Disclosures

- IP related to concussion and brain injury assessment
- IP related to assessment of dementia after brain injury
- IP related to treatment of intracranial hemorrhage

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Abbott Diagnostic Laboratories
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National Football League
National Neurotrauma Society
North American Brain Injury Society
Oculogica Inc.
Steven and Alexandra Cohen Foundation for Veteran Post Traumatic Stress and Traumatic Brain Injury
Texas, Minnesota, and Wisconsin High School Coaches Association
United States Veterans Administration and Office of Research and Development
USA Football
Prospective Treatment of Traumatic Brain Injuries by Vagus Nerve Stimulation

Presenters: Hannah Casey and Tessneem Abdallah

Molly Hubbard, MD, Thomas Bergman, MD, Rebekah Kroll, BA, Uzma Samadani, MD, PhD
Our Mission

"The goal of the Hennepin County Medical Center Brain Injury Research Lab is to classify, treat, and prevent brain injury, and improve brain health in the greater Minneapolis/St Paul community by creating innovative, sustainable solutions that can then be scaled to serve larger communities throughout the world."
HCMC Working On Advances In Measuring Concussions

New Eye Tracking Technology Used To Detect Concussions

Eye Motion Test Shows Promise For Concussion Detection

New Eye Technology Can Help Diagnose Brain Injuries Faster

HCMC Neurosurgeon Develops New Test For Concussions

Eye Motion Test Shows Promise For Concussion Detection

Eye Tracking Shows High Sensitivity As A Biomarker For Concussion, Study Finds

Eye Tracking Has High Sensitivity As A Biomarker For Concussion

Renowned Neurosurgeon To Join HCMC

Internationally Recognized Neurosurgeon Dr. Uzma Samadani Joins HCMC

Internationally Recognized Neurosurgeon Dr. Uzma Samadani joins Hennepin County Medical Center

Q&A With Uzma Samadani

Ophthalmology Meets Neurosurgery

Eye Movements To Diagnosis Traumatic Brain Injuries

New Eye Tracking Technology Adds Insight To Brain Injuries

Rethinking Concussions: Technology Helping To Broaden The Picture

For Older Adults, A Rising Risk Of Subdural Hematoma

Can Technology Save Football?

New Study Keeps Eye On Traumatic Brain Injuries

Shortfall Of Neurosurgeons Predicted To Treat Common Brain Injury, Study Says

New Eye Tracking Technology Can Detect Concussions

Eye Tracking May Help To Spot Concussions Quickly
I. CLASSIFY
   A. CLASSIFY-I: Biomarkers in CT + patients
   B. CLASSIFY-II: Serum biomarkers in Pediatric vs Adult population
   C. CLASSIFY-III: Serum vs CSF biomarkers
   D. CLASSIFY-IV: BDNF and TAU in Acute vs. Long Term patients
   E. CLASSIFY-V: Biomarkers in Blunt Force vs Non-trauma patients
   F. CLASSIFY-VI: Intracranial Hemorrhage size and GFAP
   G. CLASSIFY-VII: Biomarkers in Anoxia vs DAI
   H. CLASSIFY-VIII: Biomarkers in Brain Death
   I. CLASSIFY-IX: Early biomarkers in TBI
   J. CLASSIFY-X: Biomarkers in Crush Injury
      1. MRI
      2. Kinetic
      3. i-Stat

II. Chronic Effects of Neurotrauma (CENTS)

III. Eye Tracking and Neurovision Rehabilitation of Oculomotor Dysfunction in Mild Traumatic Brain Injuries

IV. Transforming Research and Clinical Knowledge in TBI (TRACK-TBI)

V. Traumatic brain injury Reduction in Athletes by Neck strengthening (TRAiN)

VI. Epidural STimulation After Neurologic Damage (E-STAND) Clinical Trial

VII. VERTEX

VIII. VANISH Clinical Trial (Vagal Activation of NeuromImmune Systems to Heal traumatic brain injury)
Vagus Nerve Stimulation (VNS)
History of VNS

- In 1937, Percival Bailey - neurosurgeon and psychiatrist - found that stimulation of the severed end of a vagus nerve would induce cortical changes on an EEG.
- In 1988, Jacob Zabara developed a vagus nerve stimulator which reduced seizure activity in dogs.
- In 1997: FDA approved VNS for seizure activity
- In 2005: It was approved as treatment for depression
Vagus Nerve (Cranial Nerve X)
<table>
<thead>
<tr>
<th>Components</th>
<th>Function</th>
<th>Central connection</th>
<th>Cell bodies</th>
<th>Peripheral distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visceral motor (efferent general visceral)</td>
<td>Involuntary muscle and gland control</td>
<td>Dorsal motor nucleus X</td>
<td>Dorsal motor nucleus X</td>
<td>Cardiac, pulmonary, esophageal, gastric, celiac plexuses, and muscles, and glands of the digestive tract</td>
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<tr>
<td>Visceral sensory (afferent general visceral)</td>
<td>Visceral sensibility</td>
<td>Nucleus tractus solitarius</td>
<td>Inferior ganglion X</td>
<td>Cervical, thoracic, abdominal fibers, and carotid and aortic bodies</td>
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<td>Visceral sensory (afferent special visceral)</td>
<td>Taste</td>
<td>Nucleus tractus solitarius</td>
<td>Inferior ganglion X</td>
<td>Branches to epiglottis and taste buds</td>
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<td>General sensory (afferent general somatic)</td>
<td>Cutaneous sensibility</td>
<td>Nucleus spinal tract V</td>
<td>Superior ganglion X</td>
<td>Auricular branch to external ear, meatus, and tympanic membrane</td>
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Man Partly Wakes From 15-Year Vegetative State—What It Means

The 35-year-old was able to turn his head and react to visual cues after doctors put a device in his chest that stimulates the vagus nerve.
Forebrain

- Cerebrum, thalamus, hypothalamus
- Complex sensory and neural functions
Thalamus

- “Relay Center” of the brain
- Regulates consciousness, sleep/alertness
Reticular Formation

- Nerve pathways that mediate level of consciousness
<table>
<thead>
<tr>
<th>Row</th>
<th>Status</th>
<th>Study Title</th>
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<td>• Procedure: Selective vagus nerve stimulation</td>
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VANISH Clinical Trial
Vagal Activation of NeuroImmune Systems to Heal traumatic brain injury
Molly Hubbard, MD
Rebekah Kroll, BA
Thomas Bergman, MD
Tessneem Abdallah, BA
Hannah Casey
Uzma Samadani, MD, PhD
Study Type

- Single-center
- Randomized (1:1)
  - Group 1: 30 subjects with concussion TBI
  - Group 2: 30 subjects with moderate TBI
    - 15 active/15 sham in each group
- Double-blind
- Sham-controlled
- Parallel-arm study
Objective

The primary objective of this study is to provide initial evidence of use of the noninvasive vagus nerve stimulator (gammaCore device) for treatment of patients recovering from concussion and moderate traumatic brain injury to improve clinical recovery.

This study generally aims to collect randomized comparative data on the safety and efficacy of the device.
Hypotheses

Stimulation of the vagus nerve results in increased cerebral blood flow and metabolism in the forebrain, thalamus and reticular formation (1), which promotes arousal and improved consciousness (2), thereby improving outcome after traumatic brain injury resulting in impaired consciousness.
Interventional Treatment Dosing

● 2 stimulation doses each day
  ○ Each dose consists of two 120 second stimulation treatments
    ■ Left side of the neck

● 12 week period

● Patient-administered
Effectiveness Endpoints

Primary Effectiveness Endpoint
The primary effectiveness endpoints are to evaluate whether vagus nerve stimulation impacts clinical recovery from moderate traumatic brain injury as assessed by the cognitive assessments, functional assessments, and depression index at all study time-points between treatment groups.

Secondary Endpoint
The secondary endpoints for concussion and moderate traumatic brain injury patients are: heart rate variability (HRV), commercially available cognitive assessments, functional recovery assessments, depression inventory, blood-based biomarkers, non-invasive physical exam, and eye tracking metrics relative to norms. The final secondary endpoint is determination of whether a large-scale prospective randomized trial evaluating the efficacy and parameters of vagus nerve stimulation for recovery from concussion and moderate traumatic brain injury is justifiable.
Time of Injury:

- 2 weeks
- 6 weeks
- 12 weeks
- 18 weeks
Time of Injury

Visit 0
Visit 1
Visit 2
T₀: Visit 0 (Screening Visit)

➢ General Medical Questions
➢ EKG
➢ Urine Pregnancy tests (females)
➢ EEG
Inclusion Criteria

- Written Informed Consent
- 18 - 60 years
- Meets the criteria of the Head Injury Interdisciplinary Special Interest Group of the American Congress of Rehabilitation Medicine, which defines a head injury as a traumatically induced physiologic disruption of brain function, as manifested by one of the following:
  - Any period of loss of consciousness (LOC),
  - Any loss of memory for events immediately before or after the accident,
  - Any alteration in mental state at the time of the accident,
  - Focal neurologic deficits, which may or may not be transient.
Inclusion Criteria (continued)

- Meets the criteria for moderate TBI as defined by the Head Injury Interdisciplinary Special Interest Group of the American Congress of Rehabilitation Medicine, which are as follows:
  - Length of stay at least 48 hours,
  - Glasgow Coma Scale (GCS score of 9-12 or higher)
  - Operative intracranial lesion,
  - Abnormal CT scan findings.
- May have had a craniotomy, but those with hydrocephalus or active intracranial pressure elevation will be excluded.
- Able to accurately communicate the sensation of amplitude of intensity by the stimulation treatment with the GammaCore device.
- Has a stable orthopedic or other traumatic body injury.
- Is capable of completing all study assessments.
Inclusion Criteria (continued)

- Agrees to use the GammaCore device as intended and follow all of the requirements of the study, including follow-up visits.
- Agrees to record usage of the GammaCore device, all required study data, and report any adverse effects to the sponsor/investigator within 24 hours of any such adverse event.
- No evidence of focal or generalized interictal discharges on EEG.
- Willing and able to complete the study.
Exclusion Criteria

- Has an active DNR/DNI (do not resuscitate/do not intubate) request.
- Has dissent among family members/next of kin regarding level of care.
- Has a penetrating injury.
- Has concurrent active severe medical problems (psychiatric or otherwise) or conditions, which could prevent survival during the course of the study.
- Has pre-existing central nervous system disease or associated comorbidities that may not allow for an 18-week follow-up visit.
- Has an abscess, infection or lesion (including lymphadenopathy) at the gammaCore treatment site.
- Has known or suspected moderate to severe atherosclerotic cardiovascular disease, carotid artery disease (e.g. bruits or history of TIA or CVA).
- Has a clinically significant irregular heart rate or rhythm.
Exclusion Criteria (continued)

- Has uncontrolled hypertension (systolic bp > 200 or diastolic bp >100), recent (within the last 3 months) heart attack, recent (within the last 3 months) stroke, known aortic aneurysm, or congestive heart failure (CHF).
- Is currently implanted with an electrical and/or neurostimulator device, including but not limited to cardiac pacemaker, defibrillator, vagal neurostimulator, deep brain stimulator, spinal stimulator, bone growth stimulator, or cochlear implant.
- Has a history of significant carotid endarterectomy, vagotomy, dysaesthesia or vascular neck surgery on either side of the neck.
- Has been implanted with metal cervical spine hardware.
- Has a recent or repeated history of syncope.
- Has a recent or repeated history of seizures.
Exclusion Criteria (continued)

- Has known clotting disorder or hemophilia.
- Has anemia (hb<12).
- Is pregnant or nursing, or of childbearing potential and is unwilling to use an accepted form of birth control (hormonal, barrier method, surgical, or abstention or is at least two years post-menopause).
- Is participating in any other therapeutic clinical investigation or has participated in a clinical trial in the preceding 30 days.
- Is an employee of the clinical study site or a relative of the Investigator.
- Has an abnormal baseline electrocardiogram (ECG), including second and third degree heart block, atrial fibrillation, atrial flutter, recent history of ventricular tachycardia or ventricular fibrillation or clinically significant premature ventricular contraction.
- Has a known history or suspicion of substance abuse or addiction.
If eligible...

- Assigned study materials
- Training on administration of treatment with the device
- Training on all aspects and requirements of the study including completion of the Subject Diary, post-treatment and adverse event reporting and follow-up visit requirements,
- Vital signs (temperature, heart rate, respiratory rate, and blood pressure)
- Neurologic and cognitive evaluations
- Functional measure of independence
- Depression questionnaire
- Eye tracking algorithm
- Non-invasive physical examination
- Heart rate variability
- 10 cc baseline serum sample will be obtained by phlebotomy
- Schedule Visit 1 Follow Up within 72 hours +/- 1 day from screening visit
\( T_1 \): Visit 1 (Baseline)

- Review subject’s general well-being
- **First interventional treatment** with the gammaCore device and review of any adverse events, discuss any unresolved or new adverse events identified

\( T_2 \): Visit 2 (Phone Call)

- Review subject’s general well-being
- Discuss interventional treatment with the gammaCore device and for any adverse events, discuss any unresolved or new adverse events identified since the previous visit, document and record according to the parameters of the Adverse Event CRF
Time of Injury

2 weeks

Visit 3
T₃: Visit 3

- Return of completed diary and is provided with new diary if needed
  - Review subject’s diary for adverse events, discuss any unresolved or new adverse events identified since the previous visit. Review medications (specifically for change in medication usage), and that all diary questionnaires have been completed.
- Perform gammaCore treatment during office visit (to assure treatment procedure is being performed accurately).
- Vital signs (temperature, heart rate, respiratory rate, and blood pressure).
- Neurologic and Cognitive evaluations
- Non-invasive physical exam
- Eye tracking algorithm
- EKG
- Heart rate variability
- Discuss requirements of the next 4-weeks with the subject and subjects’ caregiver, including completion of the Subject Diary, adverse event reporting and follow-up visit requirements
T₄: Visit 4

- Return of completed diary and is provided with new diary if needed
  - Review subject’s diary for adverse events, discuss any unresolved or new adverse events identified since the previous visit. Review medications (specifically for change in medication usage), and that all diary questionnaires have been completed.
- Perform gammaCore treatment during office visit (to assure treatment procedure is being performed accurately).
- Vital signs (temperature, heart rate, respiratory rate, and blood pressure).
- Neurologic and Cognitive evaluations
- Non-invasive physical exam
- Eye tracking algorithm
- EKG
- Heart rate variability
- Discuss requirements of the next 6-weeks with the subject and subjects’ caregiver, including completion of the Subject Diary, adverse event reporting and follow-up visit requirements
Time of Injury

- 2 weeks
- 6 weeks
- 12 weeks
- 18 weeks

Visit 5
T5: Visit 5

- **Return used device.**
- Return of completed diary and is provided with new diary.
  - Review subject’s diary for adverse events, discuss any unresolved or new adverse events identified since the previous visit. Review medications (specifically for change in medication usage), and that all diary questionnaires have been completed.
- Perform gammaCore treatment during office visit (to assure treatment procedure is being performed accurately)
- Vital signs (temperature, heart rate, respiratory rate, and blood pressure)
- Neurologic and cognitive evaluations
- Non-invasive physical exam
- Eye tracking algorithm
- EKG
- Heart rate variability
- Serum sample will be obtained by phlebotomy
- Discuss requirements of the next 6-weeks with the subject, including completion of the Subject Diary, adverse event reporting and follow-up visit requirements.
T₆: Time 6

- Return of completed diary.
- Review subject’s diary for adverse events, discuss any unresolved or new adverse events identified since the previous visit. Review medications (specifically for change in medication usage), and that all diary questionnaires have been completed.
- Vital signs (temperature, heart rate, respiratory rate, and blood pressure)
- Neurologic and cognitive evaluations
- Non-invasive physical exam
- Eye tracking algorithm
- EKG
- Serum sample will be obtained by phlebotomy,
- EEG will be done on all patients to evaluate for changes from baseline using quantitative EEG.
Eye-Tracking
Control
## Preliminary Data

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<th>% Females</th>
<th>Mean Age</th>
<th>White Only</th>
<th>More than One</th>
<th>Pedestrian v Car</th>
<th>Motorcycle</th>
<th>Falls from height</th>
<th>Fall from standing</th>
<th>Assault</th>
<th>Workplace Injury</th>
<th>Lost to Follow up</th>
<th>Withdrawn</th>
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<td>(9) 69.2%</td>
<td>(4) 30.8%</td>
<td>44</td>
<td>(9) 69.2%</td>
<td>(4) 30.8%</td>
<td>(4) 30.8%</td>
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Side Effects

- Redness at the treatment site
- Irritation at the treatment site
  - Related to previous case of shingle and existing burning from injury
- Tingling at the treatment site
- Headaches