Current OPH Efforts to Better Understand Gulf War Illness

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April 21, 2015

Background

- Gulf War Illness (GWI) is a complex debilitating condition that exhibits as cluster of medically unexplained symptoms including but not limited to: fatigue, headaches, joint pain, muscle pain, memory loss, gastrointestinal symptoms, skin conditions, respiratory disorders, and neurological/cognitive problems

- Consistently shown to disproportionately affect Veterans deployed to the Gulf War compared to non-deployed Veterans

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Background

- At this time there is no single agreed upon and validated case definition
- In 2013 VA charged the Institute of Medicine (IOM) to develop a case definition for GWI
- IOM recommended VA use the two most widely used case definitions, the Centers for Disease Control and Prevention and the Kansas definitions
- IOM also acknowledged that VA is uniquely positioned to enhance existing efforts to better understand and define GWI

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Background

- Recommended that VA examine existing administrative and clinical data to identify elements that are missing from the CDC and Kansas case definitions
    - Symptom onset
    - Duration
    - Severity
    - Frequency of symptoms
    - Exclusionary criteria
- Should consider other symptoms/measures that may not be captured by existing criteria

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GWI Case Definitions

Centers for Disease Control and Prevention Definition (Fukuda)

- Must have one or more chronic symptoms (present $\geq$ 6 months) from at least two of the following categories
- Fatigue
- Mood and Cognition
  - Symptoms of feeling depressed
  - Difficulty remembering or concentrating
  - Feeling moody
  - Feeling anxious
  - Trouble finding words
  - Difficulty sleeping
- Musculoskeletal
  - Joint pain
  - Joint stiffness
  - Muscle pain

Kansas Definition (Steele)

- Must have symptoms in 3 of 6 domains
  - Fatigue and sleep problems
  - Pain symptoms
  - Neurologic, cognitive, or mood symptom
  - Gastrointestinal symptoms
  - Respiratory symptoms
  - Skin symptoms
- Onset must be since 1990
- Exclusionary medical conditions
- Must have at least one moderately severe symptom, or two or more symptoms within one domain

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Challenges in defining GWI in 2015

- The cohort of veterans who served in 1991 are aging and are at risk for development of age-related health conditions
- The onset of age-related disorders may impact identification of GWI, as age may cause or exacerbate symptoms consistent with GWI such as cognitive function, pain, and fatigue
  - For example, in the 2012 Follow Up Study of Gulf War and Gulf Era Veterans, 72% of Gulf War Veterans and 54% of Gulf War Era Veterans met modified CDC criteria for GWI
  - However, 90% of Gulf War Veterans AND Gulf War Era Veterans who met the modified CDC GWI criteria had a chronic medical condition that could be considered exclusionary

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Challenges in defining GWI in 2015

- Careful consideration must be given to the onset of chronic health conditions that may be simultaneously characteristic of GWI, routinely reported at higher prevalence among those with history of military service, and normally associated with diseases of aging
- The burden of chronic disease among aging cohorts is comparatively high
- Caution should be taken to avoid excluding Veterans from the GWI case definition because they have a chronic illness, as it is possible that GWI can be co-morbid with other conditions

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Challenges in defining GWI in 2015

- Symptom onset
  - Kansas criteria: Since 1990
  - Should there be an endpoint?
    - Should symptoms that developed in 2005 or 2010 be considered symptoms associated with GWI?
- Symptom Severity
  - Subjective
  - May be exacerbated by or associated with co-morbid medical conditions
- Other symptoms not captured by CDC and Kansas definitions?

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GWI Discriminate Analysis Project

- Goals
  - To integrate multiple VA datasets to develop a data rich cohort
    - Increases sample size
    - Fills the gaps in existing datasets
  - Use a multi-system process to identify those with probable GWI
  - Determine any additional features of GWI not currently in the CDC and Kansas definitions
  - Test and validate model
  - Evaluate in the clinical population

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GWI Discriminate Analysis Project

- Collaborative effort with Office of Analytics and Business Intelligence
  - Use VA data to enhance quality and effectiveness of medical care
  - Staffed with physician-scientists, statisticians, and computer scientists

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Methods

- Data Sources
  - 1995 National Health Survey of Persian Gulf Veterans and Their Families
  - 2012 Follow Up Study of a National Cohort of Gulf War and Gulf Era Veterans
  - Gulf War Registry
  - Office of Public Health Epidemiology Program Gulf War and Gulf Era Roster
  - VA Electronic Medical Record

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Methods

- 1995 National Health Survey of Persian Gulf Veterans and Their Families
  - Provide exposure data
  - 11,906 Gulf War Veterans reported at least one deployment exposure
  - Data collected in 1995, soon after the exposure, therefore minimizing recall bias

- Smoke from oil well fires
- Diesel/kerosene
- Burning trash/feces
- Skin exposure to diesel
- Chemical Agent Resistant Compound (CARC)
- Other paints/solvents
- Depleted uranium
- Microwaves
- Personal pesticides
- Nerve gas
- Mustard gas/blistering agent
- Contaminated food/water
- Wore chemical protective gear
- Pyridostigmine pills (PB pills)

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Methods

- 2012 Follow Up Study of a National Cohort of Gulf War and Gulf Era Veterans
  - Self reported GWI status (N=4,585):
    - Unexplained multisymptom illness might include things like fatigue, muscle or joint pain, headaches, memory problems, digestive problems, respiratory problems, skin problems, or any other unexplained symptoms. These problems are often not labeled at all but may sometimes be diagnosed as chronic fatigue syndrome, fibromyalgia, irritable bowel syndrome, or multiple chemical sensitivity
    - Onset year
    - Most recent year in which experienced unexplained multisymptom illness

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Methods

- Gulf War Clinical Registry
  - Established in November 1992 by the "Persian Gulf War Veterans Health Status Act"
  - About 99,000 Gulf War Veterans completed a registry exam
  - Includes both VA users and non-users

- In-person exam
  - Exposures
  - Symptoms
  - Unexplained illness (as determined by examining physician)

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Methods

- Office of Pubic Health Post Deployment Health Epidemiology Program Gulf War and Gulf Era Roster
  - Provided by Defense Manpower Data Center (DMDC)
  - Gulf War Roster contains 621,901 Veterans who were deployed to the Gulf
  - Gulf War Era Roster contains 746,247 Veterans who did not deploy to the Gulf but served during that time period

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Methods

- VA Electronic Medical Record Database (Corporate Data Warehouse)
  - Contains data since 2000 on about 15 million Veterans
    - Appointments
    - Diagnoses
    - Laboratory results
    - Medications
    - Vital statistics
    - Orders
    - Notes

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Methods

- Integrating multiple datasets fills the gaps
  - Dramatically increases sample size

  - The OPH roster provides deployment status that can be merged with medical records, since the VA medical record does not have a good identifier for Gulf War deployment

  - The VA electronic medical records data is available for 2000 and later, but the GW registry and OPH Gulf War surveys can provide diagnoses and symptoms prior to 2000 (onset)

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Methods

- Integrating multiple datasets fills the gaps
  - There is no diagnostic code for GWI in the VA electronic medical record; however, the 2012 OPH Gulf War survey has self reported GWI variables and the Gulf War Registry has a measure of clinician diagnosed unexplained illness

  - The notes section in the VA electronic medical record may provide information on other symptoms not previously captured by the current case definitions or other studies that are limited by sample size and therefore may not capture less common symptoms

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Methods

1. Identify cohorts of Veterans with and without indicators of GWI

   – **Those who were deployed to GW and those who were not deployed to GW (from OPH Roster)**

   – Those who were diagnosed with unexplained illness in GW registry (and those who were not)

   – Those who self report GWI on 2012 Gulf War Study (and those who do not)

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Methods

2. Evaluate all variables in the electronic medical record data for patients in each cohort (diagnoses, labs, medications, procedures)

3. Evaluate exposure variables from Gulf War Registry and 1995 Gulf War Survey

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Methods

4. Use machine learning to find variables that are significantly different between the cohorts

5. Use random forest and stepwise methods to identify variables with the strongest association

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Methods

6. Select variables that are clinically logical and build a logistic regression model with a training set and then a validation set

7. Use receiver operator curve (ROC) and area under the curve (AUC) to characterize predictive value
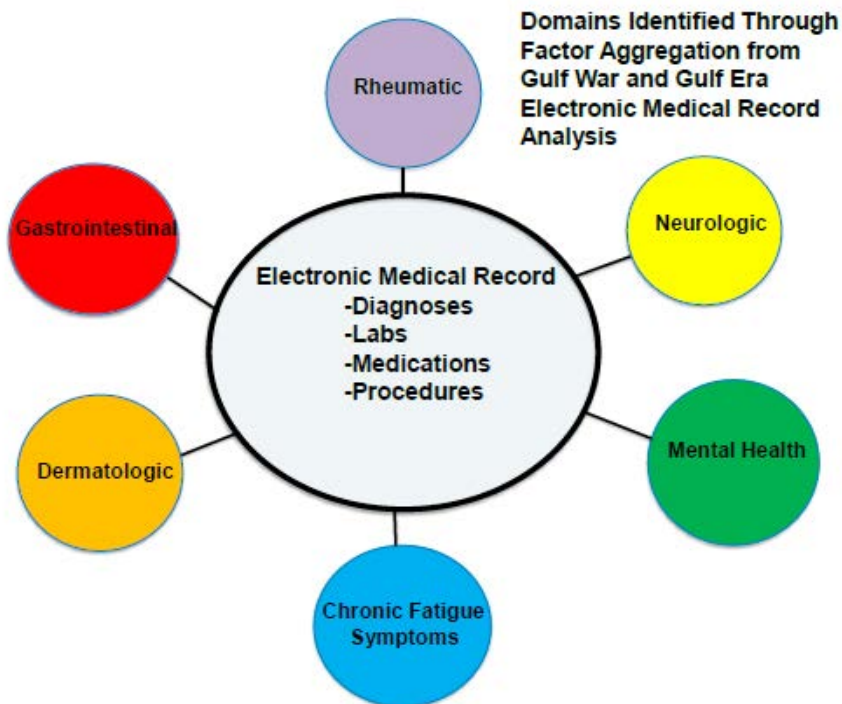
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Methods

9. Additional modification of model with bootstrap evaluation, determining interactions, and evaluation of prediction cutoffs with respect to sensitivity, specificity, and false positive results

10. Test in a clinical population (WRIISC)

Results: Preliminary

- Results presented here are findings from the first run on the **OPH Gulf War and Gulf War Era Rosters**
  - 100,000 in each group (only looked at Veterans with **current medical record**-one visit since 2013 and one visit prior to 2010)
  - There will be multiple iterations of evaluation before final results-this is nowhere near complete
  - No data on exposures in this data run. These results come from integrating the electronic medical record and the OPH Gulf War and Gulf Era rosters

Results: Preliminary

- Multiple factors were found that distinguished **Gulf War Veterans (deployed) from Gulf Era Veterans (non-deployed)**

- Many factors were consistent with the literature. Certain factors stood out and were classified into six domains
  - These are preliminary associations, not causative factors
  - These are not factors that distinguish persons with GWI from those who don't have GWI

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Domains Identified Through Factor Aggregation from Gulf War and Gulf Era Electronic Medical Record Analysis

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Results: Factors Present in Neurologic Domain

- EMG/nerve conduction study
- Magnetic image-brain stem
- Tension headache
- Memory loss
- Mild cognitive impairment
- Headache
- Abnormal involuntary movement in neck
- Migraine
- Sumatriptan prescription
- Outpatient neurology visit

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Results: Factors Present in Rheumatic Domain

- C- reactive protein
- Westergren erythrocyte sedimentation rate
- Antinuclear antibody panel
- Rheumatoid factor
- Outpatient rheumatology visit
- Polyarthritis
- Joint pain
- Myalgia

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Next Steps

- Continue analysis to refine the model
  - Onset
    - Integrate data from the OPH GW Surveys, GW Registry, and Electronic Medical Record

  - Exclusionary medical conditions
    - Suggestions from RAC Scientific Committee?

  - Exposures
    - 1995 GW Survey
    - GW Registry

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Next Steps

- Use natural language processing to analyze information in the "Clinical Notes" section of the VA electronic medical record
- Possibly look to other data sources to get information on non-VA users
  - Centers for Medicare and Medicaid (CMS)

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Questions and Contact Information

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