Breast cancer affects more than 20 thousand women in Poland per year and is the second most common, after lung cancer, cause of death resulting from any cancer. Ovarian cancer is less frequent, with 4 thousand cases annually, but much more lethal with 2.7 thousand women dying due to this disease per year. The major factors which increase the risk of both malignancies and affect their treatment are mutations of *BRCA1*, *BRCA2* and other DNA damage repair-associated genes.

BRCA1 and *BRCA2* are key players in DNA damage repair through the homologous recombination (HR) pathway, which allows the cells to repair breaks of both strands of genomic DNA due to internal or external stress factors such as radical oxygen species (ROS) or ionizing radiation. Inherited mutations of these genes, present in all cells of an individual's body, affect the cells' capability to initiate or conduct HR leading to alternative, more erroneous pathways being used for repair. These are more error-prone, lead to the accumulation of mutations and ultimately development of cancer. Carriers of mutations in either gene are prone to the rapid progression of malignancies, with few clinical symptoms observable in the early phases. Moreover, once *BRCA1/2* tumors develop they are often resistant to hormonal and/or targeted therapies such as anti-HER2 drugs. However, the presence of *BRCA1/2* mutations makes the cancer cells susceptible to synthetic lethality – exploiting of the DNA repair deficiencies, which makes the prompt identification of those vulnerabilities crucial for optimal choice of treatment.

The lack of effective tests for the development of malignancies or diagnosing them in early, curable stages make the core concept of the project innovative and clinically-relevant. One method of identifying HR-deficient (HRD) individuals is using microRNAs circulating in the serum as biomarkers of this state. In prior studies, our team has shown that mutations of *BRCA1/2* lead to altered expression levels of multiple miRNAs and allow for the design of a clinically-viable classification model. Moreover, the expression patterns of circulating microRNAs were also reported to have diagnostic capabilities for multiple tumors, including ovarian cancer. The overlap of DNA repair and malignancy signatures is, however, unknown and hinders the formulation of clinically-feasible diagnostic tests. This issue will be resolved through the activities of this project, which will lead to the design of a simplified, robust diagnostic test for malignancies in high risk individuals.

The project's aims will be achieved through a prospective cohort study conducted during this project and a comparison between *BRCA1/2* mutation carriers and mutation-free individuals of already assembled cohorts of patients with high familial risk of cancer. We also plan to perform a functional validation of the defined HRD signature and convert the test onto qPCR level (a cheap, accessible microRNA quantification technique) to allow for widespread clinical use of a cheap diagnostic test. Subsequently, we will perform repeated testing of microRNAs' levels in periodically-collected samples and associate them with the development of malignancies. Ultimately, this will enable us to determine the predictive potential for a microRNA-based surveillance program for high risk individuals.