Genetics-Genomics Research Newsletter

Winter 2024

Newsletter

Welcome to the TPMG Genetics-Genomics Research Newsletter!

Here, we present current or recently completed research projects led by clinician researchers as well as ongoing studies led by investigators at the Division of Research (DOR) that involve our clinician researchers.

Conducting research to improve care is important to many KPNC TPMG clinicians and DARE is proud to provide our physicians with research collaboration opportunities through several DARE funding mechanisms.

In this issue, we will provide you with updates regarding research interests among TPMG clinicians and a list of the incredible recently published research.

A Deeper Look Inside This Update:

- Research Highlight
- Upcoming events & funding
- Specialty Announcements
- Active and recent research projects
- Recent peer reviewed publications

DARE Delivery Science and Applied Research

The Permanente Medical Group

Research Highlight:

Mainstream Germline Genetic Testing with Expanded Eligibility for Early Breast Cancer Patients in a Large Integrated Health System

Veronica Shim 1, Audrey Karlea 2, Leslie Manace Brenman 2, Jamila Gul 3, Elizabeth Hoodfar 4, Tracy D Chan 5, Poline C Engeman 6, Vanessa M Sheldon 7, Deirdre M Thorne-Hadfield 8, Patience Odele 9, Brooke Vuong 6, Jennifer McEvoy 7, C K Chang 5, Dinesh Kotak 10, Laurel A Habel

Background: This study evaluated a new mainstream genetic testing pathway for hereditary cancer, with expanded eligibility for early-stage breast cancer patients.

Methods: The study compared multigene panel (62 genes) germline testing uptake and results for breast cancer patients at 4 pilot sites (n = 502 patients) and 10 non-pilot sites (n = 1792 patients) within Kaiser Permanente Northern California from December 2020, to June 2021. At the pilot sites, breast care coordinators (BCCs) offered and consented patients for testing, with eligibility expanded to include all patients age 65 years or younger. At the non-pilot sites, eligible patients were referred to genetics for pre-test counseling, ordering, and follow-up evaluation with the standard guideline that included all patients age 45 years or younger.

Results: Demographic and disease characteristics were similar at the pilot and non-pilot sites. At the pilot verses non-pilot sites, a higher percentage of patients was tested overall (61.6% vs 31.7%) and across all age groups. The median time from breast biopsy to test result also was reduced (22 vs 33 days, respectively). A higher percentage of patients at the pilot sites was identified as having a pathogenic/likely pathogenic variant (PV/LPV) in a breast cancer-related gene (3.6% vs 1.6%). Although the percentage of total patients tested was nearly twofold higher at the pilot sites than at the non-pilot sites, the percentage of total patients seen by genetics was estimated to be similar (33.7% vs 31.7%).

Conclusion: Mainstream genetic testing of breast cancer patients facilitated by BCCs makes it feasible for a large health care system to expand germline genetic testing to early breast cancer patients age 65 years or younger.

Shim V, Karlea A, Brenman LM, et al. Mainstream Germline Genetic Testing with Expanded Eligibility for Early Breast Cancer Patients in a Large Integrated Health System. *Ann Surg Oncol*. Published online September 18, 2024. doi:10.1245/s10434-024-16223-7

Upcoming Events

ACMG American College of Medical Genetics

March 18-22 2025, Los Angeles
https://www.acmgmeeting.net/

ASHG American Society of Human Genetics

October 14-18, 2025, Boston
https://www.ashg.org/meetings/2025meeting/

Internal Funding & Research Resources

- **General Funding Opportunities**
- **Delivery Science and Applied Research**
- **Specialty Research Networks**
- **Getting Started with Research**
- **Division of Research**

Announcements

The Invitae lab interface and Epic Genomic Module will go live in early 2025! This pivotal technology development for Precision Medicine & Genomics enables improved access and care for our high-risk members with hereditary conditions. Genetics will be making the rounds to orient interest holders, and is eager to partner for workflow innovation and delivery science research: contact Dr. Leslie Manace Brenman to find out how this impacts your patient populations and teams.

Active or Recently Completed Research Projects and Collaborations (2022-2024)

- **Genome-wide Pleiotropy Scan across Multiple Cancers**

  Doug Corley | CH |Completed

- **Genetic and non-genetic factors affecting weight loss variability after bariatric surgery**

  Hélène Choquet | CH | Completed

- **Comparison of Preimplantation and prenatal genetic testing**

  Nikhil Joshi | Other | Ongoing

- **Up-Front Vs. Genetic Consultation for Genetic Testing Increases Compliance, Reduces Time to Test, and Increases Detection**

  Veronica Shim, Laurel Habel | TAP |Completed

Recent Peer Reviewed Genetics-Genomics - Authored Publications (2022-2024)

(1-13)

1. Choufani S, McNiven V, Cytrynbaum C, Jangjoo M, Adam MP, Bjornsson HT, et al. An HNRNPK-specific DNA methylation signature makes sense of missense variants and expands the phenotypic spectrum of Au-Kline syndrome. Am J Hum Genet. 2022;109(10):1867-84. Epub 20220920. doi: 10.1016/j.ajhg.2022.08.014. PubMed PMID: 36130591; PubMed Central PMCID: PMC9606382.

2. Grant N, Sohn YB, Ellinwood NM, Okenfuss E, Mendelsohn BA, Lynch LE, et al. Timing is everything: Clinical courses of Hunter syndrome associated with age at initiation of therapy in a sibling pair. Mol Genet Metab Rep. 2022;30:100845. Epub 20220202. doi: 10.1016/j.ymgmr.2022.100845. PubMed PMID: 35242576; PubMed Central PMCID: PMC8856919.

3. Katler QS, Stepien KM, Paull N, Patel S, Adams M, Balci MC, et al. A multinational study of acute and long-term outcomes of Type 1 galactosemia patients who carry the S135L (c.404C > T) variant of GALT. J Inherit Metab Dis. 2022;45(6):1106-17. Epub 20220926. doi: 10.1002/jimd.12556. PubMed PMID: 36093991; PubMed Central PMCID: PMC9643640.

4. Paul MS, Duncan AR, Genetti CA, Pan H, Jackson A, Grant PE, et al. Rare EIF4A2 variants are associated with a neurodevelopmental disorder characterized by intellectual disability,

hypotonia, and epilepsy. Am J Hum Genet. 2023;110(1):120-45. Epub 20221216. doi: 10.1016/j.ajhg.2022.11.011. PubMed PMID: 36528028; PubMed Central PMCID: PMC9892767.

5. Schwab ME, Lianoglou BR, Gano D, Gonzalez Velez J, Allen IE, Arvon R, et al. The impact of in utero transfusions on perinatal outcomes in patients with alpha thalassemia major: the UCSF registry. Blood Adv. 2023;7(2):269-79. doi: 10.1182/bloodadvances.2022007823. PubMed PMID: 36306387; PubMed Central PMCID: PMC9860434.

6. Slavotinek A, Rego S, Sahin-Hodoglugil N, Kvale M, Lianoglou B, Yip T, et al. Diagnostic yield of pediatric and prenatal exome sequencing in a diverse population. NPJ Genom Med. 2023;8(1):10. Epub 20230526. doi: 10.1038/s41525-023-00353-0. PubMed PMID: 37236975; PubMed Central PMCID: PMC10220040.

7. Tise CG, Verscaj CP, Mendelsohn BA, Woods J, Lee CU, Enns GM, et al. MT-ATP6 mitochondrial disease identified by newborn screening reveals a distinct biochemical phenotype. Am J Med Genet A. 2023;191(6):1492-501. Epub 20230308. doi: 10.1002/ajmg.a.63159. PubMed PMID: 36883293.

8. Török F, Tezcan K, Filippini L, Fernández-Quintero ML, Zanetti L, Liedl KR, et al. Germline de novo variant F747S extends the phenotypic spectrum of CACNA1D Ca2+ channelopathies. Hum Mol Genet. 2023;32(5):847-59. doi: 10.1093/hmg/ddac248. PubMed PMID: 36208199; PubMed Central PMCID: PMC9941835.

9. Berro T, Zayhowski K. Toward depathologizing queerness: An analysis of queer oppression in clinical genetics. J Genet Couns. 2024;33(5):943-51. Epub 20231025. doi: 10.1002/jgc4.1819. PubMed PMID: 37876321.

10. Jamal L, Zayhowski K, Berro T, Baker K. Queering genomics: How cisnormativity undermines genomic science. HGG Adv. 2024;5(3):100297. Epub 20240417. doi: 10.1016/j.xhgg.2024.100297. PubMed PMID: 38637989; PubMed Central PMCID: PMC11129102.

11. Sewani S, Azamian MS, Mendelsohn BA, Mau-Them FT, Réda M, Nambot S, et al. Neurodevelopmental and other phenotypes recurrently associated with heterozygous BAZ2B loss-of-function variants. Am J Med Genet A. 2024;194(3):e63445. Epub 20231023. doi: 10.1002/ajmg.a.63445. PubMed PMID: 37872713.

12. Sharaf RN, Udaltsova N, Li D, Pai RK, Sinha S, Li Z, Corley DA. Population-Level Identification of Patients With Lynch Syndrome for Clinical Care, Quality Improvement, and Research. JCO Clin Cancer Inform. 2024;8:e2300157. doi: 10.1200/cci.23.00157. PubMed PMID: 38838280.

13. Shim V, Karlea A, Brenman LM, Gul J, Hoodfar E, Chan TD, et al. Mainstream Germline Genetic Testing with Expanded Eligibility for Early Breast Cancer Patients in a Large Integrated Health System. Ann Surg Oncol. 2024. Epub 20240918. doi: 10.1245/s10434-024-16223-7. PubMed PMID: 39292401.