### Enabling Personalized Medicine Through Exome Sequencing in the U.S. Air Force

**Green, Robert C**

*Integrative and Collaborative Biomedical Research for the 21st Century, Fort Detrick Maryland, 29-30 November 2018*

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**Abstract**

Integrative and Collaborative Biomedical Research for the 21st Century, Fort Detrick Maryland, 29-30 November 2018
INSTRUCTIONS FOR COMPLETING SF 298

1. REPORT DATE. Full publication date, including day, month, if available. Must cite at least the year and be Year 2000 compliant, e.g. 30-06-1998; xx-06-1998; xx-xx-1998.

2. REPORT TYPE. State the type of report, such as final, technical, interim, memorandum, master's thesis, progress, quarterly, research, special, group study, etc.

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5a. CONTRACT NUMBER. Enter all contract numbers as they appear in the report, e.g. F33615-86-C-5169.

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8. PERFORMING ORGANIZATION REPORT NUMBER. Enter all unique alphanumeric report numbers assigned by the performing organization, e.g. BRL-1234; AFWL-TR-85-4017-Vol-21-PT-2.

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14. ABSTRACT. A brief (approximately 200 words) factual summary of the most significant information.

15. SUBJECT TERMS. Key words or phrases identifying major concepts in the report.

16. SECURITY CLASSIFICATION. Enter security classification in accordance with security classification regulations, e.g. U, C, S, etc. If this form contains classified information, stamp classification level on the top and bottom of this page.

17. LIMITATION OF ABSTRACT. This block must be completed to assign a distribution limitation to the abstract. Enter UU (Unclassified Unlimited) or SAR (Same as Report). An entry in this block is necessary if the abstract is to be limited.
Enabling Personalized Medicine through Exome Sequencing in the U.S. Air Force

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Director, Genomes2People Research Program
Brigham and Women’s Hospital and Broad Institute
# Dr. Green’s Support and Disclosures

**Research:**
- US National Institutes of Health
- US Department of Defense
- Broad Institute of MIT & Harvard
- Franca Sozzani Fund for Preventive Genomics

**Advisory:**
- AIA, Applied Therapeutics, Helix, Ohana Biosciences, OptraHealth, Prudential, Verily, Veritas

**Co-Founder:**
- Genome Medical – a company providing telegenetics expertise to patients, providers, employers and care systems

**Disclaimer:**
The views expressed are those of the author(s) and do not reflect the official views or policy of the Department of Defense or its Components. The voluntary, fully informed consent of the subjects used in this research was obtained as required by 32 CFR 219 and DODI 3216.02_AFI 40-402.
The MilSeq Project: A Military-Academic Collaboration

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*Baylor College of Medicine
1. Genomics will soon become part of everyday medicine and will provide health benefits.

2. Managing genomic information will require a nimble multi-disciplinary approach.

3. Understanding genomics will be profoundly important to the military for:
   a. Health of service members and families
   b. Optimizing performance of the warfighter
   c. Maintaining military security
The MilSeq Project

- Initially funded by the United States Air Force (USAF) through Air Force Medical Support Agency (FA8650-17-2-6704)
- Continuation funding through 59th Medical Wing (Joint Base San Antonio-Lackland Air Force Base) and 711th Human Performance Wing (Wright-Patterson Air Force Base)
- Goal is to pilot the implementation of sequencing in day-to-day medicine (consent, sample collection, sequencing, interpretation, report generation, report disclosure, follow up care)
  - Recruit 75 active-duty Airmen and 12 USAF healthcare providers at Lackland to participate in a pilot trial of implementing genomic medicine in the USAF
  - Assess short term medical, behavioral and economic impact
  - Examine the special circumstances associated with implementation of genomic medicine within the active duty military
Experimental Design
The MilSeq Project Protocol

Airmen
- Consent/Baseline Data Collection
- Consent and Enrollment
- Exome Sequencing & Report

Healthcare Providers (HCPs)
- Pre-Education Data
- Genomic Education
- Post-Education Data

HCPs disclose results from exome report to Airmen
*Exome Reports integrated into Airmen’s electronic medical records*

- HCP Post-Disclosure Checklist
- End of Study Data
- 6-Week Post-Disclosure Data
Safety of Participants
Risk Mitigation in the MilSeq Project

• IRB approved with robust consent process.

• Optional recruitment without coercive messaging.

• Entire sequencing/interpretation process is CLIA/CAP certified and positives confirmed before disclosure.

• Genetic counselor onsite with additional 24-7 availability of experts.

• Patient-HCP disclosures taped and transcribed to be reviewed by study personnel.
Study Recruitment
Recruitment Methods

- Brochure
- Base newsletter
- Facebook posting
- Direct coordinator approach

What is the MilSeq Project?
The MilSeq Project is a clinical research study funded by the US Air Force designed to explore how genomic sequencing can be used in the practice of medicine.

What is the purpose of the study?
Genomic sequencing may soon be available to almost everyone. The purpose of this study is to explore how military health care providers (HCPs) and active service Airmen feel about genomic sequencing information and ultimately how they use this information in healthcare.

Who may participate?
We are enrolling healthy active duty Air Force members and military health care providers.

What will happen in this study?
Interested Active duty Air Force members are invited to participate in a baseline survey asking about their thoughts about genomic sequencing. At the end of the survey, they will be asked about their interest in participating in a study where they may have the opportunity to have whole exome sequencing, a type of genomic sequencing.

To learn more please contact: Megan Maxwell Genetic Counselor at (210) 292-7556

To Participate Use this Link: https://is.gd/milseq
Health Care Provider Preparation
HCP Education and Support

- 3-hour, military-specific didactic lecture from a genetic counselor
- Inheritance ACTion Sheets (4)

**YOUR PATIENT’S FINDING**

Your patient’s finding is associated with an autosomal dominant condition. This means:

1. **Variable expressivity** - the extent to which symptoms vary among affected individuals (e.g., some affected individuals may exhibit only minor symptoms while others exhibit more severe symptoms).
2. **Reduced penetrance** - an autosomal dominant condition where not all individuals with the gene variant exhibit symptoms (e.g., some individuals may carry the gene variant but not express the phenotype).

- The patient may already be symptomatic or is likely to develop symptoms in the future, unless the condition has variable expressivity or reduced penetrance.
- The patient may exhibit minor or partial symptoms.
- The patient may have variable expressivity.
- The patient may have reduced penetrance.
- Reproductive risk to any pregnancy is 50%, regardless of the sex of the fetus.
- In very rare circumstances, this risk can increase and also result in more severe symptoms if the patient’s partner has the same autosomal dominant condition as the patient (e.g., hypercholesterolemia).

**Wha t do I do now?**

Post-test counseling

- Familiarize yourself with the features of the condition.
- If possible, assess whether the patient has symptoms.
- If the patient has symptoms, they may exhibit any finding.
- Reproductive risk to any pregnancy is 50%, regardless of the sex of the fetus.
- In very rare circumstances, the risk can increase and also result in more severe symptoms if the patient’s partner has the same autosomal dominant condition as the patient (e.g., hypercholesterolemia).

**How can I find more information?**

- Clinical Sequencing Exploratory Research (CSER)
- GenoReviews®
- OMIM®
- Clinical Genome Resources (ClinGen)

**AUTOSOMAL DOMINANT**

- Clinical Sequencing Exploratory Research (CSE)
- GenoReviews®
- OMIM®
- Clinical Genome Resources (ClinGen)
Exome Sequencing
Exome Sequencing at Partners Healthcare Laboratory for Molecular Medicine
How Many Genes Were Analyzed?

16
All (~ 5000) known monogenic (Mendelian) genes

Dominant (e.g. *BRCA1*, *MLH1*, *MYH7*, *KCNQ1*, *RYR1*)

Recessive (e.g. *CFTR*, *HBB*)
All (~ 5000) known monogenic (Mendelian) genes

Dominant (e.g. BRCA1, MLH1, MYH7, KCNQ1, RYR1)

Recessive (e.g. CFTR, HBB)

Selected (9) genes with risk alleles (e.g. APOE, F5)
All (~ 5000) known monogenic (Mendelian) genes

Dominant (e.g. BRCA1, MLH1, MYH7, KCNQ1, RYR1)

Recessive (e.g. CFTR, HBB)

Selected (9) genes with risk alleles (e.g. APOE, F5)

Selected pharmacogenomic variants (~ 60 medications)
All (~ 5000) known monogenic (Mendelian) genes

Dominant (e.g. \textit{BRCA1, MLH1, MYH7, KCNQ1, RYR1})

Recessive (e.g. \textit{CFTR, HBB})

Selected (9) genes with risk alleles (e.g. \textit{APOE, F5})

Selected pharmacogenomic variants (~ 60 medications)

Genetic determinants of (~ 333) RBC/platelet antigens
All (~ 5000) known monogenic (Mendelian) genes

Dominant (e.g. BRCA1, MLH1, MYH7, KCNQ1, RYR1)

Recessive (e.g. CFTR, HBB)

Selected (9) genes with risk alleles (e.g. APOE, F5)

Selected pharmacogenomic variants (~ 60 medications)

Genetic determinants of (~ 333) RBC/platelet antigens

Polygenic Risk Scores
>5 million variants

\[ \text{Variants} \geq 10\% \text{ in WGS Cases} \]

ClinVar >5%

Medical exome >1%

\[ \text{Gene exclusions} \approx 200-300 \text{ variants} \]

\[ \text{Variant exclusions} \]

\[ \text{Data Set A} \geq 10\% \text{ MAF WGS Cases} \]

\[ \text{Excludes common technical FPs} \]

\[ \text{Common indels wrong nomenclature} \]

\[ \text{Exceptions FV, HFE, SERPINA1} \]

\[ \text{Data Set B - Gene Exclusions} \]

\[ \text{Evidence for gene-disease association} = \text{none, limited, or disputed} \]

\[ \text{Non medically relevant phenotype} \]

\[ \text{Data Set C - Variant Exclusions} \]

\[ \text{Benign interpretation} \]

\[ \text{LOF but LOF not disease mechanism} \]

\[ \text{GWAS or PGx association only} \]

\[ \text{Not reported variants: 82\%} \]

\[ \text{• VUS, Likely Benign, Benign} \]

\[ \text{• False positive variants} \]

\[ \text{McLaughlin et al, BMC Med Genetics, 2014} \]
ACMG Criteria for Variant Pathogenicity and Inclusion in MilSeq Reports

MilSeq Exome Sequencing Report

- Pathogenic
- Likely pathogenic
- Uncertain significance
- Likely benign
- Benign

Standard Indication-Based Genetic Testing Reports
Report Design
RESULT: VARIANTS OF CLINICAL SIGNIFICANCE IDENTIFIED
One variant conferring carrier status and one variant with disease-associated risks were identified.

RESULT SUMMARY
Sequencing of this individual's exome did NOT identify variants with strong evidence to cause a highly penetrant disorder, but identified one variant associated with an increased risk of disease. In addition, sequencing identified carrier status for one variant that may impact disease risk in future children or other family members, depending on the carrier status of the partner(s). All results are summarized on page 1 with further details provided on subsequent pages.

INTERPRETATION SUMMARY
A. MONOGENIC DISEASE RISK VARIANTS
This test did NOT identify variants with strong evidence to cause a highly penetrant disorder.

B. CARRIER STATUS VARIANTS
This test identified carrier status for one recessive disorder. In the heterozygous state, this variant is not known to play a role in disease, since pathogenic variants in both copies of the X gene are necessary to cause disease. Being a carrier of this variant does NOT put this individual at risk for disease, but it may impact disease risk in future children, depending on the carrier status of this individual's future partner(s).

Please note, we cannot conclusively rule out a pathogenic variant on the other copy of the gene given test and analysis limitations.

Disease, Gene, Variant Allele state Classification Penetrance Carrier
Inheritance Transcript Phenotype

| Adenylosuccinate lyase deficiency, Autosomal recessive | ADSL NM_000026.2 c.1277G>A Heterozygous Pathogenic High None reported |

C. DISEASE-ASSOCIATED RISK ALLELES
This test identified one variant associated with an increased risk of developing clinical manifestations. Please see below and subsequent pages for more detailed variant information.

Disease, Inheritance Gene Transcript Variant Allele state Classification Relative Risk

| Pulmonary Fibrosis | MUC5B NM_002458.2 c.-3133G>T Heterozygous Established Risk Allele 3.7 |

D. PHARMACOGENOMIC ASSOCIATIONS
This test identified the following pharmacogenomic associations with a potential change in management. Additional pharmacogenomic associations can be found on subsequent pages.

Drug Gene, Variant(s) Genotype Risk and dosing information

| Clopidogrel | CYP2C19 NM_000069.1 c.(-806C( ; )681G(;)636G ) ; '1/' 2 Decreased response to clopidogrel |

| Digoxin | ABCB1 NM_000927.4 c.3435T>C, p.Leu1145Lle TT Decreased metabolism and increased serum concentration of digoxin |
Recruitment Progress to Date
Patient-Participants

93 completed Phase I (baseline survey)

75 consented and enrolled

51 results disclosed and integrated into EMR
24 pending result disclosure

Provider-Participants

12 HCPs: 5 staff physicians, 5 resident physicians, 2 NPs

12 consented, received education, and completed pre/post-education surveys

All HCP-participants have disclosed at least 1 result
Health Care Provider Education
HCP’s reported significantly higher feelings of confidence in each domain after attending the education session (all p<0.05).
HCP’s reported significantly higher feelings of preparedness (scale 1-4, p=0.037) and self-efficacy (scale 1-5, p=0.018) after attending the education session.
Cohort Description and Baseline Data
# Patient-Participant Demographics

<table>
<thead>
<tr>
<th>Characteristic – N (%) unless otherwise noted</th>
<th>N=93</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (n=87)</strong></td>
<td></td>
</tr>
<tr>
<td>Mean in years (SD)</td>
<td>33.75 (±8.25)</td>
</tr>
<tr>
<td><strong>Gender (n=93)</strong></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>48 (51.6%)</td>
</tr>
<tr>
<td>Female</td>
<td>45 (48.4%)</td>
</tr>
<tr>
<td><strong>Race/Ethnicity (n=93)</strong></td>
<td></td>
</tr>
<tr>
<td>Hispanic or Latino</td>
<td>17 (18.3%)</td>
</tr>
<tr>
<td>Non-Hispanic White</td>
<td>61 (65.6%)</td>
</tr>
<tr>
<td>Non-Hispanic Other*</td>
<td>13 (13.9%)</td>
</tr>
<tr>
<td>Prefer Not to Answer</td>
<td>2 (2.2%)</td>
</tr>
<tr>
<td><strong>Education (n=93)</strong></td>
<td></td>
</tr>
<tr>
<td>Did not graduate from college</td>
<td>36 (38.7%)</td>
</tr>
<tr>
<td>College graduate or higher</td>
<td>57 (61.3%)</td>
</tr>
<tr>
<td><strong>Annual Household Income (n=93)</strong></td>
<td></td>
</tr>
<tr>
<td>≤ $99,999</td>
<td>64 (68.8%)</td>
</tr>
<tr>
<td>≥ $100,000</td>
<td>29 (31.2%)</td>
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</table>

* Non-Hispanic Other includes African American, Asian, and Other
### Healthcare Provider Demographics

<table>
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<th>Characteristic</th>
<th>N=12</th>
</tr>
</thead>
<tbody>
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<td><strong>Age (n=11)</strong></td>
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</tr>
<tr>
<td>Mean in years (SD)</td>
<td>39 (±9.25)</td>
</tr>
<tr>
<td><strong>Gender (n=12)</strong></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>8 (66.7%)</td>
</tr>
<tr>
<td>Female</td>
<td>4 (33.3%)</td>
</tr>
<tr>
<td><strong>Race/Ethnicity (n=12)</strong></td>
<td></td>
</tr>
<tr>
<td>Hispanic or Latino</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Non-Hispanic White</td>
<td>6 (50%)</td>
</tr>
<tr>
<td>Non-Hispanic Other*</td>
<td>6 (50%)</td>
</tr>
<tr>
<td><strong>Years in Practice (n=12)</strong></td>
<td></td>
</tr>
<tr>
<td>1-10</td>
<td>10 (83.4%)</td>
</tr>
<tr>
<td>21-30</td>
<td>2 (16.6%)</td>
</tr>
<tr>
<td><strong>Genetics Training (n=12)</strong></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>11 (91.7%)</td>
</tr>
<tr>
<td>Yes</td>
<td>1 (8.3%)</td>
</tr>
</tbody>
</table>

* Non-Hispanic Other includes African American and Asian
Airmen’s Motivations to Participate in a Genomic Sequencing Project

- Curiosity about Genetic Make-Up: 71%
- Desire to Advance Research: 70%
- Desire for Own Genomic Results: 60%
- Learn Results that may Impact Children/Pregnancy: 57%
- Learn about Condition that Runs in Family: 55%
- Learn Chance of Disease: 50%
- Influence USAF Policy about Genomic Sequencing: 26%
- Financial Compensation: 5%

Percent of Airmen that endorsed each motivation.
Airmen’s Concerns about Participating in a Genomic Sequencing Project

- I Don't Have Any Concerns: 70%
- Impact Current or Future Children: 49%
- Results Placed in My Medical Record: 29%
- Unable to Understand Results: 26%
- Results with Uncertain Meaning: 21%
- Impact on My Career: 19%
- How the AF Might Use My Results: 18%
- Receiving Results I Can't Do Anything About: 14%
- Receiving Information I Don't Want: 9%
- Ability to Cope with Results: 7%

Percent of Airmen that Strongly Agree/Agree
Monogenic Disease Risk: 58 Exome Reports

- 4 participants (6.8%) with autosomal dominant findings

  - Familial hypercholesterolemia
    - Male, self-reported high cholesterol first diagnosed at 20 years of age
    - Cholesterol level of 300 on most recent lipid panel (2013)
    - Prescribed CRESTOR®* as a result of this finding

  - Dehydrated hereditary stomatocytosis I
    - Male, normal CBC, splenectomy contraindicated for affecteds

  - Familial exudative vitreoretinopathy
    - Female, no visual symptoms reported

  - Nonsyndromic hearing loss
    - Female, no hearing impairment reported

*The views of AstraZeneca are not necessarily the official views of, or endorsed by, the U.S. Government, the Department of Defense, or the Department of the Air Force. No Federal endorsement of AstraZeneca is intended.
Carrier Status Variants: 58 Exome Reports

• 50 participants (86%) identified as carriers
  – Range: 0-6 per report; average: 2 per report

• Repeated findings:
  – Hereditary hemochromatosis: n=17
  – Stargardt disease: n=5
  – Primary ciliary dyskinesia: n=4
  – Thrombocytopenia with absent radius syndrome: n=4
  – Nonsyndromic autosomal recessive hearing loss: n=3
Carrier Status Variants: 58 Exome Reports
13 Possible Manifesting Heterozygotes!

- Congenital hypothyroidism: n=2
- Cystinuria: n=2
- Fanconi anemia: n=1
- Hypogonadotrophic hypogonadism: n=1
- Myotonia congenita: n=1
- Nijmegen breakage syndrome: n=1
- Pseudocholinesterase deficiency: n=3
- Rippling muscle disease: n=1
- Sickle cell: n=1
All Participants have at Least One Atypical Pharmacogenomic Variants

**Selection Criteria**

- Clinical Annotation Level A
- Clinical Annotation Levels 1A/1B
- Differ from standard dosage
- Sensitivity and specificity
- Strategic Research Objectives
  - Precision Medicine
  - Operational Readiness

**PGx Panel Classifications & USAF Applications**

<table>
<thead>
<tr>
<th>Analgesic*</th>
<th>Anticoagulant</th>
<th>Anesthetic</th>
<th>Anticonvulsant</th>
<th>Psychiatric*</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Combat casualty care&lt;br&gt;- Chronic pain management for combat-related disability&lt;br&gt;- Musculoskeletal training injury</td>
<td>- Combat casualty care&lt;br&gt;- Prophylaxis for post-amputation deep vein thrombosis</td>
<td>- Combat casualty care&lt;br&gt;- Continuum of care for subsequent surgical interventions</td>
<td>- Combat casualty care&lt;br&gt;- Traumatic brain injury</td>
<td>- Post traumatic stress disorder&lt;br&gt;- Combat-related depression and anxiety&lt;br&gt;- Sleep disturbances</td>
</tr>
</tbody>
</table>

*CYP2D6 variants are salient for informing pain management and mental health treatments in the USAF. WES may not be reliable for the detection of CYP2D6 whole-gene duplications (decreased sensitivity). Therefore, supplemental CNV analysis is performed for inclusion in the MilSeq Project PGx panel.*
Lessons from the MilSeq Study

• Multi-disciplinary team has demonstrated that sequencing can be integrated into the practice of military medicine

• Substantial number of Airmen interested in sequencing and are not deterred by thorough informed consent process.

• Participants are not distressed, even for positive findings.

• High motivation to learn about their own health (personal and reproductive)

• HCPs do not initially rate themselves as prepared but the 3-hour education module modestly improves their self-perceived level of preparedness

• Surprising amount of information pertinent to operational readiness (disease risk, performance vulnerabilities, pharmacogenomics, rapid and accurate typing for blood transfusion)
Genomic medicine in the military

Mauricio De Castro¹, Leslie G Biesecker², Clesson Turner³, Ruth Brenner⁴, Catherine Witkop⁴, Maxwell Mehlman⁵,⁶, Chris Bradburne⁷ and Robert C Green⁸

Military genomics: a perspective on the successes and challenges of genomic medicine in the Armed Services

Mauricio J. De Castro¹ & Clesson E. Turner²

¹United States Air Force Medical Genetics Center, 81st Medical Group, Keesler AFB, Mississippi 39534
²Division of Genetics, Department of Pediatrics, Walter Reed National Military Medical Center, Bethesda, Maryland 20889
MilSeq Project Scientific Conference Presentations

2017
• Military Operational and Readiness Precision Medicine
• American Society of Human Genetics

2018
• Law and the Biosciences
• American Society of Law, Medicine and Ethics
• American College of Medical Genetics and Genomics
• Military Health System Research Symposium
• American Society for Bioethics and Humanities
• American Society of Human Genetics
• National Society for Genetic Counselors
• US Army Center for Environmental Health Research Science
• Integrative and Collaborative Biomedical Research
Future Potential
Potential Benefit to Warfighter

- Health and morale of warfighters and their families
- Identification of rare donors for blood transfusions
- Awareness of increased occupational risks
- Leveraging of genetic advantages
- Countermeasures for security vulnerabilities
The MilSeq Project – Future Potential

• Evaluate scalability by expanding the number of active duty military in MilSeq Project
  – Improve overall health of service members and families
  – Tailor warfighter performance with genetic/physiological strengths
  – Identify rare blood donors and recipients for transfusion

• Utilize existing DNA repositories and create DHA biobanks to improve knowledge base

• Contribute to ongoing security discussions
Thank you!

Carrie L. Blout, MS, CGC
Ruth Brenner, MD, Lt Col, USAF
Kurt D. Christensen, PhD, MPH
Mauricio DeCastro, MD, Maj, USAF
Cubby Gardner, PhD, Maj, USAF
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Matthew Lebo, PhD

Amy L. McGuire, JD, PhD
Megan D. Maxwell, MS, LCGC
Maxwell J. Mehlman, JD
Debra Neimeyer, PhD, CIV, USAF
Efthimios Parasidis, JD, MBioethics
Stacey Pereira, PhD
Jill O. Robinson, MA
Jason L. Vassy, MD, MPH, SM
Jameson Voss, MD, MPH, Maj, USAF

Clifton Dalgard, PhD, USUHS
Lydia Hellwig, ScM, CGC
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