

# LONG-TERM IMPACT OF MILITARY-RELEVANT BRAIN INJURY CONSORTIUM - CHRONIC EFFECTS OF NEUROTRAUMA CONSORTIUM GOVERNMENT STEERING COMMITTEE MEETING APRIL 2021

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# CURRENT STATE OF THE CONSORTIUM

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David X. Cifu, M.D.



# BLUF

- COVID adjustments have allowed for continuation of prospective study follow-ups, extensive research analyses, and development of knowledge translation products.
- All studies and cores are fully operational and on track according to our approved SOW.
- All approved sub-contractual agreements have been established. CRADAs and MTAs will be finalized once we receive Walter Reed IRB approval.
- Expanded and systemized collaborations with other Consortia and researchers.
- Fall 2021 Brain Injury Special Edition on mTBI and risk for cognitive decline on schedule.





# LIMBIC CENC



Long-Term Impact of Military-Relevant  
Brain Injury Consortium

## Research Cores

### Coordinating Center

- ★ Virginia Commonwealth University, Richmond, VA

### Neuroimaging Core

- ◆ VA Salt Lake City Health Care System/University of Utah, Salt Lake City, UT

### Biomarkers Core

- ◆ Uniformed Services University of the Health Sciences/ National Institutes of Health, Bethesda, MD

### Data and Biostatistics Core

- ◆ Hunter Holmes McGuire VA, Richmond, VA
- ◆ Virginia Commonwealth University, Richmond, VA
- ◆ VA Salt Lake City Health Care System/ University of Utah, Salt Lake City, UT
- ◆ University of Hawaii, Department of Speech, Honolulu, HI

## Prospective Longitudinal Study

### Enrollment Sites

- Hunter Holmes McGuire VA, Richmond, VA
- Michael E. DeBakey VA Medical Center, Houston, TX
- James A. Haley Veterans Hospital, Tampa Florida
- South Texas Veterans Hospital, San Antonio, TX
- Fort Belvoir Community Hospital, Alexandria, VA
- VA Portland Health Care System, Portland, OR
- Minneapolis VA Health Care System, Minneapolis, MN
- VA Boston Healthcare System, Boston, MA
- WG Hefner VA Medical Center, Salisbury, NC
- Eisenhower Army Medical Center, Fort Gordon, GA
- VA San Diego Health System/University of California- San Diego/Camp Pendleton, San Diego, CA

### Recruiting Sites

- MacDill Air Force Base, FL
- Joint Base Lewis-McChord, WA
- Fort Steward, Columbia, SC
- Naval Amphibious Base, Coronado, CA

## Additional Research Studies

### Retrospective Database Study

- ▽ San Francisco VA Medical Center/University of California- San Francisco, San Francisco, CA

### Phenotypes Study

- ▽ VA Salt Lake City Health Care System/ University of Utah, Salt Lake City, UT

### Health Economics Study

- ▽ VA Palo Alto Health Care Systems/Stanford University

### Biomarkers Discovery Study

- ▽ USUHS/NIH, Bethesda, MD
- ▽ North Florida/South Georgia Veterans Health System, Gainesville, FL

### Novel Neuroimaging Study

- ▽ VA Salt Lake City Health Care System/ University of Utah, Salt Lake City, UT

## LIMBIC-CENC Legacy Study Sites

### Epidemiology of mTBI and Neurosensory Outcomes

- ▲ San Francisco VA Medical Center, San Francisco, CA

### Tau Modification Study

- ▲ Boskamp Institute, Sarasota, FL/Barrows Institute, Phoenix AZ

### Otolith Dysfunction

- ▲ Mountain Home VA Medical Center, Mountain Home, TN

### Novel White Matter Imaging to Improve Diagnosis of Mild TBI

- ▲ VA San Diego Healthcare System, San Diego, CA

### ADAPT/EVOLVE

- ▲ University of Washington, Seattle, WA

### Structural and Functional Neurobiology of Veterans Exposed to Primary Blast Forces

- ▲ WG Hefner VA Medical Center, Salisbury, NC

### DTI Phantom Study

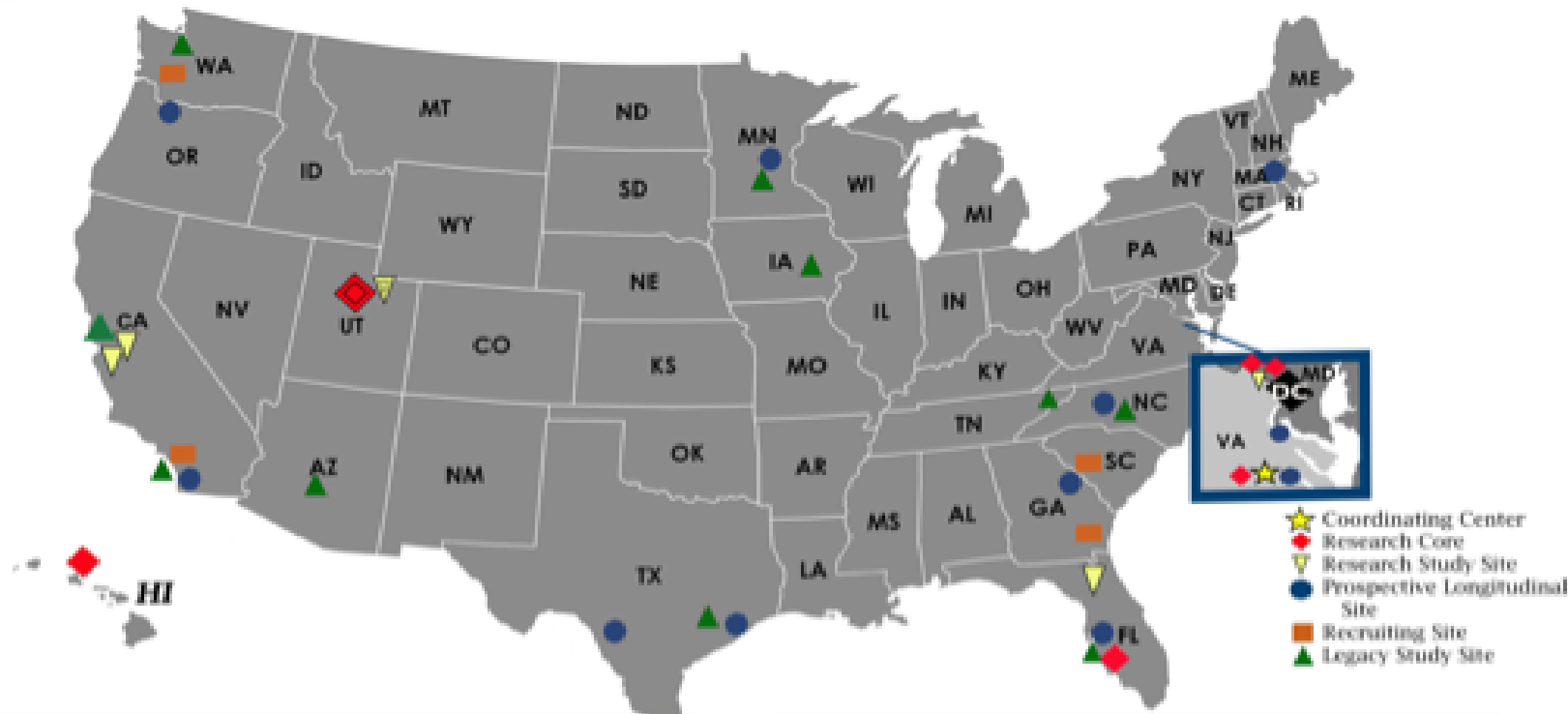
- ▲ Baylor College of Medicine, Houston, TX

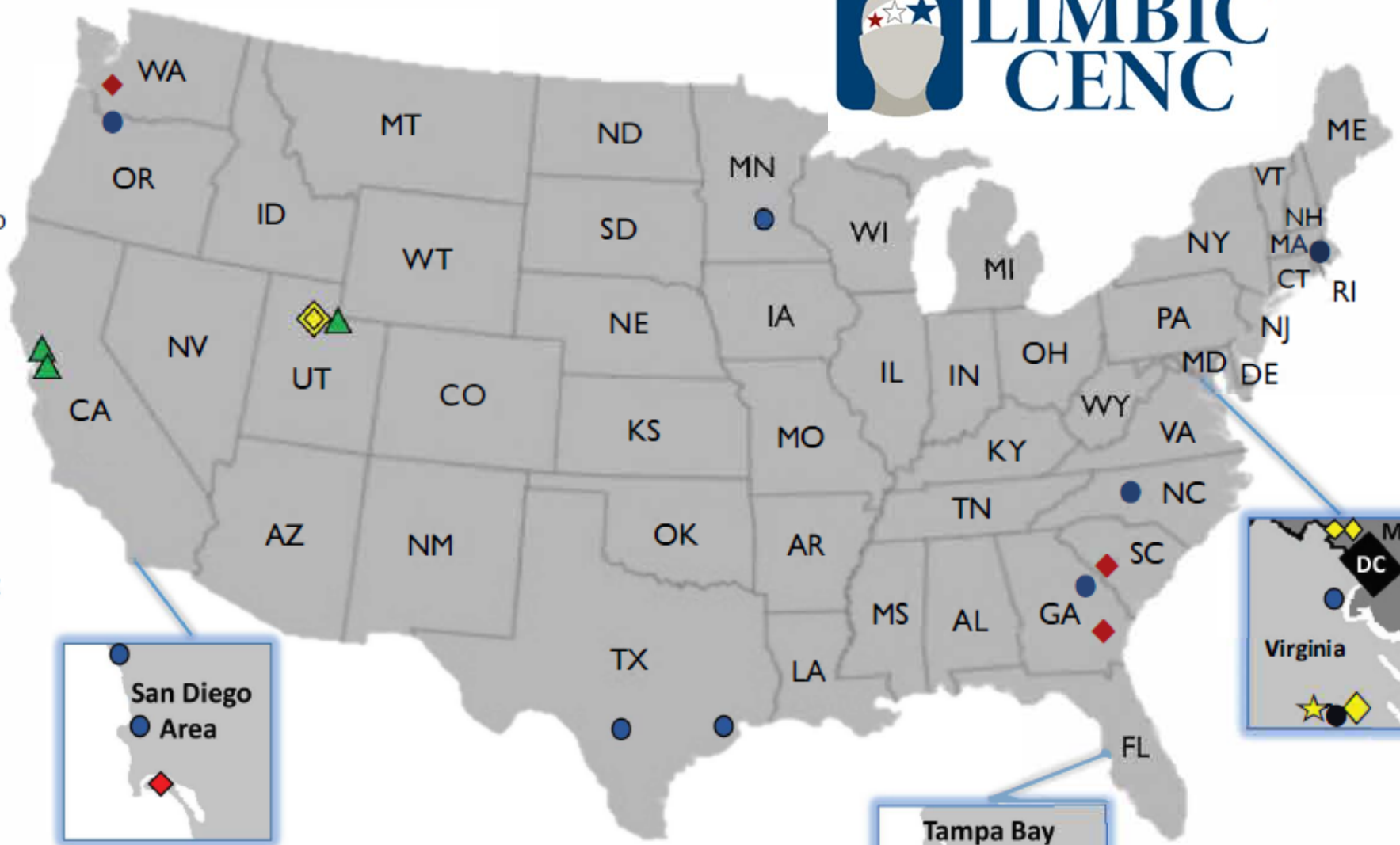
### Clinical and Neuroimaging Correlates of Neurodegeneration in Military mTBI

- ▲ Minneapolis VA Health Care System

### Visual Sensory Impairments

- ▲ Iowa City VA Health Center, Iowa City, IA





**LIMBIC-CENC Cores**

**Coordinating Center**

- Virginia Commonwealth University, Richmond, VA

**Imaging Core**

- VA Salt Lake City Health Care System/University of Utah, Salt Lake City, UT

**Biomarkers Core**

- Uniformed Services University of the Health Sciences/National Institutes of Health, Bethesda, MD

**Data Management and Biostatistical Core**

- Hunter Holmes McGuire VA, Richmond, VA
- Virginia Commonwealth University, Richmond, VA
- VA Salt Lake City Health Care System/University of Utah, Salt Lake City, UT

**LIMBIC-CENC Studies**

**Prospective Longitudinal Study Enrollment Sites**

- Hunter Holmes McGuire VA, Richmond, VA
- James A. Haley Veterans Hospital, Tampa, FL
- VA Boston Healthcare System, Boston, MA
- VA Portland Health Care System, Portland, OR
- Michael E. DeBakey VA Medical Center, Houston, TX
- South Texas Veterans Healthcare Center, San Antonio, TX
- WG Hefner VA Medical Center, Salisbury, NC
- Minneapolis VA Health Care System, Minneapolis, MN
- Eisenhower Army Medical Center, Fort Gordon, GA
- Fort Belvoir Community Hospital, Alexandria, VA
- VA San Diego Health System/University of California/Camp Pendleton, San Diego, CA

**Prospective Longitudinal Recruiting Sites**

- MacDill Air Force Base, FL
- Joint Base Lewis-McChord, WA
- Fort Stewart, GA
- Fort Jackson, Columbia, SC
- Naval Amphibious Base Coronado, Coronado, CA

**Retrospective Study Sites**

- San Francisco VA Medical Center/University of California-San Francisco
- VA Palo Alto Health Care Systems/Stanford University
- University of Utah/VA Salt Lake City Health Care System

- ★ Coordinating Center
- ◆ Research Core
- Prospective Longitudinal Study Enrollment Site
- ◆ Prospective Longitudinal Recruiting Site
- ▲ Retrospective Study Site

# LIMBIC-CENC Organizational Chart

Department of Defense

Government Steering Committee

Department of Veterans Affairs

## Leadership Team

**Consortium Director/PI**  
David Cifu, MD

**Associate Consortium Director/Co-PI**  
COL Kristofer Radcliffe, MD

**External Collaborations Director/Co-PI**  
COL (R) Sidney Hinds, MD

**Associate Consortium Director/Co-PI**  
Kristine Yaffee, MD

**Coordinating Center Director**  
Kevin Sickinger

**Biomarkers**  
Kim Kenney, MD  
Jessica Gill, PhD

## Core Facilities

**Data and Biostatistics**  
Amma Agyemang, PhD  
Mary Jo Pugh, PhD

**Neuroimaging**  
Elisabeth Wilde, PhD

**Biomarkers Discovery Study**  
(Kenney/Gill/Wang)

**Novel Neuroimaging Study**  
(Wilde)

**Prospective Longitudinal Study**  
(Walker)

## Research Studies

**Retrospective Database Study**  
(Yaffe)

**Health Economics Study**  
(Dismuke)

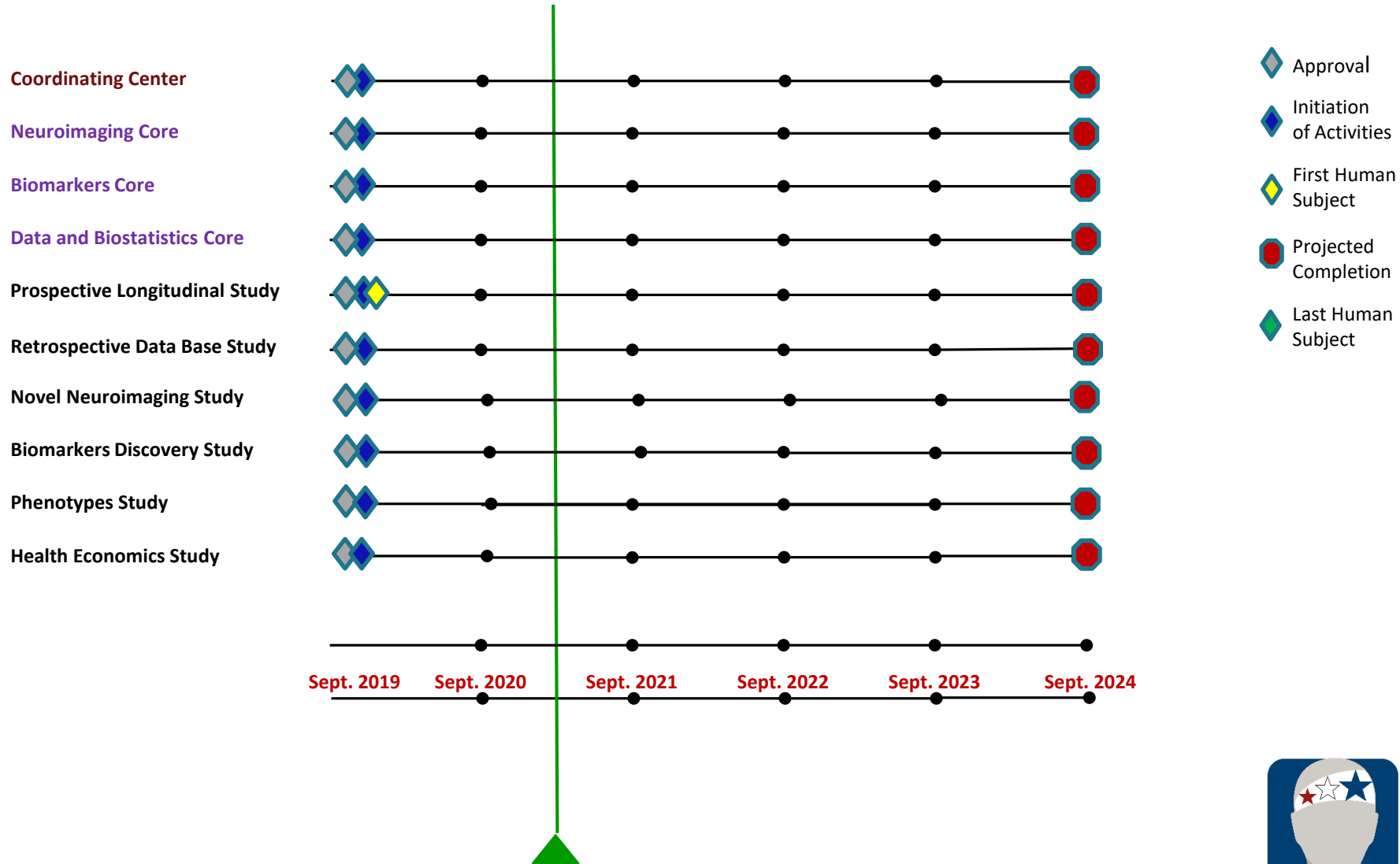
**Phenotypes Study**  
(Pugh)

**11 Clinical Study Sites**  
2 DoD  
8 VA  
1 DoD/VA

**Regulatory Oversight**  
HRPO-VAIRB- IRB of Records

**Aggregated VA and DoD Databases**

# LIMBIC-CENC Cores & Studies Timeline



# Brain Injury Special Edition – November 2021

- **Practical Approaches to Assessing and Mitigating the Risk of Cognitive Decline after Concussion: *Findings from the Long-term Impact of Military-relevant Brain Injury Consortium (LIMBIC)***
  1. *Relationship of Advanced Neuroimaging Findings to Symptom Burden and Dementia Risk after Concussion*
  2. *Relationship of Fluid Biomarker Findings to Symptom Burden and Dementia Risk after Concussion*
  3. *Role of Physical Activity following Combat-related Concussion in Impacting Dementia Risk*
  4. *Association of TBI History and Dementia in Veterans: A Mega-Database Analysis*
  5. *Clinical Phenotypes of Post-TBI Symptoms and Risk for Dementia*
  6. *Sleep disorders in TBI patients: potential new targets for reducing dementia risk*
  7. *Health Economics of Concussion, TBI and Dementia*
  8. *The Role of Transcranial Magnetic Stimulation in Post-Traumatic Cognitive Dysfunction*
  9. *Impact of PTSD on Symptom Burden and Dementia Risk After Concussion*
  10. *Long-term Cognitive Outcomes Following Military Concussion: LIMBIC 2021*
- **Supporting Resources from KTC for each topic area:** Consumer Knowledge Cards, Lay Person Abstracts, Clinical and Research Pearls, Podcast





# COVID-19 Impacts

- PLS interrupted 3 times due to outbreaks. Close connection between PLS leadership and each research site.
- In-person research has resumed in 10 of the 11 enrollment sites. Delay in initial recruitments.
- Other studies and cores have had no impact due to COVID. The Imaging Core has not been able to travel to all sites but has completed Zoom calls to ensure compliance.
- The Coordinating Center has been able to continue to manage the consortium.
- The hiring of new personnel has been limited or delayed at most sites.



# COVID Mitigation Strategy

- Worked with all enrollment sites to purchase needed PPE.
- Supported personnel in obtaining vaccinations at all sites.
- Shared lessons learned from early opening sites to newly opening sites.
- Worked on Redcap for enrollments to reduce face-to-face time.
- Will still exceed our target enrollment goal of 1,500 additional participants for PLS (total = 3,000)
  - Shifted the Enrollment targets further to the right on the calendar
  - Enrollment numbers in years 3 and 4 are limited by VA yearly budget restraints
- Research analyses are most reliant on longitudinal (follow-up) data
  - Overall retention rate = 89%
  - F/U visits Comprehensive = 76%
  - F/U visits Brief = 67%



# COVID Mitigation Strategy Enrollment Numbers

LIMBIC 2019-2024 Target = 1500

## Projected Quarterly New Enrollments for Study A: Prospective Longitudinal Study

*Subject enrollment will be expected at a rate of 2-5 per month for the duration of the study period*

Target Enrollment Study A	Year 1				Year 2				Year 3				Year 4				Year 5				Total
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	
(01) Hunter Holmes McGuire	0	0	0	0	0	6	9	9	9	9	9	9	9	9	9	9	5	3	3	0	107
(02) Michael E. DeBakey	0	0	0	0	0	3	8	8	8	8	8	8	6	6	6	6	4	4	2	0	85
(03) James A. Haley	0	0	0	0	0	9	9	9	9	9	9	9	9	9	9	9	6	6	4	0	115
(04) South Texas Veterans	0	0	0	0	0	3	9	9	9	9	9	9	9	9	9	9	8	8	7	4	120
(05) Fort Belvoir	0	0	0	0	0	3	6	9	9	9	9	9	9	9	9	9	8	8	8	2	116
(06) Portland Health Care	5	6	0	0	10	10	12	12	12	12	12	12	12	12	12	12	8	8	6	0	173
(07) Minneapolis VA	0	0	0	0	0	6	12	12	12	12	12	12	12	12	12	12	12	12	12	0	162
(08) Boston Healthcare System	0	0	0	0	0	0	6	9	12	12	12	12	12	12	12	12	12	12	8	4	147
(09) W.G. (Bill) Hefner VA	0	0	0	0	0	6	15	15	15	15	15	15	15	15	15	15	15	15	15	9	210
(10) Dwight D. Eisenhower	0	0	0	0	0	6	9	12	15	15	15	15	15	15	15	15	15	15	15	9	201
(11) San Diego Healthcare System	0	0	0	0	0	0	9	12	14	14	14	14	14	14	14	14	14	14	14	10	185
<b>Target Enrollment (cumulative)</b>	<b>5</b>	<b>6</b>	<b>0</b>	<b>0</b>	<b>10</b>	<b>52</b>	<b>104</b>	<b>116</b>	<b>124</b>	<b>124</b>	<b>124</b>	<b>124</b>	<b>122</b>	<b>122</b>	<b>122</b>	<b>122</b>	<b>107</b>	<b>105</b>	<b>94</b>	<b>38</b>	<b>1621</b>

LIMBIC is on target to exceed 2019-2024 target of 1,500 and anticipates having >3,200 total participants by 2024. Assuming the current 75% 5-year f/u completion rate, this will allow for an ongoing longitudinal cohort of >2,400 participants



# LIMBIC-CENC Regulatory Highlights

- Prospective Longitudinal Study: All 11 sites have IRB and HRPO approval.
- All other studies and cores have IRB and HRPO approval with one HRPO still in progress.
- We have now moved to the Continuing Review stage of regulatory issues.



# Consumer Advisory Board

- Held our second meeting in February 2021. All members attended
- Dr. Seel gave a demonstration of the Dementia Prognostic Indicator and received extensive feedback that was incorporated into the product.
- Co-Chairs of the CAB have participated on last 3 monthly Consortium-wide calls.
- Outstanding support of the CAB for the LIMBIC projects and progress.
- Next CAB meeting scheduled for August.



# LIMBIC-CENC PI Changes

- COL Hinds and COL Radcliffe transition completed.
- Two PLS PI changes and paperwork to be completed by end of April
  - Dr. (LtCdr) Christina La Croix is replacing Dr. Hee Chin Chae at Fort Belvoir
  - Dr. Melissa Guerra is replacing Dr. Carlos Jaramillo at our San Antonio site.



# LIMBIC-CENC Roadmap 2024

## Plotting the Course

- 2013-2021 – Define, Describe and Delineate Common Effects, Symptom Burden and Neurodegeneration after Combat-related Mild TBI
- 2021-2024 – Define and Disseminate Tools to Diagnosis and Prognosticate Symptom Burden and Neurodegeneration after Combat-related Mild TBI. Begin Intervention Trials Using Established Well-Characterized Cohorts.
- 2024-2029 – Expand and Study Innovative Interventions Across Well-Characterized Cohorts with Combat-related Mild TBI Using Validated, Standardized Assessment Approaches

## Staying on the Path



# LIMBIC Roadmap – A Productive Journey 2013-2021

## Describe the Common Effects after mTBI

Area	Contributing Studies
Neurosensory Vision Hearing Vestibular	<ul style="list-style-type: none"> <li>Described in 5 completed CENC projects (<b>Aiken, MacDonald, Kardon, Yaffe, Walker</b>)</li> <li>Being addressed in 3 active LIMBIC studies (<b>Walker, Yaffe, Pugh</b>)</li> </ul>
Neuroendocrine	<ul style="list-style-type: none"> <li>Described in 1 completed LIMBIC study (<b>Walker, Kenney</b>)</li> <li>Being addressed in VA CSP collaborative study with LIMBIC (<b>Walker</b>)</li> </ul>
Seizures	<ul style="list-style-type: none"> <li>Described in 2 completed CENC project (<b>Yaffe, Walker</b>)</li> <li>Being addressed in VA Epilepsy CoE collaborative study with LIMBIC (<b>Pugh</b>)</li> </ul>
Sleep	<ul style="list-style-type: none"> <li>Described in 5 completed CENC project (<b>Jak, MacDonald, Jak, Yaffe, Walker</b>)</li> <li>Being addressed in TBIMS/TBICoE collaborative study with LIMBIC (<b>Richardson, Dismuke</b>)</li> <li>Being addressed in 2 LIMBIC studies (<b>Werner, Richardson, Kenney, Wilde</b>)</li> </ul>
Pain	<ul style="list-style-type: none"> <li>Described in 4 completed CENC projects (<b>MacDonald, Taber, Yaffe, Walker</b>)</li> <li>Being addressed in 3 active LIMBIC studies (<b>Walker, Yaffe, Pugh</b>)</li> </ul>
Cognitive	<ul style="list-style-type: none"> <li>Described in 5 completed CENC projects (<b>Mufson, Crawford, MacDonald, Taber, Yaffe, Walker</b>)</li> <li>Being addressed in all 6 active LIMBIC studies (<b>Wilde, Kenney, Yaffe, Walker, Pugh, Dismuke</b>)</li> <li>Fall 2021 <i>Brain Injury</i> special issue dedicated to risks for cognitive decline after TBI</li> </ul>
Psychological	<ul style="list-style-type: none"> <li>Described in 5 completed CENC projects (<b>Jak, MacDonald, Taber, Yaffe, Walker</b>)</li> <li>Being addressed in 4 active LIMBIC Studies (<b>Walker, Yaffe, Pugh, Dismuke</b>)</li> </ul>
Neurological	<ul style="list-style-type: none"> <li>Described in 6 completed CENC projects (<b>Mufson, Crawford, MacDonald, Yaffe, Taber, Jak, Walker</b>)</li> <li>Being addressed in 4 active LIMBIC Studies (<b>Walker, Yaffe, Pugh, Dismuke</b>)</li> </ul>

## Define the Association Between mTBI, Symptom Burden And Neurodegeneration

Area	Contributing Studies
Symptom Burden	<ul style="list-style-type: none"> <li>Described in 7 completed CENC projects (<b>Aiken, MacDonald, Yaffe, Taber, Jak, Mufson, Crawford, Walker</b>)</li> <li>Being addressed in 4 active LIMBIC studies (<b>Walker, Pugh, Yaffe, Dismuke</b>)</li> </ul>
Neurodegeneration	<ul style="list-style-type: none"> <li>Described in 6 completed CENC projects (<b>MacDonald, Yaffe, Taber, Jak, Mufson, Crawford, Walker</b>)</li> <li>Being addressed in 6 active LIMBIC studies (<b>Walker, Pugh, Yaffe, Dismuke, Wilde, Kenney</b>)</li> <li>Fall 2021 <i>Brain Injury</i> special issue and knowledge translation products dedicated to risks for cognitive decline after TBI (<b>Cifu, Hinds, Seel</b>)</li> </ul>





# LIMBIC Roadmap – The Journey Ahead 2021-2024 (and Beyond)

## Define and Disseminate Tools to Diagnosis and Prognosticate Symptom Burden and Neurodegeneration

Research Question	Contributing Studies
Symptom Burden	<ul style="list-style-type: none"> <li>• Described in 8 completed CENC projects (<b>Wilde, MacDonald, Yaffe, Taber, Jak, Davenport, Aiken, Walker</b>)</li> <li>• Being addressed in 6 active LIMBIC studies (<b>Walker, Pugh, Kenney, Wilde, Dismuke, Yaffe</b>)</li> <li>• Knowledge Translation Core developing suite of tools (<b>Seel, Hinds</b>)</li> <li>• KTC: Risk Assessment Tool linked with Amelioration Strategies (<b>Seel</b>)</li> <li>• Completed rTMS for cognitive deficits after mTBI at LIMBIC site (<b>Manning</b>) **</li> <li>• Examining sleep interventions to reduce cognitive symptoms (<b>Werner</b>) **</li> <li>• Collaborating with VA-CSP NeuroEndocrine Assessment and Intervention trial across nine LIMBIC VA sites (<b>Walker</b>) **</li> </ul>
Neurodegeneration	<ul style="list-style-type: none"> <li>• Described in 8 completed CENC projects (<b>Wilde, MacDonald, Yaffe, Taber, Jak, Davenport, Walker, Mufson, Crawford</b>)</li> <li>• Being addressed in 6 active LIMBIC studies (<b>Walker, Pugh, Kenney, Wilde, Yaffee Dismuke</b>)</li> <li>• Knowledge Translation Core developing suite of tools (<b>Seel, Hinds</b>)</li> <li>• KTC: Risk Assessment Tool linked with Amelioration Strategies (<b>Seel</b>) Fall 2021 <i>Brain Injury</i> special issue and knowledge translation products dedicated to risks for cognitive decline after TBI (<b>Cifu, Hinds, Seel</b>)</li> </ul>



### Next Exit: Interventions 2024-2029

- **Continue Active Research applying interventions:**
  - Multiple LIMBIC collaborators with additional grant funding to study mTBI interventions
- **Partner with other investigators to leverage LIMBIC PLS site infrastructure and participants for intervention trials**
- **Mentor and Support next generation of TBI researchers**
  - Co-Investigators on LIMBIC projects
  - Mentors on CDA/K-award grants



# Questions

