Atellica IM High-Sensitivity Troponin I Assay

Performance Evaluation of the Atellica IM High-Sensitivity Troponin I Assay

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Abstract

Background

The 2015 European Society of Cardiology guidelines propose algorithms for faster rule-in or rule-out of acute myocardial infarction (AMI) in patients and for the management of NSTEMI. High-sensitivity cardiac troponin I (hs-cTnI) assays will more accurately and precisely measure changes in cTnI concentrations in serial blood draws, providing useful data to assist in identifying acute versus chronic cTnI elevations and acceptable rule-in and rule-out performance within 1 to 3 hours of presentation. This study evaluated the performance of the Siemens Healthineers High-Sensitivity Troponin I (TnIH) Assay developed for use on the Atellica® Immunoassay (IM) Analyzer. The assay is a dual-capture sandwich immunoassay using magnetic latex particles, a proprietary acridinium ester for chemiluminescence detection, and three monoclonal antibodies.

Methods

The limit of blank (LoB) and limit of detection (LoD) assessments used three reagent lots on two Atellica IM Analyzers with both lithium heparin (LiHep) and serum matrices and were run according to CLSI EP-17A2. LoD studies collected 60 replicate measurements for each of 10 serum and 10 LiHep samples per lot and per analyzer. CLSI protocol EP12-A2 was followed to compare the Atellica® IM TnIH Assay to the ADVIA Centaur® TNIH assay with n = 144 AMI patient samples spanning the range of reportable results. The 99th percentile cutoff values were established using a well-characterized population of apparently healthy subjects (n = 2007) in both LiHep and serum matrices. Clinical correlation of the Atellica IM TnIH Assay cTnI levels above the 99th percentile to adjudicated AMI diagnosis was assessed in all-comer emergency department (ED) population in both sample matrices.

Results

The LoB was 0.50 ng/L (pg/mL) across two Atellica IM Analyzers and three reagent lots. LoD was determined to be 1.60 ng/L (pg/mL). The cTnI concentration at 20% CV Total (LoQ) had a pooled value of 2.50 ng/L (pg/mL). Of the normal healthy population, 75% of the serum and 66% of the LiHep samples had values greater than the LoD.

The observed assay repeatability on the Atellica IM Analyzer ranged from 4.0 to 5.4% CV, and within-lab precision ranged from 5.2 to 7.0% CV between 9 and 20 ng/L (pg/mL). Above 20 ng/L (pg/mL), repeatability on the Atellica IM Analyzer ranged from 0.9 to 3.2% CV, and within-lab precision ranged from 1.9 to 5.2% CV.

The repeatability and within-lab precision at the pooled (female and male) 99th percentile (45.2 ng/L, pg/mL) were 2.8% CV and 3.7% CV, respectively. The 99th percentile observed for females was 34 ng/L (pg/mL) and for males 53 ng/L (pg/mL). Method comparison between the Atellica IM TnIH Assay and ADVIA Centaur TNIH assay yielded slopes of 1.01 to 1.04 across the three reagent lots. Clinical sensitivity and clinical specificity in pooled genders at 1, 2, 3, and 6 hours post-ED presentation ranged from 84.3% to 94.7% and 86.9% to 91.1%, respectively.

Conclusion

The Atellica IM TnIH Assay has a 10% total CV at a cTnI concentration 10-fold lower than the 99th percentile. This new TnIH Assay allows the establishment of gender-specific 99th percentile cutoffs and shows acceptable clinical utility in an all-comer ED population with signs and symptoms suggestive of acute coronary syndrome. The IFCC criteria for a high sensitivity cardiac troponin assay are met.[1]

Background

In 2015, the European Society of Cardiology published guidelines that propose algorithms for faster rule-in or rule-out of acute myocardial infarction (AMI) in patients admitted in the acute care setting and for the management of non-ST-elevation myocardial infarction (NSTEMI) patients. Serial measurements with high-sensitivity cardiac troponin I (hs-cTnI) assays will more accurately and precisely measure changes in cTnI concentrations, enabling the discrimination of acute from chronic cTnI elevations and affording acceptable rule-in and rule-out claims within 1 to 3 hours.[2] The Atellica IM High-Sensitivity Troponin I (TnIH) Assay is an in vitro diagnostic immunoassay for the quantitative determination of cTnI in lithium heparin (LiHep) plasma or serum (no EDTA). The primary objective of this study was to demonstrate the analytical performance of the TnIH Assay on the Atellica IM Analyzer from Siemens Healthineers.

Principles of the Procedure

The Atellica IM TnIH Assay uses the same reagent formulation as the ADVIA Centaur TNIH assay. The TnIH Assay is a dual-capture sandwich immunoassay. The detection reagent is a recombinant sheep Fab antibody covalently linked to tri-sulfopropyl acridinium ester-BSA conjugate. The sample is incubated with magnetic solid-phase capture and detection reagents that are subsequently washed and treated with acid and base reagents to initiate chemiluminescence. The relative light units are proportional to the cTnI concentration. The time to first result is 9.8 minutes.

Methods

Repeatability (within-run) and total (within-lab) precision (CLSI EP05-A3)

Experimental design involved three reagent lots, one calibrator lot per reagent lot (lot-locked), two Atellica IM Analyzers, calibration every 14 days, 20 test days, 2 runs per test day, minimum of 2 hours in between and duplicate measurements. Sample types included four control serum pools and contrived high and low spiked LiHep plasma and serum samples. New frozen aliquots were thawed daily.

Limit of blank and limit of detection (CLSI EP17-A2)

Limit of blank (LoB) and limit of detection (LoD) testing was conducted with three TnIH reagent lots consistent with *CLSI EP17-A2: Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures; Approved Guideline-Second Edition*. For LoB, two LiHep and two serum (total of four) blank samples were processed with three TnIH reagent lots for 3 days (non-consecutive), on two Atellica IM Analyzers. Each day 10 replicates were taken for each sample for a total of 240 LoB measurements per reagent lot. Determination of LoB is at the 95th percentile of all values (sorted from highest to lowest), using a nonparametric approach.

In addition, 13 serum and LiHep plasma low samples were processed with all three TnIH verification reagent lots for 20 days (2 runs per day and 2 replicates per run), on two analyzers for a total of 2080 measurements per lot to calculate the LoD. LoD is taken as the highest determination of reagent lot and analyzer combinations.

Functional sensitivity (limit of quantitation) (CLSI EP17-A2 and CLSI EP05-A3)

- Limit of quantitation (LoQ) for TnI assays is defined as the functional sensitivity, the cTnI dose at 20% CV, and the largest concentration determined from the individual reagent lot and analyzer combination.
- Three reagent lots (1, 2, 3), two Atellica IM Analyzers.
- Sample types: six low cTnI LiHep plasma pools, seven low cTnI serum pools, four control serum pools. Each testing day, a new aliquot of each sample was thawed.
- For each reagent lot, the within-lab precision over 20 days for each sample, expressed as %CV, was plotted against the mean concentration of each sample. Data were fitted using a power function to give a precision profile.

Reference interval or reference range (99th percentile of normal healthy population) (CLSI EP28-A3c)

Approximately 2000 apparently healthy subjects were enrolled prospectively with informed consent. Subjects included blood donors or patients from primary-care practices with a target male-to-female ratio of 1:1. The study involved:

- Four serum-pool controls
- One Atellica IM Analyzer
- LiHep plasma and serum samples drawn from each subject
- Non-parametric analysis.

Clinical performance

- LiHep plasma and serum samples (baseline and four other time points) were collected prospectively from subjects presenting to the emergency department (ED) with signs and symptoms suggestive of acute coronary syndrome, under informed consent.
- Twenty-nine collection sites in the U.S. shipped frozen samples to a central laboratory, where they were sorted and shipped in batches to three qualified clinical testing sites, one of which was an internal Siemens Healthineers laboratory. One lot of Atellica IM TnIH Assay reagent was used.
- Diagnostic accuracy was defined as the medical concordance between the 99th percentile cutoff point previously established using the population of apparently healthy subjects and the presence or absence of an adjudicated AMI diagnosis at each of the time points. Statistical analyses: SAS System for Windows (ver. 9.3).

Results

Table 1. Repeatability and total precision.

Atellica IM TnIH Assay					
	Mean cTnI (ng/L, pg/mL)	Repeatability (within-run)		Within Lab (total precision)	
		SD (ng/L, pg/mL)	%CV	SD (ng/L, pg/mL)	%CV
Lot 1					
Serum Pool 1	9.56	0.52	5.5	0.63	6.6
Serum Low	20.48	0.61	3.0	0.90	4.4
Plasma Pool Low, LiHep	27.87	0.78	2.8	0.93	3.4
Serum Pool 2	39.18	1.09	2.8	1.34	3.4
Serum Pool 3	147.59	2.41	1.6	3.58	2.4
Serum Pool 4	1626.99	29.82	1.8	36.24	2.2
Plasma Pool High, LiHep	15820.68	230.65	1.5	315.27	2.0
Serum High	21513.76	302.52	1.4	404.69	1.9
Lot 2					
Serum Pool 1	9.54	0.48	5.0	0.71	7.5
Serum Low	18.90	0.57	3.0	1.02	5.4
Plasma Pool Low, LiHep	27.50	0.77	2.8	1.38	5.0
Serum Pool 2	39.10	0.92	2.4	1.52	3.9
Serum Pool 3	147.37	2.56	1.7	4.39	3.0
Serum Pool 4	1610.40	28.61	1.8	50.95	3.2
Plasma Pool High LiHep	15822.86	200.07	1.3	395.37	2.5
Serum High	21392.14	411.79	1.9	534.59	2.5
Lot 3					
Serum Pool 1	9.78	0.42	4.3	0.65	6.6
Serum Low	20.89	0.55	2.6	1.03	4.9
Plasma Pool Low, LiHep	28.67	0.69	2.4	1.26	4.4
Serum Pool 2	39.42	1.06	2.7	1.60	4.0
Serum Pool 3	148.67	3.19	2.1	4.94	3.3
Serum Pool 4	1618.23	22.54	1.4	52.52	3.2
Plasma Pool High LiHep	15947.22	236.74	1.5	421.06	2.6
Serum High	21629.95	313.38	1.4	552.87	2.6

The LoB for the Atellica IM TnIH Assay was established as 0.50 ng/L (pg/mL) and the LoD as 1.60 ng/L (pg/mL).

Table 2. LoB and LoD.

Atellica IM TnIH Assay				
Reagent Lot	# Analyzers	# samples LoB; LoD	LoB (ng/L, pg/mL)	LoD (ng/L, pg/mL)
1	2	240; 160	0.45	1.53
2	2	240; 160	0.44	1.34
3	2	240; 160	0.43	1.13

The functional sensitivity (LoQ) estimate was derived using three reagent lots run on two Atellica IM Analyzers determined as the largest cTnI concentration of the individual reagent lot and instrument combination with ≤20% within-lab CV. The Atellica IM TnIH Assay has an LoQ of 2.50 ng/L (pg/mL). A composite precision curve is shown in Figure 1.

Table 3. Functional sensitivity.

Atellica IM TnIH Assay			
		Analyzer 1	Analyzer 2
Reagent Lot	CV %	cTnI (ng/L, pg/mL)	cTnI (ng/L, pg/mL)
1	20	2.50	2.25
	10	4.86	5.43
2	20	2.13	2.38
	10	4.56	5.37
3	20	2.33	2.18
	10	4.64	4.63

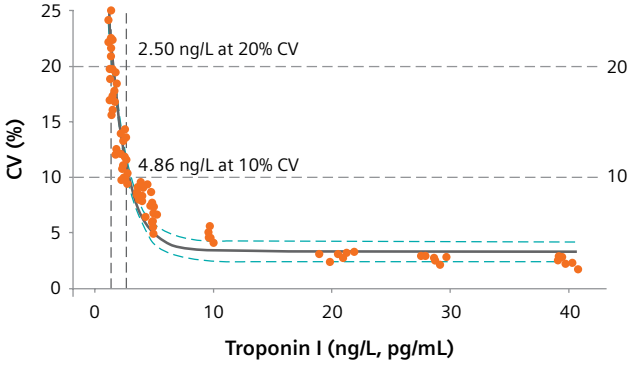

Figure 1. Atellica IM TnIH Assay composite precision data: two Atellica IM Analyzers, three reagent lots, 20 days, 40 runs. n = 4320 measurements; 480 measurements for each of nine samples.

The 99th percentile values determined for LiHep plasma and serum samples (female, male, and combined) are shown in Table 4. The 99th percentile was determined to be 45.20 ng/L (pg/mL).

Table 4. Reference interval or reference range (99th percentile of an apparently healthy population).

	LiHep			Serum		
Group	**N**	**99th percentile (ng/L, pg/mL)**	**90% CI (ng/L, pg/mL)**	**N**	**99th percentile (ng/L, pg/mL)**	**90% CI (ng/L, pg/mL)**
Pooled	2007	45.20	(33.21, 64.30)	2001	45.43	(35.47, 63.63)
Male	1000	53.48	(38.73, 80.22)	994	53.53	(33.77, 78.03)
Female	1007	34.11	(27.36, 66.23)	1007	38.64	(28.58, 72.36)

The reference interval study was performed with one lot of reagent. The LoD for this lot was determined to be 1.27 ng/L (pg/mL). Of the 2007 apparently healthy individuals, 75% of the serum and 66% of the LiHep plasma samples have values greater than the collective LoD (1.60 ng/L, pg/mL).

Table 5. Statistics for the LiHep and serum sample types.

	LiHep				Serum			
	Male		Female		Male		Female	
	99th Percentile 53.5 ng/L (pg/mL)		99th Percentile 34.1 ng/L (pg/mL)		99th Percentile 53.5 ng/L (pg/mL)		99th Percentile 38.6 ng/L (pg/mL)	
Age Range (Years)	**Mean cTnI (ng/L)**	**SD (ng/L)**	**Mean cTnI (ng/L)**	**SD (ng/L)**	**Mean cTnI (ng/L)**	**SD (ng/L)**	**Mean cTnI (ng/L)**	**SD (ng/L)**
≥22 to <30	3.57	5.18	3.08	12.91	4.00	5.51	3.31	13.17
≥30 to <40	5.03	13.55	2.67	11.29	4.98	12.42	2.97	11.53
≥40 to <50	4.04	4.76	2.90	5.92	4.75	5.18	3.09	6.22
≥50 to <60	5.18	7.85	3.35	5.84	5.67	8.28	3.72	5.94
≥60 to <70	7.34	12.25	3.05	3.84	7.63	12.79	3.36	3.94
≥70	6.23	8.32	5.97	13.49	6.50	8.52	6.25	12.64

The very slight increase across age is not statistically significant.

Clinical performance

Table 6. Demographic information for the ED all-comer population included in the Atellica IM TnIH Assay analysis.

N = 2409	Mean Age (Years)	Age Range (Years)
	56.96	23–93
Sex	**N**	**%**
Female	1046	43.4
Male	1363	56.6

Race	**N**	**%**
White	1350	56.0
Black	958	39.9
Asian	22	0.9
Hawaiian	3	0.1
American Indian	16	0.7
Multiple	20	0.8
Other	40	1.7

The clinical status of the subjects was assessed established by adjudication, performed by panels of cardiologists and emergency physicians, and based on the Third Universal Definition of Myocardial Infarction Consensus Guideline.[3]

For adjudication purposes, and the establishment of a gold standard AMI diagnosis, the local hospital cTnI results were used. The adjudicators were blinded to all Siemens Healthineers investigational troponin test results and to the final local hospital diagnosis.

Up to five blood draws were obtained from the subjects, and each draw included a serum and a LiHep collection tube. All samples collected were tested and the results were compared to the 99th percentile cutoff to assess if the interpretation of individual test result was positive or negative. The test interpretations were then compared to the subject adjudicated diagnosis to assess sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV).

Finally, the data were grouped based on the time windows during which the blood samples were collected. This grouping was done using different time window definition, as shown in Tables 7–9.

Clinical sensitivity and clinical specificity in pooled-sex samples across LiHep/serum samples at presentation, and 1, 2, 3, and 6 hours post-ED presentation ranged from 84.3% to 94.7% and 86.9% to 91.1%, respectively (Table 9).

Table 7. Atellica IM TnIH Assay clinical concordance for female samples calculated using the female-specific 99th percentile cutoff of 34.11 ng/L (pg/mL) for LiHep and 38.64 ng/L (pg/mL) for serum samples.

		Sensitivity			Specificity			PPV			NPV		
Matrix	**Timepoint hr**	**N**	**%**	**95% CI**	**N**	**%**	**95% CI**	**N**	**%**	**95% CI**	**N**	**%**	**95% CI**
LiHep	Baseline	106	87.7	80.1–92.7	903	91.4	89.4–93.0	171	54.4	46.9–61.7	838	98.4	97.4–99.1
	1 (≥0.75 to 1.5)	92	90.2	82.4–94.8	835	91.5	89.4–93.2	154	53.9	46.0–61.6	773	98.8	97.8–99.4
	2 (≥1.5 to 2.5)	43	97.7	87.9–99.6	435	91.7	88.8–94.0	78	53.8	42.9–64.5	400	99.8	98.6–100.0
	3 (≥2.5 to 3.5)	41	95.1	83.9–98.7	318	87.7	83.7–90.9	78	50	39.2–60.8	281	99.3	97.4–99.8
	6 (≥3.5 to 9)	92	94.6	87.9–97.7	468	88.2	85.0–90.9	142	61.3	53.1–68.9	418	98.8	97.2–99.5
	16 (≥9 to 24)	77	93.5	85.7–97.2	360	86.1	82.2–89.3	122	59	50.1–67.3	315	98.4	96.3–99.3
Serum	Baseline	101	86.1	78.1–91.6	911	91.7	89.7–93.3	163	53.4	45.7–60.9	849	98.4	97.3–99.0
	1 (≥0.75 to 1.5)	88	88.6	80.3–93.7	830	91.7	89.6–93.4	147	53.1	45.0–60.9	771	98.7	97.6–99.3
	2 (≥1.5 to 2.5)	40	95	83.5–98.6	431	92.3	89.4–94.5	71	53.5	42.0–64.6	400	99.5	98.2–99.9
	3 (≥2.5 to 3.5)	38	94.7	82.7–98.5	322	88.8	84.9–91.8	72	50	38.7–61.3	288	99.3	97.5–99.8
	6 (≥3.5 to 9)	87	95.4	88.8–98.2	476	89.1	86.0–91.6	135	61.5	53.1–69.3	428	99.1	97.6–99.6
	16 (≥9 to 24)	76	93.4	85.5–97.2	360	88.6	84.9–91.5	112	63.4	54.2–71.7	324	98.5	96.4–99.3

PPV: Positive predictive value; NPV: Negative predictive value.

Table 8. Atellica IM TnIH Assay clinical concordance for male samples calculated using the male-specific 99th percentile cutoff of 53.48 ng/L (pg/mL) for LiHep samples and 53.53 ng/L (pg/mL) for serum samples.

		Sensitivity			Specificity			PPV			NPV		
Matrix	**Timepoint hr**	**N**	**%**	**95% CI**	**N**	**%**	**95% CI**	**N**	**%**	**95% CI**	**N**	**%**	**95% CI**
LiHep	Baseline	193	81.9	75.8–86.7	1100	91.1	89.3–92.6	256	61.7	55.6–67.5	1037	96.6	95.3–97.6
	1 (≥0.75 to 1.5)	163	89	83.2–92.9	1036	91	89.1–92.6	238	60.9	54.6–66.9	961	98.1	97.1–98.8
	2 (≥1.5 to 2.5)	95	88.4	80.4–93.4	607	89.8	87.1–92.0	146	57.5	49.4–65.3	556	98	96.5–98.9
	3 (≥2.5 to 3.5)	77	90.9	82.4–95.5	364	91.2	87.9–93.7	102	68.6	59.1–76.8	339	97.9	95.8–99.0
	6 (≥3.5 to 9)	159	93.1	88.0–96.1	652	86.8	84.0–89.2	234	63.2	56.9–69.2	577	98.1	96.6–98.9
	16 (≥9 to 24)	147	91.2	85.5–94.8	525	87.4	84.3–90.0	200	67	60.2–73.1	472	97.2	95.3–98.4
Serum	Baseline	193	82.9	77.0–87.6	1124	91.2	89.4–92.7	259	61.8	55.7–67.5	1058	96.9	95.7–97.8
	1 (≥0.75 to 1.5)	164	87.2	81.2–91.5	1051	91.2	89.4–92.8	235	60.9	54.5–66.9	980	97.9	96.7–98.6
	2 (≥1.5 to 2.5)	94	87.2	79.0–92.5	617	89.8	87.1–91.9	145	56.6	48.4–64.3	566	97.9	96.3–98.8
	3 (≥2.5 to 3.5)	75	90.7	82.0–95.4	358	91.3	88.0–93.8	99	68.7	59.0–77.0	334	97.9	95.7–99.0
	6 (≥3.5 to 9)	158	93	88.0–96.1	648	87.8	85.1–90.1	226	65	58.6–71.0	580	98.1	96.6–98.9
	16 (≥9 to 24)	149	89.9	84.1–93.8	535	87.9	84.8–90.4	199	67.3	60.5–73.5	485	96.9	95.0–98.1

Table 9. Atellica IM TnIH Assay clinical concordance for pooled-sex samples calculated using the overall 99th percentile cutoff of 45.20 ng/L (pg/mL).

		Sensitivity			Specificity			PPV			NPV		
Matrix	**Timepoint hr**	**N**	**%**	**95% CI**	**N**	**%**	**95% CI**	**N**	**%**	**95% CI**	**N**	**%**	**95% CI**
LiHep	Baseline	299	84.3	79.7–88.0	2003	90.8	89.4–92.0	437	57.7	53.0–62.2	1865	97.5	96.7–98.1
	1 (≥0.75 to 1.5)	255	90.6	86.4–93.6	1871	90.8	89.4–92.0	403	57.3	52.4–62.1	1723	98.6	97.9–99.1
	2 (≥1.5 to 2.5)	138	92.8	87.2–96.0	1042	89.8	87.8–91.5	234	54.7	48.3–61.0	946	98.9	98.1–99.4
	3 (≥2.5 to 3.5)	118	93.2	87.2–96.5	682	90	87.6–92.1	178	61.8	54.5–68.6	622	98.7	97.5–99.3
	6 (≥3.5 to 9)	251	94	90.4–96.3	1120	86.9	84.8–88.7	383	61.6	56.7–66.4	988	98.5	97.5–99.1
	16 (≥9 to 24)	224	92.4	88.2–95.2	885	86.6	84.1–88.6	326	63.5	58.1–68.5	783	97.8	96.6–98.6
Serum	Baseline	294	84.7	80.1–88.4	2035	91	89.7–92.2	432	57.6	52.9–62.2	1897	97.6	96.8–98.2
	1 (≥0.75 to 1.5)	252	88.1	83.5–91.5	1881	91.1	89.8–92.3	389	57.1	52.1–61.9	1744	98.3	97.6–98.8
	2 (≥1.5 to 2.5)	134	91.8	85.9–95.4	1048	90	88.0–91.7	228	53.9	47.5–60.3	954	98.8	97.9–99.4
	3 (≥2.5 to 3.5)	113	92	85.6–95.8	680	90.4	88.0–92.4	169	61.5	54.0–68.5	624	98.6	97.3–99.2
	6 (≥3.5 to 9)	245	94.7	91.1–96.9	1124	87.7	85.7–89.5	370	62.7	57.7–67.5	999	98.7	97.8–99.2
	16 (≥9 to 24)	225	91.6	87.2–94.5	895	87.4	85.0–89.4	319	64.6	59.2–69.6	801	97.6	96.3–98.5

Conclusions

The Atellica IM TnIH Assay demonstrates the following:

- LoB of 0.50 ng/L (pg/mL), LoD of 1.60 ng/L (pg/mL), and LoQ of 2.50 ng/L (pg/mL).
- Demonstrated accuracy and precision for use in detecting low cTnI levels.
- 99th percentile is 45.20 ng/mL (pg/mL). Of the 2007 apparently healthy individuals, 75% of the serum and 66% of the LiHep samples had values greater than the LoD (1.60 ng/L, pg/mL).
- The LoB, LoD, LoQ, and 99th percentile values for the Atellica IM Analyzer TnIH Assay are comparable to those of the TNIH assay on the ADVIA Centaur system (0.5, 1.60, 2.50, and 47.34 ng/L, pg/mL, respectively).
- Clinical concordance study of sensitivity, specificity, PPV, and NPV demonstrates acceptable performance for use as an aid in diagnosing AMI. Clinical concordance study of sensitivity, specificity, PPV and NPV demonstrates acceptable performance for use as an aid in diagnosing AMI.

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