Early Stage Endometrioid Endometrial Cancer Recurrence Risk Stratification Using a Machine Learning RNA-Seq Gene Expression Signature

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INTRODUCTION

Early stage endometrioid endometrial cancer (EEC) adjuvant therapy decisions rely on risk stratification using histology, grade, stage, and lymphovascular space invasion (LVSI). Recently, molecular classification systems originating from TCGA, evaluated in GOG-210 and PORTEC-3 defined four prognostic subtypes based on POLE, MSI-H/MMR-D, and Copy number alterations/p53 mutations status..

Although valuable, this molecular approach still has significant limitations such as applicability to the majority of EEC patients categorized as no-specific molecular profile (NSMP) and the potential need to resolve pathogenic and prognostic heterogeneity within MMR-D, and TP53 subtypes.

These clinical unmet needs were key motivators for Tempus to develop a molecular classifier predicting distant recurrence risk in early-stage EEC with a specific focus on high intermediate-risk (HIR) patients where there is the most adjuvant treatment ambiguity.

METHODS

An RNA-seq-based gene expression profiler (GEP) was trained using a machine-learning pipeline with TCGA data (n=323) followed by further model development with Tempus data to generate a GEP-based molecular risk (MR) test for patients with EEC. The resulting model is a 24-gene signature that classifies EEC patients as MR-high or MR-low.

The GEP MR test was then evaluated on EEC patients (N=1037) from the Tempus Database to test associations with known pathologic and molecular prognostic features. Finally, a clinical evaluation of the GEP MR test was performed to assess performance on a retrospective clinical research cohort of early-stage EEC patients using the clinical endpoint of distant recurrence free survival (DRFS).

Table 1. Patient Characteristics of the EEC Cohorts

Characteristic	TCGA Training Cohort (n=323)	Tempus Evaluation Cohort (n=1037)	Stanford Evaluation Cohort (n=109)
Age 18-49	32	140	8
Age 50-69	200	649	77
Age 70+	89	248	24
G1	86	202	61
G2	99	176	31
G3	138	79	17
Stage I-II	323	146	108
Stage III-IV	N/A	148	N/A

Unknown statuses were excluded from the table. All samples had endometrioid carcinoma histology.

SUMMARY

- We developed a gene expression profiler (GEP) predicting distant recurrence risk in early-stage EEC to inform adjuvant clinical management.
- The GEP test showed expected associations with known pathologic and molecular prognostic features verifying the test design and gene features.
- In a clinical evaluation, the GEP test shows significant performance in distant recurrence risk stratification across all early-stage EEC patients, and critically in the high unmet need groups of HIR patients and NSMP patients, necessitating the need for future definitive clinical validation studies.

RESULTS

Figure 1. MR Score Associates with Known Pathologic Features in the Tempus Evaluation Cohort

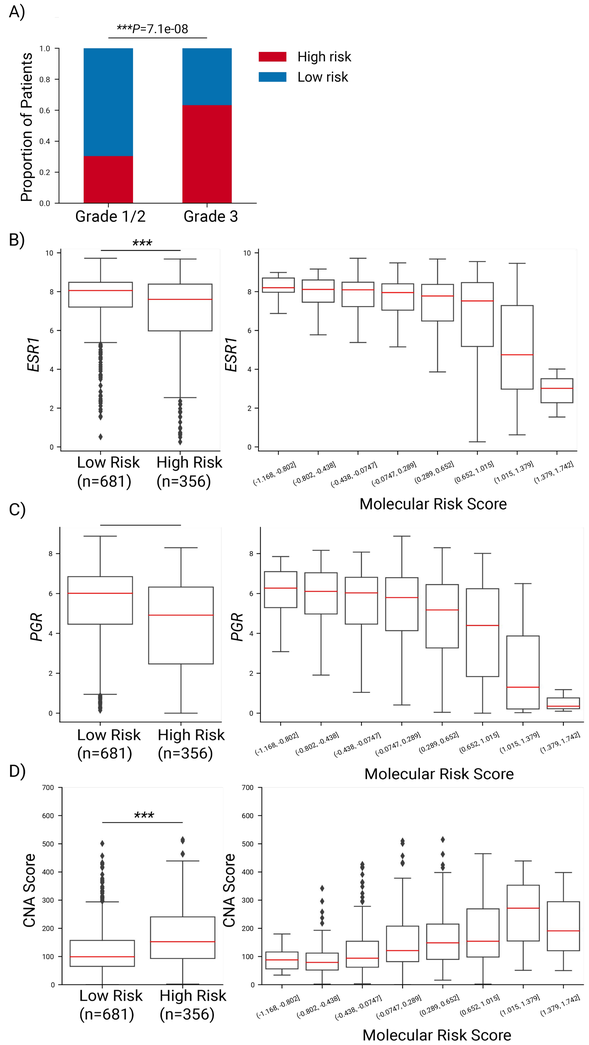

Figure 1. A) MR-high samples associated with G3 versus G1/2 histology. B) and C) ESR1 and PGR expression show inverse correlation with MR scores (low expression in high-risk disease). D) CNA and MR scores show high correlation indicating that high MR scores are associated with a known biomarker of poor prognosis and serous-like histology.

Figure 2. MR Score Associates with DRFS in the Stanford Evaluation Cohort

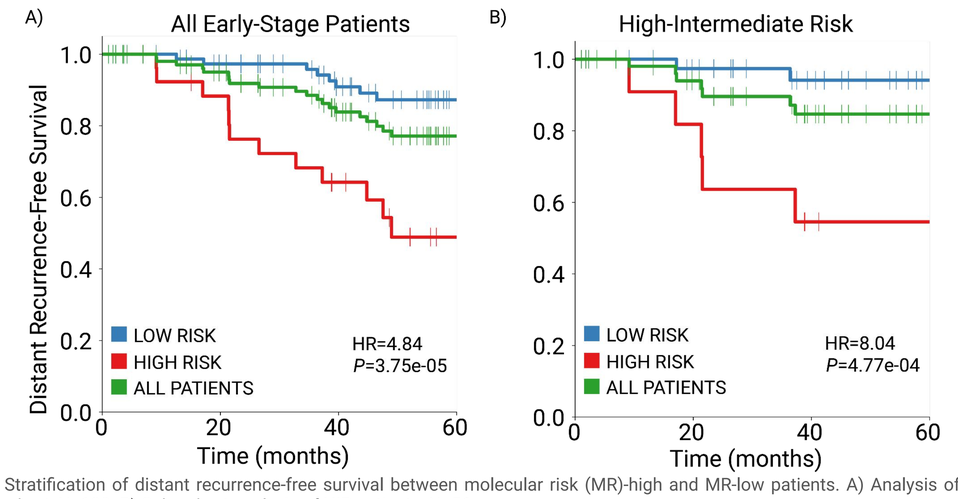

Figure 2. Stratification of distant recurrence-free survival between molecular risk (MR)-high and MR-low patients. A) Analysis of the entire Stanford cohort, N=109. B) Sub-cohort analysis of HIR patients, N=56.

Figure 3. MR Score Associates with DRFS When Stratified by TCGA Subtypes in the Stanford Evaluation Cohort

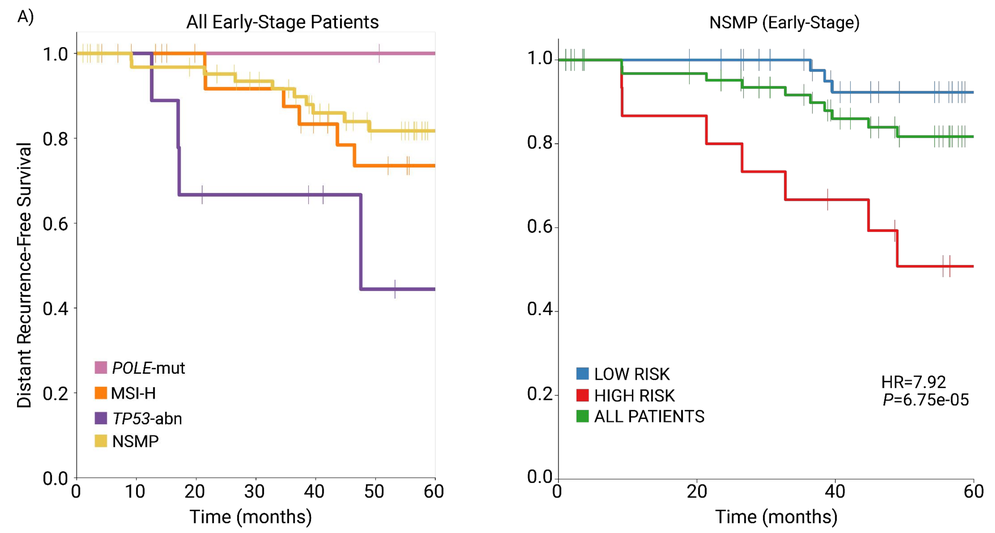

Figure 3. Stratification of distant recurrence-free survival by The Cancer Genome Atlas (TCGA) subgroups in the Stanford cohort. A) Analysis of the entire Stanford cohort by established TCGA subtypes, N=109. B) Sub-cohort analysis of NSMP patients stratifying by molecular risk (MR)-high and MR-low to demonstrate the significance in the clinically meaningful NSMP subgroup, N=67.

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