Original Article

# The Mastocytosis Society Survey on Mast Cell Disorders: Part 2—Patient Clinical Experiences and Beyond

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***What is already known about this topic?*** Mastocytosis and mast cell activation syndrome (MCAS) are disorders that are challenging to diagnose, and may go unrecognized for many years. Patients can have symptoms that mimic allergies and are at increased risk of anaphylaxis.

***What does this article add to our knowledge?*** This publication of a second set of data concerning a US mastocytosis and MCAS patient survey includes diagnostic sources, clinical/laboratory tests, comorbidities, dietary practices, familial occurrence, and perceptions of US care needs.

***How does this study impact current management guidelines?*** Goals of this article are to provide clinicians, patients, and others with a real-life–based understanding of the perceptions and experiences of patients who are evaluated and treated for mastocytosis and/or MCAS.

**BACKGROUND: Mast cell diseases such as mastocytosis and mast cell activation syndrome involve abnormal proliferation and/or activation of these cells, leading to many clinically relevant symptoms.**

**OBJECTIVE: To determine the characteristics and experiences of people known or suspected to have a mast cell disorder, The Mastocytosis Society, a US-based patient advocacy, research, and education organization, conducted a survey of patients.**

**METHODS: This Web-based survey was publicized through specialty clinics and the society's newsletter, Web site, and online blogs. Both online and paper copies of the questionnaire were provided together with required statements of consent.**

**RESULTS: The first set of results from this survey of 420 respondents has been previously published; the second set is presented in this article. These results include source(s) of diagnosis, clinical and laboratory tests reported, comorbidities, dietary practices, possible familial occurrence of mast cell disorders, and perceptions concerning mast cell disorder–related medical care needs in the United States.**

**CONCLUSIONS: These patient survey results are provided to assist medical professionals in learning patients' perceptions of**

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*Abbreviations used*
*BM- bone marrow*
*CM- cutaneous mastocytosis*
*MC- mast cell*
*MCA- mast cell activation*
*MCAS- mast cell activation syndrome*
*MCD- mast cell disorder*
*SM- systemic mastocytosis*
*TMS- The Mastocytosis Society, Inc*



***Key words:*** *Survey; Mast cell disorders; The Mastocytosis Society; Mast cell activation syndrome; Dermatologist; Allergist; Hematologist; Diet; Clinical laboratory tests; Family occurrence*

## INTRODUCTION

Abnormal proliferation, accumulation, and/or activation of mast cells (MCs) characterize mast cell disorders (MCDs). MCs are distributed in many tissues from the skin and mucosal membranes to the connective tissue, spleen, liver, and lymph nodes. MC activation (MCA), through both IgE-dependent and IgE-independent mechanisms, is associated with the release of mediator components, such as histamine, tryptase and other proteases, metabolites of arachidonic acid (such as prostaglandins and leukotrienes), cytokines, and chemokines. Binding of mediators to their respective cellular receptors in tissues can initiate and/or aggravate various acute and chronic, and sometimes debilitating, symptoms, which may induce anaphylaxis.[1-5]

MCDs include mastocytosis and MCA syndrome (MCAS).[6-11] Systemic mastocytosis and (mono)clonal MCAS are primary variants involving clonal MCs that harbor D816V or other gain-of-function *KIT* mutations, show abnormal morphology, and/or abnormally express CD25.[6-11] Cutaneous mastocytosis (CM) is more frequent in children; systemic mastocytosis (SM), with or without skin involvement, is more common in adults. Secondary and idiopathic forms of MCAS exist where no known clonal abnormalities in MCs are found. Many of these patients have IgE-dependent allergies.[12-14] Other patients presenting with acute life-threatening MCAS have idiopathic anaphylaxis. Diagnostic criteria for MCAS have been described and include signs and symptoms indicative of massive systemic MCA as well as a significant, event-restricted, increase in the serum tryptase level above the individual's baseline.[7,9] However, patients can experience symptoms of MCA without fulfilling the criteria for MCAS.[7] Patients with CM or SM may present with acute and/or chronic symptoms of MCA.

A 2010 Web-based survey on MCDs was conducted by The Mastocytosis Society, Inc (TMS) (www.tmsforacure.org), a US-based patient advocacy, research, and support organization. The first survey publication reported demographic characteristics, diagnoses, symptoms, allergies, provoking factors of MC symptoms, and disease impact.[15] This article reports the second set of results: physician types consulted, clinical laboratory tests, comorbidities, diet and nutrition, MCDs in families, and perceptions concerning US MCD-related medical care needs.

**TABLE I.** Respondents to the question "Who diagnosed your mast cell disorder?"

| Physician type(s) recalled as source(s) of diagnosis | Total respondents, n (% of 420)*† | Respondents recalling single physician diagnosis, n (% of 252) |
|---|---|---|
| Dermatologist | 196 (46.7) | 103 (40.9) |
| Allergist/immunologist | 130 (31.0) | 61 (24.2) |
| Hematologist/oncologist | 111 (26.4) | 38 (15.1) |
| Primary care physician | 57 (13.6) | 6 (2.4) |
| Gastroenterologist | 49 (11.7) | 18 (7.1) |
| Other‡ | 26 (6.2)* | 9 (3.6) |
| Unspecified no./type (eg, "doctor," hospital name) | 21 (5.0) | |

*Slightly more than a third (143 [34.0%]) of survey respondents noted more than 1 specific type of physician.
†Details concerning respondents who had not yet received a diagnosis or who did not list a doctor type are provided in this article's Online Repository at www.jaci-inpractice.org.
‡Other includes endocrinologist (13), internist-internal medicine specialist (5), pediatrician (4), rheumatologist (3), gynecologist (2), surgeon (2), cardiologist (2), neurologist (2), emergency room/"ER" doctor (2), urologist (2), otolaryngologist ("ENT") (2), geneticist (2), nephrologist (1), and rehabilitation/physical medicine specialist (1).

## METHODS

Methods and the survey questionnaire have been previously published.[15] Briefly, patients with mastocytosis, MCAS, or other MCDs were invited to complete this cross- sectional survey posted online (April 15 through May 24, 2010), with paper copies mailed upon request. Chi-square analyses were performed using Microsoft Excel. Valid responders were defined as those who answered at least some questions beyond the opening section for Demographics and Diagnosis. Of the 420 valid responders providing demographic characteristics, 62.6% were female, 22.1% male (age, 1-80 years; average, 44.8 years; median, 48 years) and primarily white (93.6%). Diagnoses obtained from physicians, as reported by respondents, included 51.2% SM, 23.8% CM, and 12.4% MCAS, 4.5% idiopathic anaphylaxis, and 6.4% not determined.[15] The denominator value for each survey section was derived from the number of participants who entered and completed at least some questions in that particular section.

## RESULTS

### Sources of diagnoses

Of 420 valid responders completing the Demographics and Diagnosis section, 400 (95.2%) responded to "Who diagnosed your mast cell disorder?" by selecting checkboxes or writing in physician types. Dermatologists, allergist/immunologists, and hematologists were the leading sources of initial diagnoses (Table I).

### Clinical and laboratory tests

Questions concerning tests related to MCDs were answered by 389 (92.6%) participants (Table II; for write-in responses, see this article's Online Repository at www.jaci-inpractice.org). Of 221 respondents recalling a bone marrow (BM) biopsy, 217 (98.2%) were adults 18 years and older. Of the remaining 43

**TABLE II.** Clinical examinations and laboratory tests reported by 389 respondents

| Examinations/tests | Total respondents,*† n (%) | Frequency per year, n (%)‡ | | | |
|---|---|---|---|---|---|
| | | ≥4 | 2-3 | 1 | Not routine |
| Clinical examinations | | | | | |
| General for symptoms (history & physical)§ | 323 (83.0) | 38 (11.8) | 69 (21.4) | 76 (23.5) | 113 (35.0) |
| Visual skin assessment | 321 (82.5) | 37 (11.5) | 72 (22.4) | 76 (23.7) | 101 (31.5) |
| Photographic skin documentation | 100 (25.7) | 6 (6.0) | 6 (6.0) | 14 (1.4) | 52 (52.0) |
| Diagnostic/biologic tests | | | | | |
| Complete blood cell counts (CBCs) | 337 (86.6) | 74 (22.0) | 90 (26.7) | 99 (29.4) | 62 (18.4) |
| Serum chemistries | 147 (37.8) | 22 (15.0) | 41 (27.9) | 42 (28.6) | 36 (24.5) |
| Serum ferritin | 76 (19.5) | 10 (13.2) | 5 (6.6) | 26 (34.2) | 30 (39.5) |
| Skin biopsy | 237 (60.9) | Frequency not queried | | | |
| BM biopsy§ | 221 (56.8) | 1 (0.5) | 7 (3.2) | 28 (12.7) | 154 (69.7) |
| Diagnostic markers | | | | | |
| Serum tryptase§ | 300 (77.1) | 29 (9.7) | 69 (23.0) | 77 (25.7) | 105 (35.0) |
| 24-h urine for histamine/histamine metabolites§ | 198 (50.9) | 6 (3.0) | 16 (8.1) | 29 (14.6) | 128 (64.6) |
| 24-h urine for prostaglandins | 84 (21.6) | 2 (2.4) | 12 (14.3) | 15 (17.9) | 44 (52.4) |
| *KIT* mutation/other molecular test | 123 (31.6) | Frequency not queried | | | |
| Radiographic tests | | | | | |
| Bone scan§ | 132 (33.9) | 1 (0.8) | 2 (1.5) | 28 (21.2) | 83 (62.9) |
| Bone density§ | 213 (54.8) | 1 (0.5) | 2 (0.9) | 58 (27.2) | 109 (51.2) |
| X-rays or CT scan | 239 (61.4) | 6 (2.5) | 20 (8.4) | 26 (10.9) | 148 (61.9) |

*CT*, Computed tomography.
*Total of those selecting "yes" (test ever performed) plus those not answering "test ever performed" but selecting or noting a frequency. "Not sure" responses were ≤10% for all tests other than serum ferritin (54.2%), serum chemistries (45.2%), and 24-h urine for prostaglandins (25.2%).
†Percent of 389 respondents.
‡Percent of total for each individual test.
§Greater than 4% of these respondents listed different timing than the options provided for these tests.

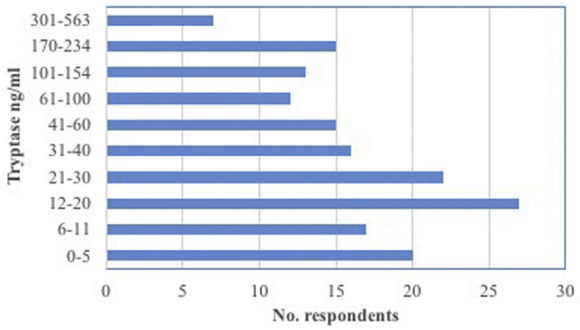


**FIGURE 1.** Most recent baseline serum tryptase level reported by 164 respondents. Respondents were asked to leave the answer blank if the most recent baseline level was not known. Data for 4 reporting the tryptase level "above 200" and one "above 300" were entered as 201 or 301 ng/mL, respectively. Five people reported their tryptase level as "normal" and these are not included in the graph. Number ranges missing from the graph had no entries at those levels.

respondents in the survey who were younger than 18 years, 3 (7.0%) reported having had this test. Diagnoses reported by those who recalled a BM biopsy are included in this article's Online Repository at www.jaci-inpractice.org.

Bone density assessment was recalled by 213 respondents, of whom 142 (66.7%) were female, 32 (15.0%) male, and 39 (18.3%) did not report sex. For the 211 of these providing birth months and years, ages ranged from 17 to 80 years (average, 52.5 years; median, 53 years); 130 (61.6%) were 50 years or older, 6.6% in their 30s, and 7.1% in their twenties or teens. Sixty-two percent of women recalling a bone density test were 50 years or older.

Although the baseline serum tryptase level is a sensitive, specific surrogate marker of MC burden in mastocytosis, an acute increase over baseline during a clinical event, such as anaphylaxis, is usually indicative of substantial systemic MCA. Once a certain threshold is reached, this increase serves as an MCAS criterion.[7] A third of 389 respondents (133 [34.2%]) recalled having had their tryptase level measured at symptom-free intervals to establish a baseline, but 188 (48.3%) did not and 56 (14.4%) were unsure. Seventy-eight people (20.1%) recalled it measured at times of maximum symptoms ("acute MC degranulation attack symptoms or anaphylaxis"), 252 (64.8%) did not, and 49 (12.6%) were unsure. For the 56 respondents (14.4%) who had it measured at both symptom-free and maximum symptom times, 23 (41.1%) had it measured "often." Respondents provided their most recent baseline tryptase level (Figure 1). For levels by diagnosis type, see this article's Online Repository at www.jaci-inpractice.org.

In most adult patients, SM is associated with the somatic gain-of-function D816V mutation in *KIT* (stem cell factor receptor).[16-18] Less than a third (123 [31.6%]) of respondents recalled *KIT* mutation or other molecular testing, queried as "c-kit (or other genetic testing)" (Table II). Participants responded to a separate question concerning a positive *KIT*D816V mutation test result (Table III). For additional genetic mutations and MC expression of CD2 and/or CD25, see this article's Online Repository at www.jaci-inpractice.org.

**TABLE III.** SM diagnosis cross-tabulated with responses regarding testing positive for the *KIT*D816V mutation and recollection of this or other molecular testing having been performed

| | n (%)* | | | |
|---|---|---|---|---|
| Tested positive for *KIT*D816V? | Total respondents | SM diagnosis† | *KIT* or other molecular test recalled | SM diagnosis and *KIT* or other molecular test recalled |
| Yes | 47 (12.1) | 42 (20.9) | 47 (38.2) | 42 (46.7) |
| No | 61 (15.7) | 31 (15.4) | 39 (31.7) | 25 (27.8) |
| Not sure | 85 (21.9) | 48 (23.9) | 32 (26.0) | 20 (22.2) |
| Test not performed | 191 (49.1) | 77 (38.3) | 4 (3.3) | 2 (2.2) |
| Total | 389 | 201 | 123 | 90 |

*Percent of column total, but note that 5 people did not answer the question.
†Total with SM answering questions in this section of the questionnaire.

## Comorbidities

In addition to symptoms and the possible presence of allergies (previously reported[15]), participants were asked about 6 common comorbidities. Of 382 respondents to this section, 120 (31.4%) reported "osteopenia or osteoporosis confirmed by a bone scan or bone density scan (dexascan)," 11 (2.9%) "coronary artery disease," 10 (2.6%) "a heart attack," 88 (23.0%) "high blood pressure," 82 (21.5%) "hypercholesterolemia (high blood cholesterol)," and 53 (13.9%) various cancer types (see this article's Online Repository at www.jaci-inpractice.org). Age and sex comparisons with the US population for osteoporosis or "low bone mass" (not reaching the criterion of osteoporosis; also referred to as osteopenia) are provided in Table IV.[19] Age comparisons with the US population for specific cancer types and other comorbidities are provided in Tables E2 to E5 in this article's Online Repository at www.jaci-inpractice.org. "Other conditions" written in by 3% or more of respondents are listed in Table E6 in this article's Online Repository at www.jaci-inpractice.org.

Of 198 SM respondents answering demographic and osteopenia/osteoporosis questions, 85 (42.9%) reported confirmed osteopenia/osteoporosis; 56 (65.9%) of these were 50 years or older, of whom 36 were female, 13 male, and 7 did not report sex (for additional diagnoses and details, see this article's Online Repository at www.jaci-inpractice.org). For respondents of all ages with osteopenia/osteoporosis, 55 (45.8%) reported taking medication for these conditions. See Figure 2 for calcium and/or vitamin D supplement responses.

## Diet and nutrition

Dietary questions were answered by 382 (91.0%) survey participants; just 41 (10.7%) had been referred to a dietitian by a physician. "Low histamine" diets had been recommended by a physician to 46 (12.0%) and by a dietitian/nutritionist to 22 (5.8%). "Low histamine" diets had been followed by 94 (24.6%), including 55 who had also tried an "elimination" diet. An "elimination" diet had been tried by 132 (34.6%), of whom 69 had not followed a "low histamine" diet.

Of the 94 reporting a "low histamine" diet, 48 (51.1%) perceived improvement in their MCD-related symptoms; however, 18 (19.1%) had not and 28 (29.8%) were not sure. Somewhat larger percentages of participants trying diet(s) felt that they might not be receiving adequate nutrition (Table V).

## Possible MCDs in family members of respondents

More than one-fifth (86 [22.9%]) of 376 respondents reported possible MCDs in family members. Six respondents reporting mastocytosis "confirmed by test results" noted relatives with a "confirmed" MCD. However, no details concerning diagnostic assays or criteria used to define MCD in relatives were reported. Details regarding relationships and disease types reported are presented in the Appendix and Table E10 in this article's Online Repository at www.jaci-inpractice.org.

## Care needs in the United States

Of 376 respondents who answered the question on location of MCD-related care, 317 (84.3%) reported receiving it in the United States. Responses of these 317 concerning US care needs and adequacy of physician-provided information are provided in this article's Online Repository at www.jaci-inpractice.org (Appendix and Figure E1).

# DISCUSSION

TMS conducted this cross-sectional survey to describe characteristics, concerns, and experiences of patients with MCDs and to increase communication between patients and physicians. As previously noted, this survey had some important strengths and weaknesses.[15] The survey likely included some patients with MCA without a definitive diagnosis of mastocytosis or proven MC involvement, because review of medical records was beyond the realistic scope of this patient-reported survey, and consensus statements on MCAS diagnosis were not published until after the survey was conducted.[7] In addition, respondents' perceptions of disease may differ from actual disease, for example, related to overestimation of true allergy.[1] However, it was important to include a broad spectrum of MCD cases and even patients with suspected disease to explore daily practice issues. Also, the findings of various professional sources of MCD diagnoses may reflect diverse clinical presentations and other challenges of MCD assessment.

If mastocytosis is suspected, specialists suggest measuring total basal serum tryptase.[26] A basal tryptase level above 20 ng/mL constitutes a minor criterion of SM.[6,27-29] However, a slight or marked increase in tryptase level can also be seen in patients with other hematologic disorders, such as myeloid leukemia, myelodysplastic syndrome, or eosinophilic leukemia, and in hereditary α-tryptasemia.[30-32] In addition, even healthy subjects can have a slightly elevated basal serum tryptase level. However, a tryptase level below 20 ng/mL does not rule out mastocytosis, because patients with CM and isolated BM mastocytosis often have lower levels.[26,33,34]

In patients with SM and elevated basal tryptase level, routine testing can help track MC burden.[6,35,36] Acute increases above baseline indicate MCA, and when the event-related increase

**TABLE IV.** Osteopenia/osteoporosis in 313 respondents providing age and sex with "yes" or "no" answers to osteopenia/osteoporosis question compared with estimated US population prevalence

| Sex<br>Age group (y) | TMS<br>Site not specified, proportion* (%) | US age group estimates, total hip or lumbar spine (%) |
|---|---|---|
| Female | (All = 78 of 230) | |
| <20 | 0 of 13 (0.0) | † |
| 20-29 | 2 of 14 (14.3) | ‡ |
| 30-39 | 5 of 24 (20.8) | |
| 40-49 | 15 of 65 (23.1) | |
| 50 or older | 56 of 114§ (49.1) | Osteoporosis 15.5%; "Low bone mass"‖ 51.4%<br>Combined osteoporosis/"low bone mass"‖ 66.8%¶[19] |
| Male | (All = 20 of 79) | |
| <20 | 1 (17 y old) of 25 (4.0) | † |
| 20-29 | 1 of 5 (20.0) | ‡ |
| 30-39 | 2 of 4 (50.0) | |
| 40-49 | 2 of 14 (14.3) | |
| 50 or older | 14 of 31§ (45.2) | Osteoporosis 4.3%; "Low bone mass"‖ 35.2%<br>Combined osteoporosis/"low bone mass"‖ 39.4%¶[19] |

*Sixty-nine cases not included because of missing information: answered question but did not report sex (58); no answer to question (1 male and 1 female); not sure (3 females, 4 males); birth year not reported for age calculation (2 females). Of the 58 who did not report sex, 21 reported osteopenia/osteoporosis.

†Statistical comparisons not feasible because of differing definitions and rarity of condition; bone density values change with growth; diagnosis of "osteoporosis" or "low bone mass"/"osteopenia" in ages less than 49 y is not made solely on density values; occurrence is disease- or medicine-related, congenital, or idiopathic.[20,21]

‡Prevalence percentages for US statistics on osteoporosis/"low bone mass" (osteopenia) not available for these age groups; bone density values vary with age, but not dramatically until ages 50 y and older, and are also influenced by other factors; "low bone mass" may not be related to risk of fracture; primary osteoporosis is rare; usually related to disease or medicine, or is idiopathic.[22-24]

§Twenty-one women and 7 men, 50 y or older, who reported not having been diagnosed with osteopenia/osteoporosis also reported in a separate question regarding testing that they had never had a bone density test performed.

‖"Low bone mass" (not reaching the criterion of osteoporosis; also referred to as osteopenia)[19,25]

¶$\chi^2$ statistical comparisons between TMS survey and US population should be interpreted with caution because US population was age-adjusted and underlying ages were not provided in reference.[19] Also, corresponding respondent age groups would have been too small to detect significant differences. No indication of significance (less than chance occurrence of differences) was detected. Women ($\chi^2 = .0000$, $P > .995$); Men ($\chi^2 = .5142$, $P > .9$).

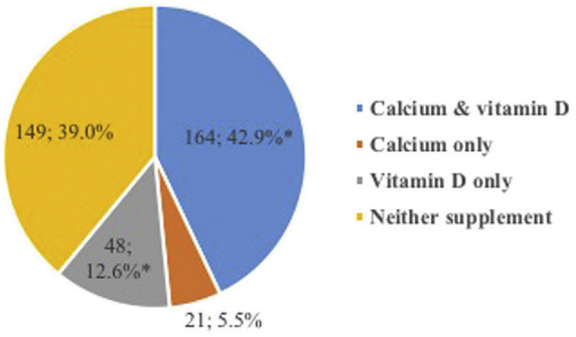


**FIGURE 2.** Calcium and vitamin D supplement use by 382 respondents. *Of 212 (55.5%) respondents taking vitamin D, 120 (56.6%) had had those levels measured; an additional 24 (11.3%) not taking vitamin D had had their levels measured. Of all 120 (31.4%) with osteopenia/osteoporosis, 55 (45.8%) took "medication," 84 (70.0%) took calcium plus vitamin D, 12 (10.0%) vitamin D only, 5 (4.2%) calcium only, and 19 (15.8%) neither supplement.

exceeds 20% + 2 ng/mL absolute above baseline, MCAS may be diagnosed.[7] Although most survey respondents reported having tryptase level measured, most of these at least annually, as recommended,[26] only 14.4% of respondents recalled measurement of both basal and event-related levels.

There is an ongoing discussion concerning elevated versus normal basal serum tryptase levels.[3,10,27,37,38] Range categories in Figure 1 were chosen to allow for normal boundaries estimated in the literature at 11 and 20 ng/mL and to accommodate the wide range of values. Some recent literature suggests similar boundaries, but several European centers consider a 15 ng/mL boundary a more realistic threshold.[26,30] In fact, based on comparison with a larger group of apparently healthy individuals, the 15 ng/mL threshold may be the most reliable parameter to discriminate between elevated and normal in daily practice, and this approach may also help avoid unnecessary referrals.[26,30]

If the serum tryptase assay is not available, serum tryptase is not elevated, or a rise cannot be captured during an MCA event, additional tests (24-hour urine analysis for histamine metabolites, prostaglandin D2 or its metabolite, or 11β-prostaglandin F2α) may be conducted, even though they may be less specific and/or sensitive.[7,26]

Visual skin assessment may identify lesions that are sometimes the first indication of possible mastocytosis.[6] Most respondents reported dermatologic assessment, more than half of these at least annually. Photographic skin documentation, although not frequently conducted for most, can provide a record of skin involvement, and changes over time or in response to therapy.[6] Verification of mastocytosis in the skin involves both clinical identification and biopsy analyzed with MC-specific markers (including tryptase) and sometimes, *KIT* mutation analysis.[6,39] More than 60% of respondents recalled a skin biopsy related to their MCD, with 88.2% of these reporting a diagnosis of mastocytosis (see this article's Online Repository at www.jaci-inpractice.org).

**TABLE V.** Perception of adequate nutrition with diet(s) or no diet for 345 respondents providing information

| | Adequate nutrition | | | |
|---|---|---|---|---|
| Dietary group | Yes, n (%)* | No, n (%)* | Not sure, n (%)* | Total, n (%)† |
| "Low histamine" only | 19 (52.8) | 12 (33.3) | 5 (13.9) | 36 (10.4) |
| "Elimination" only | 41 (59.4) | 16 (23.2) | 12 (17.4) | 69 (20.0) |
| Both diets | 27 (49.1) | 19 (34.5) | 9 (16.4) | 55 (15.9) |
| No diet | 123 (66.5) | 32 (17.3) | 30 (16.2) | 185 (53.6) |
| Total | 210 (60.9) | 79 (22.9) | 56 (16.2) | 345‡ |

$\chi^2$ analysis of percentage differences for adequate nutrition: "low histamine" vs no diet ($P = .019$); "elimination" vs no diet ($P = .25$); both diets vs no diet ($P = .055$); details provided in Tables E7-E9.
*Percent of row total.
†Percent of column total.
‡An additional 25 were not sure whether they had followed either a "low histamine" diet, an "elimination" diet, or both, and an additional 12 did not answer at least 1 of these questions or the question related to adequate nutrition. (Of *all* those who followed a "low histamine" diet, 14 of 94 [14.9%] and of *all* those who tried an "elimination" diet, 22 of 132 [16.7%] were not sure about obtaining adequate nutrition.)

Diagnosing SM usually requires a BM investigation. However, in children, a BM study is required only when hepatosplenomegaly, lymphadenopathy, blood cell count abnormalities, or other signs of a systemic BM disease are found.[6,26,40] Accordingly, the lower number of BM studies performed in children is reflected in this survey's findings. In adults with typical mastocytosis-related skin lesions, a BM biopsy is recommended, because most ultimately meet the criteria for SM.[6,41] Therefore, it is of concern that 60% of adult respondents reporting a CM diagnosis had not recalled a BM biopsy, as previously reported.[15] Additional indications for BM investigations in patients with suspected MCD have been recently reviewed.[26,30,40] If performed, appropriate harvesting and analysis techniques are required with specific cytomorphological, immunohistochemical, and molecular studies (tryptase, KIT/CD117, CD25, *KIT* mutation analysis).[6,35,42] Most reported not having the CD2/CD25 tests or were unsure, despite the fact that MC expression of CD2/CD25 is a minor criterion for diagnosing SM (see this article's Online Repository at www.jaci-inpractice.org).[6,27-29]

An additional SM minor criterion is identification of an activating mutation in *KIT* (commonly D816V).[6,27-29] Although studies indicate that more than 80% of patients with SM have a *KIT*D816V mutation,[16,18,39,43] nearly 40% of survey respondents with SM did not recall being tested for this mutation, a test performed in BM samples when this survey was conducted. In this regard it is noteworthy that molecular testing for *KIT*D816V using a highly sensitive PCR technique can now be performed in blood leukocytes and that this blood test is a useful screen for patients with suspected SM without typical skin lesions.[26,44] However, at the time of this survey, such methods were not readily available in the United States, even in specialty clinics. Guidelines for peripheral blood *KIT* mutation testing in mastocytosis are now available, and suggest that peripheral blood testing for *KIT*D816V should be part of a screening algorithm to help determine the need for a BM investigation in cases of suspected MCD without skin lesions.[26,39] Although detection of *KIT*D816V in peripheral blood is less likely in patients who have serum tryptase levels below 25 ng/mL, it is still often found, and so the recommendation is to screen for it in all patients with suspected SM.[26] In addition, measurements of *KIT*D816V allele burden can be useful for disease monitoring and for determining the prognosis.[17,45] Patients with SM with *KIT*D816V in non-MC hematopoietic lineages may have increased risk of disease progression.[16,46] In symptomatic patients in whom full criteria for SM are not met and no skin involvement is found, *KIT* mutation presence may contribute to a diagnosis of (mono)clonal MCAS.[7,9]

Additional testing may be necessary to monitor for possible disease progression and secondary complications. Some tests may be required for classification and treatment monitoring of more aggressive forms of MCD.[35,36] These tests include a complete blood cell count with differential counts (performed at least annually by nearly half reporting this test), serum chemistries (many respondents unsure, but this term may have been unfamiliar), and osteodensitometry.[26,35,39] Additional follow-up investigations such as ultrasonographic analysis of liver and spleen, computed tomograms, x-rays, bone scans, or cytogenetics may also be necessary to detect disease progression.[6,27-29,36]

Given the risk of bone mass loss in adult patients with SM, specialists recommend repeat bone density testing,[6,47-49] with timing dependent on previous diagnosis, additional risk factors, or therapy response assessment.[35,39] There are no consensus guidelines on how to follow bone disease in mastocytosis, but in patients with SM, we recommend consideration of bone density testing in 2- to 3-year intervals if previous bone density values (*T* scores) were normal, and yearly bone density if osteopenia or osteoporosis was diagnosed. This test was reported by more than half the respondents; however, questionnaire frequency options may have been inappropriate, because bone density examinations are not commonly performed more than every 1 to 2 years.[50] Most respondents reporting this test were women of postmenopausal ages, which may reflect an overlap with routinely recommended examinations for all such women. However, as per consensus recommendations, repeated examination of bone density values (*T* score) is standard in *all* adult patients with SM.

The tests and examinations discussed in this article are not all-inclusive of those that may be required for diagnosis, monitoring, and determination of secondary complications. Recommended tests and examinations have been described by the European Competence Network on Mastocytosis.[26,39] Survey results regarding allergy testing have been previously reported.[15]

Respondents were asked whether or not they had any of 6 common diseases: osteopenia/osteoporosis, cancer, high blood pressure, hypercholesterolemia, coronary artery disease, and heart attacks. Comparisons of comorbidities in this survey (Table IV

and Tables E2-E5) with frequencies from other studies, or estimated US prevalences, must be considered with caution because of differences in study design and participant characteristics.

"Confirmed" osteopenia/osteoporosis, reported by 31.4% of total and 42.9% of SM respondents, has been reported in patients with SM, along with other bone abnormalities.[47-49,51] MC mediators such as histamine act on both osteoclasts and osteoclast precursors.[52] Bone loss severity has been associated with MC amount and distribution in indolent SM.[53] Prevalences of 20% osteoporosis and 33% osteopenia have been reported in mastocytosis.[47,51]

Estimating the proportion of osteopenia/osteoporosis cases attributable to MCDs versus aging, especially at menopause, is challenging. One survey limitation was to query regarding "osteopenia or osteoporosis" without specifying any anatomic site, whereas the US National Health and Nutrition Examination Surveys (NHANES) separate these 2 conditions and specify site(s).[19] Also, actual bone density values were the basis of the US estimated prevalence, whereas recall of a diagnosis of "osteopenia" or "osteoporosis" was the basis for TMS survey frequency. Considering these limitations, "confirmed osteopenia/osteoporosis" was reported by 49.1% of female survey respondents and 52.2% of female respondents with SM, who were 50 years or older. This compares with estimated percentages of 51.4% "low bone mass" (osteopenia) and 15.5% osteoporosis in US women 50 years and older based on prevalences of sample surveys 2005-2010 applied to the 2010 population (see Table IV and Table E1 in this article's Online Repository at www.jaci-inpractice.org).[19] The percentage of osteopenia/osteoporosis in male survey respondents 50 years and older was 45.2%, compared with 54.2% of male respondents in that age group with SM. This contrasts with an estimated 35.2% "low bone mass" and 4.3% osteoporosis in the US 2010 population.[19] Manually combining the numbers provided in the reference for either osteoporosis or "low bone mass" in either the hip or lumbar spine (women 66.8%, men 39.4%) and then performing a statistical ($\chi^2$) comparison with TMS survey respondents did not detect any significant difference in prevalence (all $P$ values >0.9 except for males with SM, $P > .7$) (Tables IV and Table E1).

Although statistical comparison with the US population did not detect any significant differences, the greater occurrence of osteopenia/osteoporosis in TMS males with SM age 50 years or older is noteworthy. Significant differences might have been detected if this study had had more power; that is, if there had been more respondents reporting test results, sex, and age. Elevated risk of osteoporotic fractures in patients with SM has been associated with increased age, and especially male sex, in a European study.[48]

Although the majority of osteopenia/osteoporosis in both males and females in the TMS survey occurred in those who were 50 years or older, it was also reported by 21.4% of younger (20-49 years) women and 21.7% of younger men, plus 1 teenage male (Table IV). Because this condition is mainly a disease of aging,[54] comparative statistics for younger age groups are lacking.[24] Thus, osteopenia/osteoporosis in the young adults of the TMS survey is a serious concern and deserves further investigation and attention.

Cancer, as reported by 13.9% of respondents, included various solid tumors and 1.0% with possible hematologic/lymphatic cancers, but also nonmelanotic skin cancers, which are not part of national cancer statistics. The overall percentage for those with nonskin cancers was 7.3%, compared with the overall estimated percentage of 6.1% crude or 5.8% age adjusted (both SEs 0.2%) for the 2010 US population.[55] It is not possible to make a statement about the differences between survey respondents and the US population because there were not enough respondents with any particular cancer type to have the statistical power to detect such differences. Percentage comparisons of TMS and US prevalence estimates by age groups for 3 cancer types with at least 5 respondents (breast, cervix uteri, and thyroid) are presented in this article's Online Repository (Appendix and Table E2).

High blood pressure was reported by 23.0% of respondents, compared with 25.5% estimated for the US population in 2012 (for age breakdown, see Table E3).[56] Estimates for 3 large US surveys from 2007 to 2008 were 27.8%, 28.5%, and 30.7%.[57]

Hypercholesterolemia/high blood cholesterol was reported by 21.5% of all respondents, none for those younger than 20 years, and 27.0% for those 20 years or older. These percentages could not be compared directly with US population statistics, which reported actual measures of 200 to 240 mg/dL as "borderline high" and 240 mg/dL or more as "high" and included those taking medicine to control cholesterol levels (Table E4).[58]

Coronary artery disease was reported by 2.9% of all respondents, and by 3.3% of those 18 years or older, as compared with 6.5% estimated for the 2012 US adult population (Table E5).[56]

Heart attacks were reported by 2.6% of all respondents and 3.0% of those 20 years and older (Appendix). Comparison with US population percentages who have survived heart attacks is challenging because of small numbers in TMS survey age groups and wide variance in occurrence of cardiac arrests/myocardial infarctions within and out of hospitals. Nevertheless, US estimates indicate an overall prevalence of 3.6% in adults 20 years or older.[58]

Histamine released from MCs can cause various symptoms, whether due to allergies or due to MCD.[59,60] Exogenous histamine consumed in aged, fermented, and/or spoiled foods may also cause symptoms, but is usually deactivated by intestinal enzymes such as diamine oxidase and histamine *N*-methyltransferase; however, these enzymes are not routinely assessed.[60] Although diamine oxidase has been considered as a potential therapy, no controlled clinical trials of these concepts have been conducted so far.[60,61]

Dietary conclusions of this survey are limited because "low histamine" and "elimination" diets were not defined in the survey questionnaire, nor was actual consumption or duration assessed. Furthermore, a "low histamine" diet would, by definition, be an "elimination" diet and more than half (58.5%) of those who checked "low histamine" diet also checked "elimination" diet. In addition, many respondents were "not sure" about adequacy of nutrition. Nevertheless, analysis indicated that those who had followed a "low histamine" only diet and those who had tried both diets were significantly more likely to fear that they were not obtaining adequate nutrition ($P$ values of .019 and .004, respectively; see Tables E7-E9 in this article's Online Repository at www.jaci-inpractice.org). This finding indicates that patients attempting dietary changes need reliable guidance.

Studies of genetically linked diseases require extensive family histories combined with clinical and laboratory data, such as histopathological documentation, which was beyond the scope and capability of this survey. The 22.9% of respondents who reported possible MCDs in family members (Appendix and Table E10) may

be an overestimate, because individual family members who had an MCD were each encouraged to fill out a separate survey. In addition, the nature and confirmation of these disorders in specific relatives were not determined for any survey participants responding to this section; further studies are warranted. Some studies have identified familial MCD, and although the frequency for clonal disorders appears to be low, this field of study requires continued exploration.[31,32,62-66]

Survey findings indicate a need for increased numbers of MCD specialists, collaboration with local physicians, and improved communication between physicians and their MCD patients (Appendix and Figure E1). Efforts to establish a US network of centers similar to the European Competence Network on Mastocytosis,[67,68] established in 2002, have been initiated to address these and other unmet needs in the MCD community.

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### REFERENCES

1. Gonzalez de Olano D, de la Hoz Caballer B, Nunez Lopez R, Sanchez Munoz L, Cuevas Agustin M, Dieguez MC, et al. Prevalence of allergy and anaphylactic symptoms in 210 adult and pediatric patients with mastocytosis in Spain: a study of the Spanish network on mastocytosis (REMA). Clin Exp Allergy 2007;37:1547-55.
2. Brockow K, Jofer C, Behrendt H, Ring J. Anaphylaxis in patients with mastocytosis: a study on history, clinical features and risk factors in 120 patients. Allergy 2008;63:226-32.
3. Lim KH, Tefferi A, Lasho TL, Finke C, Patnaik M, Butterfield JH, et al. Systemic mastocytosis in 342 consecutive adults: survival studies and prognostic factors. Blood 2009;113:5727-36.
4. Valent P. Mast cell activation syndromes: definition and classification. Allergy 2013;68:417-24.
5. Gulen T, Hagglund H, Dahlen B, Nilsson G. High prevalence of anaphylaxis in patients with systemic mastocytosis—a single-centre experience. Clin Exp Allergy 2014;44:121-9.
6. Valent P, Akin C, Escribano L, Fodinger M, Hartmann K, Brockow K, et al. Standards and standardization in mastocytosis: consensus statements on diagnostics, treatment recommendations and response criteria. Eur J Clin Invest 2007;37:435-53.
7. Valent P, Akin C, Arock M, Brockow K, Butterfield JH, Carter MC, et al. Definitions, criteria and global classification of mast cell disorders with special reference to mast cell activation syndromes: a consensus proposal. Int Arch Allergy Immunol 2012;157:215-25.
8. Sonneck K, Florian S, Mullauer L, Wimazal F, Fodinger M, Sperr WR, et al. Diagnostic and subdiagnostic accumulation of mast cells in the bone marrow of patients with anaphylaxis: monoclonal mast cell activation syndrome. Int Arch Allergy Immunol 2007;142:158-64.
9. Akin C, Valent P, Metcalfe DD. Mast cell activation syndrome: proposed diagnostic criteria. J Allergy Clin Immunol 2010;126:1099-1104.e4.
10. Alvarez-Twose I, Gonzalez de Olano D, Sanchez-Munoz L, Matito A, Esteban-Lopez MI, Vega A, et al. Clinical, biological, and molecular characteristics of clonal mast cell disorders presenting with systemic mast cell activation symptoms. J Allergy Clin Immunol 2010;125:1269-1278.e2.
11. Valent P, Horny HP, Triggiani M, Arock M. Clinical and laboratory parameters of mast cell activation as basis for the formulation of diagnostic criteria. Int Arch Allergy Immunol 2011;156:119-27.
12. Schwartz LB, Metcalfe DD, Miller JS, Earl H, Sullivan T. Tryptase levels as an indicator of mast-cell activation in systemic anaphylaxis and mastocytosis. N Engl J Med 1987;316:1622-6.
13. Zanotti R, Lombardo C, Passalacqua G, Caimmi C, Bonifacio M, De Matteis G, et al. Clonal mast cell disorders in patients with severe Hymenoptera venom allergy and normal serum tryptase levels. J Allergy Clin Immunol 2015;136:135-9.
14. Bonadonna P, Bonifacio M, Lombardo C, Zanotti R. Hymenoptera allergy and mast cell activation syndromes. Curr Allergy Asthma Rep 2016;16:5.
15. Jennings S, Russell N, Jennings B, Slee V, Sterling L, Castells M, et al. The Mastocytosis Society survey on mast cell disorders: patient experiences and perceptions. J Allergy Clin Immunol Pract 2014;2:70-6.
16. Garcia-Montero AC, Jara-Acevedo M, Teodosio C, Sanchez ML, Nunez R, Prados A, et al. KIT mutation in mast cells and other bone marrow hematopoietic cell lineages in systemic mast cell disorders: a prospective study of the Spanish Network on Mastocytosis (REMA) in a series of 113 patients. Blood 2006;108:2366-72.
17. Erben P, Schwaab J, Metzgeroth G, Horny HP, Jawhar M, Sotlar K, et al. The KIT D816V expressed allele burden for diagnosis and disease monitoring of systemic mastocytosis. Ann Hematol 2014;93:81-8.
18. Kristensen T, Vestergaard H, Bindslev-Jensen C, Moller MB, Broesby-Olsen S, Mastocytosis Centre, Odense University Hospital (MastOUH). Sensitive KIT D816V mutation analysis of blood as a diagnostic test in mastocytosis. Am J Hematol 2014;89:493-8.
19. Wright NC, Looker AC, Saag KG, Curtis JR, Delzell ES, Randall S, et al. The recent prevalence of osteoporosis and low bone mass in the United States based on bone mineral density at the femoral neck or lumbar spine. J Bone Miner Res 2014;29:2520-6.
20. Bianchi ML. Osteoporosis in children and adolescents. Bone 2007;41:486-95.
21. Gordon CM, Leonard MB, Zemel BS, International Society for Clinical Densitometry. 2013 Pediatric Position Development Conference: executive summary and reflections. J Clin Densitom 2014;17:219-24.
22. Cosman F, de Beur SJ, LeBoff MS, Lewiecki EM, Tanner B, Randall S, et al. Clinician's guide to prevention and treatment of osteoporosis. Osteoporos Int 2014;25:2359-81.
23. Bone health and osteoporosis: a report of the Surgeon General. Rockville, MD: U.S. Department of Health and Human Services, Office of the Surgeon General; 2004.
24. Wade SW, Strader C, Fitzpatrick LA, Anthony MS, O'Malley CD. Estimating prevalence of osteoporosis: examples from industrialized countries. Arch Osteoporos 2014;9:182.
25. Schousboe JT, Shepherd JA, Bilezikian JP, Baim S. Executive summary of the 2013 International Society for Clinical Densitometry Position Development Conference on bone densitometry. J Clin Densitom 2013;16:455-66.
26. Valent P, Escribano L, Broesby-Olsen S, Hartmann K, Grattan C, Brockow K, et al. Proposed diagnostic algorithm for patients with suspected mastocytosis: a proposal of the European Competence Network on Mastocytosis. Allergy 2014;69:1267-74.
27. Valent P, Horny HP, Escribano L, Longley BJ, Li CY, Schwartz LB, et al. Diagnostic criteria and classification of mastocytosis: a consensus proposal. Leuk Res 2001;25:603-25.
28. Horny HP, Akin C, Metcalfe DD, Escribano L, Bennett JM, Valent P, et al. Mastocytosis (mast cell disease). In: Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, et al., editors. World Health Organization (WHO) classification of tumours. Pathology and genetics. Tumours of haematopoietic and lymphoid tissues. Lyon, France: IARC Press; 2008. p. 54-63.
29. Valent P, Horny H-P, Li CY, Longley JB, Metcalfe DD, Parwaresch RM, et al. Mastocytosis. In: Jaffe ES, Harris NL, Stein H, Vardiman JW, editors. World Health Organization (WHO) classification of tumours. Pathology and genetics. Tumours of haematopoietic and lymphoid tissues. Lyon, France: IARC Press; 2001. p. 291-302.
30. Sperr WR, El-Samahi A, Kundi M, Girschikofsky M, Winkler S, Lutz D, et al. Elevated tryptase levels selectively cluster in myeloid neoplasms: a novel diagnostic approach and screen marker in clinical haematology. Eur J Clin Invest 2009;39:914-23.
31. Lyons JJ, Sun G, Stone KD, Nelson C, Wisch L, O'Brien M, et al. Mendelian inheritance of elevated serum tryptase associated with atopy and connective tissue abnormalities. J Allergy Clin Immunol 2014;133:1471-4.
32. Lyons JJ, Yu X, Hughes JD, Le QT, Jamil A, Bai Y, et al. Elevated basal serum tryptase identifies a multisystem disorder associated with increased TPSAB1 copy number. Nat Genet 2016;48:1564-9.
33. Schena D, Galvan A, Tessari G, Girolomoni G. Clinical features and course of cutaneous mastocytosis in 133 children. Br J Dermatol 2016;174:411-3.
34. Akin C, Valent P. Diagnostic criteria and classification of mastocytosis in 2014. Immunol Allergy Clin North Am 2014;34:207-18.
35. Alvarez-Twose I, Morgado JM, Sanchez-Munoz L, Garcia-Montero A, Mollejo M, Orfao A, et al. Current state of biology and diagnosis of clonal mast cell diseases in adults. Int J Lab Hematol 2012;34:445-60.
36. Gotlib J, Pardanani A, Akin C, Reiter A, George T, Hermine O, et al. International Working Group-Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) & European Competence Network on Mastocytosis (ECNM)

consensus response criteria in advanced systemic mastocytosis. Blood 2013; 121:2393-401.
37. Horny HP, Sotlar K, Valent P. Mastocytosis: state of the art. Pathobiology 2007; 74:121-32.
38. Bonadonna P, Perbellini O, Passalacqua G, Caruso B, Colarossi S, Dal Fior D, et al. Clonal mast cell disorders in patients with systemic reactions to Hymenoptera stings and increased serum tryptase levels. J Allergy Clin Immunol Pract 2009;123:680-6.
39. Arock M, Sotlar K, Akin C, Broesby-Olsen S, Hoermann G, Escribano L, et al. KIT mutation analysis in mast cell neoplasms: recommendations of the European Competence Network on Mastocytosis. Leukemia 2015;29: 1223-32.
40. Theoharides TC, Valent P, Akin C. Mast cells, mastocytosis, and related disorders. N Engl J Med 2015;373:163-72.
41. Berezowska S, Flaig MJ, Rueff F, Walz C, Haferlach T, Krokowski M, et al. Adult-onset mastocytosis in the skin is highly suggestive of systemic mastocytosis. Mod Pathol 2014;27:19-29.
42. Horny HP. Mastocytosis: an unusual clonal disorder of bone marrow-derived hematopoietic progenitor cells. Am J Clin Pathol 2009;132:438-47.
43. Kristensen T, Vestergaard H, Moller MB. Improved detection of the KIT D816V mutation in patients with systemic mastocytosis using a quantitative and highly sensitive real-time qPCR assay. J Mol Diagn 2011;13:180-8.
44. Jara-Acevedo M, Teodosio C, Sanchez-Munoz L, Alvarez-Twose I, Mayado A, Caldas C, et al. Detection of the KIT D816V mutation in peripheral blood of systemic mastocytosis: diagnostic implications. Mod Pathol 2015;28:1138-49.
45. Hoermann G, Gleixner KV, Dinu GE, Kundi M, Greiner G, Wimazal F, et al. The KIT D816V allele burden predicts survival in patients with mastocytosis and correlates with the WHO type of the disease. Allergy 2014;69:810-3.
46. Escribano L, Alvarez-Twose I, Sanchez-Munoz L, Garcia-Montero A, Nunez R, Almeida J, et al. Prognosis in adult indolent systemic mastocytosis: a long-term study of the Spanish Network on Mastocytosis in a series of 145 patients. J Allergy Clin Immunol 2009;124:514-21.
47. Guillaume N, Desoutter J, Chandesris O, Merlusca L, Henry I, Georgin-Lavialle S, et al. Bone complications of mastocytosis: a link between clinical and biological characteristics. Am J Med 2013;126:75.e1-7.
48. van der Veer E, van der Goot W, de Monchy JG, Kluin-Nelemans HC, van Doormaal JJ. High prevalence of fractures and osteoporosis in patients with indolent systemic mastocytosis. Allergy 2012;67:431-8.
49. Rossini M, Zanotti R, Viapiana O, Tripi G, Orsolini G, Idolazzi L, et al. Bone involvement and osteoporosis in mastocytosis. Immunol Allergy Clin North Am 2014;34:383-96.
50. U.S. Preventive Services Task Force. Screening for osteoporosis: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med 2011; 154:356-64.
51. Rossini M, Zanotti R, Bonadonna P, Artuso A, Caruso B, Schena D, et al. Bone mineral density, bone turnover markers and fractures in patients with indolent systemic mastocytosis. Bone 2011;49:880-5.
52. Chiappetta N, Gruber B. The role of mast cells in osteoporosis. Semin Arthritis Rheum 2006;36:32-6.
53. Seitz S, Barvencik F, Koehne T, Priemel M, Pogoda P, Semler J, et al. Increased osteoblast and osteoclast indices in individuals with systemic mastocytosis. Osteoporos Int 2013;24:2325-34.
54. Seeman E. Invited review: pathogenesis of osteoporosis. J Appl Physiol 2003; 95:2142-51.
55. National Center for Health Statistics. Health, United States, 2010: with special feature on death and dying. Hyattsville, MD: Centers for Disease Control and Prevention; 2011.
56. Blackwell DL, Lucas JW, Clarke TC. Summary health statistics for U.S. adults: national health interview survey, 2012. Vital Health Stat 2014;10:1-161.
57. Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Blaha MJ, et al. Heart disease and stroke statistics–2014 update: a report from the American Heart Association. Circulation 2014;129:e28-292.
58. Lloyd-Jones D, Adams RJ, Brown TM, Carnethon M, Dai S, De Simone G, et al. Heart disease and stroke statistics–2010 update: a report from the American Heart Association. Circulation 2010;121:e46-215.
59. Siddiqui AA, Miner PB Jr. The role of mast cells in common gastrointestinal diseases. Curr Allergy Asthma Rep 2004;4:47-54.
60. Schwelberger HG. Histamine intolerance: a metabolic disease? Inflamm Res 2010;59:S219-21.
61. Vlieg-Boerstra BJ, van der Heide S, Oude Elberink JN, Kluin-Nelemans JC, Dubois AE. Mastocytosis and adverse reactions to biogenic amines and histamine-releasing foods: what is the evidence? Neth J Med 2005;63:244-9.
62. Fett NM, Teng J, Longley BJ. Familial urticaria pigmentosa: report of a family and review of the role of KIT mutations. Am J Dermatopathol 2013; 35:113-6.
63. Wohrl S, Moritz KB, Bracher A, Fischer G, Stingl G, Loewe R. A c-kit mutation in exon 18 in familial mastocytosis. J Invest Dermatol 2013;133:839-41.
64. Zanotti R, Simioni L, Garcia-Montero AC, Perbellini O, Bonadonna P, Caruso B, et al. Somatic D816V KIT mutation in a case of adult-onset familial mastocytosis. J Allergy Clin Immunol 2013;131:605-7.
65. Sabato V, Van De Vijver E, Hagendorens M, Vrelust I, Reyniers E, Fransen E, et al. Familial hypertryptasemia with associated mast cell activation syndrome. J Allergy Clin Immunol 2014;134:1448-1450.e3.
66. Alvarez-Twose I, Jara-Acevedo M, Morgado JM, Garcia-Montero A, Sanchez-Munoz L, Teodosio C, et al. Clinical, immunophenotypic, and molecular characteristics of well-differentiated systemic mastocytosis. J Allergy Clin Immunol 2016;137:168-178.e1.
67. Valent P, Arock M, Bischoff SC, Buhring HJ, Brockow K, Escribano L, et al. The European Competence Network on Mastocytosis (ECNM). Wien Klin Wochenschr 2004;116:647-51.
68. Valent P, Arock M, Bonadonna P, Brockow K, Broesby-Olsen S, Escribano L, et al. European Competence Network on Mastocytosis (ECNM): 10-year jubilee, update, and future perspectives. Wien Klin Wochenschr 2012;124:807-14.

## ONLINE REPOSITORY

## APPENDIX

## RESULTS

### Sources of diagnoses

Twenty-two respondents (5.2%) of the TMS survey on MCD also selected "self-diagnosed" and/or "I have not received a mast cell disorder diagnosis" in addition to noting medical professional(s) as diagnostic sources. Twenty additional respondents did not list a doctor type. Nineteen of the 20 noted either medical tests or doctor involvement in a previous question concerning timing of first consideration of possibility of an MCD, or noted testing performed in the subsequent section on Clinical and Laboratory Tests. (The 1 additional respondent who did not note physician involvement in the Demographics and Diagnosis section left the survey before that subsequent section.) More than half (12 [60.0%]) of the 20 had noted in a previous question concerning disease classification that their disease diagnosis was "suspected, but not confirmed" by test results; the remainder said that their diagnosis was "confirmed by test results" or were "not sure."

### Clinical and laboratory tests

Skin biopsies were recalled by 237 respondents (Table II, main text), of whom 88.2% reported a diagnosis of mastocytosis (136 with SM and 73 with CM). Of the 221 respondents who reported having had a BM biopsy, 66 reported receiving a diagnosis from their physicians other than SM, including 27 reporting CM, 20 MCAS, 10 idiopathic anaphylaxis, and 9 diagnosis not determined/not sure, not provided, or other.

Of the 164 people who reported their most recent baseline serum tryptase level, 127 (77.4%) reported levels above 11.5 ng/mL, 123 (75.0%) greater than or equal to 15 ng/mL, 100 (61.0%) greater than 20 ng/mL, and 91 (55.5%) greater than 25 ng/mL. Of the 110 survey respondents who reported a diagnosis of SM and provided baseline serum tryptase levels (51.2% of 215 reporting SM), 103 (93.6%) reported levels above 11.5 ng/mL, 101 (91.8%) greater than or equal to 15 ng/mL, 86 (78.2%) above 20 ng/mL, and 80 (72.7%) above 25 ng/mL. For the 100 survey participants determined to have a diagnosis of CM, 24 (24.0%) reported their most recent baseline serum tryptase level. Of these 24 participants, 14 (58.3%) reported levels above 11.5 ng/mL, 13 (54.2%) greater than or equal to 15 ng/mL, 9 (37.5%) above 20 ng/mL, and 6 (25.0%) above 25 ng/mL. For the 52 respondents determined to have a diagnosis of MCAS, 18 (34.6%) provided their most recent baseline serum tryptase level. Of those 18, only 5 (27.8%) reported levels above 11.5 ng/mL, all of which were also greater than or equal to 15 ng/mL, and 2 (11.1%) above 20 ng/mL; levels reported by those 2 respondents were above 25 ng/mL.

Of all people responding to questions in this section, just 15 (3.9%) reported testing positive for other genetic mutations (6 of whom reported "*JAK2*" mutations), but 193 (49.6%) answered that such tests had not been performed, 98 (25.2%) were not sure, and 73 (18.8%) had not tested positive. Similarly, only a small percent of these respondents (24 people or 6.2%) reported that their MCs expressed CD2 and/or CD25, and 13 (3.3%) reported that their MCs did not express these markers, but most either had not had tests performed (162 or 41.6%) or were not sure (185 or 47.6%). Of the 221 survey participants who recalled having had a BM biopsy, 10.4% reported a positive test result for 1 of these markers, 5.0% negative test results, 24.9% that these tests had not been performed, and 58.8% that they were not sure.

Respondents were given the opportunity to write in up to 4 additional tests and 77 wrote in 1 or more tests that had not been previously noted. Tests noted by more than 1 respondent included endoscopies (12), colonoscopies (11), thyroid tests (11), "MRI" (magnetic resonance imaging) (13), immuno-antibody tests (11), ultrasounds (10), "EKG" (electrocardiograph)/cardiac tests (4), "EEG" (electroencephalograph) (3), and test to "rule out carcinoid" (2).

### Comorbidities

Because of the known association of postmenopausal ages with osteopenia/osteoporosis, and reported association with SM, a cross-tabulation by diagnosis, age group, and sex is provided (Table E1).

The prevalence of comorbidities among TMS survey respondents was compared with the expected prevalence of the US population by consulting published statistics of the National Health and Nutrition Examination Survey (NHANES) and the National Cancer Institute Statistical Epidemiology and End Results (SEER) (Tables E2-E5). Statistics concerning different morbidities within these databases have been published at various times based on different updates and definitions of data. Comparisons of US prevalences with TMS survey responses were chosen from US surveys done as close as possible to 2010, the year the TMS survey was conducted.

Nonskin cancers were reported by 28 (7.3%) survey participants, including 6 (1.6%) with breast cancer, 5 each with thyroid or cervical cancer (1.3% each), as compared with the US population in Table E2 and 4 (1 response questionable) with hematologic/lymphatic cancers (1.0%). Twelve respondents reporting a diagnosis of SM with an associated hematologic disorder in the Demographics and Diagnosis section of the survey remained to answer questions on cancer. Of these 12, only 1 reported having been diagnosed with a "hematologic/lymphatic" cancer. Eight additional respondents noted 7 other types of cancer. Skin cancers were noted by 32 (8.4%), including 9 (2.4%) with basal cell skin cancer but no other cancer types and 16 (4.2%) with other types of skin cancer, with or without basal cell cancer, but no other types of cancer. Seven of the 32 with skin cancer also reported nonskin cancers.

Heart attacks were reported by 3.0% of those 20 years or older (10 out of 329 with "yes" or "no" answers to this question and providing age information, all of whom were in the age range 47 to 80 y). This is similar to the US age-adjusted estimate (NHANES from 2003 to 2006 [2010 update]) of 3.6% in adults 20 years or older.[E3]

An open-ended/write-in question asked participants to list any "other conditions" with which they had been diagnosed (beyond those directly queried) and those conditions listed by 3% or more of respondents are provided in Table E6.

### Diet and nutrition

Responses regarding perception of adequate nutrition with/without "low histamine" and/or "elimination" diets are presented in Tables E7 to E9.

### Possible MCDs in family members of respondents

Of 388 people logging into the section on Family Tendencies, 376 responded to the question "Does anyone else in your family have a mast cell disorder?" Options provided included "yes, confirmed," "yes, suspected, but not medically confirmed," "no" and "not sure." Respondents included 78 (20.7%) who indicated confirmed or suspected MCD in 1 or more family members (20 [25.6%] confirmed; 58 [74.4%] suspected). An additional 8 did not indicate family members on this question, but indicated family member type(s) on subsequent questions, bringing the final number of respondents reporting *possible* MCDs in family members to 86 (22.9%). Seventy-eight of the 86 respondents (90.7%) indicated 1 or more specific family member type(s), with 44 reporting parent(s), 32 reporting 49 siblings, 32 reporting 46 children, and 28 listing 37 other relatives. More frequent patterns were parent only (15 [19.2%]), child or children only (13 [16.7%]), parent and sibling(s) (9 [11.5%]), sibling only (6 [7.7%]), and other relative only (6 [7.7%]). More than 1 family type was reported by 38 people. Table E10 presents the confirmed and/or suspected diagnostic group(s) of both the respondents and their possibly affected family members. Some people selected multiple forms of MCDs for affected family member(s). At the time of this survey, MCAS was sometimes referred to as MCAD in the literature, so the term "MCAS/MCAD" was included in the survey questionnaire.

### Care needs in the United States

Responses to questions about patient care were limited to the 317 respondents (84.3%) who received care in the United States. Most (255 [80.4%]) said that the number of centers treating MCDs in the United States was not sufficient, and 198 (62.5%) said it was not easy to access good local MCD care.

Although more than a third (124 [39.1%]) were being treated by a specialist in MCD, more than half (169 [53.3%]) were not and 21 (6.6%) were not sure. Of the 169 people who said they were not treated by an MCD specialist, 99 (58.6%) said the *KIT* D816V test was not performed. Of the 124 participants who said they were treated by a specialist, 42 (33.9%) said they did not have this test.

More than a third of US-treated participants (118 [37.2%]) said a physician had told them that he or she could not treat them because of their MCD. Most (263 [83.0%]) said they would be comfortable if a local physician managed their care in conjunction with a mast cell specialist. US-treated respondents also answered questions on how well they were informed by their physicians concerning diagnostic procedures, required follow-up investigations, prognosis/future health prospects, and therapy options (Figure E1).

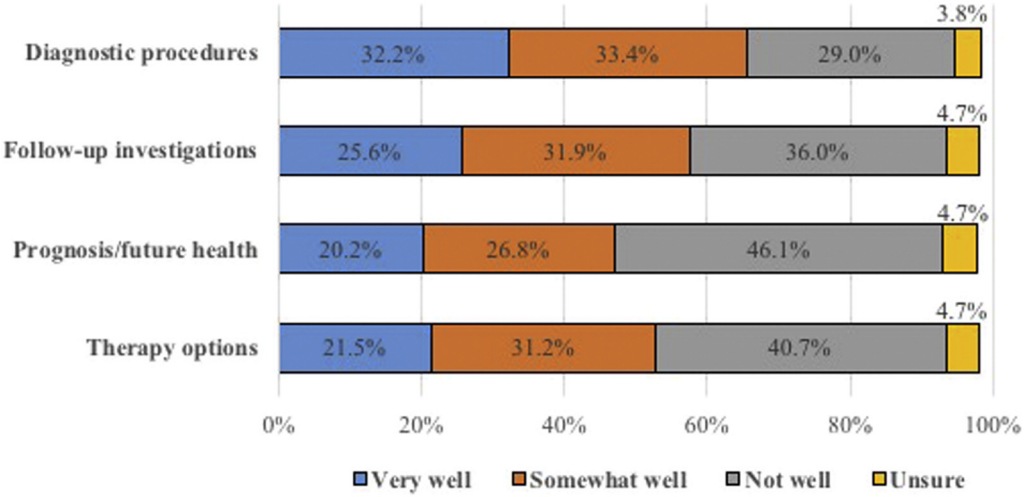


**FIGURE E1.** Percentages representing how well 317 US-treated respondents believed they were informed by their physicians concerning aspects of diagnosis and treatment (not shown are 1.6%-2.2% with no response to these questions).

**TABLE E1.** Osteopenia/osteoporosis in TMS survey subjects by diagnosis and age

| All ages | | | Age 50 y and more with osteopenia/osteoporosis | | | |
|---|---|---|---|---|---|---|
| **Diagnosis** | **Remaining in survey, n** | **Osteopenia/osteoporosis, n** | **Total, n** | **Female, n** | **Male, n** | **Sex not reported, n** |
| SM | 198 | 85 | 56* | 36† | 13‡ | 7 |
| CM | 93 | 14 | 12* | 9† | 0‡ | 3 |
| MCAS | 44 | 7 | 4* | 4† | 0‡ | 0 |
| IA | 18 | 9 | 5* | 3† | 1‡ | 1 |
| Not determined | 23 | 4 | 4 | 4 | 0 | 0 |
| Other | 4 | 0 | 0 | 0 | 0 | 0 |
| Not provided | 2 | 1§ | — | — | — | — |
| Total | 382 | 120 | 81 | 56 | 14 | 11 |

*IA*, Idiopathic anaphylaxis.
*Total number of respondents remaining in the survey, 50 y and older, including those not sure if they had osteopenia/osteoporosis, by diagnosis: SM, 107; CM, 26; MCAS, 17; IA, 11.
†Total number of female respondents remaining in the survey, 50 y and older, including those not sure if they had osteopenia/osteoporosis by diagnosis: SM, 69; CM, 17; MCAS, 15; IA, 8. SM diagnosis ($\chi^2 = .0000$; $P > .995$).
‡Total number of male respondents remaining in the survey, 50 y and older, including those not sure if they had osteopenia/osteoporosis, by diagnosis: SM, 24; CM, 4; MCAS, 1; IA, 2. SM diagnosis ($\chi^2 = 0.1397$; $P > .7$).
§Age not provided for the 1 person who reported osteopenia/osteoporosis, but did not provide a diagnosis. All remaining respondents reporting osteopenia/osteoporosis provided age information.

**TABLE E2.** Three cancer types of respondents answering questions in this section and providing age information compared with estimated US population prevalence[E1]

| Cancer, sex age group | TMS survey, proportion (%) | US 2012-adjusted age group estimate, % | Expected TMS count if same percent as US, n |
|---|---|---|---|
| Breast, female 60-69* | 5 of 39 (12.8) | Females<br>All ethnic 4.2%<br>White only 4.5% | 2† |
| Thyroid, both sexes 30-59 | 5 of 223 (2.2) | Both sexes<br>All ethnic 0.2%<br>White only 0.2% | <1† |
| Cervix uteri female 44-59‡ | 4 of 104 (3.8) | Female<br>All ethnic 0.2%<br>White only 0.2% | <1† |

*One additional respondent age 73 y had breast cancer.
†$\chi^2 \geq 0.25$, $P > .9$, but statistics with less than 5 expected occurrences are generally unreliable.
‡One additional person within this age range reported this cancer type, but did not list sex.

**TABLE E3.** High blood pressure in 356 respondents providing "yes" or "no" answers and age information compared with estimated US population prevalence[E2]

| Age group (y) | TMS survey, proportion* (%) | US 2012-adjusted age group estimate, % | Expected TMS survey count if same percent as US population prevalence, n |
|---|---|---|---|
| 1-17 | 0 of 33 (0.0) | Not available | — |
| 18-44 | 12 of 108 (11.1) | 8.3 | 9 |
| 45-64 | 59 of 175 (33.7) | 33.6 | 59 |
| 65-74 | 14 of 33 (42.4) | 52.2 | 17 |
| 75 or older | 3 of 7 (42.9)† | 58.9 | 4 |

$\chi^2$ analyses of age group differences between TMS and US: 18-44 ($\chi^2 = 0.28$; $P > .5$), 65-74 ($\chi^2 = 0$; $P > .995$); not done for 45-64 age group as no difference between TMS survey and US population prevalence.
*Seven additional people who provided ages did not answer the question and 16 were not sure.
†Percentage not reliable because less than 5 occurrences of condition.

**TABLE E4.** Hypercholesterolemia in 339 respondents providing "yes" or "no" answers compared with estimated US population prevalence[E3]

| | | US 2006-adjusted age group estimate, % | |
|---|---|---|---|
| Age group (y) | TMS survey, proportion (%)* | ≥200 mg/dL† | ≥240 mg/dL |
| 1-11 | 0 of 29 (0.0) | ‡ | ‡ |
| 12-19 | 0 of 6 (0.0) | 10 | ‡ |
| 20 or older | 82 of 304 (27.0) | 46.8 | 16.2 |

*Three additional people who provided ages did not answer the question and 37 were not sure.
†Data for 2003-2006 applied to the 2006 population; subsequent US updates not used because only those with measures of ≥240 mg/dL were included.
‡Not available/unreliable statistic.

**TABLE E5.** Coronary artery disease in 373 respondents providing "yes" or "no" answers compared by age with estimated US population prevalence[E2]

| Age group (y) | TMS survey, proportion* (%) | US 2012-adjusted age group estimate, % | Expected TMS count if same percent as US population prevalence, n |
|---|---|---|---|
| 1-17 | 0 of 41 (0.0)† | Not available | — |
| 18-44 | 0 of 108 (0.0)† | 0.9% | <1 |
| 45-64 | 6 of 184 (3.3) | 7.1% | 13‡ |
| 65-74 | 3 of 32 (9.4)† | 16.2% | 5 |
| 75 or older | 2 of 8 (25.0)† | 25.7% | 2 |

*Three additional people who provided ages did not answer question, 3 did not provide age information, and 3 were not sure.
†Percentage not reliable because less than 5 occurrences of condition.
‡$\chi^2$ for ages 45-64 ($\chi^2 = 0.00029$; $P > .9$).

**TABLE E6.** Other conditions reported through write-in option by 3% or more of 382 respondents

| Other conditions (no. in subcategory) | Total respondents, n (% of 382) |
|---|---|
| Gastrointestinal/gastroesophageal including GERD*/acid reflux (19), IBS (19), celiac disease or gluten intolerance (15) | 69 (18.1) |
| Connective tissue including arthritis (26), fibromyalgia (16), joint pain,* bursitis, tendonitis, joint hypermobility, joint degeneration | 45 (11.8) |
| Thyroid including Hashimoto disease/hypothyroid (35) | 44 (11.5) |
| Cardiac,* including arrhythmias and valvular disorders (excluding heart attack as reported in separate question) (23) | 27 (7.1) |
| Asthma* | 26 (6.8) |
| Prediabetes/diabetes type 1 and 2 | 24 (6.3) |
| Spinal/disc | 18 (4.7) |
| Gynecological | 16 (4.2) |

*IBS*, Irritable bowel syndrome; *GERD*, gastroesophageal reflux.
*Condition may overlap with previously reported symptoms in first survey article.[E4]

**TABLE E7.** Perception of adequate nutrition with/without "low histamine" diets

| | Adequate nutrition for 186 respondents | | |
|---|---|---|---|
| Diet type | Yes | No | Total observed, n (%) |
| "Low histamine" only | 19 observed<br>23.7 expected | 12 observed<br>7.3 expected | 31 (16.7) |
| No diet | 123 observed<br>118.3 expected | 32 observed<br>36.7 expected | 155 (83.3) |
| Total observed, n (%) | 142 (76.3) | 44 (10.4) | 186 |

$\chi^2$ probability of finding another difference by chance = 0.019.

**TABLE E8.** Perception of adequate nutrition with/without "elimination" diets

| | Adequate nutrition for 212 respondents | | |
|---|---|---|---|
| **Diet type** | **Yes** | **No** | **Total observed, n (%)** |
| "Elimination" diet only | 41 observed<br>44.1 expected | 16 observed<br>12.9 expected | 57 (26.9) |
| No diet | 123 observed<br>119.9 expected | 32 observed<br>35.1 expected | 155 (73.1) |
| Total observed, n (%) | 164 (77.4) | 48 (22.6) | 212 |

$\chi^2$ probability of finding another difference by chance = 0.25.

**TABLE E9.** Perception of adequate nutrition with/without either or both "low histamine" and "elimination" diets

| | Adequate nutrition for 299 respondents | | |
|---|---|---|---|
| **Diet type** | **Yes** | **No** | **Total observed, n (%)** |
| Either or both diets | 94 observed<br>104.5 expected | 50 observed<br>39.5 expected | 144 (48.2) |
| No diet | 123 observed<br>112.5 expected | 32 observed<br>42.5 expected | 155 (51.8) |
| Total observed, n (%) | 217 (72.6) | 82 (27.4) | 299 |

$\chi^2$ probability of finding another difference by chance = 0.004.

**TABLE E10.** Types of MCD reported for respondents and family members for 78 survey participants who indicated family members possibly affected

| | | | Possible type(s) of MCD in families of respondents* | | |
|---|---|---|---|---|---|
| **Diagnosis group** | **Respondents remaining in survey, n** | **Respondents with possible family occurrence, n (%)** | **SM, n** | **CM, n** | **MCAS/MCAD, n** |
| SM | 201 | 34† (16.9) | 17 | 12 | 11 |
| CM | 93 | 10‡ (10.8) | 0 | 5 | 4 |
| MCAS/MCAD | 45 | 22 (48.9) | 2 | 3 | 15 |
| IA | 18 | 10§ (55.6) | 0 | 1 | 8 |
| Not determined | 24 | 10 (41.7) | 2 | 0 | 7 |
| Total | 388 | 86 (22.2) | 21 | 21 | 45 |

*IA*, Idiopathic anaphylaxis.
*Totals for types of MCDs in families may not agree with totals in diagnosis groups because respondents were allowed to select more than 1 diagnostic type in family member(s) and for each survey respondent, a given disease type in family members was counted only once.
†Includes 3 people who checked "no" or "not sure" but then selected a family member.
‡Includes 2 people who checked "no" or "not sure" but then selected a family member.
§Includes 3 people who checked "no" or "not sure" but then selected a family member.

## REFERENCES

E1. Howlader N, Noone AM, Krapcho M, Garshell J, Miller D, Altekruse SF, et al., editors. SEER Cancer Statistics Review, 1975-2012, (Prevalence Tables). Bethesda, MD: National Cancer Institute; 2014. November SEER data submission, posted to the SEER web site, April 2015. Available from: http://seer.cancer.gov/csr/1975_2012/; 2014.

E2. Blackwell DL, Lucas JW, Clarke TC. Summary health statistics for U.S. adults: national health interview survey, 2012. Vital Health Stat 2014;10:1-161.

E3. Lloyd-Jones D, Adams RJ, Brown TM, Carnethon M, Dai S, De Simone G, et al. Heart disease and stroke statistics–2010 update: a report from the American Heart Association. Circulation 2010;121:e46-215.

E4. Jennings S, Russell N, Jennings B, Slee V, Sterling L, Castells M, et al. The Mastocytosis Society survey on mast cell disorders: patient experiences and perceptions. J Allergy Clin Immunol Pract 2014;2:70-6.