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Reproducibility of Lung and Liver Volume Measurements on Fetal Magnetic Resonance Imaging in Left-Sided Congenital Diaphragmatic Hernia

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Keywords
Congenital diaphragmatic hernia · Fetal magnetic resonance imaging · Fetal therapy · Pulmonary hypoplasia · Prenatal diagnosis

Abstract
Introduction: Congenital diaphragmatic hernia (CDH) affects 1 in 3,000 live births and is associated with significant morbidity and mortality. ***Methods:*** A review of fetal magnetic resonance imaging (MRI) examinations was performed for fetuses with left CDH and normal lung controls. Image review and manual tracings were performed by 4 pediatric radiologists; right and left lung volumes in the coronal and axial planes as well as liver volume above and below the diaphragm in the coronal plane were measured. Intra- and interreviewer reproducibility was assessed using intraclass correlation coefficient (ICC) and Bland-Altman analysis. ***Results:*** Excellent intra- and interreviewer reproducibility of the right and left lung volume measurements was observed in both axial planes (interreviewer ICC: right lung: 0.97, 95% CI: 0.95–0.99; left lung: 0.97, 95% CI: 0.95–0.98) and coronal planes (interreviewer ICC: right lung: 0.97, 95% CI: 0.95–0.98; left lung: 0.96, 95% CI: 0.93–0.98). Moderate-to-good interreviewer reproducibility was observed for liver volume above the diaphragm (ICC 0.7, 95% CI: 0.59–0.81). Liver volume below the diaphragm had a good-to-excellent interreviewer reproducibility (ICC 0.88, 95% CI: 9.82–0.93). ***Conclusions:*** The present study demonstrated an excellent intra- and interreviewer reproducibility of MRI lung volume measurements and good-to-moderate inter- and intrareviewer reproducibility of liver volume measurements after standardization of the methods at our fetal center.

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Introduction

Congenital diaphragmatic hernia (CDH), which affects 1 in 3,000 live births, is characterized by abnormal formation of the diaphragm with subsequent thoracic herniation of abdominal viscera [1]. CDH is associated with significant morbidity and mortality due to pulmonary hypoplasia and pulmonary arterial hypertension [2–

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5]. Fetal endoscopic tracheal occlusion (FETO) has been shown to improve lung development in severe CDH [6–10], and accurate disease prognostication is essential for appropriate selection of candidates that could benefit from FETO.

Sonographic and MRI prognostic markers have been proposed to facilitate the selection of potential FETO candidates and prenatal counseling [11]. Compared to ultrasound, fetal magnetic resonance imaging (MRI) offers significantly increased soft tissue contrast of the fetal lungs and mediastinal structures, allows for improved multiplanar imaging, and is not hindered by factors such as maternal habitus [12]. The MRI-derived observed-to-expected total fetal lung volume (O/E-TFLV) and the percentage of liver herniation above the diaphragm (%LH) have both been correlated with the need for extracorporeal membrane oxygenation (ECMO), risk of chronic lung disease, and pulmonary hypoplasia as well as perinatal morbidity and mortality [13, 14].

In order to optimize postnatal outcomes of perinatal CDH management, it is imperative to develop, validate, and standardize prenatal prognostic tools used for CDH evaluation. The process of measuring lung and liver volumes with MRI is well documented [13, 15–17], but the reproducibility of these measurements is seldom reported [14, 18, 19]. The objective of the present study was to assess the reproducibility of manually generated lung volumes and liver volumes above and below the diaphragm, after standardization of the methods at our fetal center.

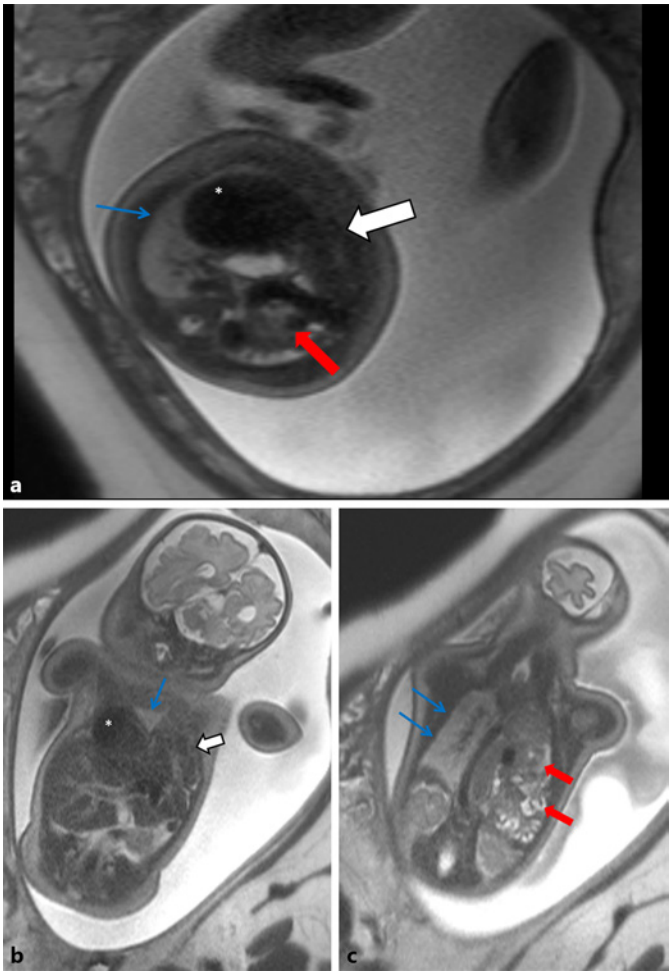

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Fig. 1. Example SSFSE axial and coronal images from prenatal MRI performed for left-sided CDH with bowel and liver herniation. **a** Axial slice through the lower thorax shows loops of herniated small bowel and colon (red arrow) and a portion of left lobe of the liver (white arrow) herniated in the left chest. The heart is shifted into the right chest (asterisk). A portion of normally developing right lung is seen (blue arrow). **b** Coronal slice through the anterior chest shows a portion of left lobe of the liver herniated through the CDH into the left chest (white arrow). The heart is shifted into the right chest (asterisk). The hypoplastic left lung is seen shifted high in the left chest (blue arrow). **c** Coronal slice through the posterior chest shows normally developing left lung (blue arrows) and herniated small bowel and colon extending to the apex of the left chest (red arrows). SSFSE, single-shot fast spin echo; MRI, magnetic resonance imaging; CDH, congenital diaphragmatic hernia.

Methods

Study Design

We performed a prospective, blinded evaluation of 38 fetal MRI examinations to access the reproducibility of the measurements of fetal lung volumes and herniated liver volumes. Our institution's radiology informatics system was used to identify all fetal MRI evaluations performed between January 2017 and December 2018 at out fetal center. Of these, 16 prenatal MRI evaluations (involving 12 patients) performed for left CDH evaluation were identified as fetal CDH lung cases and 22 MRI evaluations performed for other indications were identified to serve as normal lung controls. The Institutional Review Board approved the study (IRB# 16-008333). All patients gave written consent. The present study was conducted ethically in accordance with World Medical Association Declaration of Helsinki.

MRI Evaluation

We utilize 1.5-T imaging for fetal MRI at our institution, performing standard single-shot fast spin echo (SSFSE) and balanced steady-state free precession (b-SSFP) series in the axial and coronal planes including the lungs and upper abdomen. Typical SSFSE scanning parameters include TE 1,500–3,000, TR 90 ms, slice thickness 3–5 mm skip 0 mm, and matrix 256 × 128. Field of view is prescribed to maximize spatial resolution and signal. T1 spoiled gradient echo imaging can occasionally assist with delineating the mildly hyperintense liver from adjacent structures, following the methods previously described [12, 15].

A single radiologist (A.B.K.) reviewed all series in each MRI to identify axial and coronal SSFSE series with the least motion (as

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shown in Fig. 1). Four board-certified pediatric radiologists with fellowship and post-fellowship years of subspecialty experience of 4 years (N.C.H.), 8 years (A.B.K.), 9 years (P.G.T.), and 20+ years (K.B.T.) reviewed the MRI series in a randomized and blinded fashion. The dataset was reviewed by each radiologist twice with 3 months between both iterations in an attempt to mitigate recall bias. VISAGE PACS workstation (Visage Imaging, San Diego, CA, USA) was used for image review and to generate manual tracings. Reviewers were also blinded to their first set of results and to one another's results.

The following were evaluated from the MRI series: left and right lung volumes on the axial series; left and right lung volumes on the coronal series; and volume of the liver above and below the diaphragm on the coronal series. Manual tracing of the region of interest was performed independently by each radiologist (as shown in Fig. 2). The left and right lung volumes were calculated as the sum of the areas of the region of interest on each slice multiplied by the slice thickness. Liver volumes were determined similarly.

CDH Management

All cases of CDH were managed with a standard protocol developed at our fetal center. Since early 2017, we have also offered prenatal management (FETO) for eligible candidates according to our protocol [9]. Postnatally, all neonates affected with CDH are intubated immediately after delivery, provided with ventilator support, and transferred to the neonatal intensive care unit. ECMO is performed as indicated, and surgical diaphragmatic closure is performed in the early neonatal period after hemodynamic and respiratory stability is achieved.

Statistical Analysis

Statistical analysis was performed using R 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria) software. Within-reviewer variability was measured with intraclass correlation coefficient (ICC) and Bland-Altman analysis. To compare all reviewers, generalized linear mixed models with random effect were used to assess ICC among reviewers. The reviewer with 20+ years of experience was defined as the expert reviewer for comparisons within the Bland-Altman analysis [3]. We classified the level of reproducibility as excellent, good, moderate, or poor based on the 95% confidence intervals (CIs) of the ICC estimates (>0.9, between 0.75 and 0.9, between 0.5 and 0.75, and <0.5, respectively) [20]. Correlation between fetal lung volumes measured in axial and coronal views was evaluated using the Spearman test.

Results

A total of 34 patients met our inclusion criteria, with 22 normal lung controls and 12 left CDH patients. The mean gestation age (GA) at MRI evaluation of the CDH patients and controls was 28 ± 5 weeks and 27 ± 5 weeks, respectively ($p > 0.05$). In the CDH group ($n = 12$), the mean GA at delivery was 36. 8 ± 3.1 (median, 38.9; range, 30.6–39.3) weeks, 63.6% delivered vaginally ($n = 7$), 33.3% were managed prenatally with FETO ($n = 4$), 16.7% required ECMO ($n = 2$), and 72.7% survived to discharge ($n = 11$) (Table 1).

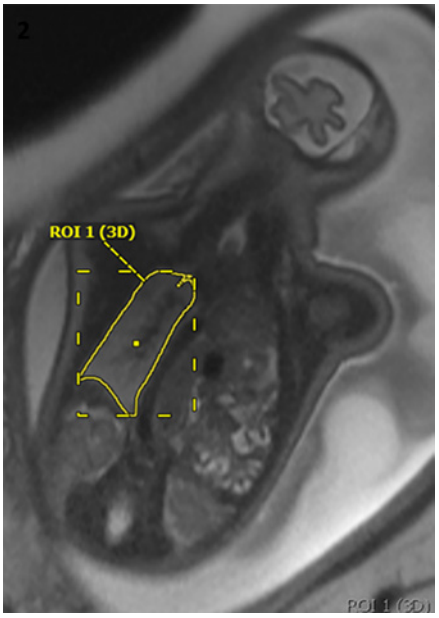

Fig. 2. Example of manual tracing of the lung in fetus with CDH. Coronal image through the chest of a fetus with left CDH containing multiple loops of bowel. Region of interest tracing delineates the right lung shown on this slice. The area is automatically calculated by the PACS software. CDH, congenital diaphragmatic hernia.

A total of 380 measurements were performed per operator, with a total of 1,520 measurements). Right and left lung volumes had excellent intra- and interreviewer reproducibility in both the axial (interreviewer ICC: right lung: 0.97, 95% CI: 0.95–0.99; left lung: 0.97, 95 CI: 0.95–0.98) and coronal series (interreviewer ICC: right lung: 0.97, 95% CI: 0.95–0.98; left lung: 0.96, 95% CI: 0.93–0.98) (Table 2). Good reproducibility was observed for fetal lung volumes measured before and at 28 weeks for axial series (interreviewer ICC: right lung: 0.85, 95% CI: 0.75–0.93; left lung: 0.91, 95 CI: 0.84–0.96) and coronal series (interreviewer ICC: right lung: 0.92, 95% CI: 0.80–0.98; left lung: 0.81, 95% CI: 0.78–0.90), as well as those volumes measured after 28 weeks for axial series (interreviewer ICC: right lung: 0.97, 95% CI: 0.94–0.99; left lung: 0.99, 95 CI: 0.97–0.99) and coronal series (interreviewer ICC: right lung: 0.95, 95% CI: 0.89–0.98; left lung: 0.98, 95% CI: 0.96–0.99). Good correlations were observed for fetal lung volumes when measured in the axial view or coronal view (right lung volumes – R: 0.97, $p < 0.001$, and left lung volumes – R: 0.78, $p = 0.001$).

The liver volume above the diaphragm had moderate-to-good interreviewer reproducibility (ICC 0.7, 95% CI: 0.59–0.81) and intrareviewer ICC ranged from 0.72 to

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Table 1. Patient demographics and outcomes of CDH patients

Patient ID	GA at fetal MRI scan	Diagnosis*	FETO‡	GA at FETO‡	GA at delivery	Mode of delivery†	ECMO	Survival to discharge
1	23.9 34.4	Isolated left CDH	Yes	28.6	38.6	V	No	Yes
2	24.4	Isolated left CDH	Yes	28.3	32.3	EXIT	No	Yes
3	24.3	Isolated left CDH	No	na	39.3	V	No	No
4	21 33.7	Isolated left CDH	Yes	28	39.1	V	No	Yes
5	33.6	Isolated left CDH	Yes	29.3	34.6	V	Yes	No
6	24.6	Isolated left CDH	No	na	Missing data	Missing data	Missing data	Missing data
7	24.7	Twins; 1 with isolated left CDH	No	na	30.6	C-section	No	Twin with CDH did not survive
8	24 34.6	Isolated left CDH	No	na	39.1	V	No	Yes
9	30.9	Isolated left CDH	No	na	39.1	V	No	Yes
10	28.1	Isolated left CDH	No	na	38.9	V	No	Yes
11	25 36.3	Isolated left CDH	No	na	39.1	C-section	Yes	Yes
12	24.4	Isolated left CDH	No	na	34.1	C-section	No	Yes

ECMO, extracorporeal membrane oxygenation. * CDH, congenital diaphragmatic hernia. ‡ FETO, fetal endoscopic tracheal occlusion; GA, gestational age; na, not applicable. † C-section, cesarean section; EXIT, extrapartum intrauterine treatment; V, vaginal delivery.

0.98. On the other hand, the liver volume below the diaphragm had a good-to-excellent interreviewer reproducibility (ICC 0.88, 95% CI: 9.82–0.93) and the intrareviewer ICC ranged from 0.83 to 0.98 (Table 2). ICC models were fit for normal and CDH patients with no meaningful differences considering the lung and liver volumes.

Reviewer 2 consistently had the lowest bias when compared to reviewer 1 (the designated expert reviewer), with the lowest bias noted for coronal left lung volume (bias 95% CI: −0.73 [−4.81 to 3.35]). Bias was consistently highest in volume of the liver below the diaphragm with a bias ranging from 1.36 to 4.14 units (Table 3).

Discussion

FETO is rapidly becoming a viable alternative for fetuses affected by severe CDH (O/E-LHR <25%) since early trials first demonstrated its feasibility and safety [7, 21]. As such, disease prognostication and accurate selection of potential FETO candidates have become a priority for optimal treatment outcomes. In light of this, several sonographic and MRI tools have been proposed and are an integral part of prenatal CDH work up in most fetal centers. Although sonographic O/E-LHR [3] and LiTR [5] have been shown to be highly reproducible, stomach position only has a fair-to-moderate interoperator reproducibility [13]. In the present study, we evaluated the reproducibility of manually generated lung and liver volume tracings on fetal MRI.

This study shows that right and left lung volume measurements have excellent inter- and intrareviewer reproducibility in both the axial and coronal planes. A moderate-to-good interreviewer reproducibility was observed for the liver volume above the diaphragm, and a good-to-excellent interreviewer reproducibility was observed for the liver volume below the diaphragm. Furthermore, intrareviewer reproducibility was good for liver volume above and below the diaphragm.

Fetal MRI lung volume measurements have been correlated with postnatal outcomes of CDH. Gorincour et al. [22] demonstrated a significant association between sur-

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Table 2. Inter- and intrareviewer ICC of lung and liver volume measurements

Volume measurement	Reviewer	Intrareviewer ICC (95% CI)	Interreviewer ICC (95% CI)
Axial right lung volume	1	1 (0.99–1)	0.97 (0.95–0.99)
	2	0.99 (0.98–0.99)	
	3	0.99 (0.99–1)	
	4	1 (0.99–1)	
Axial left lung volume	1	0.99 (0.99–1)	0.97 (0.95–0.98)
	2	0.99 (0.98–0.99)	
	3	0.99 (0.98–1)	
	4	0.99 (0.98–1)	
Coronal right lung volume	1	0.99 (0.98–1)	0.97 (0.95–0.98)
	2	0.97 (0.94–0.98)	
	3	0.99 (0.99–1)	
	4	0.99 (0.99–1)	
Coronal left lung volume	1	0.99 (0.98–1)	0.96 (0.93–0.98)
	2	0.97 (0.94–0.98)	
	3	0.99 (0.99–1)	
	4	0.99 (0.99–1)	
Liver volume above the diaphragm	1	0.72 (0.52–0.85)	0.7 (0.59–0.81)
	2	0.97 (0.95–0.99)	
	3	0.93 (0.88–0.96)	
	4	0.72 (0.53–0.85)	
Liver volume below the diaphragm	1	0.98 (0.93–0.99)	0.88 (0.82–0.93)
	2	0.94 (0.88–0.97)	
	3	0.83 (0.7–0.91)	
	4	0.79 (0.64–0.89)	

ICC, intraclass correlation coefficient; CI, confidence interval.

Table 3. Bland-Altman analysis

Variable	Reviewer	Bias, 95% CI (Bland-Altman analysis)
Axial right lung volume	1	Reference
	2	−1.92 (−6.04 to 2.21)
	3	−3.61 (−11.12 to 3.91)
	4	−3.45 (−7.87 to 0.97)
Axial left lung volume	1	Reference
	2	−1.2 (−4.05 to 1.64)
	3	−3.3 (−8.35 to 1.75)
	4	−2.74 (−6.78 to 1.29)
Coronal right lung volume	1	Reference
	2	−1 (−5.9 to 3.89)
	3	−4.16 (−12.71 to 4.38)
	4	−2.97 (−7.89 to 1.95)
Coronal left lung volume	1	Reference
	2	−0.73 (−4.81 to 3.35)
	3	−3.22 (−8.91 to 2.46)
	4	−2.31 (−6.45 to 1.83)
Liver volume above the diaphragm	1	Reference
	2	0.98 (−5.76 to 7.73)
	3	1.53 (−6.44 to 9.5)
	4	−1.82 (−11.57 to 7.94)
Liver volume below the diaphragm	1	Reference
	2	−1.36 (−17.08 to 14.36)
	3	−7.88 (−31.1 to 15.34)
	4	−4.14 (−28.58 to 20.3)

CI, confidence interval.

vival and the measured/expected fetal lung volume ratio in a retrospective cohort of 77 fetuses with isolated CDH. Cannie et al. [23] also reported a similar finding with MRI O/E-TFLV. These findings are further supported by the reports of Zamora et al. [14] and Ruano et al. [13] who demonstrated that not only were MRI O/E TFLV <35% (area under curve = 0.74; $p < 0.001$) and %LH >20% (area under curve = 0.78; $p < 0.001$) predictive of postnatal outcomes, but also a combination of both parameters had an even better prediction of the need for ECMO and mortality (accuracy of 83%).

The measurement of fetal lung volume by MRI is a tedious process. The most important requirement is an adequate MRI series of the fetus which is as motion free as possible and provides adequate soft tissue contrast and spatial resolution to depict the lung relative to adjacent structures. Ultrafast sequences which freeze in-plane motion are utilized such as b-SSFP and SSFSE. For lung volume measurements, SSFSE is preferred for the superior soft tissue contrast between the hyperintense lung and adjacent structures which appear hypointense relative to the lungs.

Ward et al. [18] previously described a good inter- (r = 0.68–0.76) and intraobserver (r = 0.89–0.91) reproducibility of fetal lung volume measurements on MRI using normal lung controls and demonstrated that lung volume measurements were independent of the imaging plane. Similarly, Büsing et al. [19] replicated this finding using CDH fetuses and also showed a high interobserver reproducibility (ICC, 0.928) of fetal lung volume measurements independent of the imaging plane, sequence, or total volume. At our institution, both axial and coronal planes are used to determine the lung volumes, and the present study confirms the high reproducibility of fetal lung volume measurements.

The reproducibility of MRI liver volume above the diaphragm previously described in the literature [13] is

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slightly higher (intraobserver ICC, 0.95; 95% CI: 0.83–0.98 and interobserver bias, 0.18; limits of agreement, −2.64 to 3.00) [14] than that we observed. Furthermore, the better reproducibility of lung volume measurements compared to liver volume measurements noted in our study may be explained by the technical aspects of the measurement technique. The liver volume measurement is read off the coronal series in order to delineate the expected location of the diaphragm. As the diaphragm is deficient or absent in CDH, the liver becomes increasingly displaced into the fetal chest. The normal hemidiaphragm, usually the right side, is used as a surrogate from the expected location of the left hemidiaphragm with any liver above this being abnormally positioned. Estimating the normal location of the diaphragm is therefore a source of operator-dependent variability.

In addition, the MRI signal of the liver is slightly hypointense relative to the normal lungs but similar to the signal of the heart, central mediastinal structures, collapsed bowel, spleen, chest, and abdominal wall. This makes precise delineation of the liver more difficult, contributing to more variability. Given that 20% is the critical value of liver herniation associated with poor postnatal outcomes [14], we recommend that when a value close to or greater than this is obtained, multiple measurements be taken; when in doubt, it is better to err on the lower end of the measurements obtained as there is a higher possibility that portions of other structures may be included in this area.

The main strength of the present study is that the reproducibility of fetal lung and liver measurements using MRI is evaluated specifically by multiple reviewers with extensive experience. The retrospective review of the patients could be considered as a potential limitation. However, this did not interfere with our results since only a select number of appropriate images were evaluated by different operators blinded to each other results in our study. Lastly, the small number of patients in our study limited the assessment of any potential association between lung and liver volumes and postnatal outcomes, and this was beyond the scope of our study. In addition, the small sample size limited the evaluation of the reproducibility of these measurements according to the severity of the CDH. However, similar reproducibility of these measurements was observed in fetuses with CDH (hypoplastic lungs) and those with normal lungs.

In conclusion, the present study demonstrated an excellent intra- and interreviewer reproducibility of MRI lung volume measurements and good-to-moderate inter- and intrareviewer reproducibility of liver volume measurements after standardization of the methods at our fetal center. Large multicenter studies are necessary to confirm our results for the generalizability to other centers.

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Statement of Ethics

The Institutional Review Board approved the study (IRB# 16-008333). All patients gave written consent. The present study was conducted ethically in accordance with the World Medical Association Declaration of Helsinki.

Conflict of Interest Statement

All authors declare no conflicts of interest.

Funding Sources

No funding was directed to this study.

Author Contributions

Amy B. Kolbe, MD, Kristen B. Thomas, MD, Nathan C. Hull, MD, and Paul G. Thacker, MD: MRI measurements, manuscript writing, and review. Matthew Hathcock: statistical analysis. Amy B. Kolbe, MD, Eniola R. Ibirogba, MBBS, and Rodrigo Ruano, MD, PhD: project conception, manuscript writing, and review.

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