

Axiom PolMut1 - polish custom genetic test for cancer predispositions and other genetically determined diseases.

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The aim of the study was to develop a unique genetic test for the Polish population that would enable the detection of all known mutations associated with an increased predisposition to cancer and other genetically determined non-cancerous diseases. The test needed to be cost-effective, rapid, and widely accessible.

Based on available literature data and the results of our previous studies on high hereditary predisposition to cancer, a database of genetic variants (so-called genetic markers) present in the Polish population and linked to a predisposition to cancer and other non-cancerous diseases was created. Ultimately, 2,136 genetic markers were approved for genotyping after thorough scientific evaluation and technological consultation. These markers included pathogenic, likely pathogenic, and VUS (variants of uncertain significance) variants in cancer-predisposing genes, non-cancer disease genes, as well as variants in microelement-metabolism genes, and markers for the breast cancer polygenic risk score (PRS 313).

In the subsequent step, microarrays (under the acronym PolMut1; Thermo Fisher Scientific) containing the selected genetic markers were designed and manufactured, followed by large-scale DNA genotyping. The PolMut1 microarray study included 5,376 genomic DNA samples. Among the genotyped samples, 104 contained previously detected and confirmed pathogenic or likely pathogenic variants in one of the following cancer-predisposing genes: *ABRAXAS*, *ATM*, *BLM*, *BRCA1*, *BRCA2*, *BRIP1*, *CHEK2*, *MLH1*, *MSH2*, *MSH6*, *MUTYH*, *PALB2*, *PMS2*, *RAD50*, *RAD51C*, *STK11*, *TP53*, and *VHL*. These samples served as ‘positive’ controls for analysis using the PolMut1 microarray. Other samples were from individuals with a family history of cancer (HBC/HBOC/HOC, CFA, HNPCC, HPC, HSC, Familial MM syndromes), with approximately 3,800 individuals affected by cancer.

Quality control (QC) assessment revealed that genotyping using the PolMut1 microarray passed QC with a sample pass rate of 98.1% and an average QC call rate of 99.6% (thresholds were set at $\geq 95\%$ and $\geq 98.5\%$, respectively). Results from genotyping ‘positive’ controls showed that the PolMut1 array confirmed 87% of the variants. The remaining 13% will be sequenced to investigate the reasons for non-compliance.

Additionally, we plan to verify all detected variants using Sanger sequencing, identify variants that may correlate with cancer incidence and other diseases, and calculate PRS 313 for the Polish population. Ultimately, we aim to establish whether analysis using the „Axiom PolMut1” array has scientific and diagnostic value.

Funding: research task carried out within the framework of the programme of the Minister of Science and Higher Education called ‘Regional Excellence Initiative’ in the years 2019-2022 project number 002/RID/2018/19 amount of funding 12 000 000 PLN.