CXCL9 is a recognized biomarker of IFNγ-driven hyperinflammation in HLH/MAS[1,2]

Specialized inflammatory biomarkers, in addition to routine tests, can aid diagnosis and monitoring of HLH/MAS[1]

Many HLH/MAS-associated biomarkers also indicate parallel inflammatory processes (e.g., elevated LDH in thrombotic microangiopathy)[1]

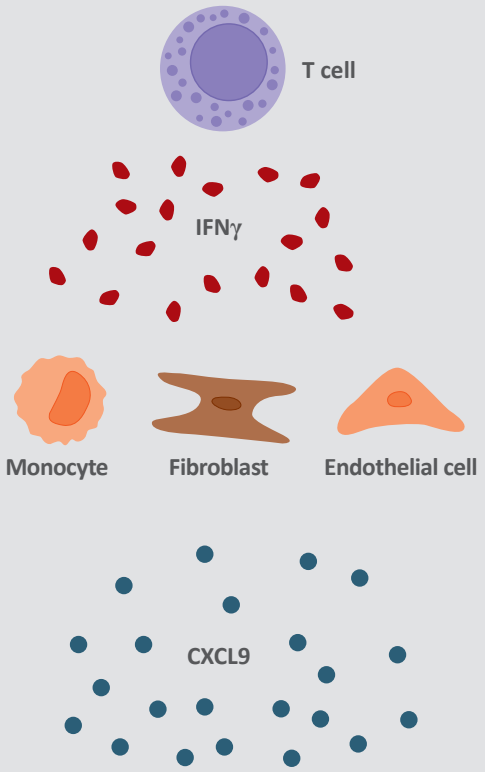
More specialized inflammatory biomarkers can assess IFNγ activity (e.g., CXCL9), inflammasome activity (e.g., IL-18), T cell activation (e.g., sCD25 [sIL-2Rα], HLA-DR), and macrophage activation (CD163, neopterin)[1]

Evidence suggests serum CXCL9 is a more useful biomarker of IFNγ activity than serum IFNγ levels[2,3]

	CXCL9	IFNγ	
		Free (active)	Antibody-bound (inactive)
Half-life in serum	**Stable[3]** Easily measurable in serum at nanogram concentrations	**Short (~1 min)[4]** Difficult to accurately measure	**Long[4]** Stabilized by drug binding and readily measurable
Representation of IFNγ activity	CXCL9 production is dependent on IFNγ activity	Free IFNγ is disproportionately retained in tissues versus serum	Antibody-bound IFNγ is neutralized and inactive

CXCL9 is an emerging inflammatory biomarker that can provide insight into underlying disease process in hyperinflammation of HLH/MAS[1]

CXCL9 is primarily induced by IFNγ, making CXCL9 a useful marker of IFNγ activity[2,3,5]



1. T cells produce IFNγ in response to infection[3]
2. IFNγ specifically induces CXCL9, a chemokine produced by monocytes, endothelial cells, and fibroblasts[3,5]
3. CXCL9 can be used as a specific biomarker for IFNγ activity[1]

CXCL9, chemokine C-X-C motif ligand 9; HLA-DR, human leukocyte antigen DR; HLH, hemophagocytic lymphohistiocytosis; IFNγ, interferon gamma; IL, interleukin; LDH, lactate dehydrogenase; MAS, macrophage activation syndrome; sCD25, soluble CD25 (also known as soluble interleukin-2 receptor α [sIL-2Rα]).

1. Shakoory B, et al. *Arthritis Rheumatol* 2023;75:1714–1732; 2. Jacqmin P, et al. *Br J Clin Pharmacol* 2022;88:2128–2139; 3. De Benedetti F, et al. *Nat Rev Rheumatol* 2021;17:678–691; 4. Lortat-Jacob H, et al. *J Biol Chem* 1996;271:16139–16143; 5. Kuo PT, et al. *Front Med (Lausanne)* 2018;5:257.

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Elevated CXCL9 levels may be useful in diagnosis and disease monitoring in patients with HLH/MAS[1–3]

CXCL9 levels are elevated in patients with HLH/MAS, reflecting increased IFNγ activity[1,2]

CXCL9 levels are elevated in MAS compared with active sJIA flares[1,2]

In contrast, IL-18 remains elevated during active sJIA, as well during a MAS episode[2]

CXCL9 levels positively correlate with laboratory markers relating to MAS severity (e.g., neutrophil and platelet counts; LDH and ALT levels)[1]

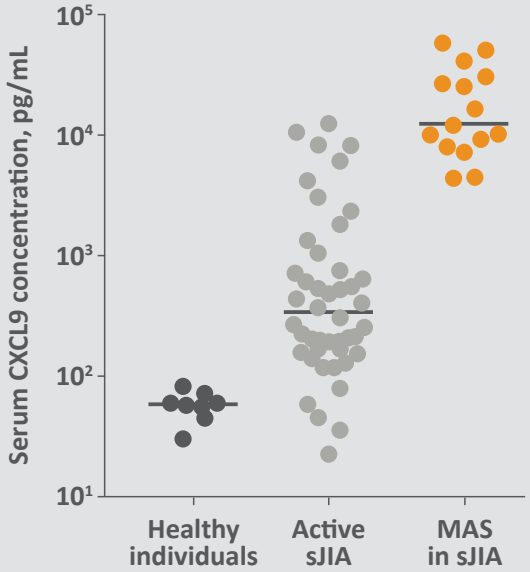

Figure adapted from Mizuta M, et al. *Cytokine* 2019;119:182–187. Bars represent median values.

CXCL9 testing availability[a]

Cincinnati Children's Hospital

LAB HOURS:
Mon – Fri
8am – 5pm (EST)

PH: **513-636-4685**

FAX: **513-636-3861**

Machaon Diagnostics

LAB HOURS:
24 hours/day
7 days/week

PH: **1-800-566-3462**

FAX: **510-839-6153**

CXCL9 is stable in EDTA plasma samples for 2 weeks (-20°C) or 6 months (-80°C)[5]

CXCL9 assessment is useful during the diagnostic workup of HLH[3]

CXCL9 assessment can be used to monitor HLH/MAS progression or resolution with less frequency than the recommended daily measures of conventional disease markers, such as ferritin and CRP[4]

[a] This is not an exhaustive list of laboratories offering CXCL9 testing. Additional laboratories continue to build new capabilities.

ALT, alanine aminotransferase; CXCL9, chemokine C-X-C motif ligand 9; EDTA, ethylenediaminetetraacetic acid; HLH, hemophagocytic lymphohistiocytosis; IFNγ, interferon gamma; LDH, lactate dehydrogenase; MAS, macrophage activation syndrome; sJIA, systemic juvenile idiopathic arthritis.

1. De Benedetti F, et al. *Nat Rev Rheumatol* 2021;17:678–691; 2. Mizuta M, et al. *Cytokine* 2019;119:182–187; 3. Jordan MB, et al. *Pediatr Blood Cancer* 2019;66:e27929;
4. Shakoory B, et al. *Arthritis Rheumatol* 2023;75:1714–1732; 5. Machaon Diagnostics. CXCL9 level. Available at: https://www.machaondiagnostics.com/test/cxcl9-level/. Accessed June 2024.

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