Award Number: W81XWH-14-1-0173

TITLE: Evaluation of the King-Devick Test to Assess Eye Movements and the Performance of Rapid Number Naming in Concussed and Non-Concussed Service Members

PRINCIPAL INVESTIGATOR: Dr. Michael Dretsch

CONTRACTING ORGANIZATION: The Geneva Foundation
Tacoma, WA 98402

REPORT DATE: July 2017

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE *(DD-MM-YYYY)*	2. REPORT TYPE	3. DATES COVERED *(From - To)*
July 2017	Annual	30Jun2016 - 29Jun2017

4. TITLE AND SUBTITLE
"Evaluation of the King-Devick Test to Assess Eye Movements and the Performance of Rapid Number Naming in Concussed and Non-Concussed Service Members"

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH-14-1-0173

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
MAJ Michael Dretsch, PhD

Email: michael.n.dretsch.mil@mail.mil

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
The Geneva Foundation
917 Pacific Ave., Ste. 600
Tacoma, WA 98402

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, MD 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for public release; distribution unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT
This study's objective is to determine to what extent the King-Devick Test results discriminate healthy individuals from both their pre-Combatives baseline and their post-Combatives assessment, to determine to what extent individuals diagnosed as having an mTBI event differ from their King- Devick Test pre-Combatives baseline, and to determine to what extent individuals who report a history of concussion during their pre-Combatives baseline differ from those who have not reported a prior concussive event.

15. SUBJECT TERMS None listed

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
Unclassified	Unclassified	Unclassified	Unclassified	16	19b. TELEPHONE NUMBER *(include area code)*

Table of Contents Page

Introduction:

The primary study objective is to determine the concurrent validity, sensitivity, and specificity of the King-Devick Test to cognitive impairment of attentional processes associated with acute mild traumatic brain injury (mTBI) in service members. The secondary objective it to explore the neurophysiological and neurostructural changes in the brain associated with both combatives training and acute concussion. In addition, we will explore changes in microRNA and other small molecules as potential biomarkers of mTBI.

Keywords:

MTBI, concussion, neurocognitive

ACCOMPLISHMENTS:

What were the major goals of the project?

1) Initiate, Plan and Design Study [Months 2-3]

2) Execute Study (collect and analyze data) [Months 3-9]

3) Conclude Study [Month 10]

What was accomplished under these goals?

Data have been collected under two protocols.

1) (A-18002) Evaluation of the King-Devick Test to Assess Eye Movements and the Performance of Rapid Number Naming in Concussed and Non-Concussed Service Members.
    a. Baselines (n=117), Post-Training (n=62), Post-Injury (n=27)
2) (A-18002.2) Imaging Assessment of Neurological Changes Associated with Subconcussive and Concussive Events in US Soldiers.
    a. Control group (n=12) and mTBI group (n=3)

In addition we -

1) Received approval of an amendment to the protocol (A-18002) with respect to changing the site PI and adding the collection of saliva samples for microRNA analysis. Funds from this award will not be used for analysis of saliva RNA. Quadrant Biosciences will provide funding for analysis saliva RNA specimen.
2) Received approval of an amendment to the protocol (A-18002.2) for adding the collection of saliva samples. Funds from this award will not be used for analysis of saliva RNA. Quadrant Biosciences will provide funding for analysis saliva RNA specimen
3) Approved for an additional six month no-cost extension in order to complete the study (approved 24 April 2017).
4) Had a team meeting at Fort Benning, with all of the investigators and associates to discuss recruitment/enrollment strategies, data management, and professional development.
5) **Our preliminary results:**
    a. For protocol A-18002, a within-subjects analysis using paired samples test revealed that mean K-D scores (smaller mean scores are better) were not significantly different between baseline (M = 41.54, SD = 7.91) and post-training phases (M = 41.67, SD = 9.54) in students (n=82) who did not sustain a concussion, t(81) = -.20, p = .841, 95% CI (-1.3, 1.1). In contrast, in individuals who sustained a concussion during Combatives (n=28), scores at baseline (M = 41.07, SD = 6.71) compared to post-injury scores (M = 45.21, SD = 10.67) were significantly different, t(27) = -2.80, p = .009, 95% CI (-7.2, -1.1), suggesting performance was markedly worse after a concussion. This finding suggests the K-D is sensitive to cognitive decrements during the acute phase of a concussive injury, and not subconcussive events occurring during Combatives training.
    b. Additional analysis will include ROC and AUC, and positive and negative predictive power, to assess sensitivity and specificity of the K-D to acute concussion as assessed via the MACE and SCAT2;

concordance between MACE and SCAT2; correlations and changes between symptom severity and cognitive functioning; and mediating effects of prior/lifetime concussions and on scores as well as other mediators/moderators.

c. For protocol A-18002.2, analysis of brain imaging and cognitive data being collected has not commenced due to the slow participant enrollment rate. However, as of Oct 2017, our number of enrolled participants has greatly increased.

6) Future analysis:

a. Future analysis (funded by Quadrant Biosciences) will include exploring saliva RNA for molecular panels (biomarkers of up or down regulation of genes and proteins associated with concussion) that might improve sensitivity/specificity to acute concussion beyond the K-D alone. In addition, linking neural network integrity with differences in salivary RNA and cognitive function and symptoms between concussed and non-concussed participants will improve our understanding of acute concussion pathophysiology, and contribute to the validation of imaging and salivary biomarkers.

What opportunities for training and professional development has the project provided?

MAJ Dretsch and Ms. Fauth met face-to-face on two separate occasions for developing data management and analysis strategies. Currently planning on submitting an abstract for Teach and Research Conference, Auburn University, AL, for Ms. Fauth to present.

How were the results disseminated to communities of interest?

Updates have been briefed to the quarterly Noninvasive Neuro-Assessment Devices In progress Review Meetings (USAMRMC CCCRP).

Press release in Army.mil and The Bayonet:
https://www.army.mil/article/172262/king_devick_study_assesses_head_injuries_in_the_army

What do you plan to do during the next reporting period to accomplish the goals?

Complete data collection. Analyze data and provide findings.

Impact

The findings from this project has the potential to impact policy for screening concussion during training in CONUS. The secondary and tertiary effects may result in continued research within other military populations and operational environments. This policy change would come through dissemination of findings to USAMRMC, MEDCOM, OTSG, and DVBIC. The results of the second protocol aimed at exploring the neuroanatomical and pathophysiologic changes associated with combatives training (both subconcussive and concussive events) will inform the community of the sensitivity and specificity of various brain imaging techniques and epigenetic changes compared to neurocognitive measures.

What was the impact on the development of the principal discipline(s) of the project?

Nothing to Report

What was the impact on other disciplines?

Nothing to Report

What was the impact on technology transfer?

Nothing to Report

What was the impact on society beyond science and technology?

Nothing to Report

Changes/Problems

Changes in approach and reasons for change
The protocol was amended to add the collection of saliva samples in order to explore changes in microRNA as a potential biomarker of acute mTBI. Funds from this award will not be used for analysis of saliva RNA.

Actual or anticipated problems or delays and actions or plans to resolve them

The rate of enrollment for the Auburn Imaging protocol has been slower than expected to unforeseen issues. Participants often do not show up for their scheduled appointments. To mitigate this delay, a one-year no-cost extension was attained.

Changes that had a significant impact on expenditures
Nothing to Report

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Nothing to Report

PRODUCTS:
Nothing to Report

Participants & Other Collaborating Organizations

What individuals have worked on the project?

Name:	Dr. Michael Dretsch
Project Role:	Principal Investigator
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	27.6
Contribution to Project:	Dr. Dretsch serves as the overall study PI on this research project.

Name:	Jenifer Fauth
Project Role:	Project Director
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	24.9
Contribution to Project:	Jenifer Fauth serves as the Project Director and on-site lead for this research project.

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?
We have had a change of site PI (Responsible for administrative oversight at Fort Benning).

What other organizations were involved as partners?
Auburn University MRI Research Center will be providing structural brain scans under a second protocol in order to assess changes in the brain associated with both combatives training and concussion.

Quadrant Biosciences has provides supplies for collecting saliva samples for microRNA analysis for both protocols (e.g., Auburn University and Fort Benning). See press release: http://www.npr.org/sections/health-shots/2017/05/04/526782407/spit-test-may-reveal-the-severity-of-a-child-s-concussion

Organization Name:
Auburn University
Quadrant Biosciences (saliva RNA analysis)

Location of Organization: (if foreign location list country)
Partner's contribution to the project (identify one or more)

X Financial support;
☐ In-kind support (e.g., partner makes software, computers, equipment, etc., available to project staff);
☐ Facilities (e.g., project staff use the partner's facilities for project activities);
X Collaboration (e.g., partner's staff work with project staff on the project);
☐ Personnel exchanges (e.g., project staff and/or partner's staff use each other's facilities, work at each other's site); and
x Other – saliva kits and analysis of saliva RNA

Special Reporting Requirements

None

Collaborative Awards

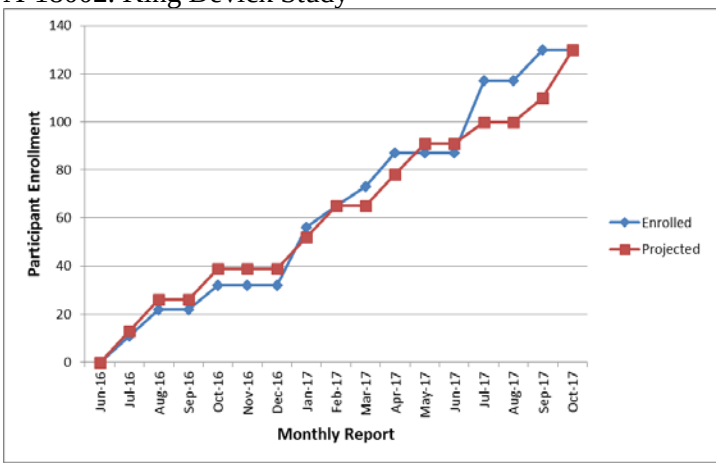
Nothing to Report

Quad Charts

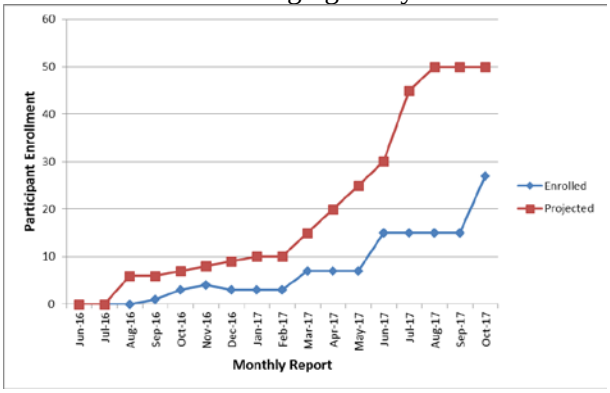
The Quad Chart (available on https://www.usamraa.army.mil) shall be updated and submitted as an appendix.

Appendices

A-18002. King Devick Study



A-18002.2. Auburn Imaging Study



AUBURN UNIVERSITY INSTITUTIONAL REVIEW BOARD for RESEARCH INVOLVING HUMAN SUBJECTS

REQUEST for MODIFICATION

For help, contact: THE OFFICE OF RESEARCH COMPLIANCE (ORC), 115 Ramsay Hall, Auburn University
Phone: 334-844-5966 e-mail: IRBAdmin@auburn.edu Web Address: http://www.auburn.edu/research/vpr/ohs

Revised 2.1.2014 **Submit completed form to IRBsubmit@auburn.edu or 115 Ramsay Hall, Auburn University 36849.**

Form must be populated using Adobe Acrobat / Pro 9 or greater standalone program (do not fill out in browser). Hand written forms will not be accepted.

1. Protocol Number: 14-542 MR 1412
2. Current IRB Approval Dates: From: 11/30/16 To: 12/16/17
3. Project Title: Imaging assessment of neurological changes associated with subconcussive and concussive events in US Soldiers

4.

Thomas S. Denney Jr.	Prof/Director	MRI/ECE	844-0214	dennets
Principal Investigator	Title	Department	Phone	AU E-Mail (primary)
PI Signature	AUMRIRC 560 Devall Drive, Suite202			rodieja
	Mailing Address			Alternate E-Mail

Faculty Advisor	FA Signature	Department	Phone	AU E-Mail

Name of Current Department Head: R. Mark Nelms AU E-Mail: nelmsrm

5. Current External Funding Agency and Grant number: The Geneva Foundation, G00009698

6. a. List any contractors, sub-contractors, other entities associated with this project:

Ft. Benning Eisenhower Army Medical Cnt, The Geneva Found, Fort Benning, GA's Comb school

b. List any other IRBs associated with this project: Eisenhower Army Medical Center IRB, MRMC IRB

7. Nature of change in protocol: (Mark all that apply)

- [x] Change in Key Personnel (attach CITI forms for new personnel)
- [ ] Change in Sites (attach permission forms for new sites)
- [ ] Change in methods for data storage/protection or location of data/consent documents
- [ ] Change in project purpose or questions
- [x] Change in population or recruitment (attach new or revised recruitment materials as needed)
- [ ] Change in consent procedures (attach new or revised consent documents as needed)
- [x] Change in data collection methods or procedures (attach new data collection forms as needed)
- [ ] Other (explain): _____

FOR ORC OFFICE USE ONLY

DATE RECEIVED IN ORC: _____ by _____
DATE OF IRB REVIEW: _____ by _____
DATE OF IRB APPROVAL: _____ by _____
COMMENTS:

MODIFICATI
PROTOCOL A
MODIFICATI
INTERVAL F

The Auburn University Institutional Review Board has approved this Document for use from 07/26/2017 to 12/16/2017
Protocol # 14-542 MR 1412

1 of 2

8. Briefly list *(numbered or bulleted)* the activities that have occurred up to this point, particularly those that involved participants.

Twelve participants have been recruited; eleven have been scanned, one was not scanned due to titanium clips. These have allowed us to obtain baseline scans prior to a combatives training course and scans after a cmTBI incident, in order to explore neural changes in service members in combatives training.

9. For each item marked in Question #7, describe the requested changes to your research protocol, with an explanation and/or rationale for each. *(Additional pages may be attached if needed to provide a complete response.)*

-Increase the recruitment to include soldiers at the TBI Clinic in Ft. Benning to allow us to meet the number of participants needed to validate the study.

-Allow for a saliva sample to be taken to explore differences in molecules such as non-coding microRNA in the saliva and correlate with imaging findings.

-Add Julio Yanes and Lily Strassberg to personnel list. Both are Psychology GRA's who are working at the MRI Research Center. They both have Level 3 Scanner Certification and they will be screening and scanning the participants for this study along with helping with analyzing data. Remove Andie Thompkins, Lucia Lazarowski, and Martha Forloines who are no longer working on this project.

10. Identify any changes in the anticipated risks and / or benefits to the participants.

none

11. Identify any changes in the safeguards or precautions that will be used to address anticipated risks.

none

12. Attach a copy of all "stamped" IRB-approved documents you are currently using. *(information letters, consents, flyers, etc.)*

DEPARTMENT OF THE ARMY
HEADQUARTERS, DWIGHT DAVID EISENHOWER ARMY MEDICAL CENTER
300 EAST HOSPITAL ROAD
FORT GORDON, GEORGIA 30905-5650

Institutional Review Board (IRB) Notification

a. Date: 25 July 2017

b. Principal Investigator: CPT Marcelo Moya

c. Project Title: Evaluation of the King-Devick Test©® to Assess Eye Movements and the Performance of Rapid Number Naming in Concussed and Non-Concussed Service Members

d. Project #: 1510001 - 4

e. Project Risk Level: Minimal Risk (MR) IAW 32CFR219.102(i)

f. IRB Review Level: Convened

g. Approval Period: No change to previously approved approval period.

h. Enrollment Limit: 100

i. Submission Type: Amendment/Modification

j. IRB Action: Approved

k. Effective Date: 13 July 2017

l. Informed Consent Process: Obtained and documented IAW 32CFR219.116(a)

m. HIPAA Authorization: Required IAW 45CFR164.508(a)(1)/DOD 6025.18R C5.1.1
Psychotherapy Notes Authorization: N/A

n. Research Monitor (RM): Not Required
(See RM appointment letter)

o. Ombudsman: Not Required
(See Ombudsman appointment letter)

Approved/acknowledged documents to support the project are:

☒ Protocol 8 June 2017
☐ Site-Specific Protocol Addendum

☐ Informed Consent Form – Control Group
☐ Informed Consent Form – Experimental Group
☒ Informed Consent Form – Combined Control and Experimental Groups 8 June 2017

☐ Parental Permission Form
☐ Children's Assent Form, 7-12 years of age
☐ Children's Assent Form, 13-age of majority
☐ Legally Authorized Representative Consent Form
☐ Information Sheet

☐ HIPAA Authorization
  ☐ HIPAA Application for Data Use and/or Disclosure for Research

☐ Recruitment Materials
  ☐ Newspaper Ad/Bulletin Board Notice
  ☐ Poster
  ☐ Social Media Posting
  ☐ Other
  ☐ Pamphlet
  ☐ Radio or TV Script
  ☐ Manual

☐ Data Collection Tools
☒ Research Project Cover Sheet 31 May 2017
☒ Research Project Amendment/Modification Request Form 30 May 2017
☒ Research Team Credentials (CV/ Résumé, CITI Training Certificate, etc.)
☒ Research Team Affirmation Statement 17 May 2017
☐ EIRB Modification Form
☐ Conflict of Interest/Financial Disclosure
☐ Memorandum of Changes

☒ Other: Impact Statement 18 May 2017

FDA Regulated Trials
☐ FDA Approval/Clearance Letters

Drugs/Biologics/Supplements
☐ Form FDA 1572 Statement of Investigator
☐ Investigational Drug Brochure

Devices
☐ Investigator Agreement
☐ Technical Manual

Required PI Actions:

The Principal Investigator is responsible for the safety and welfare of research subjects and shall comply with the DDEAMC Human Research Protection Program (HRPP) requirements to:

☒ Submit a continuing review report with applicable documentation at least six weeks prior to the approval period stated (item g).

☒ Submit a closure report when the study no longer involves human research subjects to IRB review and oversight (e.g., study completion or only de-identified data analysis remains).

☒ Upload project reports within 90 days of closure/completion to the Defense Technical Information Center (DTIC) in accordance with the DTIC site instructions (http://dtic.mil/dtic/) accompanied by an Standard Form 298.

(a) For studies funded with RDT&E, Army or RDT&E, DHP ensure technical reports are prepared in accordance with AR 70-31 and follow the format established in American National Standards Institute (ANSI) / National Information Standards Organization (NISO) 39.18-2005 or its revisions.

(b) Ensure all publications or presentations resulting from this research are cleared prior to submission in accordance with U.S. Army Public Affairs Office Regulation AR 360-1 Chapter 6, "Speakers and Clearance of Speeches, Manuscripts, and Internal Information" and other applicable local policy prior to release.

☒ Comply with the IRB approved protocol for data destruction and/or data storage.

Funding and Agreements

Do not construe this correspondence as approval for any contract funding. Only the Contracting Officer/Grants Officer can authorize expenditure of funds. The PI should contact the appropriate contract specialist or contracting officer regarding the expenditure of funds for this project.

POC: Ms. Monica Jernigan, 706-787-8053, monica.w.jernigan.civ@mail.mil or usarmy.gordon.medcom-eamc.mbx.irb@mail.mil

For use of this form, see AR 70-25 or AR 40-38; the proponent agency is OTSG

PRIVACY ACT OF 1974

Authority:	10 USC 3013, 44 USC 3101 and 10 USC 1071-1087
Principle Purpose:	To document voluntary participation in the Clinical Investigation and Research Program. The home address will be used for locating purposes.
Routine Uses:	The home address will be used locating purposes. Information derived from the study will be used to document the study; implementation of medical programs; adjudication of claims; and for the mandatory reporting of medical conditions as required by law. Information may be furnished to Federal, State and local agencies.
Disclosure:	The furnishing of your home address is mandatory and necessary to contact you if future information indicates that your health may be adversely affected. Failure to provide the information may preclude your voluntary participation in this investigational study.

PART A - VOLUNTEER AFFIDAVIT

Volunteer Subjects in Approved Department of the Army Research Studies

Volunteers under the provisions of AR 40-38 and AR 70-25 are authorized all necessary medical care for injury or disease which is the proximate result of their participation in such studies.

I, _____ having full capacity to consent and having attained my _____ birthday, do hereby volunteer to participate in the research protocol titled: **"Evaluation of the King-Devick Test to Assess Eye Movements and the Performance of Rapid Number Naming in Concussed and Non-Concussed Service Members"** under the direction of **CPT Marcelo Moya** conducted at **Fort Benning, GA's Combatives and Airborne Schools**.

The implications of my voluntary participation; the nature, duration, and purpose of the research study; the methods and means by which it is to be conducted; and the inconveniences and hazards that may reasonably be expected have been explained to me by_____.

I have been given an opportunity to ask questions concerning this investigational study. Any such questions were answered to my full and complete satisfaction. **Should any further questions arise concerning my rights on study-related injury I may contact the Center Judge Advocate at Dwight D. Eisenhower Army Medical Center, (706) 787-4097/6197.**

Evaluation of the King-Devick Test to Assess Eye Movements and the Performance of Rapid Number Naming in Concussed and Non-Concussed Service Members

Log Number 12089007

W81XWH-14-1-0173

PI: Dr. Michael Dretsch **Org:** The Geneva Foundation **Award Amount:** $500,671

Study/Product Aim(s)

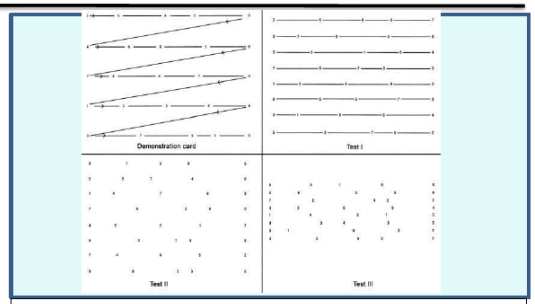
• Main Study Aim is to evaluate the ability of the King-Devick test to accurately detect concussions in Soldiers; Does the Post Incident K-D Test vary from the individual's pre-combatives baseline assessment?

•Additional Aims:

b. Does the pre-combatives baseline K-D Test assessment of individuals who report a history of concussion on their baseline questionnaires vary from the pre-combatives baseline K-D Test assessment of individuals who have not reported a prior concussion event **c. Does the** post-combatives K-D Test assessment vary from the pre-combatives baseline assessment in healthy individuals who do not suffer a concussive event.

Approach

- Subjects will be recruited at the Fort Benning Combatives School, and other Combatives training
- Recruitment will occur on the first day of training during Soldiers' in-processing
- Any Soldier that volunteers to participate will be given the informed consent and HIPAA documents
- Any volunteers that agrees to the consent process will be given a pre-combatives questionnaire and K-D test before training begins
- Volunteers who suffer a concussive event during training will be given a post-incident questionnaire (which includes the MACE and GCS) and K-D test within 24 hours after the event occurs
- Volunteers who do not have a concussive event during training will be given a post-training questionnaire and K-D test on the last day of their training
- Recruitment and testing will be conducted until 100 concussed Soldiers have been tested
- A brain imaging arm of the study will recruit from enrolled subjects, but will occur at Auburn University
- Saliva collected at Auburn and Fort Benning for microRNA analysis for potential biomarkers



Picture above shows the King-Devick test card. Each participant will be start with the demonstration card and continue through each test. Participants are instructed to read the numbers from left to right, and are informed that it is a timed event. Average test time is less than two minutes.

Timeline and Cost

Activities CY	15	16	17	18
Finalizing protocol documents, training employees, meeting with post personnel, and awaiting IRB approval				
Approved protocol. Hire additional study personnel, complete training.				
Data collection; data analysis				
Complete data analysis, and publish findings				
Estimated Budget ($500,671)	**$99,540**	**$201,835**	**$102,295**	

Updated: 13OCT2017

Goals/Milestones

CY17 Goals –

- Continued data collection
- Preliminary data analysis

CY18 Goals –

- Finish data collection, analysis, and report prior to first quarter of CY18

Comments/Challenges/Issues/Concerns

- Recruitment for Imaging protocol has been slower than expected due to "no shows" and time constraints of students.

Budget Expenditure as of 6.30.17

Projected Expenditure: $500,671

Actual Expenditure: $405,032