

## Genetic diagnostics in endometrial cancer – implications for treatment and genetic counseling

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### Introduction

Endometrial cancer (EC) is the most common cancer of the female reproductive organs in higher-income countries. Known risk factors for developing endometrial cancer include obesity, physical inactivity, ageing, diabetes, and oestrogen hormone replacement therapy. Thanks to large-scale studies, endometrial cancers have been divided into four molecular subtypes: POLE (5%), MMRd/MSI-H (30%), CNlow/NSMP (45%), and p53/CNhigh (20%). Each of these subtypes is characterised by a different prognosis and opportunities for optimal therapy. Currently, the diagnosis of molecular subtypes of endometrial cancer can be performed using the PROMISE algorithm (immunohistochemical (IHC) assessment of the expression of the following proteins: MSH2, MSH6, PMS2, MLH1, TP53, and genotyping of mutations in the POLE polymerase exonuclease domain) or using a comprehensive algorithm, i.e., next-generation sequencing (NGS), which covers coding sequences in the following genes: *POLE*, *MSH2*, *MSH6*, *PMS2*, *MLH1*, *TP53*, *KRAS*, *PIK3CA*, *BRCA1/2*, *CTNNB1*, and *POLD1*, and immunohistochemical assessment of protein expression as in the PROMISE algorithm, or only assessment of microsatellite instability (MSI) using PCR and capillary electrophoresis.

### Aim

The aim of the study was to conduct a retrospective analysis of endometrial cancer diagnostics performed between 2022 and 2025.

### Material and Methods

Between 2022 and 2025, 767 patients with endometrial cancer were tested by NGS + IHC (610 tests) or NGS + MSI (157 tests) using DNA isolated from cancer tissue samples after hysterectomy.

### Results

Applying an advanced algorithm (NGS + IHC), the following proportion of molecular subtypes were detected: POLE 7%, MSI-H (33%), CNlow (48%) and CNhigh (12%) in 610 cases. The recent application of the advanced NGS + MSI algorithm in 157 cases showed the following percentages of subtypes: POLE 3%, MSI-H (37%), CNlow (45%) and CNhigh (15%).

In addition to the genes needed to qualify a patient for a given molecular subtype, other genes of predictive significance (*MSH2*, *MSH6*, *PMS2*, *MLH1*, *BRCA1/2*, *PIK3CA*, *KRAS*) were also tested. Mutations in the *KRAS* gene were detected in 171/767 (22%) of the analysed

cases, including *KRAS* G12C mutations detected in 9/767 (1%). Mutations in the *PIK3CA* gene were detected in 370/767 (48%). The results obtained indicate the possibility of using molecularly targeted therapy, i.e. small molecule kinase inhibitors, in almost half of the patients (49%).

In 128 cases, mutations in genes associated with hereditary syndromes (BRCA-associated and Lynch syndrome) predisposing to malignant tumours were detected in endometrial cancer tissue. Seventy (55%) patients were referred to the Genetic Clinic of the Holy Cross Cancer Centre, which enabled verification of the mutations detected in the tumour tissue on a blood sample. Mutations in the blood were confirmed in 15 (21%) cases and in the following proportion in individual genes: *BRCA1* (2/7), *BRCA2* (1/16), *MLH1* (0/6), *MSH2* (1/13), *MSH6* (11/23), *PMS2* (0/5).

### **Conclusions**

Comprehensive diagnostics, in addition to molecular subtype classification, also enables the stratification of patients for targeted therapies and increases the possibility of detecting carriers of hereditary mutations in genes associated with Lynch syndrome and BRCA-associated syndromes.