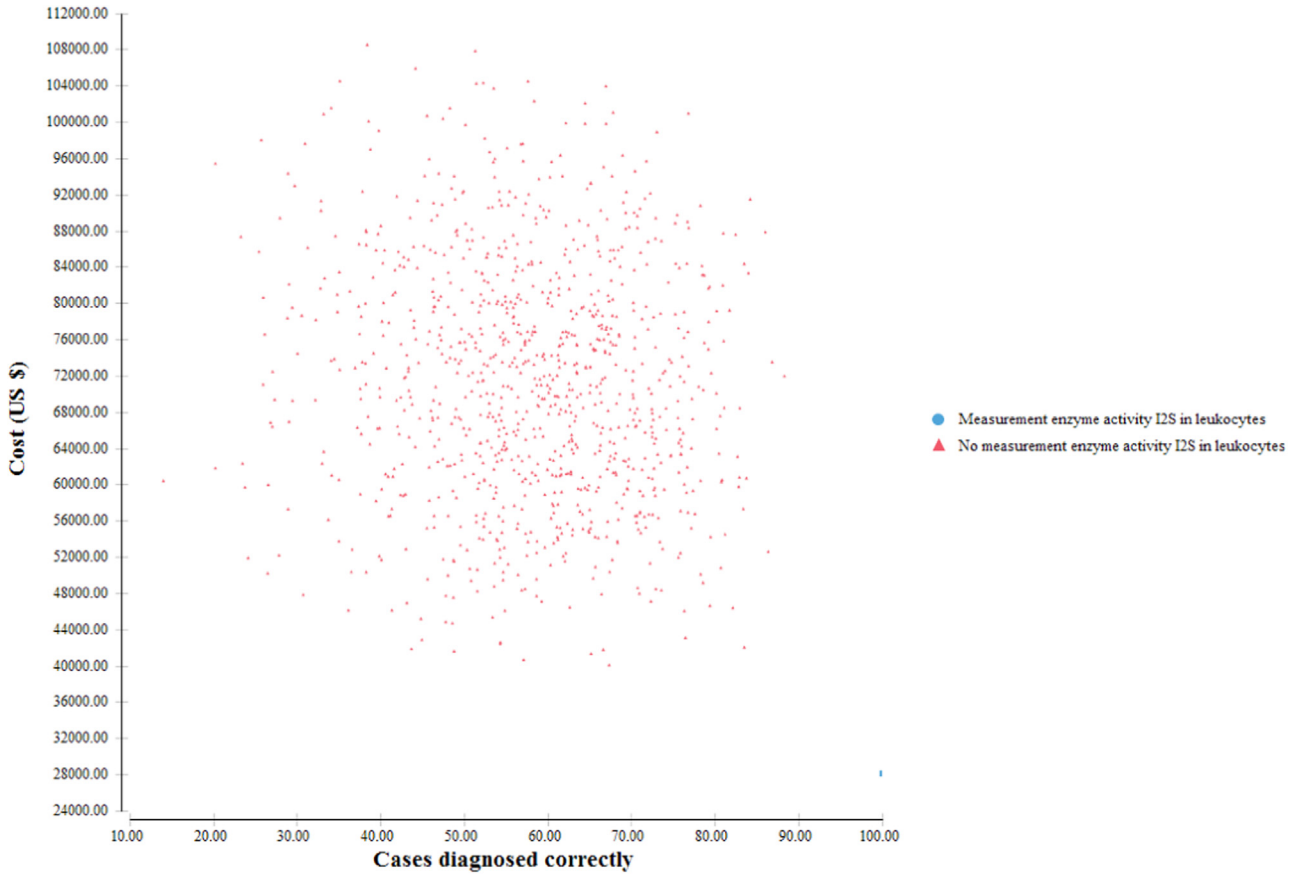


Fig. 2 – Results of probabilistic sensitivity analysis using second-order Monte-Carlo simulation of the evaluated alternatives in a hypothetical cohort of 100 patients with clinical suspicion of MPS II. I2S, iduronate-2-sulfatase; MPS II, mucopolysaccharidosis type II.

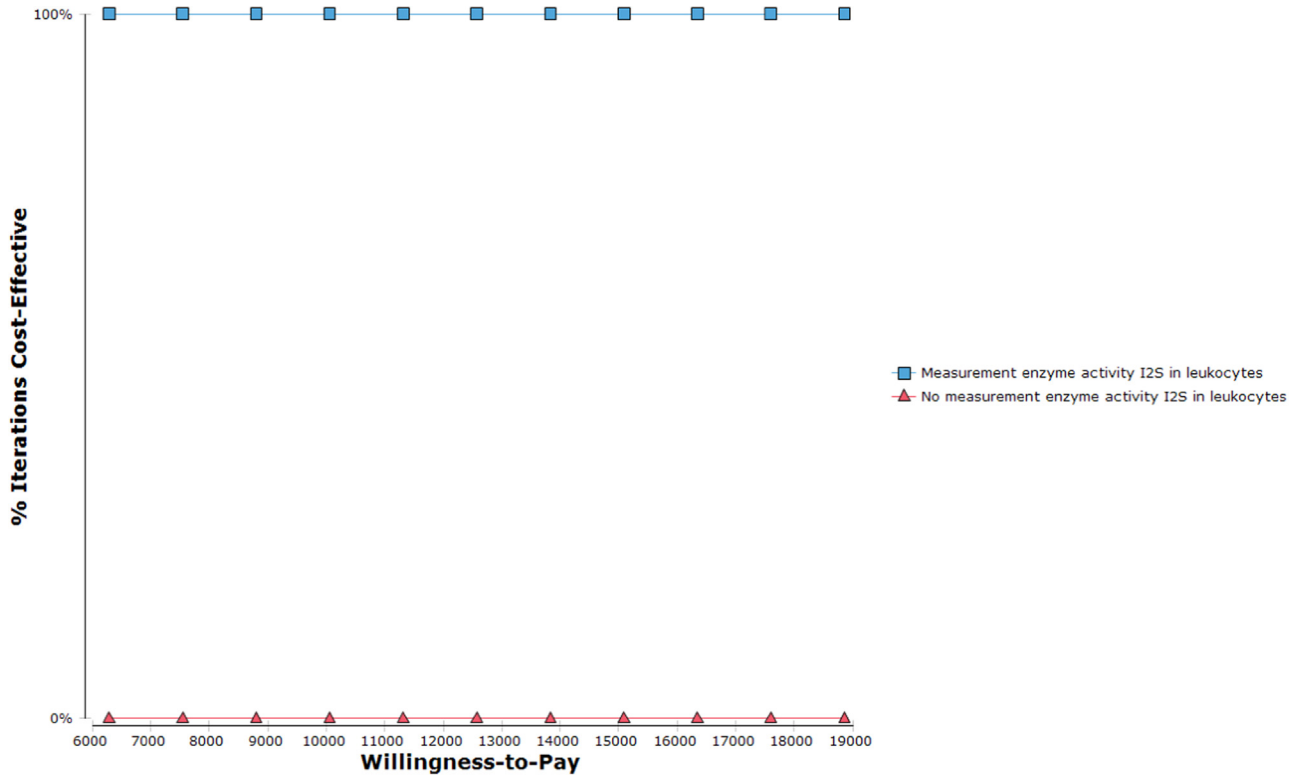


Fig. 3 – Acceptability curve of the quantification of enzymatic activity of I2S in leukocytes vs. no quantification for diagnostic confirmation of MPS II. I2S, iduronate-2-sulfatase; MPS II, mucopolysaccharidosis type II.

of GAG in urine is not considered as a diagnostic test but as a screening. Effectively, no diagnostic flow diagram was considered as a diagnostic strategy [12]. The second factor was the high proportion of false negatives (approaching 50%–75% depending on technique, age, and the method of sample collection), which makes it a tool of very low sensitivity for the diagnostic certainty required for the prescription of enzyme replacement therapy, molecular diagnosis, and genetic counseling. The third factor was that the habitual diagnostic practice, supported by clinical experts, in scenarios in which there is no enzyme availability, includes the evaluation by various specialists, the determination of GAG in urine, other clinical tests, and additional diagnostic imaging.

Regarding the costs of the test, the availability in Colombia of the measuring of enzyme activity could be considered as oligopolistic because there are only two institutions that process such samples. Despite this, the costs are not significantly higher than those of other specialized laboratory tests. There could be factors that distort the market, especially the transfer of these costs to budgets destined for investigation or the carrying out of the tests by pharmaceutical companies. Although studies to support this hypothesis are not known, the financing of this technology by those responsible for payment could eventually induce a demand or transfer of health accounts, which could cause fluctuations in the market price. This behavior was evidenced by the poor variability of technology costs in the probabilistic sensitivity analysis.

Another consideration that arose in discussions with the principal participants is related to the objective population. The diagnostic flow diagrams typically indicate the quantification of enzyme activity in patients with elevated levels of GAG in urine, giving the option of seeking other types of MPS in patients with normal levels of GAG [1]. This diagnostic consideration could eventually decrease the number of patients susceptible to benefit from the technology. Nevertheless, the evaluation considered all the patients with clinical suspicion of MPS regardless of the level of GAG in urine. This is amply justified because GAG tests are filters with an ample proportion of false negatives as stated earlier.

This study had certain limitations worth consideration. The principal limitation was the quality of the information for making an economic evaluation. The articles found in the literature review, besides the ones cited in this article, were related to enzymatic replacement and not to enzymatic quantification in leukocytes. Therefore, scarce evidence on the subject was a limitation of the study. Furthermore, the lack of studies related to the quantity of resources used and the validation of diagnostic strategies, such as physical examination, diagnostic imaging, and paraclinical examinations, were limiting factors for this study. Despite having consulted experts as a strategy to obtain information, even including consultations with clinical geneticists, the low number of patients led to a difficulty in the estimation of probabilities. This is reflected in the wide range of estimations for the parameters of the model. The experience factor also plays a fundamental part in the pretest probabilities for the different diagnostic alternatives. In this order of ideas, it seems necessary to carry out investigations aimed at estimating the prevalence of the MPS in patients under suspicion, the quantification and evaluation of resources used in diagnosing these patients, and the measuring of utilities, quality, and life expectancy in the conditions of our society aiming at calculating final outcomes centered in the patient.

The use of the technology does not pose great ethical challenges in itself because it is a technology to easily obtain samples with minimal or no risks to the patient. The principal ethical challenge lies in receiving consent to carry out the tests in adult patients with cognitive limitation. In this case, a legal tutor could be required.

Finally, there are considerations related to equality. Because this technology is outside the health benefit package, in some cases it could represent a drain on the pockets of patients. This poses a potential barrier for those who have reduced capacity to pay. In addition, in this country the samples are processed only in the capital city, Bogotá, resulting in a barrier for those who live in distant areas of Colombia. In this sense, the inclusion in the health benefit package and the development of a sample transport system based on filter paper could help to mitigate these barriers.

Conclusions

The quantification of the activity of enzyme I2S in leukocytes as a diagnostic confirmation of MPS II is the dominant technology (most effective and less costly) in comparison with the non-quantification from the point of view of the Colombian health system.

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