

Overview of Systemic mastocytosis (SM)

Abbreviated Disease State Overview



02/2023 US-BP-MED-NP-23007

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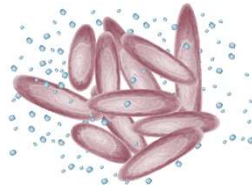
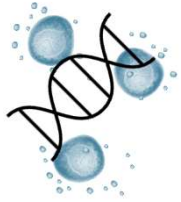
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How systemic mastocytosis develops^{1,2}



Mast cells

KIT D816V mutation driven mast cell proliferation

Symptoms of systemic mastocytosis

Mast cells express ***KIT***, a tyrosine kinase receptor^{1,3}

In ~95% of cases, the ***KIT* D816V mutation** can lead to over proliferation and survival of mast cells³

Systemic activation of mast cells can lead to **debilitating, life-threatening symptoms**, including, but not limited to: unpredictable anaphylaxis, maculopapular rash, pruritis, diarrhea, cognitive impairment, fatigue, and bone pain³

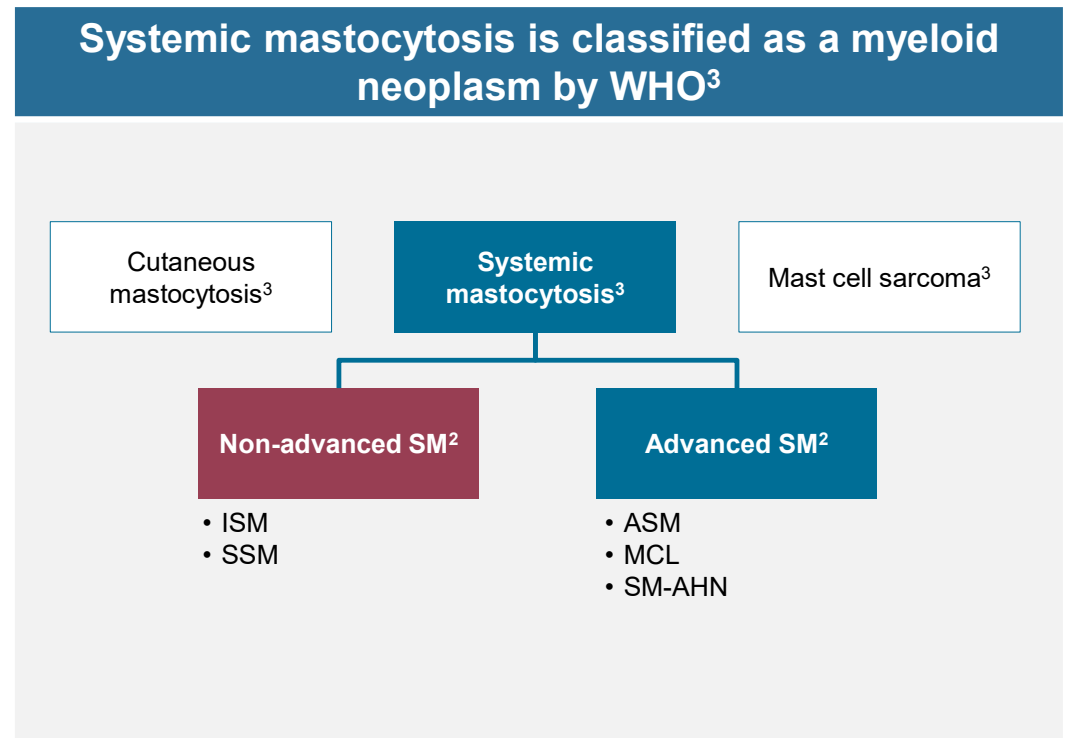
Symptom-directed therapies do not address the underlying cause of disease, offer limited control of disease, and do not prevent organ damage⁴⁻⁷

1. Metcalfe DD et al. Overview of mast cells in human biology. In: Akin C, ed. Mastocytosis. Cham, Switzerland: Springer Nature Switzerland AG; 2020:23–24.
2. Magliacane D et al. *Transl Med UniSa*. 2014;8:65-74. 3. Theoharides TC et al. *N Engl J Med*. 2015;373(2):163–172. 4. Pardanani A. *Am J Hematol*. 2019;94:363-377. 5. Pardanani A. *Am J Hematol*. 2016;91(11):1146–11591. 6. Jennings SV et al. *Immunol Allergy Clin North Am*. 2018;38(3):505–525. 7. Gilreath JA et al. *Clin Pharmacol*. 2019;11:77-92



Non-advanced systemic mastocytosis represents ~80-90% of patients with SM^{1,2}

- Prevalence of systemic mastocytosis is estimated at **≈1 in 10,000** adults¹
- According to registry data (n=1454), the majority of patients with non-advanced systemic mastocytosis present with ISM (~95%) and ~5% present with SSM²

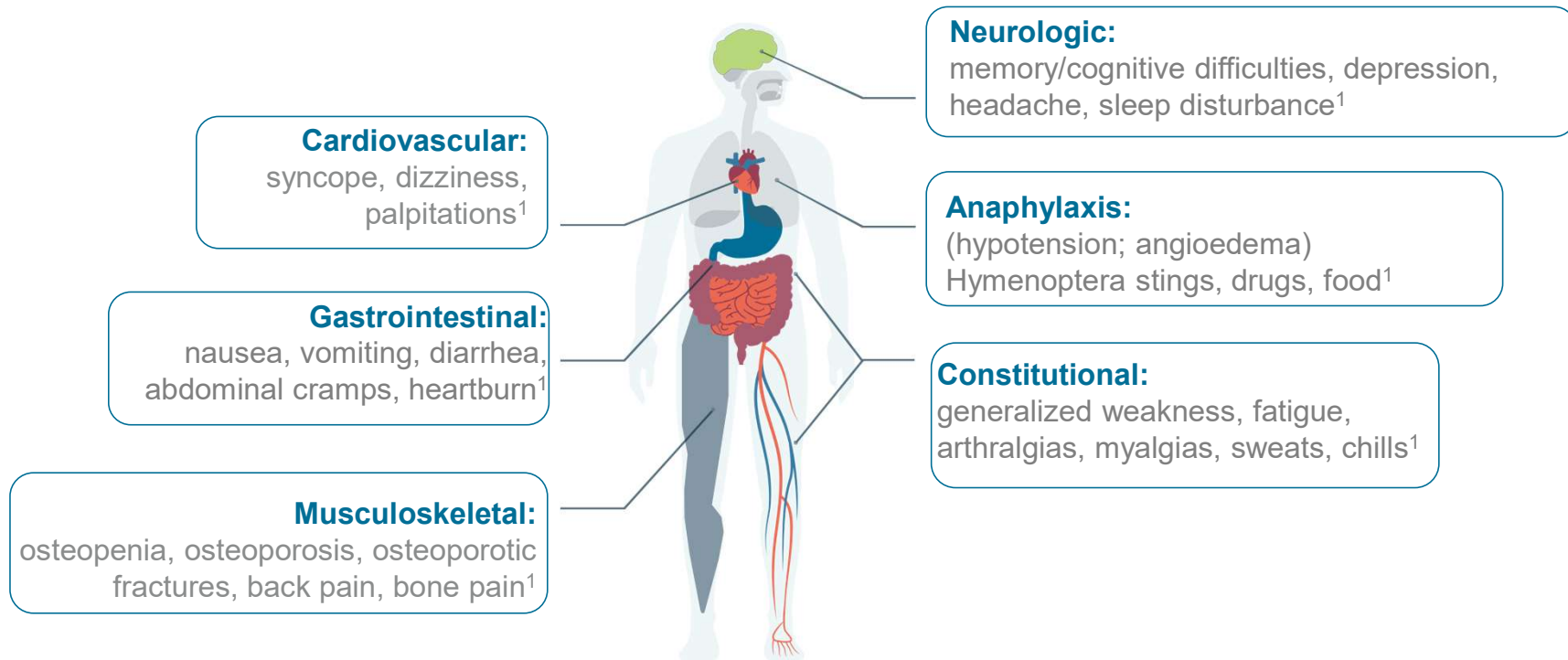


ASM, aggressive systemic mastocytosis; ISM, indolent systemic mastocytosis; MCL, mast cell leukemia; SM, systemic mastocytosis; SM-AHN, systemic mastocytosis with associated hematological neoplasm; SSM, smoldering systemic mastocytosis; BMM, bone marrow mastocytosis; WHO, World Health Organization.

1. Cohen SS et al. *Br J Haematol.* 2014;166:521–528. 2. Sperr WR et al. *Lancet Haematol.* 2019;6(12):e638–e649. 3. Khoury JD et al. *Leukemia.* 2022;36(7):1703-1719.



Systemic mastocytosis can affect several parts of the body^{1,2}



These symptoms represent the clinical spectrum of systemic mastocytosis and symptoms may vary in individuals, based on the type of systemic mastocytosis and aggressiveness of the disease.^{1,2}



Challenges in recognizing SM often result in misdiagnosis and prolonged time to diagnosis^{1,2}

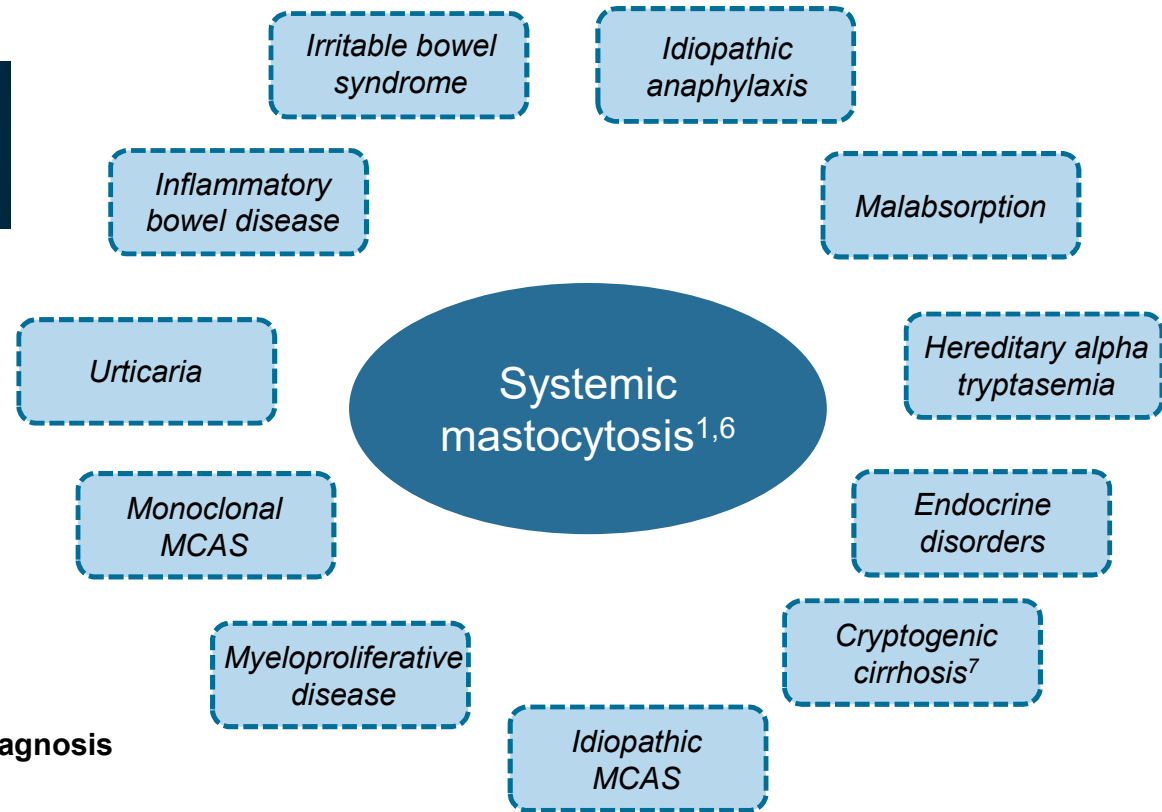
The initial symptoms of SM are heterogeneous and nonspecific, resulting in patients presenting to a diverse group of healthcare specialists and challenges in diagnosis

Some patients may remain undiagnosed until they are exposed to triggers (eg, insect sting) and experience anaphylactic reactions or even death^{3,4}

Mean time from initial symptom onset to diagnosis^{1,a}



A high index of clinical suspicion is needed to avoid misdiagnosis and delayed treatment⁵



ISM, indolent systemic mastocytosis; SM, systemic mastocytosis; SSM, smoldering systemic mastocytosis; MCAS, mast cell activation syndrome.

^aIn a Blueprint Medicines study, US adults with a self-reported SM diagnosis (N=56) completed an online survey of 100 items, including the 12-item Short-Form Health Survey, the ISM Symptom Assessment Form, and the Work Productivity and Activity Impairment Questionnaire, as well as questions about disease impact; results were analyzed using descriptive statistics.

1. Mesa et al. *Cancer*. 2022;128(20):3691-3699. 2. Trizuljak J et al. *Allergy*. 2020 Feb 28. doi: 10.1111/all.14248. 3. Reiter N et al. *Lancet*. 2013;382(9901):1380. 4. Vaughan ST et al. *Anaesthesia*. 1998;53(8):804-807. 5. Pardanani A. *Am J Hematol*. 2016;91(11):1146-1159. 6. NORD. Rare Disease Database: Mastocytosis. <https://rarediseases.org/rare-diseases/mastocytosis/>. Accessed July 7, 2021. 7. Jiang ZG, et al. *Gastroenterology*. 2018;155(1):23-24.



Hallmark symptoms may warrant investigation of systemic mastocytosis



Anaphylaxis

- **Anaphylaxis** with hypotension and syncope can occur¹
- **50% of adult patients with SM** experience recurrent or unexplained anaphylaxis^{2,3}


Skin

- **Maculopapular lesions** with **Darier's sign** is a highly specific diagnostic feature²
- Wheal-and-flare reaction is elicited by stroking lesion with a tongue spatula^{2,a}



Gastrointestinal

- Many patients report **nausea, vomiting and/or diarrhea**^{1,4}
- Symptoms can be unpredictable and severe^{1,4}

 Per WHO guidelines, it is recommended to test for **serum tryptase** and **KIT D816V** at the first sign of the disease^{3,5}

^aReprinted from Hartmann K et al. *J Allergy Clin Immunol.* 2016;137(1):35–45. Copyright 2016, with permission from Elsevier.²

1. Gilreath JA et al. *Clin Pharmacol.* 2019;11:77–92. 2. Hartmann K et al. *J Allergy Clin Immunol.* 2016;137(1):35–45. 3. Pardanani A. *Am J Hematol.* 2019;94(3):363–377.

4. Jennings SV et al. *Immunol Allergy Clin North Am.* 2018;38(3):505–525. 5. Khoury JD et al. *Leukemia.* 2022;36(7):1703-1719



High Sensitivity *KIT D816V*
Testing Labs & Blueprint
Medicines Biomarker
Testing Program
Supplementary Slides





Commercial laboratories currently offering high-sensitivity *KIT* D816V assays^{1-5,a}

Lab	Method	Sensitivity	Specimen Requirement	Reported
ARUP Laboratories ^{1,2}	Droplet digital PCR	LLD 0.03%	Whole blood (5 mL) or bone marrow (3 mL); lavender (EDTA) preferred; green (sodium heparin) also acceptable	Detected (reported as percent mutated allele) or Not detected
LabCorp ^{3†}	Droplet digital PCR	LLD 0.03%	Whole blood (3-5 mL) or bone marrow (1-2 mL); lavender-top (EDTA) or green-top (sodium heparin)	Detected (reported as percent mutated allele) or Not detected
Mayo Clinic Laboratories ⁴	Allele-specific PCR	LLD 0.1%	Whole blood (1mL); ambient preferred, refrigerated acceptable; lavender- or pink-top (EDTA) preferred	Positive or Negative

This list is not comprehensive and is not intended to be a recommendation, referral, or endorsement of a specific laboratory, service, or test. Blueprint Medicines Corporation makes no representations regarding the clinical or analytical validity, quality, or design of the testing, or services included. This list is provided as a convenience only and may not be exhaustive. Blueprint Medicines may update the list from time to time as it becomes aware of other commercial laboratories offering high-sensitivity *KIT* D816V assays.

^a*KIT* D816V mutational analysis on the bone marrow aspirate is particularly useful to establish the diagnosis of SM in patients with low mast cell burden, those with limited systemic disease who may have serum tryptase levels <20 ng/mL and lack multifocal mast cell clusters in a bone marrow biopsy.⁷ †The *KIT* D816V Digital PCR test by Labcorp is also used by Blueprint's Biomarker Testing Program.

EDTA, ethylenediaminetetraacetic acid; LLD, lower limit of detection; PCR, polymerase chain reaction; SM, systemic mastocytosis.

1. ARUP Laboratories. Accessed January 14, 2022. <https://ltd.aruplab.com/Tests/Pub/3002956>. 2. ARUP Laboratories. Accessed January 14, 2022. <https://ltd.aruplab.com/api/ltd/pdf/294>.

3. Labcorp. Accessed January 14, 2022. <https://www.labcorp.com/tests/485126/kit-d816v-digital-pcr>. 4. Mayo Clinic Laboratories. Accessed January 26, 2022.

<https://www.mayocliniclabs.com/api/sitecore/TestCatalog/DownloadTestCatalog?testId=607981>. 5. Akin C. *J Mol Diagn*. 2006;8(4):412-419.



Blueprint's biomarker testing program for systemic mastocytosis¹

Lab	Method
Blueprint's Biomarker Testing Program ¹	Droplet digital PCR

Blueprint's Biomarker Testing Program is sponsored by Blueprint Medicines as a way to help people and their doctors make more informed decisions about their health. Through this program, Blueprint Medicines, under an arrangement with Labcorp, makes *KIT D816V* testing available at no charge^a for patients who are being evaluated for systemic mastocytosis. Program eligibility criteria apply.^b **To learn more about eligibility, please visit [www.oncology.labcorp.com/blueprintsm](https://oncology.labcorp.com/blueprintsm).**

- While Blueprint Medicines provides financial support for this program, testing services are performed by an independent third party, and Blueprint Medicines assumes no liability and provides no warranties for the testing services provided by independent third parties
- Healthcare professionals shall use independent medical judgment in determining whether patients meet the program criteria for participation
- No identifiable patient data will be shared with Blueprint Medicines as part of this program
- This program is available in the United States only
- Healthcare professionals and patients who use this program have no obligation to recommend, purchase, order, prescribe, promote, administer, use, or support any Blueprint Medicines or Labcorp product or service
- No payers, including government payers, are billed for this program

^aTerms and conditions, including eligibility criteria apply. The *KIT D816V* test will be provided at no cost to patients, healthcare providers, and payers through this program. Excludes office visit, sample collection for tests not associated with this program, and any other related costs to patients. Labcorp will not bill the eligible patient's insurance for *KIT D816V* test, however, Labcorp will bill selected payer(s) for other testing services ordered.

^bTerms and conditions apply. Testing performed by Labcorp. While Blueprint Medicines provides financial support, Blueprint Medicines assumes no liability and provides no warranties for the testing services provided by independent third parties. See Labcorp website for full program details and program eligibility.

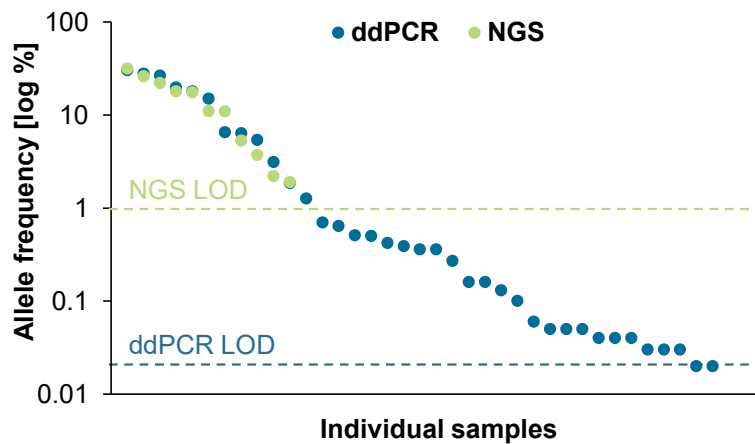
PCR, polymerase chain reaction.

1. Blueprint's Biomarker Testing Program. Accessed January 20, 2022. <https://oncology.labcorp.com/blueprintsm>.



ddPCR demonstrated 30-fold greater sensitivity over NGS for measuring *KIT* D816V MAF*1

	Local assessment n (%)	TruSight NGS n (%)	ddPCR n (%)
<i>KIT</i> D816V detected	31 (80)	11 (28)	37 (95)
<i>KIT</i> D816V not detected	8 (20)	28 (72)	2 (5)
Patients analyzed	39	39	39



The high-sensitivity ddPCR assay method demonstrated:

- *KIT* D816V mutation detection in 95% of PB samples from patients with previously confirmed ISM
- 30-fold greater sensitivity over NGS for measuring VAF; median percentage VAF (range) was 0.36 (0.02–30.22) by ddPCR and 11 (1.9–32) by NGS
- Greater diagnostic sensitivity for ISM compared with serum tryptase >20 ng/mL (77%) and presence of BM MC aggregates (90%)

*Data are from a Blueprint Medicines clinical study in systemic mastocytosis. Results were expressed as the percentage of patient PB samples testing positive for *KIT* D816V mutation (all genomic assays) and the log percent of MAF as measured by both central assay methods. NGS data at screening and ddPCR values at C1D1 were plotted for the scatter graph. BM, bone marrow; ddPCR, droplet digital PCR; ISM, indolent systemic mastocytosis; LOD, limit of detection; MC, mast cell; NGS, next-generation sequencing; PB, peripheral blood; PCR, polymerase chain reaction; VAF, variant allele frequency.

1. George et al. Presented at: 62nd American Society of Hematology Annual Meeting, Dec 5-8, 2020, Virtual format.