

VA



U.S. Department
of Veterans Affairs

Gulf War Illness(es): Planning / Developing a Case Definition

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About VA Mission



The Reason We Are Meeting



GAO Recommendation

- To increase the likelihood of making progress towards developing a single case definition of Gulf War Illness, we recommend that the Secretary of Veterans Affairs direct the Under Secretary for Health to prepare and document a plan to develop a single case definition of Gulf War Illness.
- **This plan should include near and long-term, specific actions, such as analyzing and leveraging information in existing datasets and identifying any areas for future research to help VA achieve this goal.**
- **Note: part of three GAO recommendations that centered around claims/benefits.**



VA Response

- To increase the likelihood of making progress towards developing a single case definition of Gulf War Illness, the Office of Research and Development and Post-Deployment Health Services in the Office of Patient Care Services have convened a group of subject matter experts (SMEs) to develop a plan that addresses near and long-term actions related to Gulf War Illness, as described in this report.
- This group of SMEs will also coordinate these efforts with the Veterans Health Administration's Office of Disability and Medical Assessment, the Veterans Benefits Administration, and other internal and external stakeholders.
- Veterans Affairs SMEs will interface in particular with the Department of Defense's Congressionally Directed Medical Research Program that funds much of the current research on Gulf War Illness(es).
- Specific actions within the plan will include reviewing the current literature, analyzing and leveraging information in existing datasets, and identifying any areas for future research. The status is in progress with a target completion date of March 2018.



Work Group Members

- Dr. J. Wesson Ashford – Director, CA –WRIISC
- Daniel Devine – Compensation and Benefits, VBA
- Dr. Erin Dursa – Epidemiologist, PDHS
- Brad Flohr – Special Advisor – VBA
- Dr. Drew Helmer – Director - NJ WRIISC
- Dr. Deborah Heaney – Compensation and Pension Service - Ann Arbor VAMC
- Dr. Phyllis Hollenbeck – Compensation and Pension Physician – Jackson, Mississippi VAMC
- Dr. Bob Jaeger - Director of Post-Deployment Health Research, Office of Research and Development (ORD)
- Dr. Ronit Katz - Clinical Associate Professor - Stanford University School of Medicine – CA WRIISC
- Dr. Victor Kalasinsky – Senior PM, Gulf War Research and Military Environmental Exposures, ORD
- Dr. Kristy Lidie - Program Manager, CDMRP - US Army Medical Research and Materiel Command (USAMRMC)
- Dr. Benjamin Porter – DoD - Naval Health Research Center
- Dr. Matt Reinhart – Director - DC WRIISC
- Dr. Peter Rumm – Director, Pre-911 Era Environmental Health Programs, PDHS



RAC Recommendation

An evidence-based, expert consensus-driven case definition for Gulf War illness should be developed. This process should include:

1. Review literature relevant to Gulf War Illness case definitions
2. Statistical and epidemiologic assessment of different case definition approaches using datasets that provide representative data on symptoms and medical conditions
3. Final case definition parameters / guidelines developed by an expert consensus panel

<https://www.research.va.gov/pubs/docs/GWResearch-StrategicPlan.pdf>
(2015 update)



IOM Report - CMI Case Definition

- VA asked IOM to develop a case definition for chronic multisymptom illness (CMI) for 1990-1991 Gulf War Veterans.
- IOM comprehensively evaluated and summarized the available scientific literature regarding symptoms for CMI.
- IOM evaluated the terminology currently used for CMI and provided recommendation for appropriate usage. (Mar 2014).
- Issues for IOM (Unresolved issues in defining CMI)
 - Wide variation in symptoms reported by Gulf War veterans has complicated efforts.
 - The array of symptoms suffered by many Gulf War veterans does not often point to an obvious diagnosis, etiology, or specific treatment.
 - CMI symptoms overlap with symptoms of other diseases and ill-defined conditions, such as fibromyalgia (FM) and chronic fatigue syndrome (CFS).



Case Definition – CDC 2008

Element

- **Person**
- **Place**
- **Time**
- **Clinical Features**
- **Laboratory**

Descriptive Feature

- **Age, Sex, Race, Exclusion Criteria, Occupation**
- **Geographic location**
- **Illness Onset**
- **Depend on the condition to be defined**
- **Lab tests, Imaging and so on**



Why is a CMI Case Definition So Hard?

IOM 2014 Report

- No definitive laboratory tests
- Array of symptoms
- Overlap with other syndromes
- Difficult to assign uniform criteria
- Issue of specificity and sensitivity



IOM recommended VA use definitions that capture most commonly reported symptoms:

- Centers for Disease Control and Prevention
- Kansas definitions



CDC and Kansas Definitions

CDC, CMI defined as the report by a Veteran of one or more chronic unexplained symptoms (present > 6 months) in at **least two of the following categories**:

- Fatigue
- Mood and cognition (depressed, difficulty in remembering/concentrating, moody, anxious, trouble in finding words, or difficulty in sleeping)
- Musculoskeletal (joint pain, joint stiffness, or muscle pain)
- <https://www.ncbi.nlm.nih.gov/books/NBK206740/>

Per Kansas Criteria (Symptom onset after 1990)

- Presence of symptoms in the year before the interview
- No diagnoses of other conditions (cancer, diabetes, heart disease, chronic infectious disease, lupus, MS, stroke, or serious psychiatric condition)
- **Symptoms in at least 3 of 6 symptom groups**: fatigue and sleep problems, pain, neurologic and mood, gastrointestinal, respiratory, and skin symptoms
- One moderately severe symptom or 2 or more symptoms in a symptom group
- <https://www.va.gov/RAC-GWVI/Presentation7LeaSteele.pdf>



VA Specific Recommendation

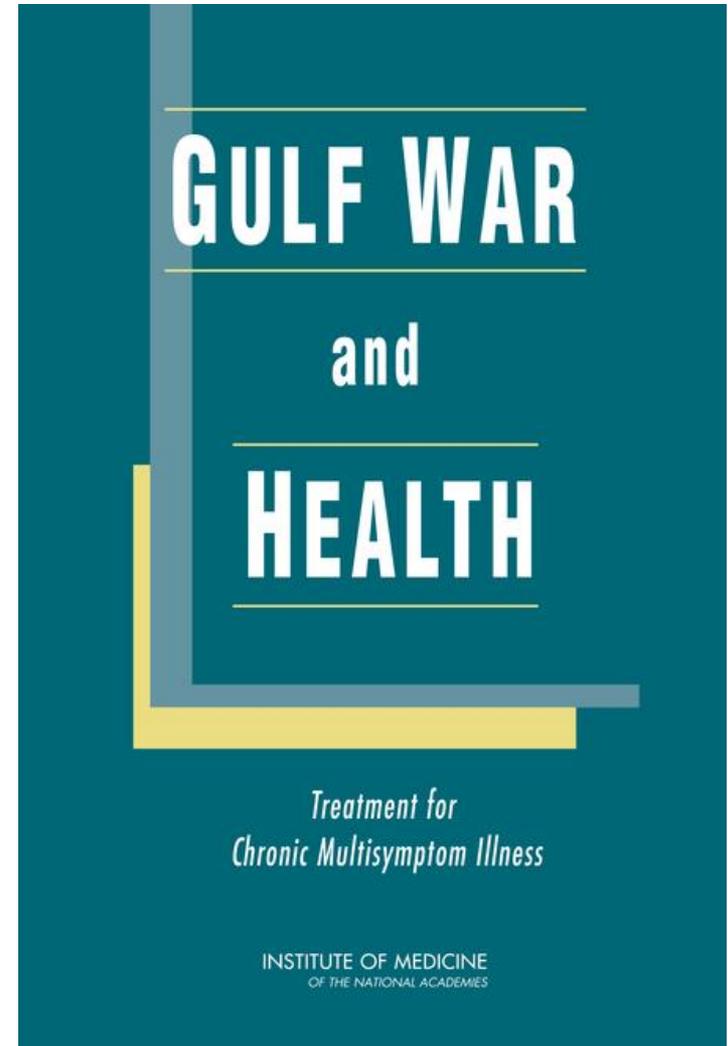
- “IOM recommends that the VA systematically assess existing data to identify additional features of CMI, such as onset, duration, severity, frequency of symptoms, and exclusionary criteria to produce a more robust case definition.”
(2014 IOM Report)



IOM Treatment Report Definition - 2013

For the purposes of this report, IOM defined CMI as:

- Presence of a spectrum of chronic symptoms experienced for >6 months
- In at least two of six categories:
 - Fatigue
 - Mood and cognition
 - Musculoskeletal
 - Gastrointestinal
 - Respiratory
 - Neurologic
- May overlap with but not captured by known syndromes (such as CFS, IBS, fibromyalgia) or other diagnoses.





VA/DOD Clinical Practice Guidelines - 2014

- CMI is a label for a diverse set of disorders including, chronic fatigue syndrome (CFS), fibromyalgia syndrome (FMS), irritable bowel syndrome (IBS).
- CMI encompasses military-specific medically unexplained illnesses, such as Gulf War Illness, Gulf War Syndrome, or post-deployment syndrome.
- **CMI also includes patients without accepted labels, defined by generally accepted criteria, who exhibit persistent or recurring symptoms negatively impacting daily function for at least 6 months duration from two or more of six categories: fatigue, mood and cognition, musculoskeletal (including pain), respiratory, gastrointestinal and neurologic (including headache).**
- Patients with symptoms lasting <6 months, or who experience only one of the listed symptoms, or with a disease with a well-established pathophysiology that explains all/most of their symptoms were not covered in this report.
- Further consideration for inclusion should be given to symptoms affecting the following systems: genitourinary, cardiopulmonary, and sleep. Individuals who meet the above descriptive criteria and also meet established criteria for specific symptom-based syndromes (e.g., fibromyalgia, IBS, CFS) may derive benefit from this guideline.



Literature Review

Very little literature on the topic of case definition for GWI/CMI since IOM 2014.

- Gwini et al; JOEM 2014 used CDC definition with some variants in a meta-analysis
 - Key finding: The pooled odds ratio comparing GW Veterans to other military groups was 2.74 (95% CI 2.15 to 3.51).
- Iannacchione et al; Methods in Neuroepid. 2011
 - Yielded evidence of 6 unique symptom patterns suggestive of syndrome variants.
- Haley et al; JAMA 1997 used a two staged factor analysis-derived of 6 syndromes.
 - Found the factor analysis-derived syndromes appeared to reflect a spectrum of neurologic injury involving the central, peripheral and autonomic nervous systems. (Ex. Impaired cognition or arthro-myoneuropathy)



Plan of Workgroup

- Literature Review including IOM report other sources. (Completed)
- Biweekly calls with workgroup - that will be increased to weekly calls on August 8th to try to move project plan forward.
- Written responses to short questions.
- Working to complete plan by end of year if at all possible.



Early Thinking of Working Group

- Could we use the CPG definition and validate it?
 - Perhaps testing with other definitions?
- Re-assess VA cohorts using the CPG.
- Not simply measuring whether those patients meeting the CPG are “better”, “worse” or “the same” based on self-reporting.
 - Other metrics should be considered (i.e. rates of hospitalization, ER visits, mortality, reproductive health, etc.)



Most Recent Workgroup Questions

1. Please provide which of the following definitions should be potentially validated by use of databases and give reasons why? (with the idea that would have clinical benefit.)
 - a. CDC
 - b. Kansas
 - c. CPG
 - d. Definition used by Compensation
 - e. other _____

2. Please provide at least three (if possible) data sources that would help to get to this (such as analyzing and leveraging information in existing datasets.)

2. Identify any areas for future research to help VA achieve this GAO recommendation goal.



How to Validate Definition?

- Can the WRIISC clinical data, and the WRIISC intake packet be used?
 - Limitation: patients tend to check every box, so the data might not be reliable or objective.
 - Using the Gulf War Survey is also a possibility.
- Re-assess established cohorts outside the VA using the CPG. VA and WRIISC visits may not be representative of the entire Gulf War population.



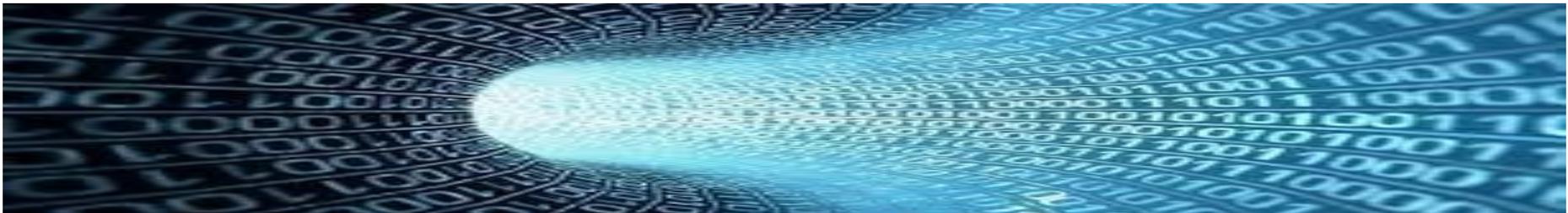
Using CPG to be Validated?

- Should the CPG be at least as a starting point for a case definition?
 - This is currently used clinically to diagnose and evaluate GW Veterans.
 - CPG was developed by SME VA and DOD clinicians and experts.
 - The CPG definition is also appealing because, to a certain extent, it combines features of both research definitions.
 - The CPG is based on clinical presentation.
 - Suggested to use CPG plus either Kansas and/or CDC (3 of 9 respondents – 1 CDC, 1 Kansas, 1 both)
 - 6/9 members who have responded favor CPG potentially.



Data Sets Proposed

- “A single representative sample of Veterans”
- “VA internal data sets”
- WRIISC clinical data
- Gulf War Survey - National Cohort of Gulf War and Gulf Era Veterans
- VA benefits data
- New prospective data collection
- Genome-wide study
 - Million Veteran Study
- CDC, Haley, Kansas cohorts





Data Sets Proposed

From DoD or Additional VA:

- Ft Devens, MA cohort – Sullivan and Kregel investigators
- US Navy Seabees – used in papers by Gray et al in early 2000s.
- USAF Female Veterans Study
- GWIRP consortia funded by the CDMRP
- USARIEM Total Army Injury and Health Outcomes Database (TAIHOD)
- CSP 585 - Gulf War Era Cohort and Biorepository
- Cohort identified from the 1995 Gulf War Study that met criteria for GWI by both Kansas and CDC definitions.
 - This would be the closest to the “gold standard” we have, since this comes from data that was collected in 1995.



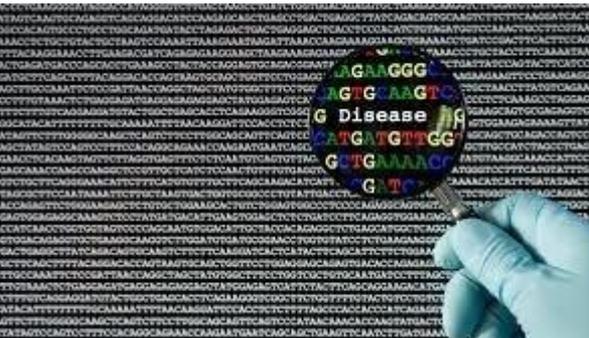
Additional DoD Data Sources

- Millennium Cohort Study: Only includes Service Members in the military in 2000. Has 9,000 Gulf War Veterans and 36,000 era Veterans
- DoD Serum Repository: Have serum for all Gulf War Veterans before and after deployment at a minimum.
 - Serum degradation might be an issue
- For recent Veterans (OEF/OIF/OND)
 - Millennium Cohort Study: >200,000 participants from this era
 - Army STARRS: Collects data from a surveys on different populations of Soldiers



Thoughts Going Forward

- Genomics is important. Not everyone in the 1991 GW and exposed developed GWI. Identifying an underlying genetic mechanism would answer many questions and perhaps improve treatments.
- A predictive algorithm, based on ICD-9/10 codes in CPRS, to identify Veterans with a high probability of CMI/GWI, might help.
 - Since many front line clinicians (VA, DoD and Community) have limitations in GWI understanding, this allows Veterans to be identified, flagged and referred for more in-depth review / exam. It would help VA with estimate prevalence.
- We have to get beyond just self-reported survey responses and add in data from the electronic medical record, other clinical records (e.g., WRIISC), and, eventually, lab and procedure results and genetic analysis.





Conclusion

- This is a difficult, but important process
 - Varied opinions on short and long term plans that could develop/test a case definition.
- At present 2/3rd of workgroup (who have answered questions) sees potential value in exploring validating the CPG definition, but 25% have opinions against the CPG. A few in the Working Group believe strongly it is untenable to develop or test a single or multiple case definitions.
- What the workgroup will be doing in near future is working with above information and holding weekly additional discussions to try to come up with a short and long-term plan per the GAO recommendation.
- Welcome input from the Committee on this.