Implementation of Endometrial Cancer TCGA Classification Using ProMisE: Experience at a Tertiary Care Center

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Background

In 2013, The Cancer Genome Atlas (TCGA) identified 4 prognostic groups of endometrial carcinomas (EMCA). The ProMisE algorithm employs IHC where possible, rendering the TCGA classification more accessible, which has been endorsed by the WHO. Other recent consensus guidelines also encourage molecular testing in EMCA (NCCN, European Society of Gynaecological Oncology), thus guiding the clinical application of EMCA classification into the 4 prognostic groups:

- *POLE* mutated
- Mismatch repair deficient (MMRd)
- p53 wild-type/No specific molecular profile (NSMP)
- p53 abnormal

Here we describe the de novo implementation of EMCA testing at one tertiary care center and the related results utilizing the Exploration, Preparation, Implementation, Sustainment (EPIS) framework (Figure 1).

Design

Following a request from our gynecologic oncology group to establish an in-house EMCA molecular testing protocol, we assembled a multi-disciplinary task force to identify need for testing and barriers, as well as solutions (Exploration and Preparation). Testing was launched in November 2020. As of July 2021, 121 EMCA had undergone this new testing protocol of IHC and next-generation sequencing (Figure 2).

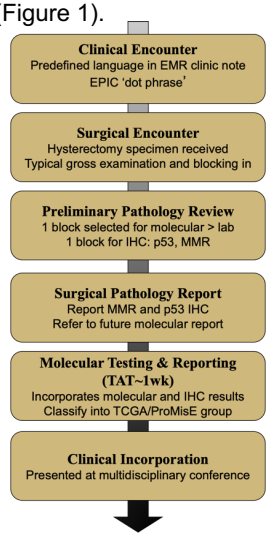
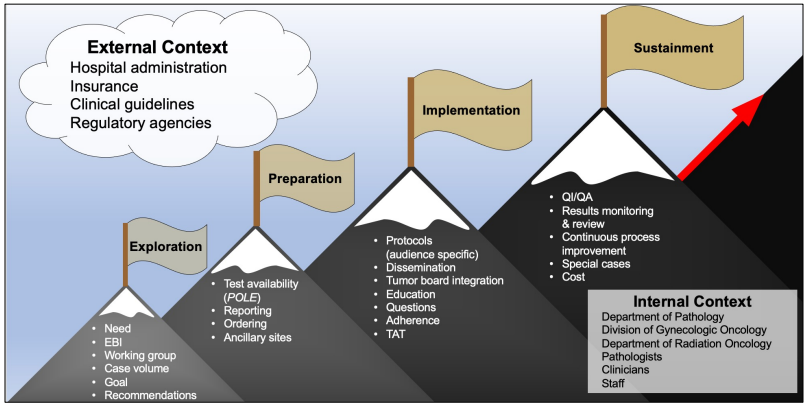


Figure 2: EMCA Testing Protocol

Figure 1: EPIS Framework



Results

The Sustainment phase includes tracking the distribution of molecular subtypes and histotypes (Table 1). There were 9 dual classifier cases:

- 2 *POLE*-p53
- 7 MMRd-p53

Notably, 13 cases (11%) harbored *TP53* mutations but were p53 IHC wild-type (wt); all were endometrioid:

- 7 (54%): dual classifiers (6 MMRd-p53, 1 *POLE*-p53)
- 6 (46%): single classifier, grade 1 endometrioid

Histotype	*POLE* n (% of *POLE*)	MMRd n (% of MMRd)	NSMP n (% of NSMP)	p53 n (% of p53)	Dual Classifier n (% of dual)
Endometrioid	5 (100)	29 (96)	50 (98)	7 (27)	7 (8)
Serous	0 (0)	0 (0)	0 (0)	8 (31)	0 (0)
Carcinosarcoma	0 (0)	0 (0)	1 (2)	9 (35)	1 (1)
Undiff/Dediff	0 (0)	1 (3)	0 (0)	1 (4)	0 (0)
Total (% of all cases)	5 (4)	30 (25)	51 (42)	26 (22)	9 (7)

Table 1: ProMisE group and EMCA histotype

Results

13% of all endometrioid carcinomas were p53 discordant, an unexpected result calling into question whether these cases, in particular endometrioid grade 1, stage I, should be classified in the p53 group. Further investigation of the *TP53* mutations suggests approximately 2/3 of discordances may be attributable to subclonality, indicating that the *TP53* mutation may be a consequence of underlying pathobiology rather than a truncal event.

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Conclusion

The highly anticipated results from the ongoing PORTEC 4a trial of molecular profile-based adjuvant therapy will inform standardized, specific, practical recommendations for EMCA testing and reporting. This study describes the implementation process at one tertiary care center using the EPIS framework and the results through July 2021, including a subset of low-stage, low-grade endometrioid carcinomas that are *TP53* mut, yet p53 wt, an unexpected result.

References

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