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| **External Collaborator Proposal** *for* **eMERGE Network Analysis**  Project/Manuscript Concept Sheet | |
| **Reference Number** | NT294 |
| **Submission Date** | June 4, 2018 |
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| **Project Title** | **Discovery of candidate SNP biomarkers for predicting the risk for periprosthetic osteolysis and other adverse outcomes in joint arthroplasties** |
| **All Other Authors** | Participating senior FDA investigators:  Vahan Simonyan, PhD  HIVE- High-performance Integrated Virtual Environment Team Lead,  Center for Biologics Evaluation and Research,  Food and Drug Administration (CBER/FDA)  Tel: 301-796-7371  E-mail: [vahan.simonyan@fda.hhs.gov](mailto:vahan.simonyan@fda.hhs.gov)  Participating NHGRI/eMERGE investigators:  Gail Jarvik (GHC/UW, gjarvik@medicine.washington.edu )  David Carrell (GHC/UW, carrell.d@ghc.org )  David Crosslin (UW, davidcr@uw.edu )  Adam Gordon (UW, agordon1@uw.edu )  Jeffrey Stanaway (UW, stanaway@uw.edu )  Ken Borthwick (Geisinger, kmborthwick@geisinger.edu )  Frank Mentch (CHOP, mentchf@email.chop.edu )  Lyam Vazquez (CHOP, vazquezl@email.chop.edu )  Jennifer Pacheco (NU, japacheco@northwestern.edu ) |
| **Other eMERGE Sites Involved** | Any sites in the eMERGE Network willing to participate |
| **Background / Significance** | CDRH’s mission for providing access to safe and effective devices as well as CDRH-coordinated efforts for National System for health Technology Assessment (NEST) imply the need for strengthening evaluation of real-world device performance. New evidentiary approaches are needed for individualizing device-related risk-benefit assessment and facilitating a more predictive evaluation of device performance in patient subgroups.  By allowing to harness the recent advances in translational epidemiology, genetics/ genomics, and bioinformatics, novel *in silico* approaches can facilitate more effective multidisciplinary evidence synthesis pertaining to medical devices.  Our proposed *in silico* framework for synthesizing epidemiologic and genetic evidence (JAMIA 2016) is expected to deliver novel biomarkers and study endpoints that can be eventually implemented in both - clinical and regulatory - settings and thus can facilitate more precise device labeling and more effective prognostic/ therapeutic management in patient subgroups. |
| **Outline of Project** | As a continuation of our on-going pilot on hip arthroplasty, the proposed project will leverage the currently available SNP findings and will extend the *in silico* discovery of SNP candidates for adverse outcomes in orthopedic implants. Similar to the pilot, epidemiologic/clinical databases such as AHRQ/ HCUPNet will be employed for identifying the trends pertaining to orthopedic implant-related adverse outcomes (*e.g.,* periprosthetic osteolysis) in patient subgroups. As a main repository of clinical genetics data, eMERGE database will serve as a main source for the *in silico* discovery of SNP biomarker candidates which will be guided by the AHRQ-derived epidemiologic trends on implant performance in sex/race-stratified subgroups.  In-house High-performance Integrated Virtual Environment (HIVE) will be used for performing statistical analysis on SNP allele distribution, exploring putative correlations between SNPs and arthroplasty-related adverse outcomes, and visualizing the results. Other repositories of genetic/genomic data and analytic tools (*e.g.,* NCBI, Ingenuity Pathway Analysis, Ensembl, 1000 Genomes, *etc.*) will be used for performing further clinical/functional plausibility analysis of the identified SNP candidates.  As the main deliverable, the project is expected to identify SNP candidates that could be used for predicting pre-implantation risk for adverse outcomes as well as for developing diagnostic/prognostic measures for post-implantation patient management. |
| **Desired Variables**  *(essential for analysis*  *indicated by* ***\*****)* | Demographic Variables: Sex, Race/Ethnicity, and Age (the subject’s age will be defined as an integer variable in association with the timing of subject’s ICD codes for arthroplasty-related diagnoses and procedures)  International Classification of Diseases – ICD9/10 codes\* pertaining to the large joint arthroplasty procedures and the corresponding adverse health outcomes as follows:  - Mechanical loosening of prosthetic joint  - Dislocation of prosthetic joint  - Broken prosthetic joint implant  - Periprosthetic fracture around prosthetic joint  - Periprosthetic osteolysis  - Articular bearing surface wear of prosthetic joint  \*Note: the data dictionary with a full list of ICD9 and ICD10 codes is provided separately.  Genetic Variables: SNP alleles for subsequent genotype-phenotype analysis in subjects with and without arthroplasty-related adverse outcomes |
| **Desired Data** | eMERGE Phase III Array data (per the aforementioned variables) will be gathered form the participating eMERGE sites for a subsequent analysis by the HIVE/CBER-DEPI/CDRH team. After mapping subjects with various arthroplasty-related procedures and adverse outcomes, the subject-level demographic and phenotypic data generated by eMERGE sites will be transferred to the DEPI-CDRH and HIVE-CBER team. Next, subject-level SNP data in conjunction with corresponding demographic and phenotypic information will be generated by the HIVE team and transferred to the DEPI-CDRH team for the subsequent phenotype-genotype analysis and *in silico* evidence synthesis aimed at SNP discovery. |
| **Planned Statistical Analyses** | Data from the Nationwide Inpatient Sample of the Agency for Healthcare Research &  Quality (NIS/AHRQ) will be used for a retrospective analysis of the large joint arthroplasty related discharges as identified by ICD9/10 codes. STATA and SAS will be applied to compare the frequencies of arthroplasty related adverse outcomes (*e.g.,* osteolysis, fracture, loosening, *etc*.) in sex/race-stratified discharges. AHRQ-derived trends on the arthroplasty related adverse outcomes in patient subgroups will be then applied to the analysis and interpretation of eMERGE-derived SNP allele distribution in arthroplasty patients with and without adverse outcomes.  The eMERGE- derived SNP data and corresponding demographic and phenotypic information will be analyzed using in house HIVE – High-performance Integrated Virtual Environment platform and analytic/visualization tools (Team Lead – V. Simonyan, CBER/FDA; for more information on HIVE capabilities, please refer to the following open-access links: <http://blogs.fda.gov/fdavoice/index.php/tag/high-performance-integrated-virtualenvironment-hive/> ; <http://www.bio-itworld.com/2014/10/22/inside-hive-fdas-multi-omicscompute-architecture.html>).  Similar to the approach used in hip arthroplasty pilot, candidate SNPs will be identified by searching for differential allele distribution patterns in arthroplasty patients *with* adverse outcomes vs. their counterparts *without* adverse outcomes. HIVE analytics will be further applied for the analysis and visualization of putative SNP-adverse outcome associations and discovery of candidate SNPs that are predictive of arthroplasty-related adverse outcomes in various patient subgroups such as sex/race-stratified populations. |
| **Ethical Considerations** | Not applicable, as the project will utilize pre-existing data, with no access to identifiable personal information and no plans for contacting patients. |
| **Available Funding or Resources** | Currently available funding:  FDA/OWH (Office of Women Health) Special Funding Initiative (2017-2018): In silico research on sex differences in the biological responses and adverse events elicited by implantable devices/biomaterials (PI – Y. Torosyan, DEPI/CDRH)  Additional funding is potentially available per long-term research needs. |
| **Milestones\*\*** | eMERGE related milestones: Phase I (by Dec 31, 2018):  - map subjects with various large joint arthroplasties  - create a transferable dataset with the subject-level GWAS data and corresponding demographic and phenotypic information, using all currently available eMERGE data  - transfer the created dataset to the FDA team  FDA related milestones:  Phase I (by Dec 31, 2018):  - analyze NIS/AHRQ data to generate putative epidemiologic evidence on the sex/race-related trends pertaining to arthroplasty related adverse outcomes  Phase II (Jan 2019 – May 2019):  - adapt HIVE-based tools for the analysis and visualization needs pertaining to the created dataset on various large joint arthroplasties  - generate putative genetic evidence on candidate SNPs indicative of arthroplasty related adverse outcomes  - test biological plausibility and clinical applicability of the discovered SNP biomarkers, using *in silico* approaches  Phase III (Jun 2019 – Dec 2019):  - integrate the eMERGE-derived genetic evidence and AHRQ-derived epidemiologic evidence pertaining to arthroplasty-related adverse outcomes  - select candidate SNPs for their further validation as potential arthroplasty-related biomarkers, based on the integrated evidence streams  Phase IV (by May 2020):  - prepare national/international presentation(s) and a manuscript for publications on SNP biomarkers pertaining to joint arthroplasties  - identify new pharmacogenetic/ pharmacoepidemiologic research possibilities using pre-existing eMERGE data pertaining to medical devices and biomaterials |

***\*\**** *This section should include the timeline for completion of project, including: approval, project duration, first and second draft of the paper and submission.*