



**BILLING CODE 4163-18-P**

**DEPARTMENT OF HEALTH AND HUMAN SERVICES**

**Centers for Disease Control and Prevention**

**42 CFR Part 88**

**[NIOSH Docket 094]**

**World Trade Center Health Program; Petition 022—Monoclonal Gammopathy of Undetermined Significance; Finding of Insufficient Evidence**

**AGENCY:** Centers for Disease Control and Prevention, HHS.

**ACTION:** Denial of petition for addition of a health condition.

**SUMMARY:** On March 11, 2019, the Administrator of the World Trade Center (WTC) Health Program received a petition (Petition 022) to add “monoclonal gammopathy of undetermined significance (MGUS)” to the List of WTC-Related Health Conditions (List). Upon reviewing the scientific and medical literature, including information provided by the petitioner, the Administrator has determined that the available evidence does not have the potential to provide a basis for a decision on whether to add MGUS to the List. The Administrator also finds that insufficient evidence exists to request a recommendation of the WTC Health Program Scientific/Technical Advisory Committee (STAC), to publish a proposed rule, or to publish a determination not to publish a proposed rule.

**DATES:** The Administrator of the WTC Health Program is denying this petition for the addition of a health condition as of [INSERT DATE OF PUBLICATION IN **FEDERAL REGISTER**].

**ADDRESSES:** Visit the WTC Health Program website at <https://www.cdc.gov/wtc/received.html> to review Petition 022.

**FOR FURTHER INFORMATION CONTACT:** Rachel Weiss, Program Analyst, 1090 Tusculum Avenue, MS: C-48, Cincinnati, OH 45226; telephone (855) 818-1629 (this is a toll-free number); email *NIOSHregs@cdc.gov*.

## **SUPPLEMENTARY INFORMATION:**

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### **A. WTC Health Program Statutory Authority**

Title I of the James Zadroga 9/11 Health and Compensation Act of 2010 (Pub. L. 111-347, as amended by Pub. L. 114-113), added Title XXXIII to the Public Health Service (PHS) Act,<sup>1</sup> establishing the WTC Health Program within the Department of

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<sup>1</sup> Title XXXIII of the PHS Act is codified at 42 U.S.C. 300mm to 300mm-61. Those portions of the James Zadroga 9/11 Health and Compensation Act of 2010 found in Titles II and III of Public Law 111-347 do not pertain to the WTC Health Program and are codified elsewhere.

Health and Human Services (HHS). The WTC Health Program provides medical monitoring and treatment benefits for health conditions on the List to eligible firefighters and related personnel, law enforcement officers, and rescue, recovery, and cleanup workers who responded to the September 11, 2001, terrorist attacks in New York City, at the Pentagon, and in Shanksville, Pennsylvania (responders), and to eligible persons who were present in the dust or dust cloud on September 11, 2001, or who worked, resided, or attended school, childcare, or adult daycare in the New York City disaster area (survivors).

All references to the Administrator of the WTC Health Program (Administrator) in this document mean the Director of the National Institute for Occupational Safety and Health (NIOSH) or his designee.

Pursuant to section 3312(a)(6)(B) of the PHS Act, interested parties may petition the Administrator to add a health condition to the List in 42 CFR 88.15. Within 90 days after receipt of a valid petition to add a condition to the List, the Administrator must take one of the following four actions described in section 3312(a)(6)(B) of the PHS Act and § 88.16(a)(2) of the Program regulations: (1) Request a recommendation of the STAC; (2) publish a proposed rule in the *Federal Register* to add such health condition; (3) publish in the *Federal Register* the Administrator's determination not to publish such a proposed rule and the basis for such determination; or (4) publish in the *Federal Register* a determination that insufficient evidence exists to take action under (1) through (3) above.

## **B. Procedures for Evaluating a Petition**

In addition to the regulatory provisions, the WTC Health Program has developed policies to guide the review of submissions and petitions,<sup>2</sup> as well as the analysis of evidence supporting the potential addition of a non-cancer health condition to the List.<sup>3</sup>

A valid petition must include sufficient medical basis for the association between the September 11, 2001, terrorist attacks and the health condition to be added; in accordance with WTC Health Program policy, reference to a peer-reviewed, published, epidemiologic study about the health condition among 9/11-exposed populations or to clinical case reports of health conditions in WTC responders or survivors may demonstrate the required medical basis.<sup>4</sup> Studies linking 9/11 agents or hazards<sup>5</sup> to the petitioned health condition may also provide sufficient medical basis for a valid petition.

After the Program has determined that a petition is valid, the Administrator must direct the Program to conduct a review of the scientific literature to determine if the available scientific information has the potential to provide a basis for a decision on whether to add the health condition to the List.<sup>6</sup> The literature review is a keyword search of relevant scientific databases; peer-reviewed, published, epidemiologic studies (including direct observational studies in the case of health conditions such as injuries) about the health condition among 9/11-exposed populations are then identified from the initial search results. The Program evaluates the scientific quality of each peer-reviewed,

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<sup>2</sup> See WTC Health Program [2014], *Policy and Procedures for Handling Submissions and Petitions to Add a Health Condition to the List of WTC-Related Health Conditions*, May 14, 2014, <http://www.cdc.gov/wtc/pdfs/WTCHPPPpetitionHandlingProcedures14May2014.pdf>.

<sup>3</sup> See WTC Health Program [2017], *Policy and Procedures for Adding Non-Cancer Conditions to the List of WTC-Related Health Conditions*, February 14, 2017, [https://www.cdc.gov/wtc/pdfs/policies/WTCHP\\_PP\\_Adding\\_NonCancers\\_14\\_February\\_2017-508.pdf](https://www.cdc.gov/wtc/pdfs/policies/WTCHP_PP_Adding_NonCancers_14_February_2017-508.pdf).

<sup>4</sup> See *supra* note 2.

<sup>5</sup> 9/11 agents are chemical, physical, biological, or other hazards reported in a published, peer-reviewed exposure assessment study of responders, recovery workers, or survivors who were present in the New York City disaster area, or at the Pentagon site, or the Shanksville, Pennsylvania site, as those locations are defined in 42 CFR 88.1, as well as those hazards not identified in a published, peer-reviewed exposure assessment study, but which are reasonably assumed to have been present at any of the three sites. See WTC Health Program [2018], *Development of the Inventory of 9/11 Agents*, July 17, 2018, [https://www.cdc.gov/ResearchGateway/Content/pdfs/Development\\_of\\_the\\_Inventory\\_of\\_9-11\\_Agents\\_20180717.pdf](https://www.cdc.gov/ResearchGateway/Content/pdfs/Development_of_the_Inventory_of_9-11_Agents_20180717.pdf).

<sup>6</sup> See *supra* note 3.

published, epidemiologic study of the health condition identified in the literature search; the Program then compiles the scientific results of each study to assess whether a causal relationship between 9/11 exposures and the health condition is supported, and evaluates whether the results of the studies are representative of the 9/11-exposed population of responders and survivors. A health condition may be added to the List if peer-reviewed, published, epidemiologic studies provide support that the health condition is substantially likely<sup>7</sup> to be causally associated with 9/11 exposures. If the evaluation of evidence provided in peer-reviewed, published, epidemiologic studies of the health condition in 9/11 populations demonstrates a high, but not substantial, likelihood of a causal association between the 9/11 exposures and the health condition, then the Administrator may consider additional highly relevant scientific evidence regarding exposures to 9/11 agents from sources using non-9/11-exposed populations. If that additional assessment establishes that the health condition is substantially likely to be causally associated with 9/11 exposures among 9/11-exposed populations, the health condition may be added to the List.

### **C. Petition 022**

On March 11, 2019, the Administrator received a petition (Petition 022) requesting the addition of “monoclonal gammopathy of undetermined significance (MGUS)” to the List.<sup>8</sup> The petition included a 2018 study by Landgren *et al.*,<sup>9</sup> which

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<sup>7</sup> The “substantially likely” standard is met when the scientific evidence, taken as a whole, demonstrates a strong relationship between the 9/11 exposures and the health condition.

<sup>8</sup> See Petition 022, *WTC Health Program: Petitions Received*, <http://www.cdc.gov/wtc/received.html>.

<sup>9</sup> Landgren O, Zeig-Owens R, Gircz O, Goldfarb D, Murata K, Thoren K, Ramanathan L, Hultcrantz M, Dogan A, Nwankwo G, Steidl U, Pradhan K, Hall CB, Cohen HW, Jaber N, Schwartz T, Crowley L, Crane M, Irby S, Webber MP, Verma A, Prezant DJ [2018], *Multiple Myeloma and its Precursor Disease Among Firefighters Exposed to the World Trade Center Disaster*, *JAMA Oncol* 4(6):821-827.

provided sufficient medical basis for the petition to be considered valid because it is a peer-reviewed, published, epidemiologic study about the health condition among 9/11-exposed populations; Landgren *et al.* is a scientific source that demonstrates a potential link between exposure to a 9/11 hazard (in this case, the identified 9/11 agents polychlorinated biphenyl (PCB), dioxins, polycyclic aromatic hydrocarbons (PAHs), and asbestos)<sup>10</sup> and the requested health condition, MGUS.

#### **D. Review of Scientific and Medical Information and Administrator Determination**

The Program policy on the addition of non-cancer health conditions to the List directs the Program to conduct a literature review of the health condition(s) petitioned.<sup>11</sup> Petition 022 requested the addition of MGUS, an asymptomatic condition characterized by the presence of a monoclonal immunoglobulin (Ig), also called an M-protein, in the blood without any evidence of multiple myeloma or another lymphoproliferative disorder. MGUS is not a cancer, and the vast majority of people with MGUS never develop the types of cancer for which it is a precursor. Immunoglobulin subtypes involved may be IgM, non-IgM (*e.g.*, IgA and IgG), or light-chain.<sup>12</sup> All pose a slight risk of progression (1-2 percent per year) to a malignant disorder. Typically, IgG and IgA MGUS are the precursors of multiple myeloma, IgM MGUS is the precursor of Waldenstrom macroglobulinemia or other lymphoproliferative conditions, and light-chain MGUS is the precursor of light-chain multiple myeloma.<sup>13</sup>

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<sup>10</sup> See *supra* note 5.

<sup>11</sup> *Supra* note 3.

<sup>12</sup> “Light-chain” refers to the antibody components made by malignant plasma cells in patients with multiple myeloma.

<sup>13</sup> Fanning SR, Hussein MA [2018], *Monoclonal Gammopathies of Undetermined Significance*, Medscape, <https://emedicine.medscape.com/article/204297-overview>.

In response to Petition 022, the Program conducted a review of the scientific literature on MGUS to identify peer-reviewed, published, epidemiologic studies of the health condition in the 9/11-exposed population.<sup>14</sup> Only one study meeting the Program's criteria for further evaluation was identified in this literature review, Landgren *et al.* [2018], referenced above.

Landgren *et al.* [2018] reported on two analyses conducted on 9/11-exposed firefighters from the New York City Fire Department (FDNY). One was a case series (a descriptive report) of 16 multiple myeloma cases identified among white male WTC-exposed FDNY firefighters. Since this analysis does not provide dispositive evidence linking 9/11 exposures to MGUS, it is not relevant to this petition and will not be further described.

The second analysis was a prevalence screening study of 781 9/11-exposed FDNY white male firefighters aged 50 to 79 years. Patients with MGUS, light-chain MGUS, and overall MGUS (*i.e.*, MGUS and light-chain MGUS combined) were diagnosed using a serum immunoglobulin assay. 9/11 exposure was assessed based on initial arrival time at Ground Zero and five exposure groups were recognized (*i.e.*, arriving the morning of 9/11 [most highly exposed]; arriving the afternoon of September 11, 2001; arriving on September 12, 2001; arriving between September 13 and 24, 2001; and arriving between September 25, 2001 and July 24, 2002 [least exposed]). 9/11 exposure was also assessed by length of time worked at Ground Zero (months in which a participant worked at least 1 day at Ground Zero).

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<sup>14</sup> Databases searched include: CINAHL, Embase, NIOSHTIC-2, ProQuest Health & Safety, PsycINFO, Ovid MEDLINE, Scopus, Toxicology Abstracts/TOXLINE, and WTC Health Program Bibliographic Database. Keywords used to conduct the search include: MGUS, monoclonal gammopathy of undetermined significance, premalignant clonal plasma cell disorder, lymphoplasmacytic proliferative disorder, monoclonal gammopathy, monoclonal gammopathies. The literature search was conducted in English-language journals on April 25, 2019.

Findings in this study were compared to those of a population-based cohort of 7,612 white male residents of Olmsted County, Minnesota, aged 50 years and older, previously assembled to estimate MGUS prevalence.<sup>15</sup> Among FDNY firefighters, the age-standardized prevalence rate (ASR) of overall MGUS (*i.e.*, MGUS and light-chain MGUS combined) was 7.63 per 100 persons (95% CI, 5.45-9.81). The ASR of light-chain MGUS was 3.08 per 100 persons (95% CI, 1.66-4.50), and for MGUS was 4.55 per 100 persons (95% CI, 2.90-6.21). The relative rate of overall MGUS (*i.e.*, MGUS and light-chain MGUS combined) was 1.76 (95% CI, 1.34-2.29) when comparing FDNY firefighters with the Olmsted County reference population; the relative rate was 3.13 for light-chain MGUS (95% CI, 1.99-4.93) and 1.35 for MGUS (95% CI, 0.96-1.91). The researchers evaluated the risk of overall MGUS (*i.e.*, MGUS and light-chain MGUS combined) by 9/11 exposure; for each of the arrival times described above, the ASRs for the 9/11-exposed FDNY firefighters were greater than in the Olmsted County reference population, although the authors did not find an exposure gradient and did not provide risk estimates for these findings. Additionally, the authors reported that there were no statistically significant differences in ASRs when length of time worked at Ground Zero was included in the analyses (the authors did not report a risk estimate for this finding). In addition, the authors did not report the results of the association between 9/11 exposures, expressed by time of arrival or duration of work at Ground Zero, and light-chain MGUS, nor for MGUS overall.

Among the strengths of Landgren *et al.* [2018] is that this is the first study to present the age-specific prevalence of MGUS or light-chain MGUS in 9/11-exposed

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<sup>15</sup> Dispenzieri A, Katzmann JA, Kyle RA, et al. [2010]. *Prevalence and Risk of Progression of Light-Chain Monoclonal Gammopathy of Undetermined Significance: A Retrospective Population-Based Cohort Study*, *Lancet* 375(9727):1721-8.

responders, and show an excess age-standardized prevalence when compared to an unexposed reference population.<sup>16</sup> Health outcomes were objectively assessed, since diagnosis was determined in all study participants by testing serum samples, collected between December 2013 and October 2015, in the laboratory.

However, Landgren *et al.* [2018] is subject to a number of limitations. The prevalence study design limits the interpretation and generalizability of findings. IgM MGUS and non-IgM MGUS were lumped together as “MGUS” and not reported separately. Risk estimates of the association between 9/11 exposure and MGUS were not reported. A temporal relationship between 9/11 exposure and the first occurrence of MGUS could also not be established; because MGUS is asymptomatic, it is possible that some FDNY members with MGUS had the condition prior to September 11, 2001 (no baseline samples were collected prior to September 11, 2001 to ascertain date of onset). Another limitation suggested by the authors is inadequate statistical power to detect a statistically significant exposure-response relationship. Landgren *et al.* [2018] addressed confounding by race, gender, and age by limiting the analysis to white men and standardizing the rates by age. However, family history of MGUS and other occupational exposures were not controlled for. A major limitation of this study is the use of the Olmsted County reference group,<sup>17</sup> which is a general population selected from a mixed rural-urban setting and not comparable to the FDNY population, a predominantly urban working population. The authors acknowledged that a comparison group composed of firefighters with no 9/11 exposure or a truly random sample of the U.S. (or the New York

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<sup>16</sup> Among FDNY firefighters, the ASR of overall MGUS was 7.63 per 100 persons (95% CI, 5.45-9.81) versus the ASR of overall MGUS among the Olmsted County reference population of 4.34 per 100 persons (95% CI, 3.88-4.81 per 100 persons and RR, 1.76; 95% CI, 1.34-2.29).

<sup>17</sup> Wi C, St Sauver JL, Jacobson DJ, *et al.* [2016], Ethnicity, Socioeconomic Status, and Health Disparities in a Mixed Rural-Urban US Community—Olmsted County, Minnesota, Mayo Clinic Proceedings 91(5):612-622.

City) population would be desirable. Finally, the authors reported that they were unable to control for all of the potential confounders between the study and reference populations.

#### Evaluation of Study Using Select Bradford Hill Criteria

Landgren *et al.* [2018] was assessed to determine whether a causal relationship between 9/11 exposures and MGUS is supported. As described in the policy on the addition of non-cancer health conditions to the List,<sup>18</sup> the WTC Health Program uses the following Bradford Hill criteria to evaluate studies of 9/11-exposed populations: strength of association, precision of the risk estimate, consistency of association, biological gradient, and plausibility and coherence.<sup>19</sup>

*Strength of association:*<sup>20</sup> Landgren *et al.* [2018] found a relatively strong association between being a 9/11-exposed FDNY member and an increased prevalence of MGUS, especially light-chain MGUS. However, Landgren *et al.* [2018] did not report risk estimates for the association between their measures of 9/11 exposure (initial arrival time and length of time worked at Ground Zero); the WTC Health Program would need such risk estimates in order to evaluate the strength of the association between 9/11 exposure and MGUS.

*Precision of risk estimate:*<sup>21</sup> Landgren *et al.* [2018] reported reasonably precise risk estimates when comparing FDNY members with the Olmsted County reference

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<sup>18</sup> *Supra* note 3.

<sup>19</sup> Aschengrau A, Seage GR [2018], *Essentials of Epidemiology in Public Health. 4th Edition*, (Burlington, MA: Jones & Bartlett).

<sup>20</sup> It is generally thought that strong associations are more likely to be causal than weak associations; however, a weak association does not rule out a causal relationship. *See supra* note 19.

<sup>21</sup> The uncertainty inherent in estimating the strength of association between exposure and health effect (effect size) from observational data is expressed as a confidence interval, illustrating a range of values that contains the true effect size. A narrow

population.<sup>22</sup> Because Landgren *et al.* [2018] did not report risk estimates and their confidence intervals for the association between 9/11 exposure and MGUS, the WTC Health Program is unable to evaluate the precision of such risk estimates.

*Consistency of association:*<sup>23</sup> Multiple studies are not available to ascertain consistency. Only the Landgren *et al.* [2018] study is available.

*Biological gradient:*<sup>24</sup> The exposure-response (biological gradient) information provided in Landgren *et al.* [2018] does not demonstrate an exposure gradient between 9/11 exposure and MGUS. In other words, the study does not provide evidence that the risk of MGUS increases with increasing levels of exposure.

*Plausibility and coherence:*<sup>25</sup> The findings of Landgren *et al.* [2018] do not demonstrate a basis for a potential relationship between 9/11 exposure and MGUS. Some FDNY members with MGUS may have had the condition prior to September 11, 2001. This lack of temporal information severely limits an evaluation of the plausibility of an association between 9/11 exposure and MGUS.

#### Evaluation of Representativeness of Study

Landgren *et al.* [2018] was reviewed to determine whether both the WTC responder cohort studied is representative of the entire 9/11-exposed population and whether the results can be extrapolated. MGUS screening study subjects were a subset of

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confidence interval indicates a more precise measure of the effect size and a wider interval indicates greater uncertainty. *See supra* note 19.

<sup>22</sup> *See supra* note 16.

<sup>23</sup> Consistent findings are demonstrated when they have been repeatedly reported by multiple studies. *See supra* note 19.

<sup>24</sup> Studies establish an exposure-response relationship by demonstrating that increases in exposure (*i.e.*, exposures of greater intensity and/or longer duration) are associated with a greater incidence of disease. A thorough evaluation of exposure-response requires analysis of multiple levels of exposure such that the investigator can demonstrate that the risk increases with increasing levels of exposure. *See supra* note 19.

<sup>25</sup> Study findings demonstrate a basis in scientific theory that supports the relationship between the exposure and the health effect and do not conflict with known facts about the biology of the health condition. *See supra* note 19.

FDNY members who were exposed to 9/11 agents on or in the aftermath of September 11, 2001 until the Ground Zero site closed in July 2002. All study subjects were white males between the ages of 50 and 79 who had serum samples taken by the FDNY WTC Health Program from December 2013 through October 2015. The findings of this study represent only a subset of white male FDNY responders and may not be generalizable to other 9/11-exposed groups.

### Summary of Evaluation

The study by Landgren *et al.* [2018] was evaluated to determine whether a causal relationship between 9/11 exposures and MGUS is supported. As described in the policy on the addition of non-cancer health conditions to the List,<sup>26</sup> the WTC Health Program uses the Bradford Hill criteria described above to evaluate whether a causal relationship between 9/11 exposures and a health condition is supported. Although Landgren *et al.* [2018] speculated that the study results demonstrate an association between 9/11 exposure and MGUS, the information available in the study is insufficient to support a claim for causation using the Bradford Hill criteria. The study reported a reasonably strong and precise association between being a 9/11-exposed FDNY firefighter and an increased prevalence of MGUS; however, an exposure-response gradient was not found. Furthermore, the temporality of the findings was not established because some FDNY members with MGUS may have had the condition prior to September 11, 2001. Finally, the consistency of an association could not be assessed as Landgren *et al.* [2018] was the only relevant study that was identified. Given the lack of an exposure-response gradient,

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<sup>26</sup> *Supra* note 3.

the questionable plausibility, the lack of other relevant studies, and the other limitations discussed above, the WTC Health Program considers the Landgren *et al.* [2018] study to be preliminary and insufficient to add MGUS to the List.

#### **E. Administrator's Final Decision on Whether to Propose the Addition of Monoclonal Gammopathy of Undetermined Significance to the List**

Pursuant to PHS Act, sec. 3312(a)(6)(B)(iv) and 42 CFR 88.16(a)(2)(iv), the Administrator has determined that insufficient evidence is available to take further action at this time, including proposing the addition of MGUS to the List (pursuant to PHS Act, sec. 3312(a)(6)(B)(ii) and 42 CFR 88.16(a)(2)(ii)) or publishing a determination not to publish a proposed rule in the *Federal Register* (pursuant to PHS Act, sec. 3312(a)(6)(B)(iii) and 42 CFR 88.16(a)(2)(iii)). The Administrator has also determined that requesting a recommendation from the STAC (pursuant to PHS Act, sec. 3312(a)(6)(B)(i) and 42 CFR 88.16(a)(2)(i)) is unwarranted.

For the reasons discussed above, the Petition 022 request to add MGUS to the List of WTC-Related Health Conditions is denied.

#### **F. Approval to Submit Document to the Office of the Federal Register**

The Secretary, HHS, or his designee, the Director, Centers for Disease Control and Prevention (CDC) and Administrator, Agency for Toxic Substances and Disease Registry (ATSDR), authorized the undersigned, the Administrator of the WTC Health Program, to sign and submit the document to the Office of the Federal Register for publication as an official document of the WTC Health Program. Robert Redfield M.D.,

Director, CDC, and Administrator, ATSDR, approved this document for publication on July 29, 2019.

John J. Howard,

Administrator, World Trade Center Health Program and Director, National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention, Department of Health and Human Services.

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