**eMERGE Network Proposal for Analysis**

Project/Manuscript Concept Sheet

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| **Submission Date** | October 16, 2015 |
| **Project Title** | The identification and reporting of actionable incidental genetic variants from large scale clinical sequencing of drug response genes. |
| **Tentative Lead Investigator (first author)** | Quinn S. Wells |
| **Tentative Senior Author (last author)** | Iftikhar Kullo/Gail Jarvik |
| **All other authors** | Dan Roden, Sara Van Driest, Sarah C. Stallings  Other interested PGx investigators |
| **Sites Involved** | All sites |
| **Background / Significance** | The decreasing cost and widening availability of next generation technology has made high-throughput genetic sequencing an increasingly routine component in the clinical evaluation of suspected genetic conditions. As clinical sequencing becomes more widespread, there will be an obligatory increase in the number of incidentally identified variants that, while unrelated to the original indication for testing, may harbor pathologic potential. Jarvik, et al ([http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3791261/#](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3791261/)) found 585 instances of 239 unique variants identified as disease causing in the Human Gene Mutation Database (HGMD) in 1,000 adult individuals screened for variants in 114 genes associated with possibly undiagnosed medical conditions. Current American College of Medical Genetics and Genomics (ACMG) guidelines recommend return of all actionable incidental findings when a patient undergoes clinical genetic sequencing for any indication. The interpretation of, and appropriate response to, such findings is complex and controversial. |
| **Outline of Project** | Summarize incidental genetic findings and the process of their return at each of the participating institutions. |
| **Desired**  **Variables (essential for analysis**  **indicated by \*)** | Incidental PGRNseq-ascertained variants interpreted as pathogenic or likely pathogenic and possibly slated for return or actually returned at each site; clinical data for subjects; details of guidance for return and associated clinical care modifications. |
| **Desired data** | See above. |
| **Planned Statistical Analyses** | Qualitative (comparative variant lists, comparative return guidance and clinical care changes) and quantitative descriptive data will be reported. |
| **Ethical considerations** | None noted. |
| **Target Journal** | XXX |
| **Milestones\*\*** | October 2015: Obtain information from all sites  November 2015: Preliminary data review & request for more information as needed from contributing sites  December 2015: First draft of manuscript circulated  Early February 2016: Second draft of manuscript circulated  Mid February 2016: Manuscript submission |

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