

Análise de custo-efetividade do teste de cadeias leves livres (Freelite®) para o diagnóstico de gamopatia monoclonal

Cost-Effectiveness Analysis of Serum Free Light Chain Assay (Freelite®) for the Diagnosis of Monoclonal Gammopathy

Bruno Salgado Riveros¹

Farmacêutico, PhD. Laboratory of Clinical Services and Synthesis of Evidences, Universidade Federal do Paraná (UFPR). Curitiba, PR

Fernando Caporal

Farmacêutico, MSc. Specialist in Hematology and Senior Technologist in Human Cytogenetics. Independent Consultant. Curitiba, PR.

Elyara Maria Soares

Biomédica, PhD. Scientific Affairs Manager, the Binding Site Brazil Ltda. São Paulo, SP.

Fulvio Facco

Farmacêutico, MSc. General Manager Latin America, the Binding Site Brazil Ltda. São Paulo, SP.

Resumo: Os protocolos de diagnóstico atuais para gamopatia monoclonal (GM) dependem da eletroforese de proteínas do soro (EFPS) como a única avaliação inicial para a proteína monoclonal, ainda que limitada no que diz respeito à sua sensibilidade. A associação do teste de cadeia leve livre no soro (CLL, Freelite®) resulta na diminuição do número de resultados falso-negativos. Buscamos avaliar a eficiência de CLLs para o diagnóstico de GM no Sistema Único de Saúde (SUS) e na Sistema de Saúde Suplementar (SSS). Os dados de um estudo publicado em pacientes com suspeita de GM (n = 652) foi usado para a árvore de decisão. O modelo foi desenvolvido para distinguir qual protocolo de diagnóstico fornece o valor mais alto para cada unidade monetária investida. Foram testados o protocolo padrão (PP) (EFPS como auxílio na via de diagnóstico), e dois comparadores, PP + CLLs (PP1) e PP + CLLs + IFS (PP2). Os resultados foram interpretados como a quantidade de moeda (BRL) gasta para cada diagnóstico correto incremental de GM. A simulação probabilística indicou um ICER médio de R\$ 1.192 e R\$ 1.470 para a PP1 e PP2, respectivamente, no SUS. Para SSS, os respectivos ICER foram BRL 3620 e 4193. Considerando um limiar superior a R\$ 1.500 (SUS) e \$ 4.000 (SSS), PP1 é a estratégia mais provável que seja custo-benefício. A adição do teste de CLLs melhora a eficiência dos recursos financeiros atribuídos ao diagnóstico de GM, no que diz respeito às abordagens adotadas tanto no SUS quanto no SSS.

Palavras chaves: Gamopatia monoclonal, análise de custo-benefício; teste de cadeia leve livre no soro.

Abstract: Current diagnosis protocols for monoclonal gammopathy (MG) rely on serum electrophoresis (SPEP) as the sole initial assessment for monoclonal protein, such as in Brazil, limited with respect to their sensitivity. Adding serum Free Light Chain (sFLC, Freelite®) determination results in a decreased number of false-negative results. We sought to assess the efficiency of sFLC for the diagnosis of MG in the Brazilian Public Health System (SUS) and Supplementary Healthcare System (SSS). Data from a published study on patients presenting with a suspicion of MG (n=652) was used to populate a decision tree model. The model was developed to distinguish which diagnosis protocol provides the highest value for each monetary unit invested. It were tested the standard protocol (SP) (SPEP as an aid in the diagnostic pathway), and two comparators, SP plus sFLC (PP1) and SP plus sFLC and Serum Immunofixation Electrophoresis (sIFE) (PP2). Results were interpreted as the amount of currency (BRL) spent for each incremental correct diagnosis of MG. Probabilistic simulation indicated an average ICER of BRL 1,192 and BRL 1,470 for PP1 and PP2, respectively in SUS. For SSS, the respective ICERs were BRL 3,620 and 4,193. Considering a threshold over BRL 1,500 (SUS) and BRL 4,000 (SSS), PP1 is the strategy more likely to be the cost-effective. The addition of sFLC assessment in the initial diagnostic work up of MG improves efficiency of financial resources allocated to MG diagnosis, with respect to the approaches taken in both SUS and SSS.

Keywords: Monoclonal gammopathies; cost-effectiveness analysis; serum free light chain.

¹riveros.bs@gmail.com

Introduction

An important application of serum free light chain (sFLC) analysis is in the assessment of patients with a suspicion of monoclonal gammopathy (MG) (1). The diagnosis of myeloma in patients with non-secretory or oligo-secretory (non secretory) myeloma can be very difficult due to the low concentration of M-protein in blood and urine. In these cases, the common strategy for screening, Electrophoresis Serum (SPEP) or Urine (UPEP), have limited sensitivity. This approach leads to many false-negative results (2). The inclusion of sFLC analysis alongside SPE has been shown to have a high sensitivity for symptomatic plasma cell dyscrasias (3). Both the International Myeloma Working Group (IMWG) and the National Comprehensive Cancer Network (NCCN) recommend the use of sFLC assays in the initial diagnostic work up of suspected myeloma patients in parallel to SPEP (2,4). It is important to highlight that delayed diagnosis may have the potential to increase the incidence and or degree of renal insufficiency and bone diseases (5).

Despite recognizing sFLC assessment as an important technique that may improve the sensitivity of MG diagnosis (2,4), there are very limited reports that consider its cost-effectiveness, i.e., the balance between additional costs after incorporating this technology in a given health system, and the incremental benefits provided to patients and health systems.

Currently, there are no studies assessing MG diagnosis strategies in Brazil. Thus, we sought to assess the cost effectiveness of including sFLC assays in both the Brazilian public and supplementary healthcare settings.

Methods

The present economic evaluation followed the precepts contained in the *Diretrizes Metodológicas: Diretriz de Avaliação Econômica* (6), Model Transparency and Validation: A Report of the ISPOR-SMDM Modeling Good Research Practices Task Force-7 (7), and Modeling Good Research Practices – Overview: A Report of the ISPOR-SMDM Modeling Good Research Practices Task Force-1 (8).

Economic model

The model addresses the use of protein electrophoresis and sFLC assessment in the diagnostic pathway for MG, thus addressing the efficiency of different strategies only in the diagnostic process. Any potential additional value related to decreased hospitalization, numbers and degree of renal insufficiency or bone diseases were not taken into account. The sensitivity and specificity of each diagnostic pathway was calculated from data presented in Vermeersch *et al.* (2008) (9), the respective incidence of false negative and false positive results were applied. Costs of laboratory tests, as well as imaging and biopsies required for each strategy were identified, quantified and valued. In the SUS and SSS perspective, costs were taken from SIGTAP (10) and CBHPM (11), respectively. Results are expressed as an Incremental Cost-Effectiveness Ratio (ICER), which corresponds to the monetary investment required for one incremental correct diagnosis of MG. The model was used to assess both the Brazilian Public Healthcare System (*Sistema Único de Saúde*, SUS) and Supplementary Healthcare System (SSS) settings.

Standard and comparator strategies

Three diagnostic pathways for MG detection were compared (Figure 1):

- The standard protocol (SP) for MG diagnosis currently used in SUS and SSS. The protocol follows the Brazilian National Guidelines for Diagnosis and Therapeutics for Multiple Myeloma (MM) (12), in which the initial diagnostic work up includes SPEP, samples that are abnormal by SPEP are reflexed to SIFE.
- The second pathway (PP1) is the addition of sFLC assessment to SP (SPEP+sFLC). Samples that are abnormal by either SPEP or sFLC are reflexed to SIFE.
- The third pathway (PP2) includes the assessment of sFLC, SPE and SIFE on all samples in parallel.

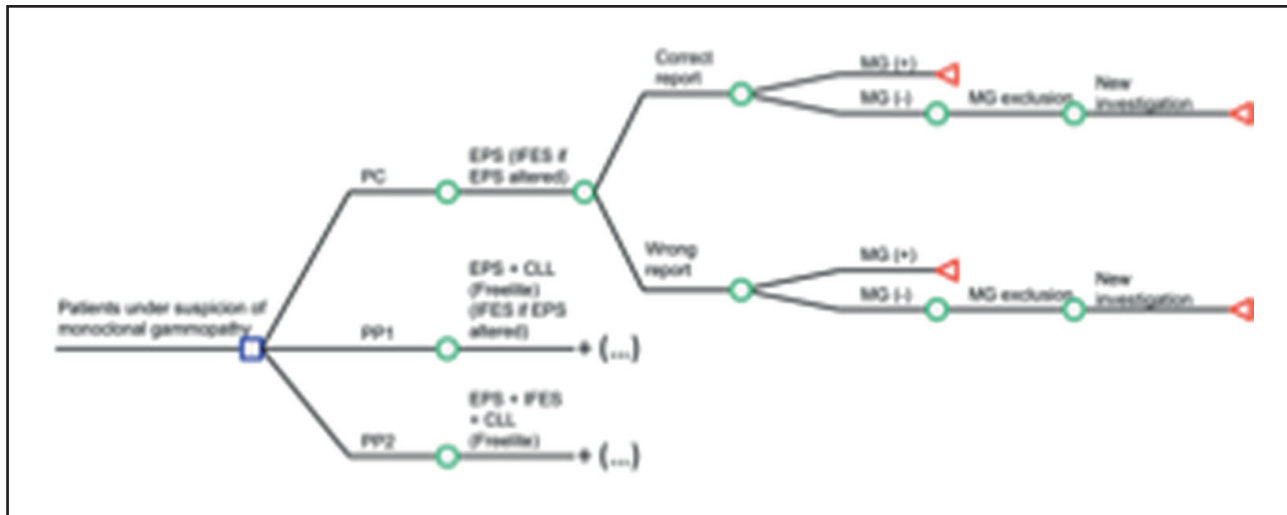


Figure 1. Decision tree developed to assess different strategies for the diagnosis of monoclonal gammopathy.

Population involved

The target population included any patient with a suspected symptomatic MG. In Brazil there is no standard strategy for following patients with MGUS and so these were not followed by the model. Overall, it corresponds to patients over 50 years old, predominantly black men. A study from 2006 (13) assessed the most important characteristics about Brazilian patients diagnosed with MM and found that they are very similar compared to other findings in literature (13). Among the different types of MG, MGUS is the most prevalent (61%), followed by MM (18%), amyloidosis (9%), lymphoproliferative diseases (3%), smoldering MM (3%), solitary extramedullary plasmacytoma (2%), macroglobulinemia (2%) and others (2%) (3).

Assumptions and limitations

As with any decision modeling, assumptions and limitations were made in developing the model and when populating the variables. It was assumed that all patients with a suspicion of MG presenting at SUS or SSS are submitted to the SP diagnostic pathway. Where patients were shown to have a MG the model assumed they had a single MG. If a patient was negative for MG, it was assumed that further assessments would be carried out in order to identify the correct diagnosis. It was assumed that facilities to deliver those strategies are available in hospitals

of reference for monoclonal gammopathy management. The results shown in this study are representative for the Freelite® sFLC assays, The Binding Site Group, Birmingham, UK. Finally, the results of this model are not representative for sFLC when it is being used for monitoring patient's disease.

Probabilities

Transition probabilities were taken from a published single-blind study that assessed sensitivity and specificity of different diagnosis strategies in 833 patients with a suspicion of MG being that 209 were known previously to have MG (9). From these patients, 18 were diagnosed with MM (8%), two light-chain MM (1%), three amyloidosis (2%), 4 lymphoproliferative diseases (2%), 1 macroglobulinemia (1%), 156 MGUS (74%) and 25 with non-Hodgkin B-cell lymphoma (12%). Each sample was assessed considering each different strategy and two independent teams analyzed the results. Clinical reports were checked by a third team who possessed the correct diagnostic for each patient's sample (9). Cases of MGUS and non-Hodgkin B-cell lymphoma were excluded from analyses. Therefore, population considered was of 652 patients, being that 28 had previous diagnostic of MG.

Probabilistic data were inserted in the model considering the absolute number of patients as shown in Table 1.

Table 1. Probabilistic data used in the model to the assessment of different diagnosis strategy of MG.

Number of patients assessed	652	Adapted from Vermeersch <i>et al.</i> (2008)(9)
Number of patients with MG	28	18 MM, 2 LCMM, 3 AL-AM, 4 LD, 1 WD
Patients without MG	624	
SP – correct reports (positive cases/negative cases)	25/624	Sensitivity 89% Specificity 100%
PP1 - correct reports (positive cases/negative cases)	27/604	Sensitivity 96% Specificity 97%
PP2 - correct reports (positive cases/negative cases)	28/604	Sensitivity 100% Specificity 97%
SP – wrong reports (false positive/false negative)	-/3	
PP1 - wrong reports (false positive/false negative)	20/1	
PP2 - wrong reports (false positive/false negative)	20/-	

MG, monoclonal gammopathy; MM, multiple myeloma, LCMM, low chain multiple myeloma; AL-AM, AL-amyloidosis; LD, linfoproliferative diseases; WD, Waldenstrom macroglobulinemia.

Costs

The costs applied to the model were are summarized in Table 2.

Table 2. Cost (BRL) variables used in the model

<i>Cost parameters</i>	<i>SUS (mean±SE)*</i>	<i>SSS (mean±SE)*</i>
Standard protocol	350 ± 10	699 ± 23
sFLC + SP	413 ± 11	874 ± 23
SPEP + sFLC + SIFE	482 ± 6	1,053 ± 12
MG typing	772 ± 18	2,706 ± 67
New investigations	964 ± 43	2,468 ± 145

* Since the costs of tests are tabulated for both perspectives, uncertainty is related to the amount of tests required for a given individual.

Where patients were shown to be positive for MG the costs of the relevant pathway was used plus the cost of MG tipification and where patients were negative for MG the costs of the relevant pathway was used plus the costs related to new investigation. For false-positive results, the costs of one of the strategies plus the cost of tipification plus cost of new investigation were taken into account. Finally, for false-negative patients the cost for one of the strategies plus new investigations was considered. These cost of newer investigations were valued by means of top-down method. Given the most important clinical suspicion for patients negative to MG, the most relevant lab and image tests as well as biopsies were identified, quantified and, eventually, valued (9,15).

Costs variables were calibrated through Gamma Distribution curves, considering the cost of each test weighted by its frequency (minimum and maximum) of use in the MG diagnosis. From the intervals obtained, the hyper parameters “ α ” and “ β ” were calculated to address the reproduction of these limits capable to reproduce these limits.

The identification of the most common tests and their frequencies were estimated by means of hematologist's opinion as well as the prevalence of different types of MG and specific tests for each disease (15). In spite of urine immunofixation being part of SP, its use in practice is reduced due to poor quality of urine 24 hours samples. Thus, its usage was considered only in cases of suspect of AL-Amyloidosis, when this test is mandatory (4,16)renal failure, anaemia, and bone lesions.

Efficacy

The efficacy of strategies was assessed by means of the percentage of correct diagnosis of MG. That

choice allows exposing the increase in sensitive attributed to newer strategies compared to the standard one.

Sensitivity analysis

It was carried out one-way sensitivity analysis for all the variables of the model. One way sensitivity analysis was assessed using the 95% confidence interval (95% CI) identified through the distributions curves. Probabilistic sensitivity analysis (2nd order Monte Carlo simulation) was used to explore the combined uncertainty of each variable, here 5000 iterations were applied.

Internal validation

A hematologist assessed all probability and costs data as well as model structure. Equations and formulas in the model were doubled checked independently. The internal validation consisted of reproducing results shown by Vermeesch *et al.* (2008) (9). Findings from the model coincided perfectly with the study, indicating the correct adaptation from literature data to the model.

Results

The base case results are shown in Table 3, indicating the mean cost per patient for a given diagnostic pathway. In addition, it is presented the percentage of an individual gets a correct diagnosis according to adopted strategy (Efficacy), the ratio of cost and effectiveness and, finally, the ICER for PP1 and PP2 compared to the standard strategy, SP.

Table 3 - Base Case results

Strategy	Average cost (BRL)	Efficacy (sensitivity)	CE*	ICER*
SUS				
SP	1,307	.89	1,468	
PP1	1,393	.96	1,451	1,228
PP2	1,461	1.00	1,461	1,400
SSS				
SP	3,176	.89	3,568	
PP1	3,435	.96	3,578	3,700
PP2	3,614	1.00	3,614	3,982

PP1 strategy presents the best ICER for SUS (BRL 1,228) and SSS (BRL 3,700). PP2 ICER corresponds to BRL 1,400 (SUS) and 3,982 (SSS).

One-way sensitivity analysis indicated the probability of a positive correct diagnosis provided by PP2 as the most critical variable for the model. Varying this variable within its 95% CI (0.25, 0.18-0.26) did not make PP2 more efficient than PP1. SP was also not shown to be more efficient than PP1 or PP2 when the probability of a positive correct diagnosis provided by SP was tested within the 95% CI (0.21, 0.16-0.25) values. When the probability of positive correct diagnosis provided by PP1 was varied (95% CI, 0.22, 0.17-0.26) the final interpretation was altered if it value was lower than .19 (favoring PP2) or greater than 0.25 when PP1 become dominant over PP2. No other variable was shown to alter the interpretation of base case scenario.

Considering results provided by probabilistic analysis, it is possible to assess the likelihood of each strategy being the most cost-effective for a different range of WTP. This is called Cost-Effectiveness Acceptability Curve (Figure 3), in which x-axis provides possible range for willingness to pay and y-axis the probability for each strategy being the most cost-effective.

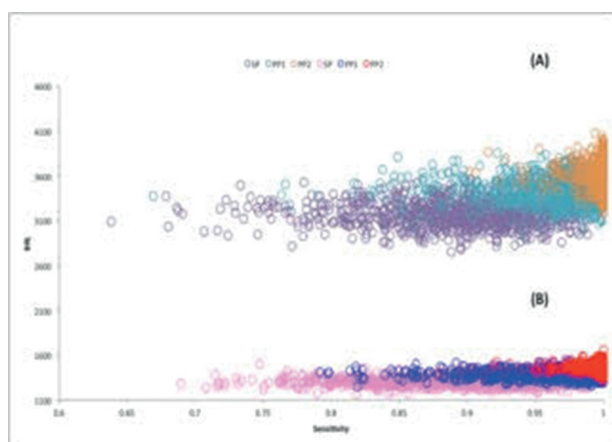


Figure 2. Scatterplot showing costs and benefits SP, PP1 and PP2 (A) Perspective of SSS (B) Perspective of SUS.

For WTP above a BRL 1,500 (SUS) and BRL 4,000 (SSS) PP1 was shown to be the most cost-effective strategy.

PP2 become more efficient when SUS is willing to pay more than BRL 3,500 and SSS more than BRL 8,000 for each incremental correct diagnosis. The cost per correct diagnosis in SP was shown to be BRL 1,468 and BRL 3,568 for SUS and SSS respectively.

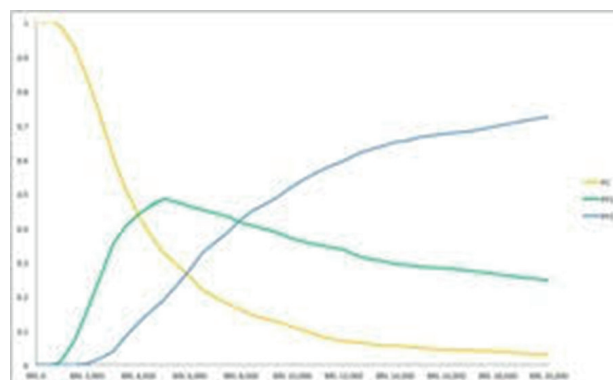
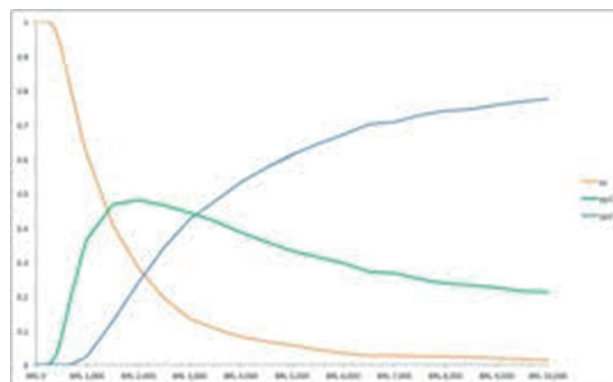


Figure 3. Cost-Effectiveness Acceptability Curve. The y-axis shows the probability of a given strategy being the most cost-effective considering a predefined willingness to pay (x-axis). (A) Perspective of SUS and (B) perspective of SSS

In a hypothetical scenario where PP2 is not a feasible strategy to be used in large scale, PP1 appears as the most efficient strategy when WTP are greater than BRL 1,250 (SUS) and BRL 3,400 (SSS). Considering the, actual expenses for one correct diagnosis of MG in SUS (BRL 1,451) and SSS (3,578), PP1 would have a probability of 75% and 68% of being more efficient, respectively, compared to SP with a trend of increasing its probability of being more efficient as higher the WTP becomes.

Discussion

The built model was capable to reproduce data obtained from Vermeesch *et al.* (2008) (sensitivity and specificity for each assessed strategy) being useful to explore different screening choices for MG diagnosis. This is the first economic evaluation model aiming to assess such a scenario.

MGUS cases were excluded from analyses since in practical terms a patient who receives a diagnostic of MGUS do not receive a treatment neither a disease monitoring (12). Therefore, increasing sensitivity/specificity for MGUS cases will not improve diagnostic work up. Non-Hodgkin B-cell lymphoma cases were excluded because such a disease does is not a monoclonal gammopathy and would be picked up by a different pathway.

Both PP1 and PP2 increased the sensitivity for MG diagnosis (from 89% to 96 (PP1) and 100% (PP2),) compared to the current strategy in both perspectives. On the other hand, specificity was decreased from 100% to 97%, that is to say the number of false positive slightly increased with PP1 and PP2 (3%). The direct impact of it is the unnecessary expenses with a patient whose it is believed to have MG (these costs were taken into account in this study). Conversely, an increase in sensitivity allows a faster classification of MG, and, therefore starting an appropriate treatment. Since a treatment will be offered sooner, it is likely that future expenses due to disease complication will be saved (these costs were not also captured in our analysis).

When sFLC assays are used in association with SPEP (PP1), the efficiency of MG diagnosis improves. Similarly, when sFLC assays are used in association with SPEP and SIFE, efficiency is also increased but in a smaller dimension.

Currently in Brazil there is a concern that tariffs of reimbursement for diagnostic tests are undervalued. In this study we showed that the efficiency strategies considering sFLC (PP1 and PP2) are unlikely to be altered by an update of the involved reimbursements. After all, in an environment where reimbursements are closer to actual expenses (SSS perspective) such efficiency is greater than current pathway (SP).

Since the assessed interventions (PP1 and PP2) are not treatment technologies, but diagnostic te-

chnologies, it is understood that population heterogeneity (e.g. age, sex and comorbidities) are not capable to change sensitivity and specificity observed in a Belgian population and extrapolated to the Brazilian setting (9). However, it is important to highlight that sensitivity and specificity are directly proportional to incidence of the different MG existing in a given population. For instance, it is known that non-secretory MM is more likely to not be detected by SP in relation to PP1 and PP2 (3,13). The clinical data used in this model were extracted from a population in which the prevalence of nonsecretory MM was 1%, whereas literature data suggest a prevalence of about 3% (3,13). Thus, our assessment might be overestimating efficiency of SP in real world.

In terms of efficiency, PP1 or PP2 are very similar. However, the challenges for implementing PP2 may hugely favor PP1. Applying PP2 in large scale across SUS or SSS implies in the clinical laboratory having access to nephelometer/turbidimeter (for sFLC assessment) and automated or semi-automated equipment to perform SIFE. If on one hand nephelometer/turbidimeter are largely present in clinical laboratories (to carry out other tests), on the other hand, specific equipment to automate SIFE tests may not be. It is expected a relative enhance in the number of SIFE tests in PP2 pathway, what would lead to workload issues in absence of automation. In addition, the minimal gain in terms of sensitivity may not justify the substantial increase in workload.

In spite of the most appropriate interpretation for cost-effectiveness results demand a known WTP in order to compare ICER of each intervention, the lack of a known threshold does not prevent of inferring about efficiency of PP1 and PP2, but limit a thorough evaluation of their advantages and disadvantages. Decision tree method is used when the follow up of the assessed scenario is as brief as possible. Therefore, the horizon of this study corresponds to the time spent to do a diagnostic of MG. Future studies aiming to carry out a broader assessment about this subject might explore the impact of earlier diagnosis in morbidity and mortality surrounding MG.

Conclusion

Adding sFLC in the initial work up diagnostic of monoclonal gammopathy in SUS or SSS improves the effectiveness of the diagnostic strategy, regardless of whether SIFE is run in parallel or not. When sFLC is used in combination with SPEP as an aid in the diagnostic pathway for patients with MG, the maximum gain in efficiency is observed.

References

1. Jenner E. Serum free light chains in clinical laboratory diagnostics. Clin Chim Acta. 2014;427:15–20. [Internet] Disponível em: <http://dx.doi.org/10.1016/j.cca.2013.08.018>
2. National Clinical Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Multiple myeloma. NCCN; 2015
3. Katzmman JA, Kyle RA, Benson J, Larson DR, Snyder MR, Lust JA *et al.* Screening panels for detection of monoclonal gammopathies. Clin Chem. Jun. 2009;55(8):1517–22.
4. Rajkumar SV, Dimopoulos MA, Palumbo A, Blade J, Merlini G, Mateos M-V *et al.* International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. Lancet Oncol, 2014 Nov;15(12):e538–48. [Internet]. Disponível em: <http://www.ncbi.nlm.nih.gov/pubmed/25439696> [cited 2014 Oct 27]
5. Leung N, Behrens J. Current approach to diagnosis and management of acute renal failure in myeloma patients. Adv Chronic Kidney Dis. 2012 Aug;19(5):297–302.
6. Ministério da Saúde. Secretaria de Atenção à Saúde. Diretrizes Metodológicas: Diretriz de Avaliação Econômica. (2. ed.) Brasília: Ministério da Saúde; 2014.
7. Eddy DM, Hollingworth W, Caro JJ, Tsevat J, McDonald KM, Wong JB. Model transparency and validation: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force-7. Value Health, 2013;5(6):843–50. [Internet]. Disponível em: <http://www.ncbi.nlm.nih.gov/pubmed/22999134> [cited 2013 Nov 18]
8. Caro JJ, Briggs A. H, Siebert U, Kuntz KM. Modeling good research practices – overview: a report of the ISPOR-SMDM modeling good research practices task force- 1. 2012;15:796–803. Disponível em: <http://eprints.gla.ac.uk/73437/>
9. Vermeersch P, Van Hoovels L, Delforge M, Marien G, Bossuyt X. Diagnostic performance of serum free light chain measurement in patients suspected of a monoclonal B-cell disorder. Br J Haematol. 2008 Aug;143(4):496–502.
10. Ministério da Saúde. Sistema de Gerenciamento da Tabela de Procedimentos, Medicamentos e OPM do SUS (SIGTAP). [Internet]. Disponível em: <http://sigtap.datasus.gov.br/tabela-unificada/app/sec/inicio.jsp>
11. Associação Médica Brasileira (AMB). Classificação Brasileira Hierarquizada de Procedimentos Médicos (CBHPM). São Paulo: AMB; 2014.
12. Ministério da Saúde. Portaria n° 708, de 6 de agosto de 2015, que ‘aprova as Diretrizes Diagnósticas e Terapêuticas do Mieloma Múltiplo’.
13. Hungria VTM, Maiolino A. Mieloma múltiplo: progressos e desafios. Rev Bras Hematol Hemoter. 2007 Mar;29(1):1–2. [Internet] Disponível em: http://www.scielo.br/scielo.php?script=sci_arttext&pid=S1516-84842007000100002&lng=en&nrm=iso&tlng=pt [cited 2015 Feb 18]
14. Associação Brasileira de Medicina (ABM). CBHPM Classificação Brasileira Hierarquizada de Procedimentos Médicos. São Paulo: AMB; 2014. [Internet]. Disponível em: <http://www.cremers.org.br/pdf/cbhpm.pdf> [cited 2015 Jun 1].
15. Faria RMD, Paula RO. Gamopatias monoclonais – critérios diagnósticos e diagnósticos diferenciais / Monoclonal gammopathies – diagnosis criteria and differential diagnosis. Rev Bras Hematol. 2007;29(1):17–22.
16. Katzmman JA. Screening panels for monoclonal gammopathies: time to change. Clin Biochem Rev. 2009 Oct;30(3):105–11.

FINANCIAL SUPPORT: There was no support needed for this article.

FINANCIAL DISCLOSURES: The authors have no conflict of interest.

ACKNOWLEDGEMENT: The authors wish to thank Richard Hughes from The Binding Site Group, Birmingham, UK, for data discussion and manuscript formatting.

Recebido em 13/03/2017.

Aceito para publicação em 10/10/2017.