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LETTER TO THE EDITOR

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Diagnostic testing for penicillin allergy: A survey of practices and cost perceptions

To the Editor,

Having a penicillin allergy label associates with worse healthcare outcomes and increased treatment costs.[1-3] However, whether penicillin allergy testing is cost-saving remains unclear, particularly as there is heterogeneity in the practice of such testing.[4]

Therefore, we developed an online questionnaire to assess the practice and cost perceptions of diagnostic tests used in penicillin allergy evaluation. Regarding cost perceptions, we asked respondents to estimate material, personnel, and facilities costs of performing each assessed diagnostic test. We also asked for estimates on the total paid amounts for each performed test (ie, perceived reimbursements by the State, insurance companies, or patients). Respondents provided a level of confidence (low, medium, or high) for each reported cost estimate. This questionnaire targeted drug allergy experts in Europe—we contacted European Network of Drug Allergy members by email, as well as first, last, and/or corresponding authors of publications in the field of drug allergy (our search was limited to publications of the last 10 years). Survey respondents were re-contacted to confirm outlier values.

To provide a broader comparison, we also contacted North American authors in the field of drug allergy, sending the same email to the Adverse Reactions to Drugs, Biologicals and Latex Committee of the AAAAI. In addition, we also (a) performed a comprehensive literature search in MEDLINE, Scopus, and Web of Science for publications assessing the costs of penicillin allergy tests, and (b) performed two cost assessments of material and personnel costs for skin tests and drug provocation tests (DPT)—one in a Portuguese private Allergy Unit and another in a Portuguese public hospital Unit.

All reported costs were converted into Euro (€) using the three-month average of June-August 2018. We performed descriptive analyses of data by standard methods. In addition, we identified factors associated with higher or lower reported cost estimates for each test by performing linear regressions with the log-transformation of summed reported costs as the dependent variable; multiple linear regression models were selected based on their AIC. Variables with missing data were excluded from regression models if missing values represented >5% of all responses; in the remaining cases, missing data were replaced by values determined by multivariate imputation by chained equations methods. We developed a Shiny-based online app to allow for interactive exploration of our results (Appendix S1 accessible at http://penallergy.med.up.pt).

We obtained 51 responses to our questionnaire from 19 countries (out of 389 individuals from 34 countries to whom the questionnaire was directly sent, corresponding to a response rate of 13.1%). Respondents were predominantly female (n = 33) and had a mean age of 46.4 years (Table S1). Most respondents were practicing allergists (n = 44) and worked in the public sector (n = 45). Forty-four responses were from Europe, and 7 were from North America. In all, 38 emails were sent to confirm outlier values, with 27 (71%) responses received.

More than 90% of respondents had experience in performing skin prick tests (SPT), DPT, and intradermal tests for penicillin allergy evaluations (Table 1). In patients with suspected penicillin allergy, intradermal tests and DPT were the most frequently performed tests (median frequency = 80%), followed by SPT (75%), specific IgE (sIgE) (30%), patch tests (15%), and basophil activation test (BAT) and lymphocyte transformation test (LTT) (10%) (Appendix S1). The median required time was of 45 minutes to perform SPT and intradermal tests; for DPT, the median time was 5 hours. More than half respondents reported performing SPT (65%), intradermal tests (57%), and patch tests (77%) in the outpatient setting; DPT were most commonly reported to be performed in the day ward (48%) (Appendix S1). A median of 2 healthcare professionals was necessary to perform all tests except DPT (with a median of 3 professionals).

Regarding cost estimates, the highest median costs for assessing a patient were reported for DPT (€190.0), followed by BAT/LTT (€90.0 for both), specific IgE quantification (€81.0), patch tests (€75.1), intradermal tests (€66.6), and SPT (€50.0) (Figure 1; Table S2; Appendix S1). Most reported cost estimates were either of medium or of low confidence (Table S2). Using multiple linear regression models, we observed that higher cost estimates were most frequently associated with the number of involved healthcare professionals (particularly for SPT and intradermal tests) and working in Northwestern Europe (for intradermal tests and DPT) (Appendix S1).

Estimates of the median paid amount for each test were highest for DPT (€112.7) and lowest for intradermal tests (€30.0), SPT (€28.8), and sIgE (€27.0) (Table S2; Appendix S1). For all assessed tests/procedures, the reimbursement to cost ratio (perceived amount paid dividing by the overall reported cost estimates) was lower than 100%, ranging from 44.4% for patch tests to 73.8% for DPT; these percentages were higher in Europe than in North America for SPT, intradermal tests, and DPT.

In our comprehensive literature review, we identified six publications assessing the costs of penicillin allergy diagnostic tests (namely skin tests and DPT),[3,5-9] five of which performed in North America[3,5-8] and one in Europe[9] (Table S3)—our median reported

TABLE 1 Description of the practice of penicillin allergy diagnosis tests reported by European and North American respondents (n = 51)

	Skin prick test	Intradermal test	Patch test	Specific IgE	Drug provocation test
Experience in performing the test/procedure—n (%)	48 (94.1)	47 (92.2)	31 (60.8)	34 (66.7)	48 (94.1)
Europe	42 (95.5)	41 (93.2)	29 (65.9)	33 (75.0)	41 (93.2)
North America	6 (85.7)	6 (85.7)	2 (28.6)	1 (14.3)	7 (100)
Percentage of patients with penicillin allergy label receiving the test/procedure—median (IQR)	75 (75)	80 (65)	15 (33)	30 (81)	80 (45)
Europe	85 (65)	80 (60)	20 (35)	30 (85)	80 (45)
North America	20 (58)	30 (53)	5 (0)	70[a]	98 (8)
Number of tests/procedures performed per patient—median (IQR)	5 (3)	5 (6)	3 (2)	3 (2)	3 (2)[b]
Europe	5 (3)	5 (6)	4 (3)	3 (2)	4 (2)[b]
North America	5 (1)	4 (5)	3 (0)	2[a]	2 (0.5)[b]
Number of drugs/determinants tested—median (IQR)	4 (2)	4 (3)	3 (2)	3 (2)	-
Europe	4 (3)	4 (2)	3 (2)	3 (1)	-
North America	4 (2)	4 (4)	5 (1)	2[a]	-
Aminopenicillin testing—n (%)	46 (95.8)	43 (91.5)	30 (88.2)	28 (90.3)	-
Europe	41 (97.6)	39 (95.1)	29 (87.9)	27 (93.1)	-
North America	5 (83.3)	4 (66.7)	1 (100)	1 (50.0)	-
Cephalosporin testing—n (%)	20 (41.7)	21 (44.7)	9 (26.5)	9 (26.5)	-
Europe	19 (45.2)	19 (46.3)	9 (27.3)	9 (27.3)	-
North America	1 (16.7)	2 (33.3)	0	0	-
Minutes required to perform each test/procedure—median (IQR)	45 (35)	45 (75)	40 (30)	180 (180)	300 (240)
Europe	45 (30)	60 (90)	40 (30)	180 (180)	300 (180)
North America	20 (30)	20 (34)	45 (15)	600[a]	120 (60)
Setting where the test/procedure is performed—n (%)					
Outpatient	31 (64.6)	27 (57.4)	24 (77.4)/24 (77.4)[c]	28 (82.4)[d]	20 (41.7)
Europe	25 (59.5)	21 (51.2)	22 (75.9)/22 (75.9)[c]	27 (81.8)[d]	13 (31.7)
North America	6 (100)	6 (100)	2 (100)/2 (100)[c]	1 (100)[d]	7 (100)
Inpatient	2 (4.2)	3 (6.4)	1 (3.2)/ 1 (3.2)[c]	1 (2.9)[d]	12 (25.0)
Europe	2 (4.8)	3 (7.3)	1 (3.5)/1 (3.5)[c]	1 (3.0)[d]	10 (24.4)
North America	0	0	0	0	2 (28.6)
Day ward	16 (33.3)	19 (40.4)	7 (22.6)/ 8 (25.8) [c]	1 (2.9) [d]	23 (47.9)
Europe	16 (38.1)	19 (46.3)	7 (24.1)/ 8 (27.6) [c]	1 (3.0) [d]	23 (56.1)
North America	0	0	0	0	0
Laboratory	0	0	1 (3.2)/1 (3.2)[c]	8 (23.5)[d]	0
Europe	0	0	1 (3.5)/ 1 (3.5)[c]	8 (24.2)[d]	0
North America	0	0	0	0	0
Number of patients assessed in the same room—median (IQR)	3 (4)	3 (4)	1 (2)/ 1 (2)[c]	-	3 (3)
Europe	4 (3)	3 (3)	2 (2)/ 1 (2)[c]	-	3 (4)
North America	1 (0.5)	1 (0.5)	1 (0)/ 1 (0)[c]	-	2 (2)
Number of healthcare professionals required to perform each test/procedure—median (IQR)	2 (1)	2 (1)	2 (1)/ 2 (1)[c]	2 (1)/ 2 (1)[e]	3 (1)
Europe	2 (1)	2 (1)	2 (1)/ 2 (1)[c]	2 (1)/ 2 (0)[e]	3 (2)
North America	2 (2)	2 (2)	3 (1)/ 2 (1)[c]	1/ 1[ae]	2 (1)

Abbreviations: IQR, interquartile range; max, maximum; min, minimum.

[a]No IQR and range are presented, as there is only one sIgE estimate from North America.

[b]These values correspond to the average number of testing doses given in a drug provocation test in the context of penicillin allergy (the median percentages for the frequency of patients requiring one, two or more than two drug provocation tests are, respectively, of 70% [IQR: 60%], 18% [IQR: 22%], and 10% [IQR: 19%]).

[c]Values for patch test preparation and application/Values for patch test results' reading.

[d]Values regarding the setting where blood sampling is performed.

[e]Values for blood sampling/Values for specific IgE quantification.

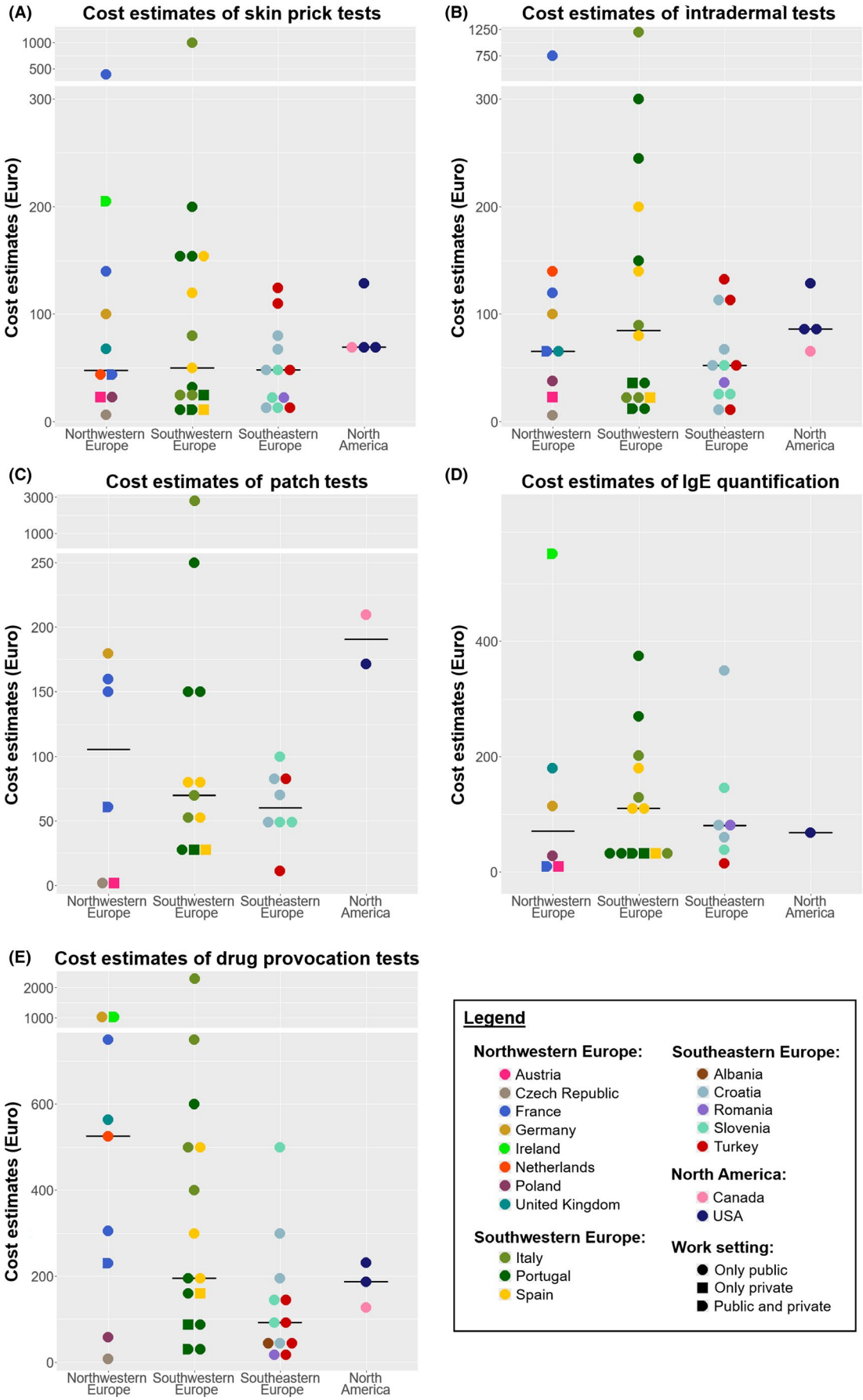

FIGURE 1 Respondent-reported cost estimates (in 2018 Euro) of skin prick tests (A), intradermal tests (B), patch tests (C), IgE quantification (D), and drug provocation tests (E) in patients with suspected penicillin allergy, by respondents' region, country, and work setting

material and personnel cost estimates were generally consistent with the values presented in those studies, while reported facilities costs may have been overestimated when compared to the value obtained in the only publication formally calculating space costs (€3).[8] Our cost assessment in a Portuguese private Allergy Unit identified a total cost per patient for skin tests of €41.7 (€14.3 for material costs + €27.4 for personnel costs) and for DPT of €78.6 (€10.1 for material costs + €68.5 for personnel costs) (Table S4). In the public sector, our cost assessment identified skin tests costs per patient of €95.0 (€73.5 for material costs + €21.5 for personnel costs) and DPT costs of €77.0 (€11.0 for material costs + €66.0 for personnel costs).

The estimates reported in this study provide unique contextual information on the need for context-based cost assessments and on when penicillin allergy testing might be cost-saving. This is particularly relevant as previous studies have shown that patients with a penicillin allergy label may have higher treatment costs due to the use of more expensive antibiotics and increased risk of hospital-acquired infections (resulting in longer hospital stays), readmissions, and more ambulatory visits[1-3]—therefore, by prompting an allergy delabeling in most patients, generalized testing could possibly be cost-saving.

This study has some important limitations regarding its sample size and low response rate. While the questionnaire length might have dissuaded some experts, we tried to minimize response fatigue by allowing skip patterns. Another potential limitation concerns the possibility of literacy-related sample biases, although we re-contacted respondents to clarify outliers/potential mistakes. Potential strengths include results novelty, the combined use of different methodologies, and the possibility of results exploration using an interactive app.

In conclusion, this study suggests that there is wide diversity in penicillin allergy testing practice and reported cost estimates, with median values ranging from €50.0 for SPT to €190.0 for DPT. Of note, respondents had not provided actual costs, but rather estimates based on their perceptions, and largely with low-medium confidence. The fact that cost estimates were largely higher than reported paid amounts merits further attention, as it might negatively influence penicillin allergy diagnostic practice, which may result in worse clinical outcomes and in an increased healthcare burden.

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CONFLICTS OF INTEREST

Eric Macy has received research grants from ALK (the sellers of Pre-Pen in the United States) and consulted for and is serving on a data and safety monitoring board for Audentes. No other author has conflicts of interest to declare within the scope of this study.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.