# Improving Endometrial cancer assessment by combining the new techniqUe of GENomic profiling with surgical Extra Uterine Disease Assessment

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EUGENIE aims to bridge the knowledge gap. As up till now disease stage was the most important prognostic factor, we aim to improve the molecular risk classification system by integrating the disease stage into the molecular subgroups. As a first...

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| **Ethical review** | Approved WMO |
| **Status** | Pending |
| **Health condition type** | Metastases |
| **Study type** | Observational invasive |

## Summary

### ID

NL-OMON57465

**Source**
ToetsingOnline

**Brief title**
EUGENIE

### Condition

- Metastases

**Synonym**
endometrial cancer

**Research involving**
Human

## Sponsors and support

**Primary sponsor:** UZ Leuven
**Source(s) of monetary or material Support:** Ministerie van OC&W

## Intervention

**Keyword:** Endometrial Cancer, Genomic profiling, Uterine

## Outcome measures

### Primary outcome

Study objectives:

The primary objective of the study is to investigate the disease spread pattern for each molecular group. This knowledge will tailor surgical staging procedures and optimize adjuvant treatment guidance. The secondary objective is to investigate the association between disease stage and prognosis in each molecular subgroup. We additionally aim to improve the current risk classification system by integrating disease stage and molecular classification allowing a more accurate estimation of the risk of recurrence or overall survival in EC patients.
Finally, we want to explore the association between molecular subtype and site of metastasis (lymph nodes, peritoneum, omentum, and/or systemic), considering both metastasis at diagnosis and as recurrence.

Primary objective:

The primary objective is to determine the association between molecular classification and disease stage.

Molecular type consists of four molecular subgroups (POLE-ultra mutated (POLE),

p53 abnormal (p53abn), mismatch repair deficient (MMRd), and nonspecific molecular profile (NSMP).

Disease stage is based on the number and type of upfront metastatic disease and contains the following levels: IA-IB; II A-IIB; III A IIIB IIIC; IVA IV B

The primary endpoint is the prevalences of the disease stages at diagnosis in each molecular subgroup.

**Secondary outcome**

The secondary objective is to evaluate if and how the disease stage in each of the molecular subgroups associates with prognosis.

Endpoints studied are time to recurrence and overall survival.

Time to recurrence is the time between diagnosis and first recurrence or death of any cause. Patients alive and without recurrence are censored at their last follow-up.

Overall survival is the time between diagnosis and death of any cause. Patients alive are censored at their last follow-up.

Site of recurrence will be studied as an exploratory time to event endpoint.

This endpoint is defined as the time between diagnosis and first recurrence, with site of recurrence (lymph nodes, peritoneum, omentum, and/or systemic) as competing events. Patients without recurrence are censored at their last follow-up.

# Study description

## Background summary

Endometrial cancer (EC) is the most common gynaecologic malignancy in developed countries. In Belgium, ~1500 patients are diagnosed with EC each year. Current treatment for EC includes a hysterectomy with bilateral salpingo-oophorectomy. Further surgical staging procedures (lymphadenectomy, peritoneum, and/or omentum biopsies) can be performed, might detect metastases, and determine the disease stage. The type and extent of this surgical staging depend on a pre-operative risk assessment and guides adjuvant treatment (chemo- or radiotherapy). However, this pre-operative risk assessment based on histology and imaging is relatively inaccurate. This strategy is far from optimal for several reasons. First, preoperative histology presents high intersubjective variability leading to poor reproducibility in the assignment of histotype, particularly in high-grade tumours.(1) Moreover, its concordance between preoperative histology and final histology is poor, as it does not correspond in ~33% of cases, most likely due to superficial sampling and tumour heterogeneity.(2,3) In addition, preoperative imaging modalities are expensive, time-consuming, hampered by non-perfect accuracies, require specialized expertise, or present limitations in reproducibility and availability.(4) As a result, this leads to an incorrect risk estimation of metastases at diagnosis in EC patients. In particular, the risk of metastasis in low- and intermediate-risk patients (representing 80% of EC patients) is underestimated, as 10-15% of these patients develop recurrent disease.(5-8) Also, not all intermediate-high and high-risk patients present with metastases at diagnosis, and ~50% of these patients do not recur. The suboptimal risk estimation of metastases at diagnosis results in an important over- and undertreatment of patients (2, 3) and inaccurate clinical trials.(9,10) Thus, there is an urgent need to develop risk stratification strategies that will better predict the presence and localization of metastases in EC patients, and therefore more efficiently tailor surgical staging procedures.
In 2013 The Cancer Genome Atlas (TCGA) Research Network developed a new molecularly driven classification system, that divides EC tumours into four molecular subgroups (POLE-ultra mutated (POLE), p53 abnormal (p53abn), mismatch repair deficient (MMRd), and nonspecific molecular profile (NSMP). The molecular classification has shown to surpass histologic subtyping and grading to more efficiently predict prognosis and has the potential to represent a paradigm shift in the management of EC patients.(11)
However, the relation between the four molecular subgroups and the risk of tumour spread beyond the uterus at diagnosis has insufficiently been investigated so far. It has been stated that the future is molecular and that surgical staging will be of reduced relevance. As a result, the new classification is being quickly incorporated, and the use of staging surgery to assess the presence of metastases dissuaded. This is incomprehensible, as the presence and localization of metastases (disease stage) have until now been the most important predictor of prognosis, and its impact on each of the four risk subgroups is so far not known.

We believe that the future is in integrating morphologic and molecular findings, so the preoperative diagnosis will also support accurate surgical decision making. If the new molecular classification is fully implemented without knowing the importance of the disease stage at diagnosis in each of the molecular subgroups, it will be extremely difficult, if not impossible, to investigate this in the future. By replacing the traditional classification (based on histotype and stage) with the molecular classification alone, we will lose important information and therefore propose to integrate stage and molecular classification.

## Study objective

EUGENIE aims to bridge the knowledge gap. As up till now disease stage was the most important prognostic factor, we aim to improve the molecular risk classification system by integrating the disease stage into the molecular subgroups. As a first step, we will prospectively collect the unique data of a large cohort of EC patients who are all fully staged. We will then evaluate if the disease stage is associated with the molecular type. This will determine the indicated surgical procedure in each subgroup. Secondly, we will assess how the information on stage combined with molecular type relates to prognosis. These data will inform us about the need for adjuvant treatment for each combination of stage and molecular subgroup. The results of the project will eventually lead to an integrated, personalized management of all EC patients.

## Study design

EUGENIE is a prospective multicentre study including 1,000 EC patients. Patients will be included during the first four years of the study and the follow-up will be two-six years. Patients with FIGO stage I-IV EC will be enrolled. A surgical staging procedure will be performed, including a hysterectomy with bilateral salpingo-oophorectomy (BSO) and assessment of lymph nodal and peritoneal/omental metastases. The molecular classification will be determined on the tumor sample. Adjuvant treatment will be proposed based on patient characteristics, pathology, and stage, according to European guidelines and local practice. Follow-up is as in routine practice and will be documented at least for two years after treatment. The primary objective is to determine the association between molecular classification and the disease stage. The secondary objective is the association between disease stage in each of the molecular subgroups and prognosis.

## Intervention

NA

## Study burden and risks

Extent of the burden and risk associated with participation are minimal.

There is an urgent need to develop risk stratification strategies that will better predict the presence and localization of metastases in EC patients, and therefore more efficiently tailor surgical staging procedures.

## Contacts

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## Trial sites

### Listed location countries

Netherlands

## Eligibility criteria

**Age**
Adults (18-64 years)
Elderly (65 years and older)

### Inclusion criteria

1. Voluntary written informed consent of the participant or their legally authorized representative has been obtained before any screening procedures
2. Women >= 18 years
3. First diagnosis of EC, all disease stages and all histo-types

### Exclusion criteria

1. Participant has a history of pelvic or para-aortic lymph node dissection or sampling, previous pelvic (and/or para-aortic) radiotherapy, previous neoadjuvant chemotherapy
2. Any disorder, which in the Investigator*s opinion might jeopardise the participant*s safety or compliance with the protocol
3. Any prior or concomitant treatment(s) that might jeopardise the participant*s safety or that would compromise the integrity of the Study

## Study design

### Design

**Study type:** Observational invasive

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| Masking: | Open (masking not used) |
| Control: | Uncontrolled |
| Primary purpose: | Diagnostic |

### Recruitment

NL

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|---|---|
| Recruitment status: | Pending |
| Start date (anticipated): | 15-12-2024 |
| Enrollment: | 160 |
| Type: | Anticipated |

## Ethics review

Approved WMO

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| Date: | 07-05-2025 |
| Application type: | First submission |
| Review commission: | METC NedMec |

## Study registrations

## Followed up by the following (possibly more current) registration

No registrations found.

## Other (possibly less up-to-date) registrations in this register

No registrations found.

## In other registers

| Register | ID |
| --- | --- |
| ClinicalTrials.gov | NCT06354738 |
| CCMO | NL88029.041.24 |