

The roles of tertiary lymphoid structures in chronic diseases

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Supplementary table 1 | Frequency of TLS-positive cases in cohorts of different tumours extracted from studies reporting histological TLS assessment

Included in organ comparison analysis	Cancer subtype	Organ	Disease details	Treatment before surgery	total cases analysed	# of TLS+ cases	% of TLS-positive cases	Details on TLS assessment method and region	Reference
Yes	IBC	Breast	Invasive ductal carcinoma, mixed subtypes	untreated	134	17	12.69	whole slide H&E, whole tissue area	1
Yes	DCIS	Breast	Ductal carcinoma in situ	untreated	68	5	7.35	whole slide H&E, whole tissue area	1
Yes	HNSCC	Tongue	Oral tongue squamous cell carcinoma	untreated	310	263	84.84	whole slide H&E, peritumoral area	2
Yes	HCC	Liver	Hepatocellular carcinoma	untreated	273	129	47.25	whole slide H&E, whole tissue area, TLS assessed intratumorally	3
Yes	PDAC	Pancreas	Pancreatic ductal adenocarcinoma	untreated	104	101	97.12	whole slide IHC for CD20, tumor-stroma interface	4
Yes	TNBC	Breast	Metaplastic breast cancer (triple negative breast cancer-like)	untreated	60	36	60.00	whole slide H&E, whole tissue area, number of positive cases extrapolated from survival graph	5
Yes	NSCLC	Lung	Non-small cell lung cancer, early stage	untreated	74	64	86.49	whole slide H&E and IHC for DC-LAMP and CD3, whole tissue area	6
Yes	BC_HER2-	Breast	HER2- invasive breast cancer and ductal carcinoma in situ	untreated	210	69	32.86	whole slide H&E and IHC for CD20, CD3, CD21, BCL6, PNAD, whole tissue area	7
Yes	BC_HER2+	Breast	HER2+ invasive breast cancer and ductal carcinoma in situ	untreated	40	26	65.00	whole slide H&E and IHC for CD20, CD3, CD21, BCL6, PNAD, whole tissue area	7
Yes	BC_HER2-	Breast	ER- invasive breast cancer and ductal carcinoma in situ	untreated	41	31	75.61	whole slide H&E and IHC for CD20, CD3, CD21, BCL6, PNAD, whole tissue area	7
Yes	BC_HER2-	Breast	PR- invasive breast cancer and ductal carcinoma in situ	untreated	56	36	64.29	whole slide H&E and IHC for CD20, CD3, CD21, BCL6, PNAD, whole tissue area	7
Yes	BC_HER2+	Breast	ER+ invasive breast cancer and ductal carcinoma in situ	untreated	208	64	30.77	whole slide H&E and IHC for CD20, CD3, CD21, BCL6, PNAD, whole tissue area	7
Yes	BC_HER2+	Breast	PR+ invasive breast cancer and ductal carcinoma in situ	untreated	120	38	31.67	whole slide H&E and IHC for CD20, CD3, CD21, BCL6, PNAD, whole tissue area	7
Yes	HNSCC	Larynx	laryngeal squamous cell carcinoma	untreated	24	5	20.83	whole slide H&E, whole tissue area	8
Yes	NSCLC	Lung	Non-small cell lung cancer	untreated	147	86	58.50	whole slide IHC for PNAD next to dense lymphocytic clusters, 10 40x regions per slide	9
Yes	HCC	Liver	Hepatocellular carcinoma	untreated	112	NA	33.00	whole slide multiplexIF, whole tissue area	10
Yes	NSCLC	Lung	Non-small cell lung cancer	untreated	103	80	77.67	whole slide H&E, whole tissue area	11
Yes	PDAC_TMBhi	Pancreas	Pancreatic ductal adenocarcinoma, SHM high (>10)	untreated	17	14	82.35	whole slide IHC for CD20 and CD3, multiplex IF, whole tissue area	12
Yes	PDAC_TMBlo	Pancreas	Pancreatic ductal adenocarcinoma, SHM low (<=10)	untreated	42	5	11.90	whole slide IHC for CD20 and CD3, multiplex IF, whole tissue area	12
Yes	PDAC	Pancreas	Pancreatic ductal adenocarcinoma	untreated	174	44	25.29	whole slide H&E, whole tissue area	12
Yes	BC_HER2-	Breast	HR- invasive breast cancer	untreated	41	19	46.34	whole slide IHC for CD20, whole tissue area	10.3969/j.issn.1673-4254.2013.05.25
Yes	BC_HER2+	Breast	HR+ invasive breast cancer	untreated	89	30	33.71	whole slide IHC for CD20, whole tissue area	10.3969/j.issn.1673-4254.2013.05.25
Yes	GACA	Stomach	Gastric adenocarcinoma, intestinal type	untreated	6	6	100.00	whole slide IHC for CD20, whole tissue area	13
Yes	PDAC	Pancreas	Pancreatic ductal adenocarcinoma	untreated	308	308	100.00	whole slide H&E, whole tissue area	14

Yes	TNBC	Breast	Triple negative breast cancer	untreated	42	21	50.00	whole slide IHC for CD21, CD20, whole tissue area	15
Yes	NSCLC	Lung	Lung adenocarcinoma	untreated	146	57	39.04	whole slide H&E, whole tissue area	16
Yes	MIBC	Bladder	Muscle invasive bladder cancer	untreated	16	13	81.25	whole slide multiplex IHC, whole tissue area	17
Yes	NonMIBC	Bladder	Non- Muscle invasive bladder cancer	untreated	12	9	75.00	whole slide multiplex IHC, whole tissue area	17
Yes	OVCA	Ovary and omentum	High-grade serous ovarian cancer	untreated	30	17	56.67	whole slide multiplex IHC, whole tissue area	18
Yes	TNBC	Breast	Triple negative breast cancer	untreated	769	733	95.32	whole slide H&E, whole tissue area	19
Yes	BC_HER2+	Breast	HER2+ invasive breast cancer	untreated	447	402	89.93	whole slide H&E, whole tissue area, TLS found peritumorally	20
Yes	BC_HER2-	Breast	HR-HER2+ invasive breast cancer	untreated	240	186	77.50	whole slide H&E, whole tissue area, TLS found peritumorally	20
Yes	BC_HR+	Breast	HR+HER2+ invasive breast cancer	untreated	207	116	56.04	whole slide H&E, whole tissue area, TLS found peritumorally	20
Yes	BC_HER2+	Breast	HER2+ invasive breast cancer	untreated	168	65	38.69	whole slide H&E, whole tissue area	21
Yes	BC_HER2-	Breast	HR-HER2+ invasive breast cancer	untreated	78	NA	43.59	whole slide H&E, whole tissue area	21
Yes	BC_HR+	Breast	HR+HER2+ invasive breast cancer	untreated	90	NA	34.44	whole slide H&E, whole tissue area	21
Yes	BC_HER2-	Breast	HER2- invasive breast cancer	untreated	191	59	30.89	whole slide H&E and IHC for CD20, CD3, CD23, whole tissue area	22
Yes	BC_HER2+	Breast	HER2+ invasive breast cancer	untreated	54	33	61.11	whole slide H&E and IHC for CD20, CD3, CD23, whole tissue area	22
Yes	BC_HR-	Breast	ER- invasive breast cancer	untreated	89	46	51.69	whole slide H&E and IHC for CD20, CD3, CD23, whole tissue area	22
Yes	BC_HR-	Breast	PR- invasive breast cancer	untreated	95	50	52.63	whole slide H&E and IHC for CD20, CD3, CD23, whole tissue area	22
Yes	BC_HR+	Breast	ER+ invasive breast cancer	untreated	157	46	29.30	whole slide H&E and IHC for CD20, CD3, CD23, whole tissue area	22
Yes	BC_HR+	Breast	PR+ invasive breast cancer	untreated	150	42	28.00	whole slide H&E and IHC for CD20, CD3, CD23, whole tissue area	22
Yes	TNBC	Breast	Triple negative breast cancer	untreated	45	22	48.89	whole slide H&E and IHC for CD20, CD3, CD23, whole tissue area	22
Yes	MIBC	Bladder	Urinary bladder	untreated	51	28	54.90	3mm TMA cores with TC and IM by IF, sequential IHC	23
Yes	RCC	Kidney	Clear cell renal cell carcinoma	untreated	105	33	31.43	IF on 3mm TMA cores with TC and IM, sequential IHC	23
Yes	CRC	Liver	Metastatic colorectal cancer	untreated	14	12	85.71	whole slide IHC for CD20, whole tissue area, TLS present peritumorally	24
Yes	CRC	Colon	Colorectal cancer	untreated	843	230	27.28	whole slide H&E, whole tissue area, TLS present peritumorally	25
Yes	MIBC_TMBhi	Bladder	Muscle invasive bladder cancer, mutation high	untreated	151	117	77.48	whole slide H&E, whole tissue area	26
Yes	MIBC_TMBlo	Bladder	Muscle invasive bladder cancer, mutation low	untreated	153	107	69.93	whole slide H&E, whole tissue area	26
Yes	MIBC	Bladder	Muscle invasive bladder cancer	untreated	40	40	100.00	whole slide multiplexIF, whole tissue area	26
Yes	CRC_TMBhi	Colon	Colorectal cancer, microsatellite instable	untreated	15	15	100.00	whole slide multiplexIF, peritumoral area	27
Yes	CRC_TMBlo	Colon	Colorectal cancer, microsatellite stable	untreated	94	91	96.81	whole slide multiplexIF, peritumoral area	27

Yes	CRC_TMBhi	Colon	Colorectal cancer, microsatellite instable	untreated	189	111	58.73	whole slide H&E, whole tissue area	28
Yes	CRC_TMBlo	Colon	Colorectal cancer, microsatellite stable	untreated	1299	588	45.27	whole slide H&E, whole tissue area	28
Yes	HNSCC_HPV-	Tongue	HPV- head and neck squamous cell carcinoma	untreated	13	13	100.00	whole slide IHC for CD20, whole tissue area	29
Yes	HNSCC_HPV-	Tonsil	HPV- head and neck squamous cell carcinoma	untreated	18	18	100.00	whole slide IHC for CD20, whole tissue area	29
Yes	HNSCC_HPV+	Tongue	HPV+ head and neck squamous cell carcinoma	untreated	15	12	80.00	whole slide IHC for CD20, whole tissue area	29
Yes	HNSCC_HPV+	Tonsil	HPV+ head and neck squamous cell carcinoma	untreated	10	9	90.00	whole slide IHC for CD20, whole tissue area	29
Yes	NSCLC	Lung	Lung squamous cell carcinoma	untreated	69	68	98.55	whole slide H&E, peritumoral area	30
Yes	BC_HER2+	Breast	HER2+ invasive ductal cancer	untreated	48	48	100.00	whole slide H&E and IHC for CD20, CD3, CD23, whole tissue area	31
Yes	TNBC	Breast	Triple negative breast cancer	untreated	20	18	90.00	whole slide H&E and IHC for CD20, CD3, CD23, whole tissue area	31
Yes	OVCA	Ovary and omentum	High-grade serous ovarian cancer	untreated	147	14	9.52	whole slide IHC for CD20 and DC-LAMP, whole tissue area	32
Yes	OVCA	Ovary and omentum	High-grade serous ovarian cancer	untreated	62	39	62.90	whole slide IHC for CD20, whole tissue area	33
Yes	OVCA	Ovary and omentum	High-grade serous ovarian cancer	untreated	35	22	62.86	whole slide IHC for CD20, whole tissue area	33
Yes	MIBC	Bladder	Muscle invasive bladder cancer	untreated	31	25	80.65	whole slide multiplex IF, whole tissue area, most TLS peritumorally	34
Yes	CRC	Colon	Colorectal cancer	untreated	418	411	98.33	whole slide H&E, whole tissue area, TLS present peritumorally	35
Yes	HNSCC_HPV-	Oral cavity excluding base of tongue and tonsils	HPV- oral squamous cell carcinoma	untreated	68	16	23.53	whole slide IHC for CD20, CD21, BCL6, whole tissue area	36
Yes	HNSCC_HPV+	Oral cavity excluding base of tongue and tonsils	HPV+ oral squamous cell carcinoma	untreated	6	1	16.67	whole slide IHC for CD20, CD21, BCL6, whole tissue area	36
Yes	CRC	Colon	Colorectal cancer	untreated	67	58	86.57	multiplex IF, whole tissue area, TLS present peritumorally	37
Yes	NSCLC	Lung	Lung adenocarcinoma, without ALK rearrangement and driver gene mutations	untreated	9	8	88.89	whole slide IHC for CD20, whole tissue area	38
Yes	NSCLC	Lung	Lung adenocarcinoma, with ALK rearrangement	untreated	39	30	76.92	whole slide IHC for CD20, whole tissue area	38
Yes	HCC	Liver	Hepatocellular carcinoma	untreated	170	142	83.53	whole slide H&E, peritumoral area	39
No		Breast	Invasive ductal carcinoma, mixed subtypes	Chemotherapy	35	0	0.00	whole slide H&E, whole tissue area	1
No		Breast	Invasive ductal carcinoma, mixed subtypes	untreated+chemotherapy	312	37	11.86	whole slide H&E, whole tissue area	1
No		Prostate	Prostate adenocarcinoma	untreated	17	NA	NA	whole slide H&E, whole tissue area	40
No		Breast	invasive breast cancer and ductal carcinoma in situ	untreated	290	146	50.34	whole slide H&E and IHC for CD20, CD3, CD21, BCL6, PNAD, whole tissue area	7
No		Lung	Non-small cell lung cancer, advanced stage	Chemotherapy	122	NA	NA	whole slide IHC for DC-LAMP and CD20, whole tissue area	41
No		Lung	Non-small cell lung cancer, early stage	untreated	74	NA	NA	whole slide IHC for DC-LAMP and CD20, whole tissue area	41

No	Lung	Non-small cell lung cancer without underlying COPD	untreated	376	NA	NA	whole slide IHC for DC-LAMP and CD8, whole tissue area	42
No	Lung	Non-small cell lung cancer	NA	91	NA	NA	whole slide H&E, whole tissue area	43
No	Breast	Invasive breast cancer, mixed subtypes	untreated	70	NA	NA	whole slide IHC, Tfh used as surrogate for TLS, whole tissue area	44
No	Pancreas	Pancreatic ductal adenocarcinoma, SHM high + low	untreated	63	29	46.03	whole slide IHC for CD20 and CD3, multiplex IF, whole tissue area	12
No	Breast	Invasive breast cancer, mixed subtypes	untreated	130	49	37.69	whole slide IHC for CD20, whole tissue area	10.3969/j.issn.1673-4254.2013.05.25
No	Stomach	Gastric adenocarcinoma	untreated	1033	NA	NA	whole slide H&E and IHC for CD20, CD21, whole tissue area	45
No	Stomach	Gastric adenocarcinoma	Chemotherapy	42	NA	NA	whole slide IHC for CD20, whole tissue area	46
No	Stomach	Gastric adenocarcinoma	untreated	40	NA	NA	whole slide IHC for CD20, whole tissue area	46
No	Stomach	Gastritis with intestinal metaplasia, non-tumor	untreated	10	0	0.00	whole slide IHC for CD20, whole tissue area	13
No	Brain	Metastatic breast cancer	untreated+chemotherapy	37	0	0.00	whole slide H&E, whole tissue area	47
No	Breast	Metastatic breast cancer, primary tumor	untreated+chemotherapy	245	112	45.71	whole slide H&E, whole tissue area	47
No	Liver	Metastatic breast cancer	untreated+chemotherapy	84	13	15.48	whole slide H&E, whole tissue area	47
No	Lung	Metastatic breast cancer	untreated+chemotherapy	127	48	37.80	whole slide H&E, whole tissue area	47
No	Ovary	Metastatic breast cancer	untreated+chemotherapy	25	0	0.00	whole slide H&E, whole tissue area	47
No	Liver	Hepatocellular carcinoma	untreated	303	102	33.66	TMA H&E, intratumoral area	48
No	Liver	Hepatocellular carcinoma	untreated	159	54	33.96	TMA H&E, intratumoral area	48
No	Liver	Hepatic hemangioma, non-tumor	untreated	50	4	8.00	TMA H&E, whole tissue	48
No	Breast	Invasive breast cancer, mixed subtypes	untreated	255	101	39.61	whole slide H&E and IHC for CD20, CD3, CD23, whole tissue area	22
No	Rectum	Rectal cancer	untreated	60	NA	NA	whole slide IHC of CD3, CD83, whole tissue area, TLS peritumorally	49
No	Liver	Metastatic colorectal cancer	Chemotherapy	51	33	64.71	whole slide IHC for CD20, whole tissue area, TLS present peritumorally	24
No	Liver	Metastatic colorectal cancer	untreated+chemotherapy	65	45	69.23	whole slide IHC for CD20, whole tissue area, TLS present peritumorally	24
No	Omentum	High-grade serous ovarian cancer	Chemotherapy	31	NA	NA	whole slide IHC for CD20, whole tissue area	50
No	Omentum	High-grade serous ovarian cancer	untreated	10	NA	NA	whole slide IHC for CD20, whole tissue area	50
No	Liver	Hepatocellular carcinoma	untreated	145	59	40.69	whole slide IHC for CD3, CD8, CD20, CD208, CD21, intratumoral area	51
No	Liver	Hepatocellular carcinoma	untreated	120	48	40.00	whole slide IHC for CD3, CD8, CD20, CD208, CD21, intratumoral area	51
No	Bladder	Muscle invasive bladder cancer	untreated	300	58	19.33	whole slide H&E, intratumoral area	26
No	Bladder	Muscle invasive bladder cancer, mutation low+high	untreated	304	223	73.36	whole slide H&E, whole tissue area	26
No	Bladder	Muscle invasive bladder cancer	Chemotherapy	30	29	96.67	whole slide multiplexIF, whole tissue area	26

No	Colon	Colorectal cancer, microsatellite stable and unstable	untreated	109	106	97.25	whole slide multiplexIF, peritumoral area	27
No	Lung	Non-small cell lung cancer, advanced stage	Chemotherapy	122	NA	NA	whole slide IHC for DC-LAMP and CD8, whole tissue area	52
No	Lung	Non-small cell lung cancer, advanced stage	untreated	39	NA	NA	whole slide IHC for DC-LAMP and CD8, whole tissue area	52
No	Lung	Metastatic colorectal cancer	untreated	140	NA	NA	whole slide IHC for DC-LAMP and CD8, whole tissue area	52
No	Lung	Metastatic renal cell carcinoma	untreated	52	NA	NA	whole slide IHC for DC-LAMP and CD8, whole tissue area	52
No	Colon	Colorectal cancer, microsatellite stable and unstable	untreated	1663	784	47.14	whole slide H&E, whole tissue area	28
No	Tonsil and base of Tongue	HPV- head and neck squamous cell carcinoma	untreated	25	25	100.00	whole slide IHC for CD20, whole tissue area	29
No	Tonsil and base of Tongue	HPV+ head and neck squamous cell carcinoma	untreated	25	21	84.00	whole slide IHC for CD20, whole tissue area	29
No	Lung	Metastatic colorectal cancer	untreated+chemotherapy	57	45	78.95	whole slide IHC of CD8, FOXP3 whole tissue area	53
No	Lung	Lung squamous cell carcinoma	Chemotherapy	51	47	92.16	whole slide H&E, peritumoral area	30
No	Lung	Lung squamous cell carcinoma	tumor non-related corticosteroids	18	18	100.00	whole slide H&E, peritumoral area	30
No	Lung	Lung squamous cell carcinoma	untreated+chemotherapy	138	133	96.38	whole slide H&E, whole tissue area	30
No	Breast	Invasive ductal carcinoma, mixed subtypes	untreated	167	148	88.62	whole slide H&E and IHC for CD20, CD3, CD23, whole tissue area	31
No	Breast	Triple negative breast cancer	Chemotherapy	108	93	86.11	whole slide H&E, whole tissue area	54
No	Lung	Non-small cell lung cancer with underlying COPD	Brochodilators	90	NA	NA	whole slide IHC for CD20 and CD3, whole tissue area	55
No	Lung	Non-small cell lung cancer without underlying COPD	untreated	43	NA	NA	whole slide IHC for CD20 and CD3, whole tissue area	55
No	Ovary and omentum	High-grade serous ovarian cancer	untreated	97	61	62.89	whole slide IHC for CD20, whole tissue area	33
No	Colon	Colorectal cancer	Chemotherapy or RT	32	NA	NA	whole slide H&E, whole tissue area, TLS present peritumorally	35
No	Colon	Colorectal cancer	untreated	117	NA	NA	whole slide H&E, whole tissue area, TLS present peritumorally	35
No	Colon	Colorectal cancer	untreated+chemotherapy+RT	149	147	98.66	whole slide H&E, whole tissue area, TLS present peritumorally	35
No	Liver	Hepatocellular carcinoma	untreated	163	10	6.13	whole slide H&E, whole tissue area, TLS assessed intratumorally	56
No	Oral cavity excluding base of tongue and tonsils	Oral squamous cell carcinoma, mixed HPV	untreated	80	17	21.25	whole slide IHC for CD20, CD21, BCL6, whole tissue area	36
No	Lung	Lung adenocarcinoma, mixed ALK status	untreated	48	38	79.17	whole slide IHC for CD20, whole tissue area	38
No	Liver	Hepatocellular carcinoma	untreated	170	73	42.94	whole slide H&E, intratumoral area	39

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Supplementary table 2 | TLS in human kidney diseases

Definition of TLS	Frequency (TLS positive patients/total patients)	Clinical findings	Ref
IgA nephropathy*			
Clusters containing CD4/CD8/CD20/DC-SIGN ⁺ cells	38.8% (59/152)	TLS ⁺ patients had higher sCr, proteinuria, BP and more severe glomerulonephritis than TLS ⁻ patients	1
T and B cell aggregates	31.4% (328/1044)	TLS frequency correlated with risk of 50% decline in eGFR or kidney failure in patients with eGFR<60 ml/min/1.73 m ² ; TLS predicted IgAN progression in earlier stage disease	2
Membranous nephropathy*			
T and B cell aggregates	34.2% (151/442)	TLS+ patients had higher sCr, proteinuria and BP, lower serum albumin, and lower remission rate than TLS- patients; TLSs were associated with anti-PLA2R antibody; TLS+ patients were older and frequently male	3
Lupus nephritis*			
T and B cell aggregates	31.3% (10/32)	In a few patients, follow-up biopsy samples showed mature TLSs despite immunosuppressive treatment	4
T and B cell aggregates with FDCs	12.5% (4/32)		
T and B cell aggregates	51.4% (35/68)	The presence of TLS was associated with clonal expansion, somatic hypermutation and immune complex deposition in tubular basement membranes	5
T and B cell aggregates with germinal centre	5.9% (4/68)		
ANCA-associated glomerulonephritis*			
T and B cell aggregates	31.3% (5/16)	No clinical findings were reported.	4
T and B cell aggregates with FDCs	6.3% (1/16)		
T and B cell aggregates	47.4% (53/112)	The presence of TLS was associated with higher risk of AKI requiring dialysis and kidney failure	6
T and B cell aggregates with nodular B cell aggregates	13.4% (15/112)		
Acute kidney allograft rejection*			
B cell clusters	45.0% (9/20)	B cell density positively correlated with glucocorticoid resistance and poor graft outcomes	7
B cell clusters	59.2% (71/120)	The presence of TLSs was not associated with time to ACR, steroid resistance, sCr or graft loss	8
Clinically stable kidney allografts*			
T and B cell aggregates with signs of proliferation	0 months: 3.8% (8/210); 1 month: 46.9% (90/192); 6 months: 53.4%	The presence of TLS with FDCs in allografts at 1-year biopsy was associated with higher risk of kidney function decline after transplantation compared with allografts without TLS or those with TLSs but no FDCs	9

	(87/163) 12 months: 53.4% (108/185)		
T and B cell aggregates with signs of proliferation and FDCs	0 months: 1.4% (3/210); 1 month: 3.6% (7/192); 6 months: 8.6% (14/163); 12 months: 18.9% (35/185)		
Kidney allografts with chronic rejection[‡]			
B cell clusters with FDCs	95% (19/20)	No clinical findings were reported.	10
Complicated pyelonephritic kidneys[‡]			
T and B cell aggregates with sign of proliferation	100.0% (16/16)	No clinical findings were reported.	11

*Needle biopsy samples; [‡]Surgically resected kidneys. sCr, serum creatinine; BP, blood pressure; PLA2R, phospholipase A2 receptor; FDCs, follicular dendritic cells; ANCA, Antineutrophil Cytoplasmic Antibody; AKI, acute kidney injury; ACR, acute cellular rejection; BCR, B cell receptor; CKD, chronic kidney disease.

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