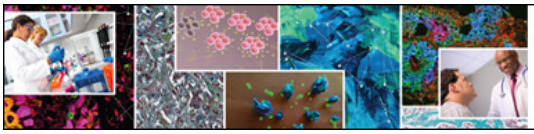

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Comparison of rare pathogenic germline variants associated with cancer predisposition syndrome in Taiwan and USA populations

Short Title:
Germline variants in Taiwan vs. US

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Abstract:
Objective To evaluate the analytical performance of a 98-gene NGS panel designed to detect highly- penetrant, rare pathogenic germline variants, strongly linked to predisposition of cancers in Taiwan and USA. **Methods** This 98-gene panel was developed following an extensive review of genes with a strong clinical and genetic linkage evidence for cancer predisposition. Probes covering the exon sequences from these 98 genes were validated using 19 samples obtained from the Platinum Genomes Project and the Genome In A Bottle Consortium. Analytical sensitivity and specificity for the detection of clinically important variants within multiple cancers types were demonstrated in 30 reference samples derived from patients with familial cancers. Additionally, two clinical cohorts of 1885 and 374 subjects from Taiwan and USA, respectively, were screened for detection of rare pathogenic germline variants in our CAP accredited laboratory in Taiwan, and CLIA certified laboratory in the USA. **Results** The analytical sensitivity and specificity of the assay panel were 99.95% and 100%, respectively. Similarly, the reportable variants for all 30 DNA samples containing clinically important SNVs in BRCA1/2, RET, APC, MEN1 and PTEN were called with no false positives. The concordance for the use of either blood (reference lab) or saliva (internal lab) as a sample source was found to be 99.9%. The mean age of the Taiwan cohort was 43, with 58% males and 42% females, while the US cohort had a mean age of 58 with 40% males and 60% females. Germline pathogenic variants were detected in 47/1885 (2.5%) and 25/374 (6.7%) individuals respectively. Outside of BRCA1 and BRCA2 positive cases in Taiwan (8.5% and 17%) and US (4% and 0%), the remaining germline positive cohort had pathogenic variants detected in MUTYH, MLH1, RET, ATM, APC, CHEK2, ERCC2, PALB2, PTCH1, WRN, BARD1, BRIP1, PMS2, PTEN, RAD51D, SDHD, RUNX1, BLM, HOXB13, and MSH6. Stratification of pathogenic variants among high risk and average risk individuals suggests these variants are distributed in both risk groups. Using a multigene approach, we identified 35/47 (87%) and 24/25 (96%) additional cases with rare pathogenic mutations respectively which would not have been identified if we were only looking for BRCA1/2 mutations. **Conclusion** We have demonstrated in 2 clinical cohorts the analytical and clinical validity of a 98-gene panel for the detection of pathogenic germline variants predisposing to cancer. High sensitivity and specificity of this panel was demonstrated irrespective of the use of blood or saliva as samples.
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Author Disclosure Information:

Z. Gulzar: ; CellMax Life. **J. Lucas:** ; CellMax Life. **A. Atkins:** ; CellMax Life. **S. Su:** ; CellMax Life. **O. Segurado:** ; CellMax Life. **R. Mei:** ; CellMax Life.
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