IRBnet Number: 409729-12
PI: MAJ Michael W. Bartoszek
Protocol Title: Patient and provider confidence and satisfaction with the clinical use of CYP genetic variability analysis to guide analgesic treatment: A randomized, controlled pilot study using the Pain Medication and Mental Health DNA Insight™ test.
Initial Date Submitted: 02/10/2015
Revision Date: 31 August 2016

Application and Request for Approval of Study Proposal

1.0 PROTOCOL TITLE: Patient and provider confidence and satisfaction with the clinical use of CYP genetic variability analysis to guide analgesic treatment: A randomized, controlled pilot study using the Pain Medication and Mental Health DNA Insight™ test.

2.0 PRINCIPAL INVESTIGATOR:

Name: Dr. Michael Bartoszek, MD
Title: Staff Anesthesiologist
Department: DOS/AO
Name/Address of Institution: Womack Army Medical Center, Fort Bragg, NC
Phone: 910-907-7209
Email: Michael.w.bartoszek.mil@mail.mil

2.1 ASSOCIATE INVESTIGATORS:

Name: Dr. Anthony R. Plunkett, MD
Title: Director of Research
Department: Anesthesiology
Name/Address of Institution: Womack Army Medical Center, Fort Bragg, NC
Phone: 910-643-2423
Email: anthonyrplunkett@gmail.com

Name: MAJ Min Ho Chang, MD
Title: Staff physician IPMC
Department: IPMC
Name/Address of Institution: Womack Army Medical Center, Fort Bragg, NC
Phone: 910-907-7209
Email: Min.h.Chang.mil@mail.mil

Name: Dr. Robert N. Agnello, D.O.
Title: Primary Care Pain Champion (PCPC)
Department: IPMC
Name/Address of Institution: Womack Army Medical Center, Fort Bragg, NC
Phone: 910-570-3375
Email: Robert.n.agnello.civ@mail.mil

Name: Dr. Melissa M. Roberts, MD

Title: Co-Chair of the CLER Committee
Department: Womack Family Medical Clinic
Name/Address of Institution: Womack Army Medical Center, Fort Bragg, NC
Phone: 910-907-9619
Email: melissa.m.roberts23.civ@mail.mil

2.2 COLLABORATORS:

Name: Amy M. McCoart RN BSN CCRC
Title: Research Manager DVCIPM /Henry M. Jackson Foundation
Department: Clinical Investigations/Anesthesiology
Name/Address of Institution: Womack Army Medical Center, Fort Bragg, NC
Phone: 910-907-6239
Email: amy.m.mccoart.ctr@mail.mil

Name: Elizabeth Dennison
Title: Research Coordinator
Department: Clinical Investigations
Name/Address of Institution: Womack Army Medical Center, Fort Bragg, NC
Phone: 910-907-9516
Email:elizabeth.m.dennison5.ctr@mail.mil

Name: Dr. Krista Highland, PhD
Title: Senior Scientist
Department: DVCIPM/ Henry M. Jackson Foundation
Name/Address of Institution: Defense and Veterans Center for Integrative Pain Management (DVCIPM), Rockville, MD
Phone: 301-816-4732
Email: khighland@dvcipm.org

2.3 ROLES AND RESPONSIBILITIES:

The PI will be involved in patient recruitment, design and oversight of experimental methodology, literature review and manuscript writing. Dr. Plunkett will assume the roles and responsibilities of PI in the event Dr. Bartoszek is unavailable to carry out his responsibilities. AIs will be involved in patient recruitment and screening and potential manuscript writing. Ms. McCoart and/ or Ms Dennison will be involved in recruitment, performing patient consent, interviews and administering surveys, specimen collection, shipping of samples and regulatory

communications. Ms McCoart will also participate in protocol development.

3.0 RESPONSIBILITIES OF THE PRINCIPAL/ASSOCIATE INVESTIGATOR IN HUMAN SUBJECTS RESEARCH:

The principal investigator is the individual who is primarily responsible for the actual execution of the clinical investigation. He/she is responsible for the conduct of the study, obtaining subjects' consent, providing necessary reports, and maintaining study documents. The Associate Investigator will assist the Principal Investigator with the responsibilities stated below.

As the Principal Investigator or Associate Investigator:

A. I will not enroll a subject into a study until the study has been approved by the appropriate authority and, when appropriate, the subject's primary care provider has granted approval for him/her to enter a study.

B. By signing this protocol, I warrant that any use of Protected Health Information (PHI) for reviews preparatory to research met the following requirements:
i. The review of PHI was done solely to prepare a research protocol, or for similar purposes preparatory to research;
ii. No PHI was taken outside the Military Health Care System or disclosed to persons not having a need for this information; and
iii. This review of PHI was necessary for research purposes

C. I am responsible for assuring that the prospective volunteer is not participating as a subject in other research that will significantly increase the research risks to the subject.

D. I am responsible for assuring the quality of each subject's consent in accordance with current federal regulations. This will include ensuring that any "designee" that obtains consent on my behalf is completely conversant with the protocol and is qualified to perform this responsibility.

E. I will obtain the WAMC IRB approval for advertisements used to recruit research subjects.

F. I will not accept any outside personal remuneration for implementation of a study.

G. I will take all necessary precautions to ensure that the study does not generate hazardous chemical waste.

H. I will obtain the proper WAMC clearance prior to all presentations, abstracts, and publications. The following require WAMC approval:

i. Reports involving WAMC subjects and/or patients.
ii. Reports that cite WAMC in the title or byline.
iii. Reports of WAMC approved clinical investigation or research.
iv. Reports of research performed at WAMC.
v. Reports of research conducted by WAMC assigned personnel.

I. I will obtain proper Office of the Surgeon General (OTSG) publication clearance prior to all presentations, abstracts, and
publications that involve:
i. Traumatic brain injury
ii. Post-traumatic stress disorder
iii. Poly-pharmacy
iv. Pain

(For assistance with publication clearance contact Ms. Jenkins, IRB Secretary at linda.j.jenkins.civ@mail.mil)

J. I must submit to the Clinical Investigation Service (CIS):

i. Any source of outside funding.
ii. An annual Continuing Review Report (CR), due in the anniversary month of the protocol's initial approval or due in the month as determined by the IRB for continuing review and approval.
iii. Reports of adverse effects occurring in subjects as a result of study participation or of any protocol deviations and submit these reports to Research Monitor if there is one for the study.
iv. An Addendum, prior to any changes made to the study or a change in the funding status.
v. Listing of presentations, abstracts, and publications arising from the study for inclusion in the CR.

K. I will maintain a Study File that must be kept for six years following completion of the study if no IND/IDE used (32 CFR 219.115(b). If IND medication or IDE appliances are used, the file must be kept for 2 years after FDA approval and can then be destroyed; or if no application is filed or approved, until 2 years after the study is discontinued and FDA notified (21CFR 312.62(c). The records should be kept in the Department/Service where the research took place (AR 40-38). If I am scheduled to PCS or ETS, I will notify the Clinical Investigation Service as soon as I am aware but at least 3 months prior to departure. Records will be given to a new WAMC PI or the Department/Service Chief.

L. I will be familiar with all applicable regulations governing research, and will adhere to all of the requirements outlined in the WAMC's DOD Assurance and Federal-Wide Assurance granted by the Office for Human Research Protections, Department of Health and Human Services.

I. Research Monitor

If it is determined that a Research Monitor is assigned to the research study, I agree to provide the name, human subject protection training and curriculum vitae of the research monitor. I acknowledge that this individual will be qualified (e.g., Medical Doctor, Nurse Practitioner, etc.). The research monitor will review all unanticipated problems involving risk to the subjects or others, serious adverse events and all subject deaths associated with the protocol and provide an unbiased written report of the event. At a minimum, the research monitor will comment on the outcomes of the event or problem, and in the case of a serious adverse event or death, comment on the relationship to participation in the study. The research monitor will also indicate whether he/she concurs with the details of the report provided by the study investigator. Reports for events determined by either the investigator or research monitor to be possibly or definitely related to participation and reports of events resulting in death will be promptly forward to the WAMC IRB.

J. Active Duty Military Personnel as Study Subjects

Special consideration will be given to the recruitment process for military personnel. The Chain of Command will not be involved in the recruitment of military personnel and will not encourage or order soldiers to participate in research study. An ombudsman will be used when conducting group briefings with active duty personnel to ensure that volunteers understand that participation is voluntary. Restrictions on compensation for active duty military members will be adhered to as applicable.

K. Title 10 United States Code 980

I acknowledge the requirements of Title 10 United States Code 980: "Funds appropriated to the Department of Defense may not be used for research involving a human being as an experimental subject unless-(1) the informed consent of the subject is obtained in advance; or (2) in the case of research intended to be beneficial to the subject, the informed consent may be obtained from a legal representative of the subject."

If an individual cannot give his or her own consent (e.g., incapacitated individuals, incompetents, minors) to participate in the research study, consent of the individual's legally authorized representative will be obtained prior to the individual's participation in the research. Moreover, such subjects will not be enrolled in Dodd sponsored research unless the research is intended to benefit each subject enrolled in the study.

4.0 LOCATION OF STUDY: Single site: Womack Army Medical Center, Fort Bragg, NC

5.0 EXPECTED COMPLETION DATE: October 2016

6.0 BACKGROUND AND LITERATURE REVIEW:

Date of Search: December 01, 2014
Period Searched: January 1990-December 2014
Sources Searched: Periodicals, journals, google scholar, PubMed internet
Keywords Searched: Genomics, Genetics, Pain, DNA, translational medicine, personalized medicine

Military service members are often injured during training (sprains, strains, etc.) or in combat (battle as well as non-battle injuries).[1] The need to effectively manage pain and its impact on rehabilitation and recovery with minimal side effects led to the formation of the Pain Management Task Force (PMTF) by the Office of The Surgeon General (OTSG).[2] This tri-service report defined both the problem and the general lack of training for providers of patients who have pain. Pain is often referred to as the "fifth vial sign" and its importance has lead the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) to evaluate adequate pain control as an important marker in quality.[3] Opioids have been a mainstay of pain management since morphine was first discovered in the 1800s. Opioids, however, can be associated with various adverse side effects including postoperative nausea and vomiting, constipation, ileus, and respiratory depression.[4] Treatment of acute pain may help prevent the development of chronic pain and lower the risk of addiction.

Chronic pain is the leading cause of disability in the United States, with the top 2 reasons being back pain and arthritis.[19] In the military, it is the leading cause of medical evaluation board initiation, and a major reason for evacuation from theaters of operation.[20-24] The annual cost to treat chronic pain in the U.S. costs hundreds of millions of dollars, and the proportion of individuals on disability has nearly doubled over the past 20 years. Interventional treatments for pain are expensive and have done little to reduce the rates of disability or need for surgery.[25] Analgesic medications such as opioids and adjuvants all possess significant adverse effects, including sedation and cognitive impairment, which can be particularly detrimental in service members. This indicates a strong need for safe, effective treatments for chronic pain.

The extraordinary variation in patients' response to medications has been attributed to genetic as well as environmental factors. However, genetic variations are generally believed to account for up to 95 % of the observed variability in drug disposition and effects.[5] The inter-individual variability in both pain sensitivity and response to medication is both fascinating and frustrating. It has long been the primary care providers biggest challenge to identify the most effective analgesic regimen in each patient. Unfortunately, beyond an individual provider's experience with analgesic medications, typically little objective data are available to assist healthcare providers in predicting an individual's response to a given medication. Several studies have

suggested specific genetic variations as responsible for the vast inter-individual differences seen in patients.[6-10] A review of cancer-related pain identified a number of genetic variations that are current targets of both diagnosis and treatment.[11] The narrow therapeutic dosing range of opioid medications combined with the highly stressful military working environment has brought significant attention to the field of pain and opioid dependence management. The concept of personalized or precision medicine, based on the human genome, is considered the next major breakthrough in healthcare. Currently the FDA has approved pharmacogenetic information for over 100 medications including popular analgesics such as tramadol, codeine and carisoprodol.[12]

Normal genetic variations in genes that encode drug metabolizing enzymes or drug receptors can result in inter-individual variations in drug response, i.e., the degree to which an individual metabolizes a drug or triggers a biological response can have a large effect on the success of the drug therapy. Therefore, genetic tests that determine gene variations can be useful in adjusting drug dosage based on patients' individual gene variations. This information allows medication plans to be tailored to the individual patient, maximizing drug efficacy while minimizing drug associated adverse effects. The CYP (Cytochrome P450 gene) superfamily is one of the most important groups of enzymes involved in the oxidation of therapeutic drugs, xenobiotics and endogenous compounds.[13] Many CYP isoforms are expressed polymorphically because of mutations in the CYP genes (**Figure 1**). The CYP2D6, CYP2C9 and CYP2C19 genes are particularly polymorphic.[14] Many of these polymorphisms have functional significance, resulting in altered enzyme activity or complete loss of enzyme expression.[14] Individuals can be classified into distinct metabolizer classes based on the CYP variants in their genome. For example, individuals can be classified based on their CYP2D6 enzyme activity into four metabolizer groups: Ultrarapid Metabolizer (UM, higher than normal enzyme activity), Extensive Metabolizer (EM, normal enzyme activity), Intermediate Metabolizer (IM, intermediate enzyme activity) and Poor Metabolizer (PM, low or no enzyme activity, **Figure 2**). Clinical studies have demonstrated that individuals that were PMs for CYP2D6 metabolized drugs and taking codeine had very low systemic exposure to the active compound morphine compared to EMs.[15,16] Therefore, PMs may experience little to no pain relief from codeine.[16,17] In contrast, UMs are at high risk of severe toxicity because of above average systemic exposure to the active compound morphine.[18] In summary, the use of genomic information has the potential for improving the utility, efficacy and safety of pain management.

In this pilot study the variability in CYP metabolism will be analyzed in a group of chronic pain patients taking opioids, using the FDA exempt Pain Medication DNA Insight™ test and Mental

Health DNA Insight™ test . The study will identify both clinician and patient confidence and satisfaction with the use of this test to guide a potential change in their analgesic regimen.

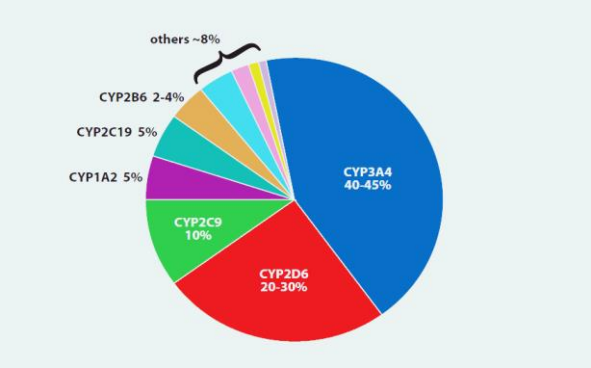


Figure 1: Relative contribution to drug metabolism by CYP type

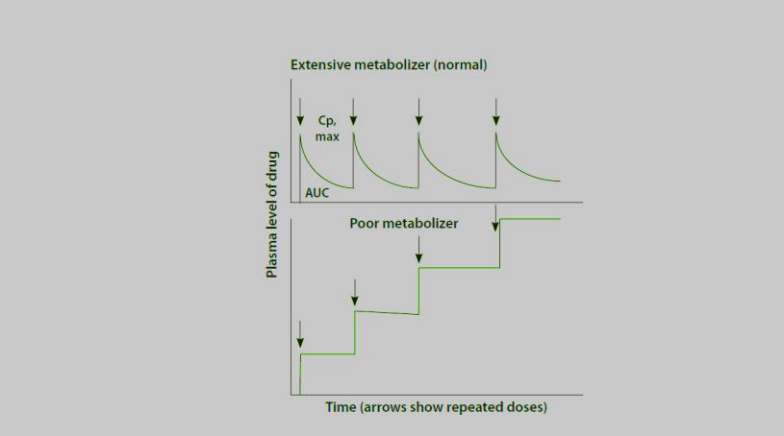


Figure 2. Variation in CYP activities has an impact on drug pharmacokinetics

6.1 REFERENCES:

1. Cohen, S.P., et al., Presentation, diagnoses, mechanisms of injury, and treatment of soldiers injured in Operation Iraqi Freedom: an epidemiological study conducted at two military pain management centers. *Anesth Analg*. 2005; 101(4): 1098-103, table of contents.

2. Office of The Army Surgeon General, P.M.T.F. Providing a Standardized DoD and VHA Vision and Approach to Pain Management to Optimize the Care for Warriors and their Families. *Final Report*. 2010.

3. Joint Commission Improving the quality of pain management through measurement and action. 2003.

4. Oderda GM, Said Q, Evans RS et al. Opioid-related adverse drug events in surgical hospitalizations: impact on costs and length of stay. *Ann Pharmacother*. 2007;41(3):400-406.

5. Eichelbaum, M., M. Ingelman-Sundberg, and W.E. Evans. Pharmacogenomics and individualized drug therapy. *Annu Rev Med*. 2006; 57: 119-37.

6. Diatchenko L, Nackley AG, Slade GD, Bhalang K, Belfer I, Max MB, Goldman D, Maixner W. Catechol-O-methyltransferase gene polymorphisms are associated with multiple pain-evoking stimuli. *Pain.* 2006; 125:216-224

7. Lee Y, Kim H, Wu T, Wang X, Dionne R. Genetically mediated inter-individual variation in analgesic responses to COX inhibitory drugs. *Clin Pharmacol Ther.* 2006; 79:407-418

8. Mogil J, Ritchie J, Strasburg K, Kaplan L, Wallace MR, Romberg R, Bijl H, Sarton E, Fillingim R. Melanocortin-1 receptor gene variants affect pain and mu-opioid analgesia in mice and humans. *J Med Genetics.* 2005; 42:583-587

9. Tegeder I, Costigan M, Griffin RS, Abele A, Belfer I, Schmidt H, Ehnert C, Nejim J, Marian C, Scholz J, Wu T, Allchorne A, Diatchenko L, Binshtok AM, Goldman D, Adolph J, Sama S, Atlas SJ, Carlezon WA, Parsegian A, Lotsch J, Fillingim RB, Maixner W, Geisslinger G, Max MB, Woolf CJ. GTPcyclohydrolaseandtetrahydrobiopterinregulate pain sensitivity and persistence. *NatMed.* 2006; 12:1269-1277

10. Zubieta JK, Heitzeg MM, Smith YR, Bueller JA, Xu K, Xu Y, Koeppe RA, Stohler CS, Goldman D. COMT val158met genotype affects mu-opioid neurotransmitter responses to a pain stressor. *Science.* 2003; 299:1240-1243

11. Turabi A, Plunkett AR. The application of genomic and molecular data in the treatment of chronic cancer pain. *J Sur Onco.* 2012; 105:494-501

12. US. Food and Drug Administration website. http://www.fda.gov/drugs/scienceresearch/researchareas/pharmacogenetics/ucm083378.htm. Accessed April 10, 2014.

13. Solus, J.F., et al., Genetic variation in eleven phase I drug metabolism genes in an ethnically diverse population. *Pharmacogenomics*. 2004; 5(7): 895-931.

14. Hiratsuka, M., In vitro assessment of the allelic variants of cytochrome P450. *Drug Metab Pharmacokinet.* 2012; 27(1): 68-84.

15. Yue, Q.Y., et al., Pharmacokinetics of codeine and its metabolites in Caucasian healthy volunteers: comparisons between extensive and poor hydroxylators of debrisoquine. *Br J Clin Pharmacol*. 1991; 31(6): 635-42.

16. Eckhardt, K., et al., Same incidence of adverse drug events after codeine administration irrespective of the genetically determined differences in morphine formation. *Pain.* 1998; 76(1-2): 27-33.

17. Sindrup, S.H., et al., Codeine increases pain thresholds to copper vapor laser stimuli in extensive but not poor metabolizers of sparteine. *Clin Pharmacol The.,* 1990; 48(6): 686-93.

18. Kirchheiner, J., et al., Pharmacokinetics of codeine and its metabolite morphine in ultra-rapid metabolizers due to CYP2D6 duplication. *Pharmacogenomics J.* 2007; 7(4): 257-65

19. Brooks PM. The burden of musculoskeletal disease- a global perspective. *Clin Rheumatol* 2006; 25: 778-81.

20. Cohen SP, Brown C, Kurihara C, Plunkett A, Nguyen C, Strassels SA. Diagnoses and factors associated with medical evacuation and return to duty for service members participating in Operation Iraqi Freedom or Operation Enduring Freedom. A prospective cohort study. *Lancet.* 2010; 375: 301-9.

21. Cohen SP, Plunkett AR, Wilkinson I, Nguyen C, Kurihara C, Flagg A 2nd, et al. Headaches during war: Analysis of presentation, treatment, and factors associated with outcome. *Cephalalgia.* 2012; 32: 94-108.

22. Cohen SP, Nguyen C, Kapoor SG, Anderson-Barnes V, Foster L, Shields C, McLean B, Wichman T, Plunkett A. Back pain during war: An analysis of factors affecting outcome. *Arch Intern Med.* 2009; 169: 1916-23

23. Cohen SP, Kapoor SG, Nguyen C, Anderson-Barnes V, Brown C, Schiffer D, et al. Neck pain during combat operations: an epidemiological study analyzing clinical and prognostic factors. *Spine.* 2010; 35: 758-63.

24. Cohen SP, Kapoor S, Anderson-Barnes VC, Turabi A, Nguyen C, Plunkett A. Non-cardiac chest pain during war. *Clin J Pain.* 2011; 27: 19-26.

25. Deyo RA, Mirza SK, Turner JA, Martin BI. Overtreating chronic back pain: time to back off? *J Am Board Fam Med*. 2009; 22: 62-8.

26. Saxon AJ. Returning veterans with addictions. *Psychiatric Times*. July 14, 2011. Available at: http://www.psychiatrictimes.com/military-mental-health/content/article/10168/1906035

27. Sehgal N, Manchikanti L, Smith HS. Prescription opioid abuse in chronic pain: a review of opioid abuse predictors and strategies to curb opioid abuse. *Pain Physician.* 2012; 15(3 Suppl): ES67-

28. Certainty Item: Bennette CS, Trinidad SB, Fullerton SM, Patrick D, Amendola L, Burke W, Hisama FM, Jarvik GP, Regier DA, Veenstra DL. Return of incidental findings in genomic medicine: measuring what patients value--development of an instrument to measure preferences for information from next-generation testing (IMPRINT). Genet Med. 2013 Nov;15(11):873-81.

29. Confidence Scale: Estes R, Hosseini J The gender gap on Wall Street an empirical analysis of confidence in investment decision making J Psychol. 1988,12.577.

30. Satisfaction Items: Holmes-Rovner M, Kroll J, Schmitt N, Rovner DR, Breer ML, Rothert ML, Padonu G, Talarczyk G. Patient satisfaction with health care decisions: the satisfaction with decision scale. Med Decis Making. 1996 Jan-Mar;16(1):58-64. PubMed PMID: 8717600.

31. Decision regret items: Brehaut JC, O'Connor AM, Wood TJ, Hack TF, Siminoff L, Gordon E, Feldman-Stewart D. Validation of a decision regret scale. Med Decis Making. 2003 Jul-Aug;23(4):281-92. PubMed PMID: 12926578.

32. Kreft, I. & De Leeuw, J. (1998). Introducing multilevel modeling. London: Sage.

33. Singer, J. D., & Willet, J. B. (2003). Applied longitudinal data analysis. Oxford: Oxford University Press.

34. Nesselroade, J. R. (1991). Interindividual differences in intraindividual change. In L. M. Collins & J. L. Horn (Eds). Best methods for the analysis of change (pp.92-105). Washington, DC: American Psychological Association.

35. Maas, C. J. M., & Hox, J., J. (2004). Robustness issues in multilevel regression analysis. Statistica Neerlandica, 58, 127-137.

36. Roberts, J. K., Monaco, J. P, Stovall, H., & Foster, V. (2011). Explained variance in multilevel models. In J J. Hox & J. K Roberts (Eds). Handbook of advanced multilevel analysis (pp.219-230). NY: Taylor and Francis.

37. Raferty, A. E. (1993). Bayesian model selection in structural equation models. In K. A. Bollen & J. S. Long (Eds). Testing structural equation models (pp. 163-180). Newbury Park: Sage.

38. Raudenbush, S., Bryk, A., Cheong, Y. F., Congdon, R., & du Toit, M. (2011). HLM 7: Hierarchical linear and nonlinear modeling. Lincolnwood, IL: Scientific Software International.

7.0 PURPOSE: To determine the confidence and satisfaction with clinical utility of the Pain Medication and Mental Health DNA Insight™ tests in optimizing analgesic regimens.

7.1 HYPOTHESES/RESEARCH QUESTIONS:

This is a pilot study and thus our goal is to explore the feasibility of an appropriately powered clinical study, which would investigate the utility of the Pain Medication and Mental Health DNA Insight ™ test to improve pain management of patients with chronic pain. Our goal is to explore how providers and patients will respond to this test and we intend to use our findings to generate hypotheses and preliminary data for a robust, fully powered clinical trial in the future.

Our research questions are:

How does the use of the Pain Medication and Mental Health DNA Insight ™ test affect provider satisfaction, certainty and confidence in dosing of opioid and non-opioid analgesics?

How does the use of the Pain Medication and Mental Health DNA Insight ™ affect patient

satisfaction, certainty and confidence in pain management plan?

How does the use of the Pain Medication and Mental Health DNA Insight ™ test affect pain related patient-reported outcomes, including DVPRS, PROMIS and BPI scores?

7.2 SPECIFIC AIMS/SIGNIFICANCE:
Specific Aims

1. Examine trends in provider decisions in prescribing analgesics and modifying analgesic treatment plans and provider outcomes for satisfaction, certainty and confidence in dosing of analgesics with and without access to Pain Medication and Mental Health DNA Insight ™ genetic testing results.

2. Examine trends in patients' satisfaction, certainty and confidence in dosing of analgesics between patient groups whose providers had access to Pain Medication and Mental Health DNA Insight ™ genetic testing results and those whose providers did not have access to the genetic information.

3. Compare patient-reported pain and mental health outcomes between patient groups whose providers had early access to Pain Medication and Mental Health DNA Insight ™ genetic testing results to those who had delayed access in the control period and subsequently following later access to the results.

The general aim of this pilot study is to assess the utility of a test that analyzes the DNA of chronic pain patients to determine their metabolic response to common analgesics, anti-depression and anxiolytic medications, to improve provider and patient confidence and satisfaction with the pain treatment plan. The results of the DNA analysis will help guide providers to change or continue the current analgesic regimen. This concept is known as "personalized" or "precision" medicine - the ability to treat patients based on their genetic profile in order to maximize therapeutic effect and minimize or eliminate unwanted side effects.

7.3 DESIGN
7.3.1 Design type:

This is a prospective, randomized, controlled, observational pilot study analyzing both providers' and patients' perceptions and responses to the DNA Insight test. For this study there will need to be a total of twelve provider groups to be enrolled and 4-8 of each provider's patients will be enrolled in the study. Enrollment will continue of providers until up to 12 providers and 48 patients have been enrolled in the study. Therefore twelve to sixteen military health system primary care providers will need to be consented due to withdrawal of providers prior to

referring patients. A total of 48 patients will be enrolled, 4-8 patients for each of the actively enrolled providers (12- 16 providers and 48 patients total). Each provider's patients will be randomized into delayed treatment (Group A) or immediate treatment (Group B) at a 1:1 ratio. Each participating provider will agree to order and interpret a Pain Medication and Mental Health DNA Insight™ test. Results for patients in Group A will be given to the provider with a 3 month delay. Those in the 3 month delay will serve as a comparison group for the period prior to receiving intervention. Results for patients in Group B will be given to the provider without delay, 2-3 weeks after saliva sample collection. The provider will use the results of the Pain Medication and Mental Health DNA Insight™ test to evaluate whether changes of medications are indicated based on the individual patient's genetic profile. A measure of the provider's certainty, confidence, satisfaction, perception of care and global impression of change will be assessed at baseline, prior to obtaining the test results, and after obtaining the test results, as outlined in the data collection section. Patients' pain related self-reported outcomes, certainty, confidence and satisfaction will be assessed at baseline, prior to obtaining the DNA Insight™ test results, and after receipt and implementation of the test results, as described in the data collection section of the protocol.

At the baseline visit (Visit 0) each enrolled patient will provide a saliva sample for the Pain Medication DNA Insight™ test that identifies genetic variation in CYP metabolism. The providers and patients will be recruited from any of the Womack Army Medical Center's Primary Care Medical Homes and family practice clinics.

Provider Inclusion:

- Licensed provider serving as a primary care manager in the Womack Army Medical Center Health Care System to include physicians, physician assistants and nurse practitioners.

Provider Exclusion

- Resident

Patient Inclusion:

- Military healthcare system beneficiary enrolled in the Womack Army Medical Center Health Care System
- Age 18 or older
- Patient of the enrolled provider for at least 3 months.
- Persisting pain for at least 3 months, with average daily pain score of 4 or higher that is not expected to improve without directed therapy.
- No history of chronic liver or kidney disease

Patient Exclusion:

- Known pregnancy or breast feeding
- Planned deployment, permanent change of station, or military separation within upcoming 6 months

7.3.3 Number of Participants: 12-16 Primary Care Managers and 48 patients enrolled in any of the Womack Army Medical Center's Primary Medical Homes or clinics with corresponding credentialed primary care managers

7.3.4 Explanation of the process from consenting to data collection:

♦ The Primary and Associate investigators along with Ms Dennison will recruit the 12-16 primary care providers from the Womack MHS. Dr. Agnello, Ms Dennison or Mr. Phillips will present a short PowerPoint presentation at the provider monthly meeting, the OIC will be ask to leave the room and be presented with the study separately. Interested providers will be asked to sign a consent form that explains there role in the study. They also will be shown a sample of what the reports will look like.

♦ A month after presenting to a clinic, providers that attended the meeting will be sent a reminder email from the research coordinator. The OIC or HSS for that clinic or Dr. Agnello will be ask to distribute a provider ad to all providers (Appendix 1). This ad will ask for volunteers and give the research team contact information.

♦ The provider ad will be posted in the WAMC bulletin along with a small description of the study.

♦ The enrolled providers will identify potential candidates within their panel based on inclusion/exclusion criteria and refer the interested patients to the study coordinator for potential inclusion in the study. They will be provided a script (Appendix A) on what to say to potential candidates. That script will refer the potential subjects to contact the study coordinator. They will be given a sheet with the study coordinator's contact information on it (Appendix B), a patient ad (Appendix 2) will also be attached that gives a small amount of information about the study and states that If the patient does not contact the coordinator after 5 business days, they will be called to ask about their interest in the study (Appendix 3). The provider will email or call the coordinator with the patients name and phone number. The providers will provide basic contact information that will include name, clinic, phone and email (Appendix C1) This appendix will also list their patient volunteers by study ID number that they will be treating.

- AIs will suggest potential candidates to enrolled providers if they deem expectable through normal clinic exposure and consults.

- The head nurses/nursing staff of each enrolled provider will be briefed on the study, inclusion/ exclusion criteria and their role in recruitment. The nurses will be ask to give potential candidates they think may qualify for the study a patient ad (Appendix 2).

- A poster that looks similar to Appendix 2 will be placed in each recruiting clinic's lobby to expose potential candidates to the idea of the study. Contact information is provided for the potential candidate to contact the research team. The poster asks for interested patients to fill out an information card with their name, phone number, and provider name. The cards can be placed in a solid box. The research coordinator will pick up all cards once a week. All patients will be called. Patients with providers not enrolled in the study will be thanked for their interest and told they cannot participate.

- The research coordinator will have access to consented providers' patient list through AHLTA. Pain patients will be identified daily through the "reason for visit" column. The patient will be sent a recruitment letter stating information about the study. A member of the research team will then call the potential patient about 4 days after sending the letter to see if the subject is interested and qualifies for the study. If the provider already has 4 patients participating or feels that patient would not be a good candidate the patient will be informed they do not qualify and they will be thanked for their time.

- Consented providers will be sent an email to inform them that their pain patients will be sent letters to see if they are interested in the study. Providers will be informed if their patient is interested in the study.

- A screen excel will be kept on a password protected computer. The spreadsheet will be used to keep track of patients who have been sent letters. There will be no PHI in the spreadsheet. Patient initials, date of sent letter, date of call and if they agreed to participate will be recorded.

♦ The study coordinator will meet with potential subjects prior to one of their scheduled appointments, explain risks/benefits of study, and obtain informed consent for inclusion in the study. These potential subjects will have the opportunity to review the consent via email prior to their meeting with the study coordinator if they choose.

♦ Once consented; subject will be allocated into one of the two study groups based on a table of randomized numbers. Subjects' demographic information such as age, gender,

race, email and phone numbers will be collected. (Appendix C2). This will also list their provider study ID number as well. Prior to the first study-related visit with the provider (Visit 0) the subject will be asked to complete the Defense and Veterans Pain Rating Scale (DVPRS) with Supplemental Items (Appendix D), the Brief Pain Inventory Short Form (BPI-SF) Perception of Relief Item over past week (Appendix E), Patient Reported Outcome Measurement Information System (PROMIS) short forms for pain interference (Appendix F), depression (Appendix G) and anxiety (Appendix H), the Patient Perceptions of Care (Appendix I), and Patient Global Impression of Change (Appendix J). The subject will be provided with a list of common opioids and NSAIDs (Appendix K) and be asked their current medications both prescription and OTC/ alternative treatments. (Appendix L).

♦ At Visit 0 a saliva sample will be collected by the study coordinator and labeled with a study ID number assigned specifically to that subject and all the samples for that day will be shipped to Pathway genomics following IATA (international air transport association) shipping regulations. Saliva is collected on all patient volunteers regardless of which group they are in. The DNA/ saliva sample will be destroyed 60 days after collection by the Pathway Genomics lab.

♦ After the first study-related visit with the provider (Visit 0) the subject will be asked to complete the patient certainty, confidence and satisfaction surveys (Appendix M). This survey will be provided by email.

♦ After Visit 0 with the subject the provider will be asked to complete the Provider Perception of Care (Appendix N), the Provider Global Impression of Change (Appendix O), and Provider Certainty, Confidence and Satisfaction surveys (Appendix P). These surveys can be hand-delivered to provider or provided over email.

♦ A member of the research team will query AHLTA to confirm the subject's current analgesic medication regiment at the time of enrollment. All analgesics will be documented as a total daily dose and all opioids will be converted to daily oral morphine equivalents using the Hopkins Opioid Program (www.hopweb.org). These data will be entered into the CRF [(Case Report Form) (Appendix L). A medication will be classified as an analgesic according to (Appendix Q).

♦ If the subject is randomized to Group A, there will be a 3-month wait period before the provider will receive the subject's DNA test result. During this time the patient will be scheduled for monthly visits (Visit 1, 2, and 3) with the provider. Each visit will be at least 1 month in advance or as the clinic allows. During these visits the medications may be changed or adjusted according to routine care. Before each visit the subject will be

asked to complete surveys of Appendix D, E, F, G, H, I, and J. After each visit the subject will be asked to complete survey of Appendix M.
After each visit the provider will be asked to complete surveys of Appendix N, O, and P.

♦ A report for the subjects study ID number will be returned to the provider within 1-3 weeks of saliva sample collection for subjects in the Group B, and after the 3-month wait period for Group A. The test report has only the subject's study ID on it, so the study coordinator will match the name of the subject with the subject study ID once it returns, so the provider is aware of the name of the subject. The report will be hand-delivered to the Primary Care Manager (PCM) by the study coordinator for use by the PCM at his/her discretion The provider will keep a copy of the results in a research folder for their use at other study visits. The provider will be informed in the ICF and when results are handed to them that the test results are not to be placed in the patient's medical record or shared with another provider.

♦ The Pain Medication and Mental Health DNA report identifies genetic variations that affect how individuals respond to commonly prescribed opioids, pain medications, antidepressants and anxiolytics. A sample report of the mental health component is shown in (Appendix R). In addition to the medications in the sample report, the Pain Medication and Mental Health DNA Insight will also test for genetic variations affecting response to carisoprodol, celecoxib, codeine, fentanyl, hydrocodone, methadone, methotrexate toxicity, oxycodone and tramadol.

♦ The provider will use his/her professional knowledge and judgment to interpret the test results and apply those results to the care of his/her patient. The consent form signed by the primary care managers will emphasize the option to consult with a pain specialist, if deemed necessary by the PCM.

♦ The subject will be scheduled for a follow-up appointment upon receipt of the Pain Medication and Mental Health DNA Insight Test. Prior to this visit (Visit 1(Group B) or Visit 3(Group A)) the subject will be asked to complete Appendices D, E, F, G, H, I, and J. At this visit the provider will discuss the test results with the subject and adjust or change the subject's medication as he sees necessary based on the genomic information. It is possible the medications will remain unchanged.

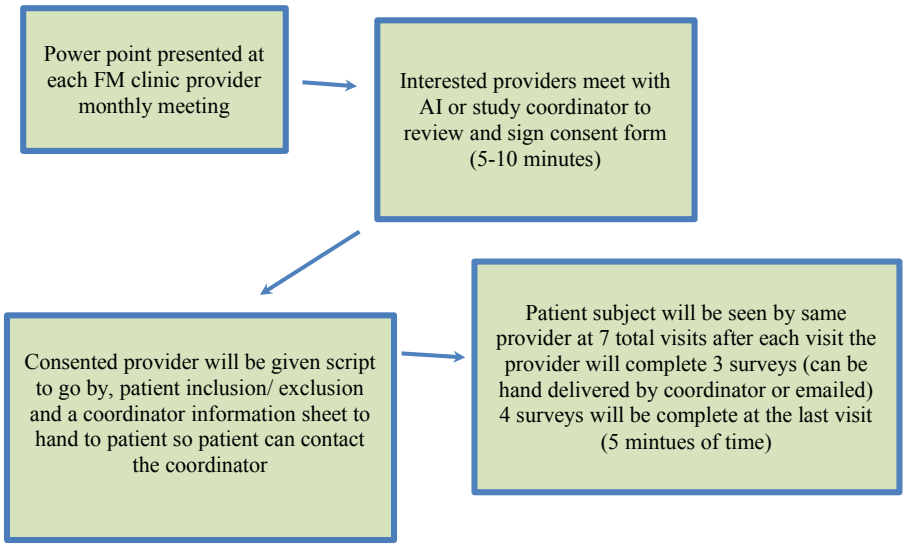
♦ After Visit 1 the subject will be asked to complete Appendix M, and the provider will be asked to complete Appendix N, O, and P.

♦ After implementation of the test results the subject will be scheduled to see the provider monthly for 6 months (Visit 2, 3, 4, 5, 6) and before each visit the patient subject will be

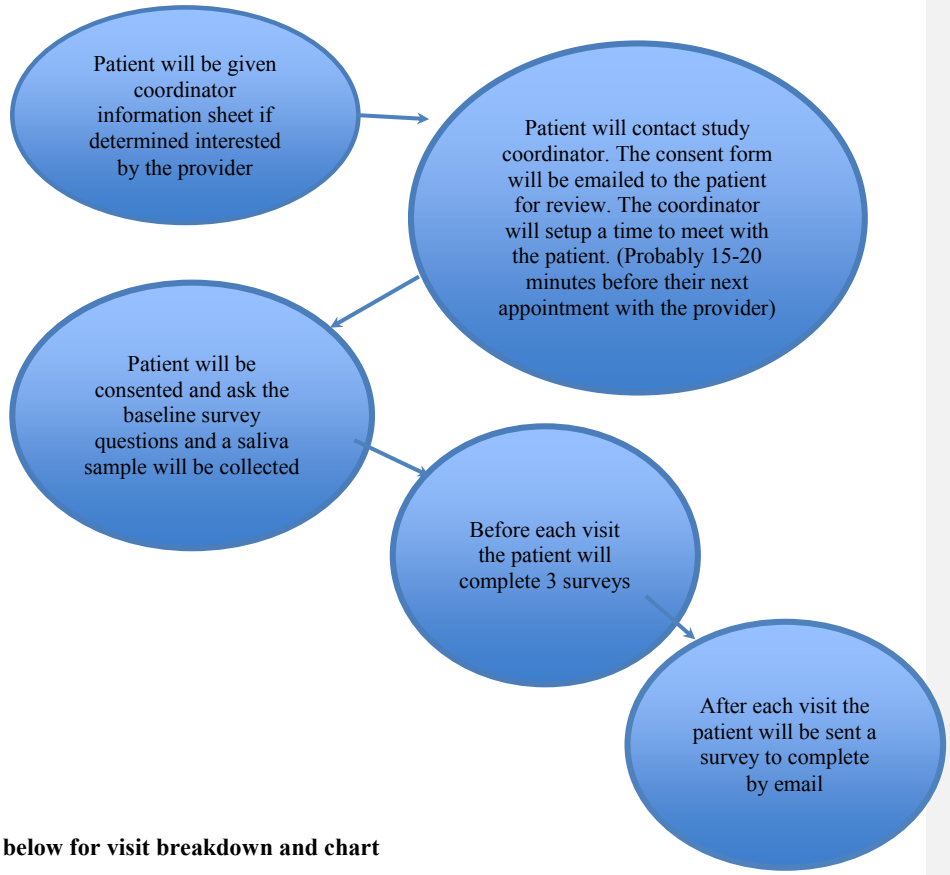
asked to complete Appendix D, E, F, G, H, I, and J. At each visit, the subjects' medications may be adjusted or changed as deemed necessary by the provider. After the visits the subject will be asked to complete Appendix M, and the provider will be asked to complete Appendix N, O, and P. At the last visit the provider will be ask to complete a question about provider usage (Appendix S).

♦ After the last visit (Visit 6), a member of the research team will query AHLTA to determine the patient's current analgesic medication regiment at the end of the study. The subject will asked at that visit what they are taking as well. All analgesics will be documented as a total daily dose and all opioids will be converted to daily oral morphine equivalents using the Hopkins Opioid Program (www.hopweb.org). These data will be entered onto the CRF.

Provider Diagram



Patient Diagram



See below for visit breakdown and chart

7.3.5 Data Collection Instruments:

Appendix 1: Provider Ad
Appendix 2: Patient Ad
Appendix 3: Coordinator Script
Appendix A: Provider Script
Appendix B: Coordinator Contact Information
Appendix C1: Provider Contact information
Appendix C2: Subject demographics and contact information
Appendix D: DVPRS side A and B
Appendix E: BPI-SF Perception of Relief Item
Appendix F: PROMIS SF v1.0 – Pain Interference-SF8a
Appendix G: PROMIS SF v1.0 – ED-Depression-SF8a
Appendix H: PROMIS SF v1.0 – ED-Anxiety-SF8a
Appendix I: Patient Perceptions of Care
Appendix J: Patient Global Impression of Change
Appendix K: Patient Medication Example List
Appendix L: Case Report Form
Appendix M: Patient Certainty, Confidence and Satisfaction
Appendix N: Provider Perception of Pain Care
Appendix O: Provider Global Impression of Change
Appendix P: Provider Certainty, Confidence and Satisfaction
Appendix Q: Medication list of acceptable analgesics
Appendix R: Sample genomics report for both
Appendix S: Provider Usage

References: See Section 6.1

7.3.6 Variables/Data Points:

Baseline (Visit 0):

<u>All subjects, regardless of group assignment</u>
Before visit with the provider

- Demographics (Appendix C), DVPRS (Appendix D), BPI perception of pain relief item (Appendix E), PROMIS short forms for pain interference (Appendix F), depression (Appendix G), anxiety (Appendix H)
- patient perception of care (Appendix I)
- patient global impression of change (Appendix J)

At the visit saliva sample is taken and sent for analysis

After visit with the provider
- certainty, confidence, satisfaction (Appendix M)

Provider
After visit with the subject
- certainty, confidence, satisfaction (Appendix P)
- provider perception of care (Appendix N)
- provider global impression of change (Appendix O)

Visits 1-6 (Group A receives test results at visit 3, Group B receives test results at visit 1)

Subjects
Before visit with the provider
- DVPRS, PROMIS short forms for pain interference, depression, anxiety, BPI perception of pain relief item
- patient perception of care
- patient global impression of change

After visit with the provider
- certainty, confidence, satisfaction

Provider
After visit with the subject
- certainty, confidence, satisfaction
- provider perception of care
- provider global impression of change
- provider usage (visit 6 only)

Table 1: Visit Chart

	Group A (Delayed)	Group B
Visit 0	Consent, saliva sample	Consent, saliva sample
Visit 1		Receive results
Visit 2		
Visit 3	Receive results	
Visit 4		
Visit 5		
Visit 6	Last visit	Last visit

At the end of the study patients' medications will be extracted from records and changes will be documented and analyzed. All opioids will be converted to oral morphine equivalents.

7.4 RISKS TO SUBJECTS:

There is little direct risk associated with the analysis of the patient's DNA. A patient will submit a saliva sample only, no invasive procedure is required. The sample will then be shipped to the testing site and results will be forwarded to the medical provider.

The only risk of data collection during the study is potential loss of privacy/confidentiality of enrollment in the study. The consent forms with the subject's name will be stored in a locked file cabinet in the research coordinator's office at WAMC. The master link between subject name and ID will be stored in a password protected excel file on the V drive at WAMC, with access limited to only the study team. This file will be separate from the file containing the collected data.

Analysis of personal genetic information potentially carries risk of future health insurance discrimination. The results of the DNA Insight Test will not become part of the patient's medical record and not be visible to potential future health insurers. While price discrimination based on genetic make-up is a theoretical risk, the nature of the information in the DNA Insight does not lend itself to discrimination by insurers.
As with any laboratory test, patients are exposed to the potential risk of results misinterpretation. In this case, misinterpretation could result in adverse medication effects up to and including death of the patient. When a clinician obtains test results, that clinician is expected to possess the appropriate knowledge and clinical judgment to accurately interpret the test and prudently act on those results. All primary care providers are trained on basic drug pharmacokinetics and pharmacodynamics during medical training. Primary care providers are expected to have knowledge of the CYP system and its genetic heterogeneities. Furthermore, primary care providers are expected to possess clinical judgment in deciding the appropriateness of specialty consultation. For this study, to address the potential risk of results misinterpretation, primary care providers will be provided with an information sheet reminding them of the availability of pain specialty consult. All analgesic dosing changes should be done with appropriate clinical judgment and prudence in accordance with standard of care for the practice of primary care medicine. Providers credentialed by Womack Army Medical Center are subject to this organization's strict and thorough credentialing process.

8.0 DATA ANALYSIS:

For this two-group design, a variety of self-report measures (confidence, certainty, etc.) will be taken up to a maximum of 8 repeated measures, including a baseline measure prior to the intervention. Given this variability where time is not a fixed factor insofar there may be variation for number of measures by individual and/or group a mixed linear modeling (or sometimes referred

to by the umbrella term: multilevel modeling-MLM) analysis will be conducted.[32] The advantage of a MLM approach is that it is sufficiently flexible insofar inter-individual variability on (1) time and (2) number of measures can be readily accommodated.[33] Moreover, in the context of a longitudinal design interindividual differences in intraindividual trajectories can be captured.[34]

When conducting a MLM analysis, the assumption is that there is a nested structure, and particularly for event-based studies, time (level 1-microlevel) will be nested within the patient (level 2- individual). For this study there are 12 provider groups with 4 patients nested within the groups, hence this could be cast as a 3-level model (time nested within patient nested within provider). However, one caveat is this is a very small sample size for MLM, and power may be a significant issue.[35] The viability of increasing the sample size or aggregating levels (if deemed appropriate insofar it does not compromise the integrity of the design) will be explored. A sequence of models will be examined, with the unconditional means model (no predictors) as the starting point, serving to compute the unconditional intraclass correlation coefficient (ICC), and hence capturing the extent of between-patient variability. Subsequent models will entail adding a variable that captures time, and then at the macro-level introducing the grouping (experimental vs. control) variable. If deemed appropriate, all time-invariant and time-varying predictors will be testing for significance ($\alpha = .05$) and moreover, the stochastic parameters (i.e., variance components) will also be examined: $\underline{u}_0$ and possibly $\underline{u}_1$ where $\underline{u}_0$ is the random coefficient for the intercept (i.e. initial basis) and $\underline{u}_1$ is the random coefficient for the slope. For the single-item ordinal-level outcomes the cumulative logit link function will be employed using residual maximum likelihood (REML) as the default estimator (otherwise the identity link function will be used for continuously measured outcomes).

Commented [1]: Can Peter address this sentence?

Selection of the best fitting model will be guided not only by the change in magnitude of the variance components, represented in part by the pseudo r^2 statistic[36], but also information-theoretic indices such as the Akaike Information Criterion (AIC) or Bayesian Information Criteiron (BIC), of which the model with the lower value evinces better fit[37]. All MLM analysis will be conducted using the HLM7.01 software.[38] Data cleaning, testing of assumptions and descriptive analysis will be performed in SPSS v. 22 or Stata v. 11.0. Moreover, as a basis of comparison (again keeping in mind small sample size) generalized estimating equations (GEE) will also be considered, with an unstructured working correlation matrix stipulated as the error variance/covariance matrix (though alternatives such as autoregressive with lag 1 (AR1) may be considered).

As for testing concordance of patients and caretakers, correlations will be computed as well as intraclass correlation coefficients (ICC) so as to assess the level of relationship between the patients and providers on like-items.

References: See Section 6.1

A database will be created in REDCap (Research Electronic Data Capture) after IRB approval. REDCap is a secure, web-based application for building and managing online surveys and databases. The data will be housed and secured on Defense and Veteran Center for Integrative Pain Management (DVCIPM) servers. Each patient will be allocated a study ID number, 01-48 and providers will be assigned study ID numbers 101-112, when they sign a consent form, and thereafter will be referred to by that number in the database. Investigators and research staff will have secure password protected access to RedCap in order to enter data.
The REDCap data will be extracted and sent to an outside DVCIPM statistician, for analysis. PHI will be removed before sending to the statistician.

9.0 MILITARY RELEVANCE:

Modern war fighters suffering from acute and chronic pain are often healing from multiple physical and psychological traumas. The National Defense Authorization Act of Fiscal Year 2010 (NDAA) mandated pain related research, including that attributable to injuries of modern warfare. The PMTF, convened by the OTSG of the Army stated in its Final Report that alternative therapeutics should be evaluated and incorporated into pain management practices across the DoD and VA health care continuum.[2] Prompt, effective and safe treatment of pain in the military population is a major healthcare goal. The treatment of both acute and chronic pain has received national attention.[19] Several media outlets have reported on the complex problem of adequately treating pain, while trying to minimize or eliminate the misuse potential of narcotic analgesics.[20-22] Furthermore, in an environment where downsizing and costs savings are required, the potential to save money on medical management and reduced adverse side effect related problems will become a major part of military healthcare in the coming years.

Chronic pain is the leading cause of medical boards across all services, and a major cause of unit attrition.[20-24] Treatment with invasive (i.e., surgery or radiofrequency) procedures is expensive and often impractical in theater, and has not been shown to reduce disability rates. By virtue of their younger age and high incidence of psychopathology (in veterans), service members are at higher risk than the general population for addiction and overdose from opioids.[26, 27] Adjuvants such as gabapentin and tricyclic antidepressants do not carry the same risks as opioids, but can affect cognition, cause psychomotor impairment, and are associated with other adverse effects (e.g. Weight gain) that may adversely impact service members. It is likely in the near future as genomic information becomes more easily obtained and interpreted that we would no more consider deploying a soldier without understanding their phenotypic response to common

medications used on the battlefield than we would allow them to deploy without knowing their blood type.

10.0 MEDICAL APPLICATION:

Personalized medicine is the ability to tailor therapy based on a patient's individual genotype. It helps eliminate the long and expensive process of trial and error, especially in the chronic pain population. This approach to medicine is being researched and utilized in the pharmaceutical industry across the globe. Genetic susceptibility has led to breakthroughs in treatment for numerous auto-immune and cancer related disease processes. Determining which patients will respond best to which class of opioids, with minimal side effects, will drastically improve the way pain medicine is practiced. Of significant importance, is the ability to reduce the risk of opioid addiction and overdose in our military beneficiary population.

11.0 BUDGET:
Will any outside organization provide funding or other resources?
☒ **Yes** The Company Pathway Genomics is funding the study and funds will be managed by the Henry M. Jackson foundation. A Statement of Work will be submitted.
☐ **No**

Item	Cost
Personnel	$90065
Supplies	$750
Other	1250
Travel	$6300
Publication costs	$2500
IRB fees	$2500
Total	$103365

12.0 HIPAA AUTHORIZATION:

i. Are you intending to collect subject's Protected Health Information (PHI) and any of the following

18 personal identifiers?
☐No – HIPAA does not apply – go to question #**iv**
☒Yes – please check which ones:

- ☒ 1. Names
- ☐ 2. Street address, city, county, 5-digit zip code
- ☒ 3. Months and dates (years are OK) and ages >89 (unless all persons over 89 years are aggregated into a single category)
- ☒ 4. Telephone numbers
- ☐ 5. Fax numbers
- ☒ 6. E-mail addresses
- ☒ 7. Social security number
- ☐ 8. Medical record number
- ☐ 9. Health plan beneficiary number
- ☐10. Account number
- ☐11. Certificate/license number
- ☐12. Vehicle identification number (VIN) and/or license plate number
- ☐13. Device identifiers and serial numbers
- ☐14. URLs (Uniform Resource Locators)
- ☐15. Internet protocol address number
- ☐16. Biometric identifiers, such as finger and voice prints
- ☐17. Full face photographic images or any comparable images
- ☐18. Any other unique identifying number, characteristic, or code such as patient initials

ii. Can you limit your collection of personal identifiers to just #2, 3 or 18 above?
☐Yes – then your dataset may qualify as a Limited Data Set – please contact usarmy.bragg.medcom-wamc.list.wamc-irb-admin@mail.mil. for further instructions before completing HIPAA authorizations or waivers thereof. Then go to question #**iv**.
☒No – Go to question #**iii.**

iii. Is obtaining patient Authorization "impracticable"?
☐Yes – Authorization may qualify to be waived by the IRB. Please contact usarmy.bragg.medcom.wamc-list.wamc-irb-admin@mail.mil. for instructions.
☒No – Research subjects will need to sign a HIPAA Authorization.

3. What precautions will you take to protect the confidentiality of research source documents (Case Report Forms, questionnaires, etc.), the research data file, and the master code (if any

Paper documents will be kept in a locked cabinet in a locked office area. Forms with names on them will be kept separate from data collection forms. Electronic files will be password protected and the master list will be kept in file separate from the data points. The master list will be destroyed 6 years after the end of the study. Only the study investigators and collaborators will have access to the research data

4. When will you destroy the research source documents, data file, and the master code?

6 years after the end of the study. All electronic data will be deleted from the computer system.

vi. Will research data including identifiable Protected Health Information be sent outside of WAMC?
☐Yes

☒No

5. Linkage of extracted data to other databases:

N/A

12.1 BENEFITS

The ability to identify how a patient will react to a medication based on their genetic make-up is a major advance for pain medicine. All too often, patients must endure months and years of adjustments in their medication regimen, many times resulting in inadequate pain control and/or intolerable side effects. Having the knowledge of how a patient will respond and metabolize a certain opioid or other pain medication before treatment is started, will lead to more effective medical care and higher patient satisfaction. This is the epitome of personalized medicine.

12.2 RISKS

There are little associated with the analysis of the patient's DNA. A patient will submit a saliva sample only, no invasive procedure is required. The sample will then be shipped to the testing site and results will be forwarded to the medical provider.

The only risk of data collection during the study is potential loss of privacy/confidentiality of enrollment in the study. The consent forms with the subject's name will be stored in a locked

file cabinet in the research coordinator's office at WAMC. The master link between subject name and ID will be stored in a password protected excel file on the V drive at WAMC, with access limited to only the study team. This file will be separate from the file containing the collected data.

12.3 HIPAA AUTHORIZATION WAIVER

If you wish to obtain and use identifiable protected health information for a study without obtaining written approval ("HIPAA Authorization") from the subject, please complete a HIPAA Authorization Waiver Form to provide justification for IRB review and approval. Contact usarmy.bragg.medcom-wamc.list.wamc-irb-admin@mail.mil. for assistance.

13.0 WAIVER OF THE REQUIREMENT TO OBTAIN INFORMED CONSENT: Note this section pertains to *obtaining* informed consent. Section 12.3(b) relates to *documenting* informed consent. All 3 of the following must be sufficiently satisfied in order for the IRB to waive this requirement. Double left click the box that applies and mark appropriately.

☐ **The research involves no more than minimal risk to the subjects** (For example, it is medical records research, risk is primarily psychosocial in nature, or attendant on breaches of privacy and confidentiality) **and,**

The waiver will not adversely affect the rights and welfare of the subjects (Explain how or why the waiver will not adversely affect the rights and welfare of the subjects, e.g. the subjects are no longer living) **and,**

The research could not practicably be carried out without the waiver. (Explain why the research could not be carried out without the waiver of informed consent. For example, it is impossible to contact the subjects or some of the subjects may no longer be alive.)

☒ Not applicable

13.1 WAIVER OF THE REQUIREMENT TO DOCUMENT INFORMED CONSENT: Note this section pertains to the *documentation* of informed consent. Documentation of informed consent can be waived by the IRB if it meets one of two criteria below. Double click the appropriate box and mark.

☐ 1. The only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality.

Each subject will be asked whether the subject wants documentation linking the subject with the research, and the subject's wishes will govern; or

☐ 2. The research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context. In cases in which the documentation requirement is waived, the IRB may require the investigator to provide subjects with a written statement regarding the research.

☒ 3. Not applicable.

14.0 IMPACT STATEMENTS:

Department/ Service	**Necessary for Which Proposals?**	**Indicate if this is required for your study.** If answered "yes", an impact statement from the Department or Service must accompany the protocol
Information Management Directorate (IMD)	Study involves use of the Internet and/or E-mail for patient recruitment and/or data collection; use of Web page design, data collection, or other Web-based applications	☐ Yes ☒No
Laboratory	Study involves laboratory staff or resources	☐ Yes ☒No
Nursing	Study requires any involvement of Nursing personnel paid by WAMC	☐ Yes ☒No If yes, complete the detailed Nursing Impact Statement found on the IRB Web site
Pharmacy	Study uses any drugs, IND or otherwise	☐ Yes ☒No
PAD/Medical Records	Study involves review of medical records	☐ Yes ☒No
Radiology	Study requires any radiological services	☐ Yes ☒No
Other	For example, a specific clinic, service or department **All family practice clinics including the WTU.**	☒ Yes ☐No

We will get impact statements prior to any provider recruiting at the individual clinics.

15.0 SIGNATURE:

I verify that the contents of this proposal are accurate and that I have read and agree to

comply with the statements above which outline my responsibilities as a Principal Investigator or Associate Investigator.

_____
Principal Investigator Signature
Name and Date: _____

15.1 OTHER SIGNATURES FOR APPROVAL:

I concur with the submission of this proposal to the Clinical Investigation Service for review and approval.

_____
Service Chief Signature
Name and Date: _____

_____
Department Chief Signature
Name and Date: _____

IRBnet Number: 409729-12
PI: MAJ Michael W. Bartoszek
Protocol Title: Patient and provider confidence and satisfaction with the clinical use of CYP genetic variability analysis to guide analgesic treatment: A randomized, controlled pilot study using the Pain Medication and Mental Health DNA Insight™ test.
Initial Date Submitted: 02/10/2015
Revision Date: 31 August 2016

Checklist of Support Documents that Must Accompany Protocol

☐ 1. **Protocol Application** Submit the entire protocol as a word document without signatures in order to allow track changes. Section 15 is the signature page(s). After it is completed, scan in as a pdf file and submit these pages as a "signature" file. Alternatively, you can submit a digitally signed word document.

☐ 2. **Investigator Letter of Support** Required for Principal Investigators, signed by the Department Chief or Directorate if PI is the Department Chief.

☐ 3. **Complete Impact Statement as applicable:**
a. Information Management Directorate (IMD)
b. Laboratory Impact Statement
c. Nursing Impact Statement
d. Pharmacy Impact Statement (required if study uses any drugs, IND or otherwise)
e. Pathology Impact Statement
d. Radiology Impact Statement
e. Examples may include specific clinic or service.

☐ 4**. Informed Consent Document if applicable** See section 13.0-13.1 above. Contact usarmy.bragg.medcom-wamc.list.wamc-irb.admin@mail.mil. for assistance.

☐ 5. **HIPAA Waiver Form, if applicable**

☐ 6. **Figures / Graphs / Appendices**

☐ 7. **Data Collection Sheets / Questionnaire**

☐ 8. **Cooperative Authorization and Development Agreement (CRADA)** If receiving outside funding, contact usarmy.bragg.medcom-wamc.list.wamc-irb-admin@mail.mil. for assistance. The Clinical Investigations Regulatory Office has final approval of this study.

☐ 9. **Conflict of Interest Statement** Must be completed for ALL Investigators

☐ 10. **Advertisement Materials, if applicable**

☐ 11. **Responsibilities of Principal Investigator and Associate Investigator** Section 3 and 16-18 must be signed.

☐ 12. **Copy of Curriculum Vitae (CV)** From Principal Investigator and all Associate Investigator(s). The IRB may request CVs from Collaborators depending on their role in the study.

☐ 13. **Certificate on Human Participant Protections Course for all Investigators**

Access at http://www.citiprogram.org/. Select New Users or login using previous username/password. Select Womack Army Medical Center as the Participating Institution. Training is good for 3 years.