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| **eMERGE Network: Manuscript Concept Sheet** |
| **Reference Number** *(to be assigned by CC)* | NT307 |
| **Submission Date** | 09/15/18 |
| **Project Title** | Risk of colorectal cancer and age of CRC onset associated with HFE C282Y/C282Y homozygosity |
| **Tentative Lead Investigator** *(first author)* | Gail P Jarvik |
| **Tentative Senior Author** *(last author)* | Gail P Jarvik |
| **All Other Authors**  | Lisa Bastarache, Adam Gordon, Melody Palmer, Elisabeth Rosenthal, David Crosslin, Ian Stanaway, Taryn Hall, David Carrell, Kathy Leppig, Lisa Bastarache, Agnes Sundaresan, Eric Larson, Marc Williams, Dan Roden |
| **Sites Participating** | All adult eMERGE sites (centralized analyses), may need age of onset of cancer from sites. |
| **Background / Significance** | Analysis of UW eMERGE-III data revealed an unexpected and significant enrichment of HFE (Hemochromatosis, *HFE* C282Y/C282Y homozygotes) among colorectal cancer patients compared to those without a cancer diagnosis, those with polyps only, and the published incidence of HFE. Previous epidemiological work has associated Hemochromatosis (HFE) with 2-3-fold increased risk of colorectal cancer (CRC) as well as breast cancer. Mechanistically, the increased iron load in these individuals is hypothesized to lead to a higher constitutive free-radical burden, promoting carcinogenesis. This association has not penetrated the clinical genetics or GI communities. We intend to evaluate the association of CRC and breast cancer in *HFE* C282Y/C282Y homozygotes across the eMERGE study, in addition to the Vanderbilt and possibly Geisinger (approval needed) biorepositories. Additionally, the relationship between hemochromatosis and colorectal cancer raises the question of appropriate colon cancer screening ages for patients with the risk of genotype. For that reason evaluation of whether age of onset of colorectal cancer is different among hemochromatosis risk genotype carriers versus noncarriers will be evaluated.REFS:Cancer risk in HFE C282Y homozygotes: results from the HUNT 2 study ARNE Åsberg, Ketil Thorstensen, Wenche ø. Irgens, PÅl R. Romundstad & Kristian Hveem Pages 189-195 | Received 06 May 2012, Accepted 15 Nov 2012, Published online: 03 Jan 2013 Download citation <https://doi.org/10.3109/00365521.2012.752028>[The risk of new-onset cancer associated with HFE C282Y and H63D mutations: evidence from 87,028 participants.](https://www.ncbi.nlm.nih.gov/pubmed/26893171) Lv YF, Chang X, Hua RX, Yan GN, Meng G, Liao XY, Zhang X, Guo QN. J Cell Mol Med. 2016 Jul;20(7):1219-33. doi: 10.1111/jcmm.12764. Epub 2016 Feb 19. PMID:26893171<https://www.ncbi.nlm.nih.gov/pubmed/26893171>[Association between hemochromatosis (HFE) gene mutation carrier status and the risk of colon cancer.](https://www.ncbi.nlm.nih.gov/pubmed/12529348) Shaheen NJ, Silverman LM, Keku T, Lawrence LB, Rohlfs EM, Martin CF, Galanko J, Sandler RS. J Natl Cancer Inst. 2003 Jan 15;95(2):154-9. PMID:12529348<https://www.ncbi.nlm.nih.gov/pubmed/12529348> |
| **Outline of Project** | 1. Extract genotype data to identify *HFE* C282Y/C282Y homozygotes
2. Review phenotype data in relevant individuals for diagnoses of hemochromatosis, colorectal cancer, likely using ICD9 codes for GWAS set and CRC derived phenotype for the eMERGESeq set
3. Statistical analysis below
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| **Desired Data - Common Variables\*** *(Available from the CC)* | [x] Demographics [x] ICD9/10 codes[ ] CPT codes[x] Phecodes hemochromatosis, CRC[x] BMI | [ ] Common Variable Labs[ ] Common Variable Meds[ ] Other: Case/Control status on Phase I and [ ] Phase II phenotypes |
| **Other Desired Data *(Available from participating sites)*** | *Please specifically list out any data elements that participating sites would collect or extract from clinical or other sources for this project (i.e. not common variables above)*  |
| **Desired Genetic Data** | [x] eMERGE I-III Merged set (HRC imputed, GWAS)[ ] eMERGE PGx/PGRNseq data set [x] eMERGEseq data set (Phase III)[ ] eMERGE Whole Genome sequencing data set[x] eMERGE Exome chip data set[ ] eMERGE Whole Exome sequencing data set[ ] Other (not listed above): |
| **Does project pertain to an existing eMERGE Phenotype?** | [x] Yes, if so please list: CRC [ ] No |
| **Planned Statistical Analyses** | Restrict to age > 50 Yrs. Stratify by sex (or add as covariate).Prediction of CRC by HFE in C282Y/C282Y homozygotes vs non-carriers that also do not carry the 63 minor allele. Covariates: sex, age of CRC onset, BMI (age 40 years), hemochromatosis diagnosis (phlebotomy status). For all cases of CRC (no age limit) contrast the age of onset of CRC between C282Y/C282Y homozygotes vs non-carriers that also do not carry the 63 minor allele. Describe distributions. |
| **Ethical Considerations** | none |
| **Target Journal** | Amer J Human Genetics |
| **Milestones***(This section should include the key dates for completion of project, including approval, project duration, draft completion, and submission.)* | Data by 11/18Analysis by 1/19Submit by 3/19 |

**\*Common Variables available across all datasets:**

* Demographics: sex, year of birth, decade of birth, race, ethnicity
* Codes: (repeated values & age at event): ICD, CPT, Phecodes
* BMI: (repeated value & age at event) height, weight, BMI
* Labs: (lab name, repeated lab value & age at event) Serum total cholesterol, LDL, HDL, Triglycerides, Glucose fasting/non-fasting/unknown, & White Blood Cell count