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| **External Collaborator Proposal** *for* **eMERGE Network Analysis**Project/Manuscript Concept Sheet |
| **Reference Number** | NT218 |
| **Submission Date** | 3/6/2017 |
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| **Project Title** | ***In Silico* Integration of Epidemiologic and Genetic Evidence on the Sex/Race-Related Modifying Effects on Hip Arthroplasty Outcomes** |
| **All Other Authors**  | **Vahan Simonyan, PhD**HIVE Team Lead,Center for Biologics Evaluation and Research,Food and Drug Administration (CBER/FDA)Tel: 301-796-7371E-mail: vahan.simonyan@fda.hhs.gov All eMERGE investigators are welcome to participate  |
| **Other eMERGE Sites Involved** | TBD by NIH/eMERGECHOP CCHMC ?Columbia Geisinger ?GHC/UW Harvard MarshfieldMayo Northwestern Vanderbilt  |
| **Background / Significance** | The current project is aligned with CDRH’s regulatory science initiatives and serves CDRH’s vision for National System for Medical Device Evaluation which can provide access to safe and effective devices and deliver “the right device to the right person”.As part of CDRH's regulatory research efforts for strengthening device evaluation, new evidentiary approaches are needed to individualize the device-related risk-benefit assessment and facilitate a more predictive evaluation of real-world device performance. This project will utilize novel *in silico* evidence synthesis approaches harnessing the recent advances in translational epidemiology, genetics/genomics, and bioinformatics. In addition to employing conventional data sources such as device registries, other pre-existing biomedical data sources will be explored for identifying device-related genetic/genomic data that can be used for discovery of new - reliable and measurable - study endpoints (*e.g.,* molecular biomarkers indicative of device performance in patient subgroups). As a result, this *in silico* approach is expected to enhance clinical and regulatory decision-making and promote device-related Precision Medicine applications. |
| **Outline of Project** | As part of the efforts for raising awareness of the need for finding cost/time-efficient solutions for device-related Precision Medicine applications, this project is intended to develop and propagate unconventional evidentiary and analytical approaches based on the re-utilization and re-purposing of disparate pre-existing data (e.g., epidemiological, clinical, 'omics, *etc.*) The current pilot is focused on hip arthroplasty and is aimed at *in silico* discovery of candidate SNP(s) that may differentially affect the hip arthroplasty related outcomes in sex/race-stratified subpopulations. |
| **Desired Variables** *(essential for analysis**indicated by* ***\*****)* | Demographic: 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 hip arthroplasty-related diagnoses and procedures)International Classification of Diseases – ICD9 codes (and their ICD10 equivalents, *not shown*) pertaining to hip arthroplasty with corresponding procedures and health outcomes:V43.64 Hip joint replacement (history)81.51 Total hip replacement 81.52 Partial hip replacement 81.53 Revision of hip replacement, not otherwise specified00.70 Revision of hip replacement, both acetabular and femoral components 00.71 Revision of hip replacement, acetabular component 00.72 Revision of hip replacement, femoral component 00.73 Revision of hip replacement, acetabular liner and/or femoral head only996.41 Mechanical loosening of prosthetic joint 996.42 Dislocation of prosthetic joint 996.43 Broken prosthetic joint implant 996.44 Periprosthetic fracture around prosthetic joint 996.45 Periprosthetic osteolysis 996.46 Articular bearing surface wear of prosthetic jointGenetic:eMERGE Phase III Array Data will be used for deriving subject-level SNP data and performing the subsequent genotype-phenotype analysis, using HIVE platform and analytic tools (see below) |
| **Desired Data** | ***Subject level*** data including the aforementioned demographic and diagnostic variables and corresponding GWAS data will be provided by the eMERGE sites and subsequently analyzed by the HIVE/CBER-DEPI/CDRH team. The demographic and phenotypic data on subjects with hip arthroplasty-related outcomes will be retrieved and provided by the eMERGE sites (see the data dictionary attached as Excel file). The subject-level genetic information on these subjects will be generated by the FDA-HIVE team after getting access to the corresponding eMERGE Phase III Array Data.  |
| **Planned Statistical Analyses** | Data from the Nationwide Inpatient Sample of the Agency for Healthcare Research & Quality (NIS/AHRQ) were used for a retrospective analysis of hip arthroplasty related discharges identified by the aforementioned ICD9 codes. STATA14 was applied to compare the hip arthroplasty related adverse outcomes (*e.g*., osteolysis, fracture, loosening, *etc.)* in sex/race-stratified discharges (*e.g*., White Males *vs*. White Females). The newly collected GWAS data and other available genetic/genomic 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, please refer to the following open-access links: <http://blogs.fda.gov/fdavoice/index.php/tag/high-performance-integrated-virtual-environment-hive/> ; <http://www.bio-itworld.com/2014/10/22/inside-hive-fdas-multi-omics-compute-architecture.html> ; <http://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=10&ved=0ahUKEwj_84bjgZDSAhWCOCYKHXoMAasQFghRMAk&url=http%3A%2F%2Fwww.fda.gov%2Fdownloads%2FScienceResearch%2FMeetingsConferencesandWorkshops%2FScienceWritersSymposium%2FUCM467971.pdf&usg=AFQjCNHRLgE2DPvZxFlPizrIl_NEHeMbmw> ).The AHRQ-derived frequencies for hip arthroplasty related adverse outcomes will be then analyzed in juxtaposition to the eMERGE-derived SNP allele distribution in hip arthroplasty patients. The GWAS data will be explored for differential allele distribution in hip arthroplasty patients with and without adverse outcomes (*e.g.,* V43.64 alone *vs.* V43.64 + 996.45, as patients with hip replacement and no reported adverse outcomes *vs*. patients with hip replacement complicated by periprosthetic osteolysis). HIVE analytics will be applied for the analysis and visualization of potential SNP-adverse outcome associations and discovery of putative sex/race-associated candidate SNPs that are predictive of hip arthroplasty related adverse outcomes. |
| **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): *In silico* research on sex differences in the biological responses and adverse events elicited by implantable devices/biomaterials (PI – Y. Torosyan, DEPI/CDRH)

Potential additional funding:* FDA grant applications including the upcoming National Evaluation System for health Technology Funding Opportunity Announcement (NEST FOA 2017)
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| **Milestones\*\*** | Pilot Phase (*Completed*):* to derive epidemiological evidence on the sex/race-associated modifying effects on hip arthroplasty outcomes
* to derive preliminary genetic evidence on candidate SNPs that may be associated with the adverse outcomes in hip-implanted patient subgroups (*i.e*., differential allele frequency in White Males with periprosthetic osteolysis)

Phase I (by Jul 2017): * to collect GWAS data, demographics, and ICD codes on subjects with hip arthroplasty using all available eMERGE data sources
* transfer the newly collected GWAS datasets to HIVE/FDA

Phase II (Jul 2017 – Dec 2017): * develop HIVE-based approaches to generation, harmonization, visualization and analysis of the collected GWAS data
* generate genetic evidence on putative candidate SNP biomarkers for hip arthroplasty related adverse outcomes
* analyze biological plausibility and clinical applicability of the newly discovered biomarker candidates, using pathway analysis and other *in silico* approaches

Phase III (Jan 2018 – May 2018): * to integrate the eMERGE-derived genetic evidence and AHRQ-derived epidemiologic evidence pertaining to hip arthroplasty
* to identify the hip arthroplasty related SNP biomarker candidates that can be pre-selected for further validation based on the integrated evidence streams and subsequent *in silico* analyses

Phase IV (by May 2019): * to prepare national/international presentation(s) and manuscript(s) for peer-reviewed publications
* to identify new pharmacogenetic/ pharmacoepidemiologic research possibilities and corresponding eMERGE genetic/genomic datasets pertaining to medical devices
* to develop and disseminate methodological recommendations for utilizing similar *in silico* framework and evidentiary approaches for various Precision/Stratified Medicine applications
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***\*\**** *This section should include the timeline for completion of project, including: approval, project duration, first and second draft of the paper and submission.*