Variant of Unknown Significance Rates Vary by Ethnicity and Genes Analyzed

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As the uptake of multi-gene panel testing (MGPT) continues to increase worldwide, a primary concern of clinicians and patients is the possibility of variants of unknown significance (VUS). The VUS rate increases with expanding genomic content and ethnic diversity. We aim to define the likelihood of identifying a VUS on MGPT across five major ethnic groups: Caucasian, Ashkenazi Jewish, Asian, Hispanic, and African American. A retrospective review of over 40,000 patients undergoing MGPT for hereditary predisposition to cancer was performed at a single diagnostic laboratory. Ethnicity was indicated on test requisition forms. The rate of identifying one or more VUS was calculated for 10 different MGPTs ranging in size from 5-42 genes. Individuals with one or more VUS, including those who carried a pathogenic or likely pathogenic mutation were included. The number of individuals within each ethnic group varied from 1,873 Asians to 37,151 Caucasians. The likelihood of a VUS was consistently lowest for Caucasian and Ashkenazi Jewish individuals across all panels (Table 1). Asians showed the highest MGPT VUS rates on all panels except PancNext. The VUS rate for Lynch syndrome genes (MLH1, MSH2, MSH6, PMS2, EPCAM) across all panels was 6. 9% in Caucasians and 16. 4% in Asians. In BRCA1 and BRCA2, the VUS rate for Asians was 5. 7%, while the VUS rate for Caucasians was 2. 1%. Our results demonstrate that VUS rates for MGPT vary based on the patient's ethnic background and the number of genes analyzed. The specific genes analyzed also play a role, as genes differ in size and some tolerate more variability than others. For example, BreastNext has higher overall VUS rates than RenalNext despite both panels containing 17 genes. Availability of population frequency data also contributes to VUS rate variation by ethnicity, although these gaps will continue to improve with the use of public population frequency databases such as the Exome Aggregation Consortium (ExAC).

Table 1: VUS Rates (%) by Ethnicity and MGPT

MGPT	**# of Genes**	**Cauca-sian**	**African Ameri-can**	**Ash-kenazi Jewish**	**Asian**	**Hispanic**
BRCAplus	5	4. 4	8. 9	2. 6	13. 7	8. 0
GYNplus	9	10. 8	17. 0	15. 6	24. 5	15. 2
PGLNext	10	10. 9	33. 3	0. 0	28. 6	16. 0
PancNext	13	18. 0	39. 4	17. 1	27. 8	29. 4
Breast-Next	17	21. 5	37. 1	24. 7	42. 2	29. 0
ColoNext	14	16. 1	21. 6	16. 6	35. 7	29. 6
RenalNext	17	18. 0	30. 0	16. 7	47. 6	27. 3
OvaNext	23	27. 4	43. 0	27. 6	54. 3	37. 2
Can-cerNext	28	29. 9	48. 3	33. 1	59. 1	36. 8
Cancer Next-**Expanded**	42	39. 4	57. 1	41. 7	74. 4	52. 7