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A comparative study of different assays for autoantibodies detection in patients with autoimmune gastritis

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ABSTRACT

Objective: Autoimmune gastritis (AIG) is an important health problem and a risk factor for gastric neoplasms. This study assessed the diagnostic performance of different assays for anti-parietal cell antibodies (APCA) and anti-intrinsic factor antibodies (AIFA) in patients with histologically confirmed AIG.
Methods: This prospective, multicenter study included 50 AIG patients and 93 controls. The diagnostic performance of fluorescent enzyme immunoassay (FEIA) and immunoblot was evaluated for the detection of both APCA and AIFA, while indirect immunofluorescence (IIF) was assessed for APCA only.
Results: Overall, AIFA detection using FEIA demonstrated slightly better performance (specificity [Sp] 100 %, positive predictive value [PPV] 100 %, negative predictive value [NPV] 75 %) compared to immunoblot (Sp 98.9 %, PPV 94.1 %, NPV 73 %). However, both methods showed low sensitivity (Se): 38 % for FEIA and 32 % for immunoblot. When the FEIA cut-off was adjusted using ROC curve analysis, Se increased to 50 %, while maintaining high Sp (98.9 %). For APCA detection, Se was similar across all methods (~80 %), but Sp varied: immunoblot showed lower Sp (89.3 %) compared to IIF (98.8 %) and FEIA (95.7 %). PPV was highest for IIF (97.5 %), followed by FEIA (89.9 %) and immunoblot (89.3 %). NPV was lowest for immunoblot (80 %), while IIF and FEIA showed comparable values (89.5 % and 90.9 %, respectively). Adjusting the FEIA cut-off for APCA increased Sp to 98.9 % without reducing Se (76 %). Combining AIFA and APCA testing improved diagnostic performance, yielding a sensitivity of 90 % and specificity of 95.7 %.
Conclusions: FEIA offers superior diagnostic accuracy for APCA and AIFA testing in AIG. The highest diagnostic yield for AIG is observed when both APCA and AIFA are assessed. This approach could be clinically applicable in the screening for AIG and diagnostic process of AIG.

1. Introduction

Autoimmune atrophic gastritis (AIG) is an immune-mediated disorder of unknown etiology, characterized by the progressive destruction of parietal cells of the gastric oxyntic mucosa but sparing the antrum [1–3]. Consequently, hypochlorhydria and impaired intrinsic factor production eventually lead to malabsorption of iron, vitamin B12, and other micronutrients [4–7]. The prevalence of AIG is estimated at 2–4 % [8,9] and increases in the elderly and women [10]. AIG is often associated with other autoimmune diseases, such as autoimmune thyroiditis and diabetes mellitus type 1 [11,12]. Importantly, AIG is also associated with an increased risk of type 1 gastric neuroendocrine neoplasms and

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possibly gastric adenocarcinoma [3,13–18]. The serological hallmarks of AIG include anti-intrinsic factor (AIFA) and anti-parietal cell (APCA) antibodies, but variable diagnostic accuracies have been reported across studies [19,20]. Additionally, up to 20 % of AIG patients may have a "seronegative" (i.e., AIFA and APCA negative) disease [21,22]. This underscores the need to improve AIG diagnostic strategies to prevent AIG-associated neoplasia and micronutrient deficiencies [7]. Indirect immunofluorescence (IIF), considered the gold standard, suffers from confounding factors [23], In another commonly used technique, immunoblot, results are expressed only in a semi-quantitative manner [24]. On the other hand, automated techniques, such as enzyme-linked immunosorbent assay (ELISA), demonstrated enhanced diagnostic performances [20,25]. Introducing another automated technique, fluorescent enzyme immunoassay (FEIA), has generalized access to autoantibody testing in AIG, but the lack of serological testing guidelines remains a major limitation. Only a few studies have compared the diagnostic performances of different assays in AIG, mostly comparing IIF with ELISA, often lacking histopathological confirmation [20,25,26]. Starting from these premises, this study aimed to evaluate the diagnostic performances of different autoantibody assays (FEIA, immunoblot, IIF) in biopsy-proven AIG.

2. Materials and methods

Patients previously included in our prospective, multicenter, cross-sectional study were selected from the biobank [27]. In brief, the original study protocol was as follows: (i) patients admitted for upper endoscopy in four French University Hospitals between 2016 and 2019 were candidates for inclusion; (ii) the upper endoscopy with gastric biopsies according to the Sydney protocol was performed in all patients, with at least two biopsies from the antrum, and two from the corpus (iii) fasting blood sample was obtained, subsequently (iv) the presence, severity, and extent of atrophy were evaluated by histopathological analysis of gastric biopsies according to the updated Sydney system [27, 28]. AIG was diagnosed histologically as corpus/fundus mucosal atrophy, with or without intestinal metaplasia and enterochromaffin-like cell hyperplasia. Patients with normal gastric mucosa or non-atrophic gastritis were included in the control group. Of 394 patients, 33 were excluded due to the absence of biopsies from two sites (corpus and antrum), four due to gastric adenocarcinoma at the initial examination, 109 samples representing *H. pylori* related-gastritis, 108 samples representing patients with non-atrophic gastritis from the control group, and 10 patients due to the lack of serum samples.

Overall, 93 were included in the control group, and 37 with AIG were included in the study group, with 13 additional samples from newly diagnosed AIG patients from CHU Nantes. Serum APCA and AIFA were assessed using immunoblot automated on BlueDiver instrument (Alphadia, Belgium) and FEIA (Fluorescence Enzyme Immunosorbent Assay) automated on Phadia™ 250 (ThermoFisher Scientific, USA), following manufacturers' protocols. For the detection of AIFA and APCA by immunoblot, purified intrinsic factor from porcine stomach and purified H^+/K^+ ATPase from porcine gastric mucosa were respectively used as antigens and immunoblot analysis was performed with the BlueScan and Dr Dot Software (D-Tek, Mons, Belgium). The threshold used was >5 UA, threshold defined as equivocal result by the manufacturer. For AIFA and APCA detection by FEIA, human intrinsic factor and purified H^+/K^+ ATPase from porcine gastric mucosa were respectively used as antigens. A positive threshold of >7U/mL, corresponding to equivocal results according to manufacturer's instructions, was used. APCA were also evaluated by IIF on rat tissue sections (Biosystems, Spain) with fluorescein-conjugated anti-human immunoglobulin (Bio-Rad, USA) and a sera dilution of 1:40 followed, in case of positivity, by serial dilutions (1:40–1:320). IgG anti-*Helicobacter pylori* were analyzed by ELISA (GastroPanel®, Biohit Oyj; positivity threshold >30 EIU). Sensitivity (Se), Specificity (Sp), Positive and Negative Predictive Value (PPV, NPV) and area under the curve (AUC) were calculated, with receiver operating characteristics (ROC) for threshold evaluations. Inter-assay agreements were measured as concordant percentages, with Cohen's kappa (κ) estimating concordance. Spearman's rank test analyzed correlations, %CV assessed variability, and chi-square/Mann-Whitney *U* test compared variables. Data were visualized using GraphPad® Prism. The study followed the Declaration of Helsinki and was approved by the Institutional Review Board on November 8, 2011. It was registered on clinicaltrials.gov under the number NCT02624271. The bio-collection derived from the study was registered under the number DC-2011-1399**.** Written informed consent was obtained from all the patients.

3. Results

Fifty AIG patients (28 females, 22 males; age 61.0 ± 16.4 years) and 93 controls [84 with normal gastric mucosa, 9 with non-atrophic gastritis (54 females, 39 males, $p = 0.8$; 54.7 ± 14.8 years, $p = 0.1$)] were included. Six (12 %) AIG patients and 2 (2.1 %) controls were *H. pylori*-positive (serum and/or histology), $p = 0.001$. The AIG and control groups were well balanced regarding age and sex ($p > 0.05$), but *H. pylori* positivity was higher in the study group ($p = 0.001$).

AIFA and APCA diagnostic performances, based on manufacturer thresholds, are summarized in Table 1.

AIFA assays presented high Sp and PPV (Sp 100 % vs. 98.9 %; PPV 100 % vs. 94.1 % for FEIA vs. immunoblot, respectively) but low Se (38 % vs. 32 %). ROC curves-based threshold adjustment improved AIFA-FEIA Se and NPV to 50 % and 78.6 %, respectively (Fig. 1A, Table 2). Concordance between FEIA and immunoblot was excellent (κ:0.873, global agreement 97.2 %, Table 1), and AIFA levels positively correlated ($r = 0.658$, $p < 0.001$; Fig. 1B). Notably, FEIA showed less variability than immunoblot (%CV FEIA: 5.4–8.5 %; Immunoblot: 23.5–30.6 %; Supplementary Table 1).

APCA detection was similar for all methods (Se ~80 %), but IIF showed the highest Sp (98.8 %; Table 1). Only 1 control tested positive by IIF, 4 by FEIA and 10 by immunoblot. All of these were low-positive results, except for one control, who was highly positive across all three assays. The 4 APCA positive cases by FEIA were also positive by immunodot. Moreover, antibody titers were significantly lower in the control group compared to AIG patients using both methods (1.4 UA vs 37 UA with immunoblot, and 1.7 U/mL vs 59.1 U/mL with FEIA; $p < 0.001$) (Supplementary Fig. 1). Again, adjusting the APCA threshold for FEIA improved Sp while preserving Se (Fig. 1C–Table 2). The concordance between methods was excellent (κ:0.882–0.965) with positive correlation (FEIA and IIF: $r = 0.826$, $p < 0.001$, FEIA and immunoblot: $r = 0.843$, $p < 0.001$, Fig. 1D and E, respectively**,** Table 1). Variability was lower in FEIA (5.6–6.8 %) than in immunoblot (18–18.9 %) (Supplementary Table 1). Intra-assay variability was also evaluated for FEIA and lead to low CVs for both APCA and AIFA after ten repeated measurements in a single run (4.2 % and 5.1 %, respectively).

Crucially, the ability to capture AIG patients improved greatly when considering FEIA positivity for AIFA and APCA, either alone or in combination with Se 90 %, Sp 95.7 %, and PPV, NPV exceeding 90 % (Table 2). Double positivity achieved 100 % specificity.

4. Discussion

Serological AIG diagnosis is challenging due to variability in detection methods and a lack of standardized guidelines, leaving assay selection dependent on local availability. Since gastric H/K ATPase was identified as the target of APCA, various immunoassays, such as ELISA, immunoblot, or FEIA, have been developed. These automated assays reduced operator dependency, a significant limitation of the IIF method. However, a lack of standardization of these methods (different antigenic sources, detection approaches and positive cut-offs) could still lead to variable diagnostic accuracy, hence affecting the concordance between APCA assays.

Table 1
Diagnostic accuracy and concordance of different assays for detecting AIG with APCA and AIFA.

AIFA										
Method	Positive results (n)		Se (%)	Sp (%)	NPV (%)	PPV (%)	AUC	Cohen's kappa	Concordance (%)	
	AIG *n=50*	Control *n=93*					ND	FEIA	FEIA	
Immunoblot	16	1	32.0	98.9	73.0	94.1	ND	0.873	97.2	
FEIA	19	0	38.0	100	75.0	100	0.781	1		
APCA										
Method	Positive results (n)		Se (%)	Sp (%)	NPV (%)	PPV (%)	AUC	Cohen's kappa		Concordance (%)	
	AIG *n=50*	Control *n=93*[1]					IIF	FEIA	IIF	FEIA	
IIF[1]	39	1	79.6	98.8	89.5	97.5	ND	1	0.965	x	98.5 %
Immunoblot	40	10	80.0	89.3	80.0	89.3	ND	0.882	0.905	94.8	95.8
FEIA	40	4	80.0	95.7	90.9	89.9	0.948	0.965	1	98.5	x
Combination of antibodies										
Assessment	Positive results (n)			Se (%)		Sp (%)		NPV (%)		PPV (%)
	AIG *n=50*	Control *n=93*								
APCA + AIFA	14	0		28.0		100		72.1		100
APCA and/or AIFA	45	4		90.0		95.7		94.7		91.8

AIG, auto-immune gastritis; AIFA, anti-intrinsic factor antibodies; APCA, anti-parietal cell antibodies; AUC, Area under curve; FEIA, fluorescent enzyme immunoassay; IIF, indirect immunofluorescence; Se, sensitivity; Sp, specificity; NPV, negative predictive value; PPV, positive predictive value; ND, not determined. Positive results for AIFA and APCA with the FEIA method were defined with a cut-off >7 U/mL. Screening dilutions for IIF for APCA were 1/40, followed by serial dilutions (1/40–1/320) for titer determinations.
[1] For IIF, eight sera were not determined, one in the AIG group and 7 in the control group.

This study found FEIA superior to immunoblot and IIF, with 90 % sensitivity and 95.7 % specificity when combining APCA and AIFA in a cohort of biopsy-proven AIG. FEIA offers higher reproducibility and less inter-assay variation (<10 %), unlike subjective IIF, which is prone to differences in interpretation and variability in cell fixation conditions [29]. Moreover, interference from heterophile antibodies can lead to nonspecific staining in IIF, as observed in eight samples from our study. For APCA detection, specificity was highest for IIF, producing fewer false positives in controls, as in other studies [23]. Adjusting the FEIA cut-off for APCA improved specificity while maintaining sensitivity, thus enhancing its diagnostic value. AIFA detection was highly specific but less sensitive (32–38 %). Although method concordance was high, immunoblot displayed greater inter-assay variability than FEIA. This can be explained by a less automated process compared to FEIA. The use of the BlueDiver system for immunoblot in our study allowed partial automation of the immunoblot procedure, including steps such as washing and reagent distribution. However, sample distribution remained a manual step, introducing a potential source of variability. Moreover, the methods of signal detection differ between FEIA which is a quantitative method that uses a calibration curve, whereas immunoblot is a semi-quantitative method based on the visual comparison of antigen dot color intensity against a negative control. This semi-quantitative approach may increase the number of borderline results, negatively impacting both sensitivity and specificity. The observed difference in sensitivity for AIFA detection between FEIA and immunoblot may also be related to the source of antigen: immunoblot uses purified porcine antigens, while FEIA employs human recombinant antigens.

It was previously shown that detection of APCA in ELISA has higher sensitivity than with IIF [25]. In a study by Lahner et al., APCA with ELISA achieved 81 % sensitivity and 90 % specificity. In our study, the results regarding sensitivity were very similar, ~80 % in each method (IIF, immunoblot, FEIA), whereas specificity was the highest in IIF (98.8 %, followed by FEIA (95.7 %), and immunoblot (89.3 %). In our study, AIFA had a sensitivity of 32 % in the immunoblot technique and 38 % in FEIA. In contrast, in the study by Laher et al., the sensitivity with ELISA was assessed at 27 %. Specificity in both our and Laher's study for AIFA was 100 % [20] While ELISA is a viable alternative to IIF, showing better APCA and AIFA detection performance with good inter-assay variability [25,26], FEIA, a newer immunoenzymatic method, offers full automation and flexibility, making it ideal for routine diagnostics. A prior study showed comparable results between ELISA and FEIA for AIG antibodies but lacked histological data [26]. Our study confirms FEIA's superior diagnostic performance over immunoblot and IIF for diagnosing AIG.

The seropositivity of APCA and AIFA is the hallmark of AIG [20]. APCA is detected in 80 % of AIG patients, including asymptomatic cases, and may predict future AIG (potential AIG) [12,25]. AIFA, present in 30–60 % of AIG cases, is highly specific. APCA are also found in ~10 % of healthy individuals (true false positives) [30], with detection rates varying by method. This suggests that antibody positivity in a healthy population might be method-dependent.

This study's strengths include a prospective, multicenter design and histological confirmation of AIG, which reduces bias. Limitations include a small AIG cohort, a lack of information about the health status of the control group beyond the absence of AIG, particularly regarding the presence of other autoimmune diseases and/or medical conditions, which could potentially act as a confounding factor. Additionally, higher *H. pylori* prevalence was noted in the AIG group, although unlikely to affect the outcomes. Several patients were receiving vitamin B12 supplementation at the time of inclusion; therefore, vitamin B12 status was not considered in the analyses of this study. It is also important to note that potential diagnostic inaccuracies regarding biopsy sampling and classification should be considered when interpreting our findings. Antibody testing used FEIA, immunoblot, and IIF, but further comparisons with automated assays are needed.

Overall, we conclude that FEIA offers superior diagnostic accuracy for APCA and AIFA testing in AIG, and that the highest diagnostic yield is observed when both APCA and AIFA are assessed. This approach could be clinically applicable as the preferred method for AIG screening and diagnosis.

CRediT authorship contribution statement

Małgorzata Osmola: Writing – review & editing, Writing – original draft, Validation, Methodology, Data curation. **Caroline Hémont:** Methodology, Data curation, Conceptualization. **Marcin Romańczyk:** Writing – review & editing, Writing – original draft, Conceptualization. **Amaury Druet:** Writing – original draft. **Nicolas Chapelle:** Writing – original draft. **Tamara Matysiak-Budnik:** Writing – review & editing, Writing – original draft, Validation, Project administration, Conceptualization. **Marco Vincenzo Lenti:** Writing – review & editing, Writing – original draft, Validation, Methodology, Conceptualization. **Jérôme C. Martin:** Writing – review & editing, Validation, Project administration, Methodology, Investigation, Funding acquisition, Data curation,

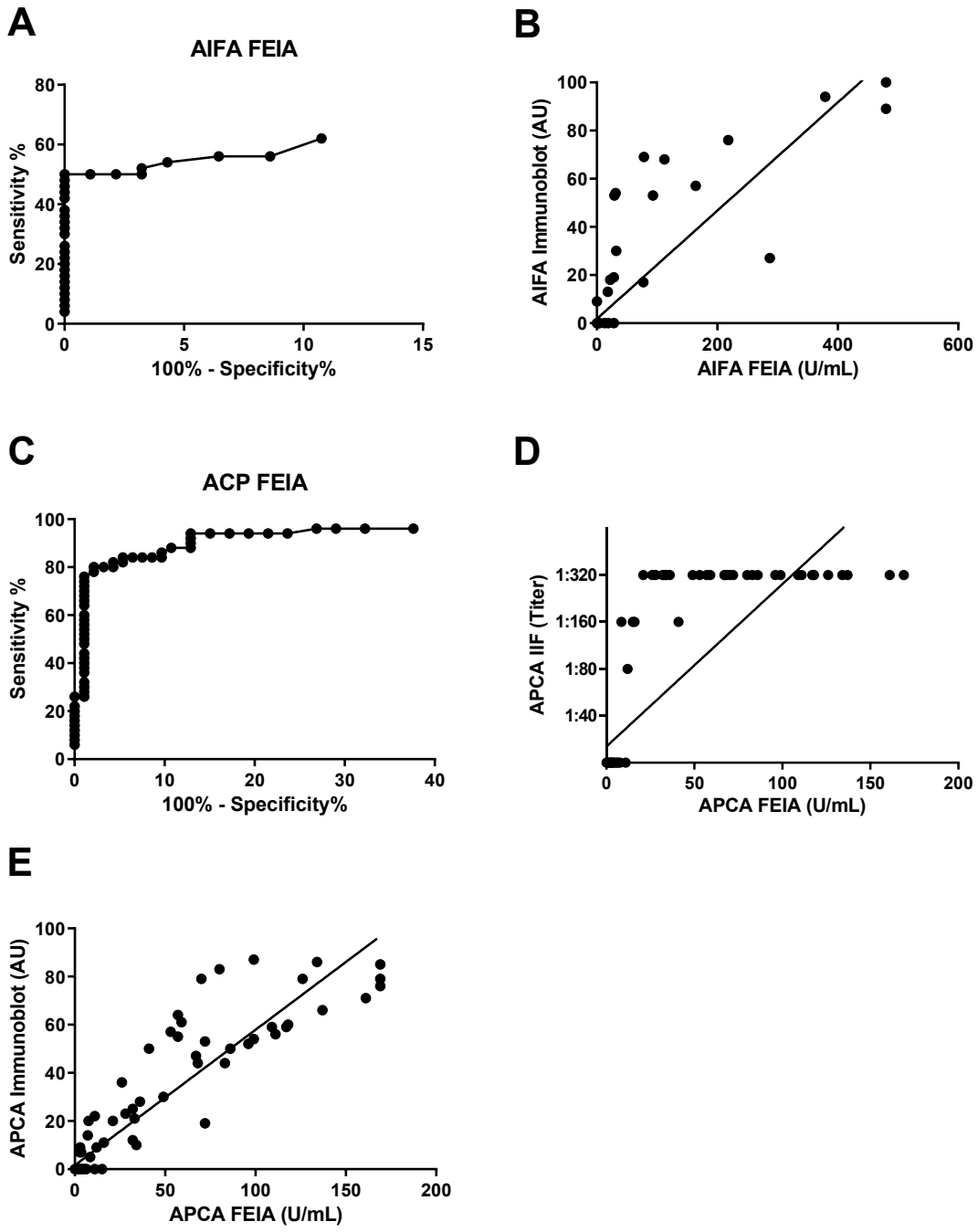

Fig. 1. Diagnostic performance for (A) anti-intrinsic factor antibodies, (C) anti-parietal cell antibodies with FEIA method. Correlation between different assays for antibody concentration (B, D, E).
Correlation between antibody concentration according to the different assays. Spearman test: B: $p < 0.001$, $r = 0.658$, D: $p < 0.001$, $r = 0.826$, E: $p < 0.001$, $r = 0.843$; APCA, anti-parietal cell antibodies; AIFA, anti-intrinsic factor antibodies; APCA, anti-parietal cell antibodies; IIF, indirect immunofluorescence; FEIA, fluorescent enzyme immunoassay; AU, arbitrary unit.

Conceptualization.

Potential competing interests

MO received travel grants from Angelini Pharma, Accord, and honoraria for lectures from Bayer, Astellas, and Sandoz, not related to the topic of this article; CH, MR, AD, NC, TMB, MVL, JCM: no conflict of interest.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Malgorzata Osmola reports a relationship with Angelini Pharma that includes: travel reimbursement. Malgorzata Osmola reports a relationship with Accord Healthcare Inc that includes: travel reimbursement.

Table 2
Diagnostic performance of APCA and AIFA after adjusting the cut-off with receiver operating characteristics for threshold evaluations.

		Cut-off (U/mL)	Se (%)	Sp (%)	PPV (%)	NPV (%)
APCA FEIA	Manufacturer's cut-off	7	80.0	95.7	90.9	89.9
	ROC cut-off	11,5	76.0	98.9	97.4	88.5
AIFA FEIA	Manufacturer's cut-off	7	38.0	100.0	100.0	75.0
	ROC cut-off	2.2	50.0	98.9	96.2	78.6

AIFA, anti-intrinsic factor antibodies; APCA, anti-parietal cell antibodies; FEIA, fluorescent enzyme immunoassay; Se, sensitivity; Sp, specificity; NPV, negative predictive value; PPV, positive predictive value; ROC, receiver operating characteristics.

Malgorzata Osmola reports a relationship with Bayer Corporation that includes: speaking and lecture fees. Malgorzata Osmola reports a relationship with Astellas Pharma Inc that includes: speaking and lecture fees. Malgorzata Osmola reports a relationship with Sandoz Inc that includes: speaking and lecture fees. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jtauto.2025.100294.

Data availability

Data will be made available on request.

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