

Prospective Registry of Multiplex Testing (PROMPT): a web-based platform to assess cancer risk of genetic variants.

Michael Francis Walsh, Pragna Gaddam, Laura Digiovanni, Judith Balmaña, Jill S Dolinsky, Taylor Sittler, Rachel Klein, Stephen E Lincoln, Brian Allen, Justin Leighton, Charles Strom, Vanessa Ranger-Miller, Kyle Brown, Judy Ellen Garber, Fergus J. Couch, Susan M. Domchek, Mark E. Robson, Kenneth Offit; Memorial Sloan Kettering, New York, NY; Clinical Genetics Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY; University of Pennsylvania, Philadelphia, PA; Vall d'Hebron Institute of Oncology, Vall d'Hebron University Hospital, Barcelona, Spain; Ambry Genetics, Aliso Viejo, CA; Color Genomics, Burlingame, CA; GeneDx, Gaithersburg, MD; Invitae, San Francisco, CA; Myriad Genetics, Inc., Salt Lake City, UT; Pathway Genomics, San Diego, CA; Quest Diagnostics Nichols Institute, San Juan Capistrano, CA; PatientCrossroads, San Mateo, CA; Dana-Farber Cancer Institute, Boston, MA; Mayo Clinic, Rochester, MN; University of Pennsylvania Perelman School of Medicine, Philadelphia, PA; Memorial Sloan Kettering Cancer Center, New York, NY

Abstract Text:

Background: Multiplex genetic testing results in detection of pathogenic mutations of low, intermediate and high penetrance, as well as variants of uncertain clinical significance.

Methods: A web-based interface was constructed to allow individual patients and families who have had germline panel testing to consent to ongoing research under an IRB approved protocol. Phase one recruitment was facilitated by engagement of 7 commercial testing laboratories, genetic counselors, academic centers and crowd sourcing. Genetic variant, personal and family history, other phenotypic data were recorded. In phase two, individuals will be asked to consent to ascertainment of samples from family members for cosegregation studies, and collection of biospecimens for functional genomic analysis. Data collected will be deposited in public databases.

Results: As of January 14th, 2016, 1537 individuals from 4 continents have enrolled onto PROMPT. Of these, 34% had no personal history of cancer, 50% were diagnosed with breast cancer, 4% ovarian cancer, 3% colon cancer, 3% skin cancer, and 6% with other cancer types. Most of the cohort (94%) was female. Of 756 variants in the PROMPT database, 36.2% were pathogenic, 3.4% pathogenic or likely pathogenic, 2% likely pathogenic, 1.9 % likely benign, 1.6% benign, 14.4% alterations with conflicting interpretation, 1.9% other designations and 38.6% variants of uncertain significance. Genes most commonly reported as altered included: *ATM*, *CHEK2*, *BRCA2*, *PALB2*, *BRCA1*, *BARD1*, *CDH1*, *BRIP1*, *TP53*, *MSH6*, *MSH2*, *APC*, *NBN*, *RAD51C*, *MUTYH*, *PMS2*, *RAD50*, *PTEN*, *RAD51D*, *MLH1*, and *NF1*.

Conclusions: The first phase of PROMPT collected and classified genotypic and phenotypic information associated with variants detected by multiplex testing. Continued ascertainment is underway. The second phase of the study will entail segregation and functional studies. Cancer care providers and laboratories are encouraged to refer their patients to PROMPT. With ENIGMA, ClinVar, ClinGen and other efforts, web based registries such as PROMPT provide a means to assess both the frequency, as well as clinical validity and clinical utility of genomic variants detected by multiplex testing.