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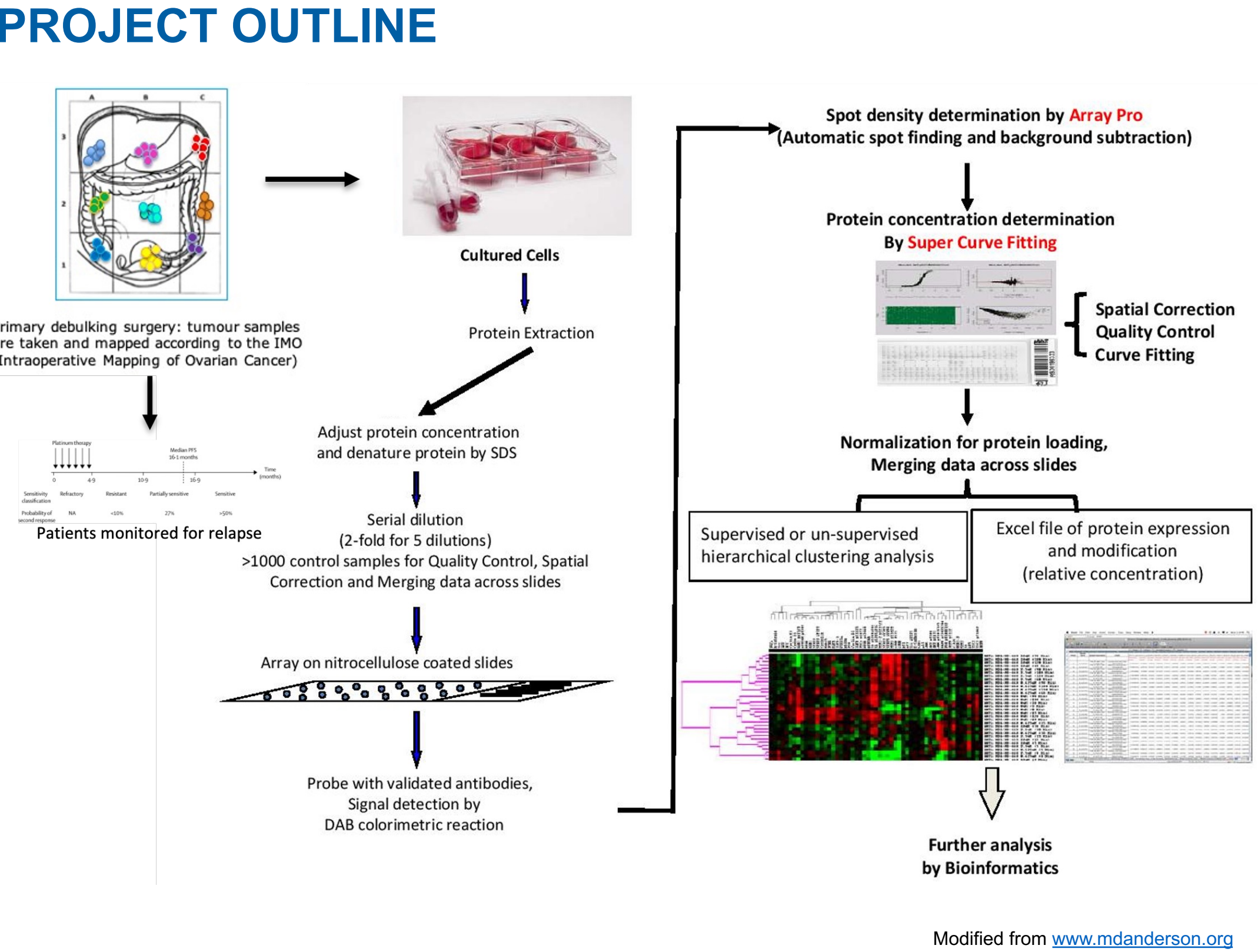
OBJECTIVES

Although initially most patients with HGSOC respond to platinum therapy, the majority of patients will develop resistance to chemotherapy and thus have poor outcomes. This study aimed:

- to understand the extent of heterogeneity related to platinum-induced cell signalling at the protein level in primary tumour cell cultures derived from multiple HGSOC samples and linked to clinical outcomes.
- to investigate the difference between platinum-induced protein changes in tumours collected from a matched primary and relapse case.

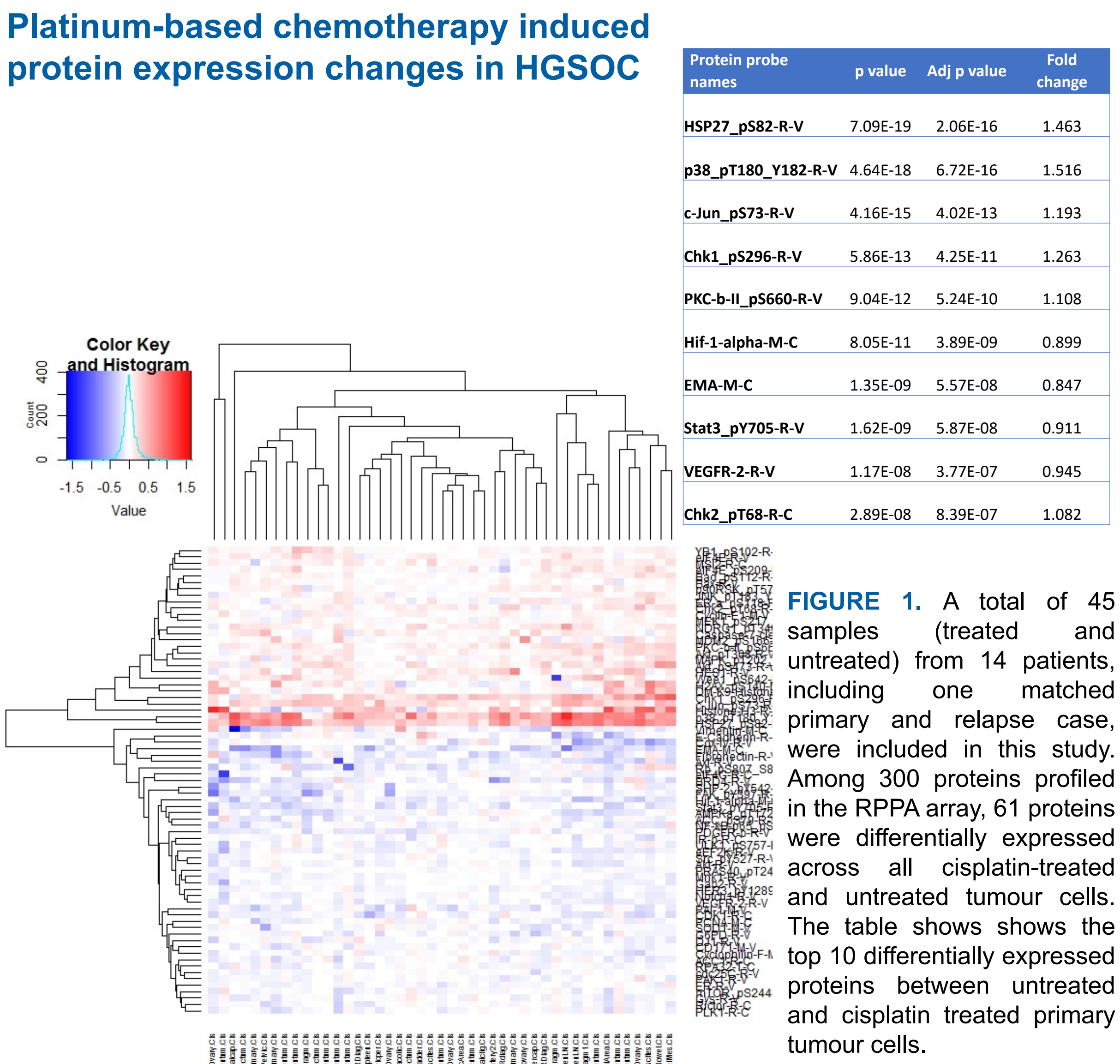
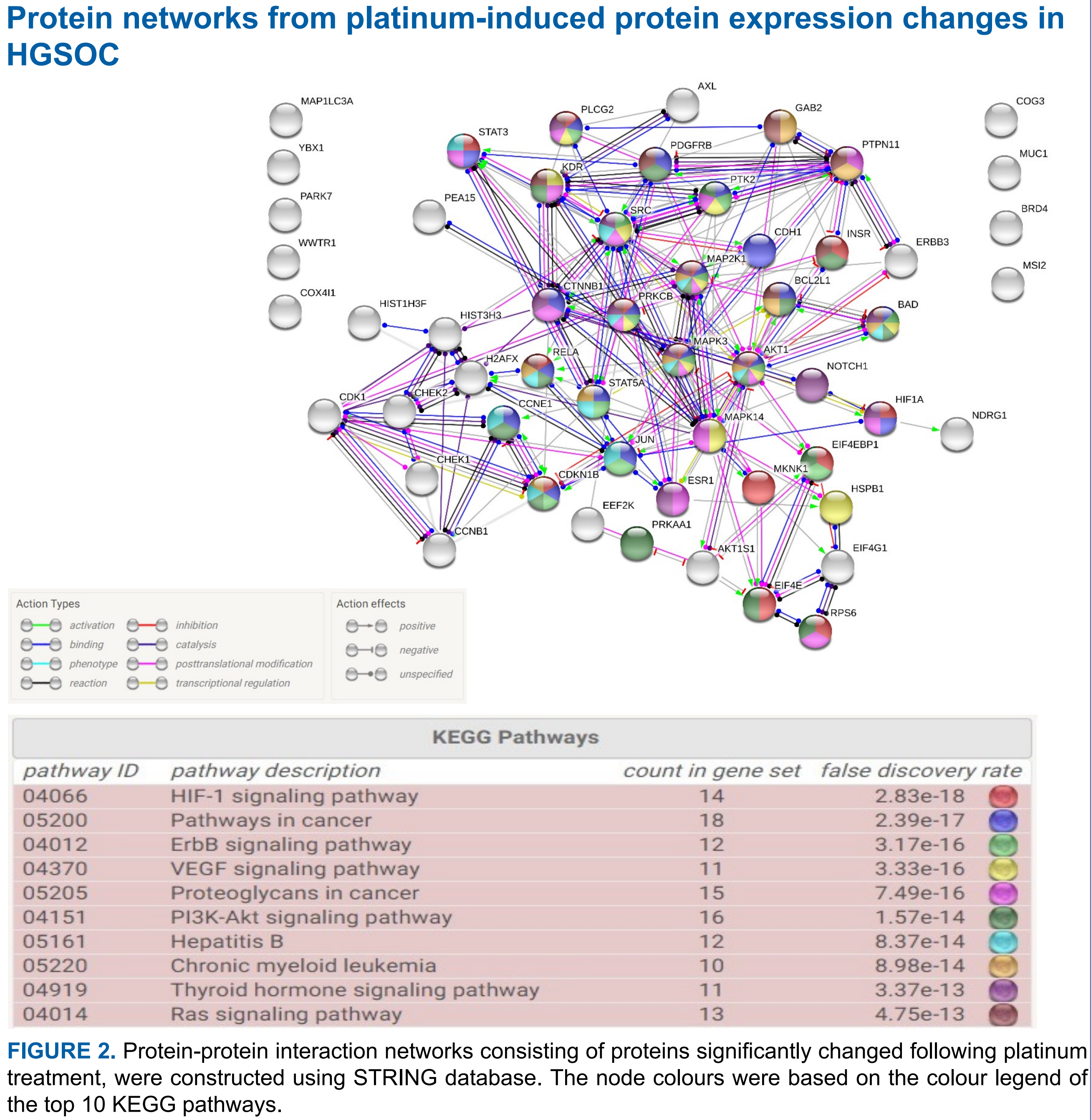
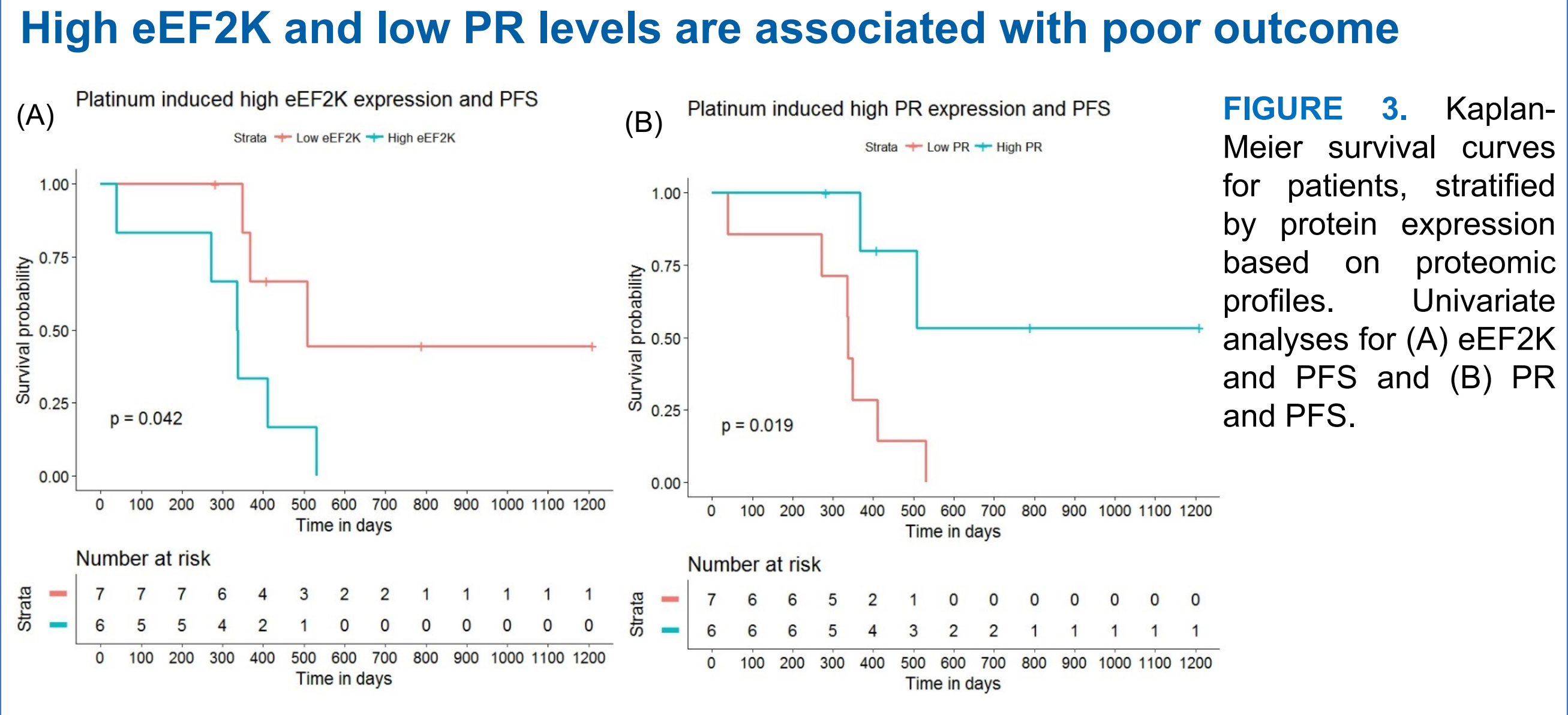
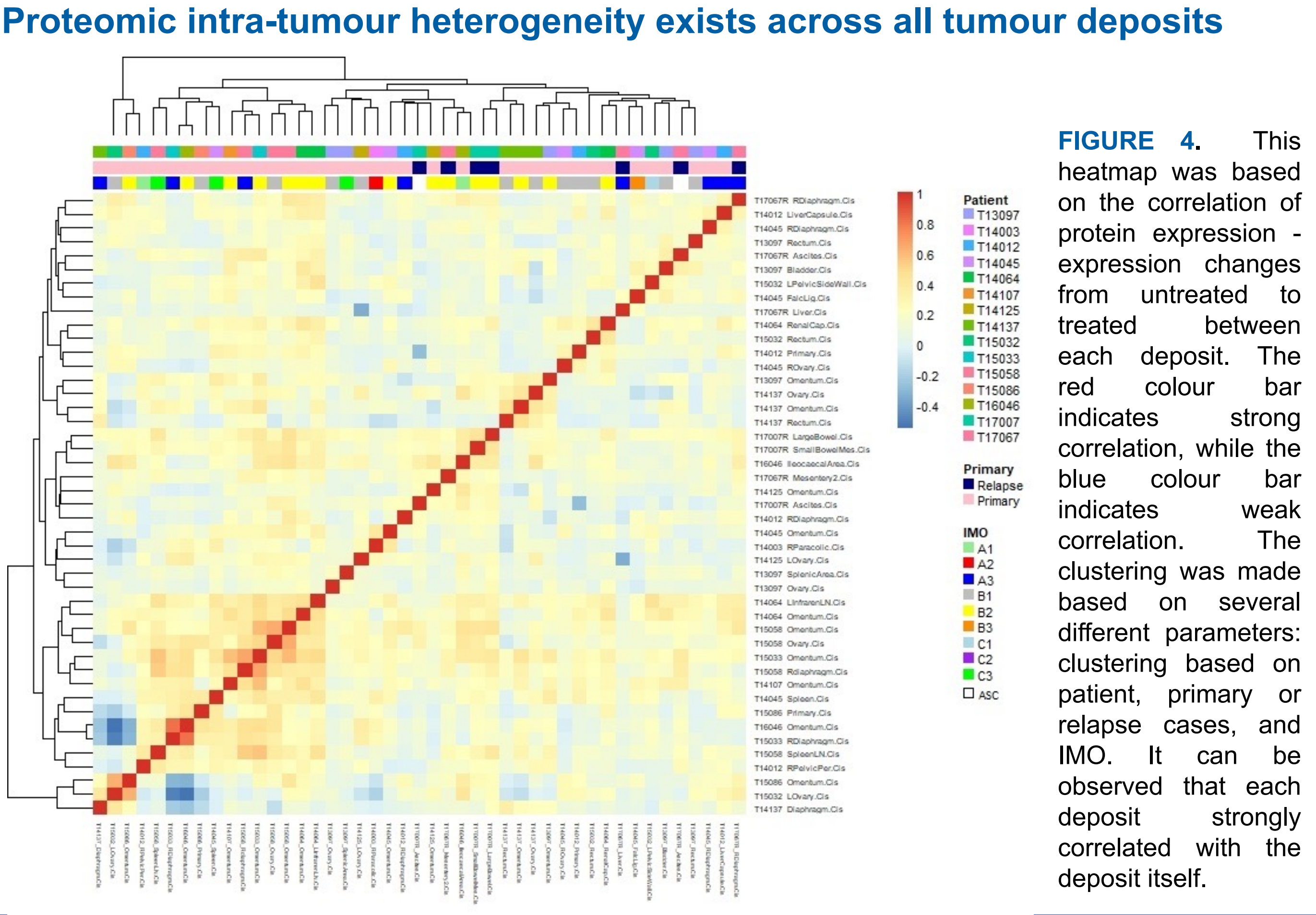
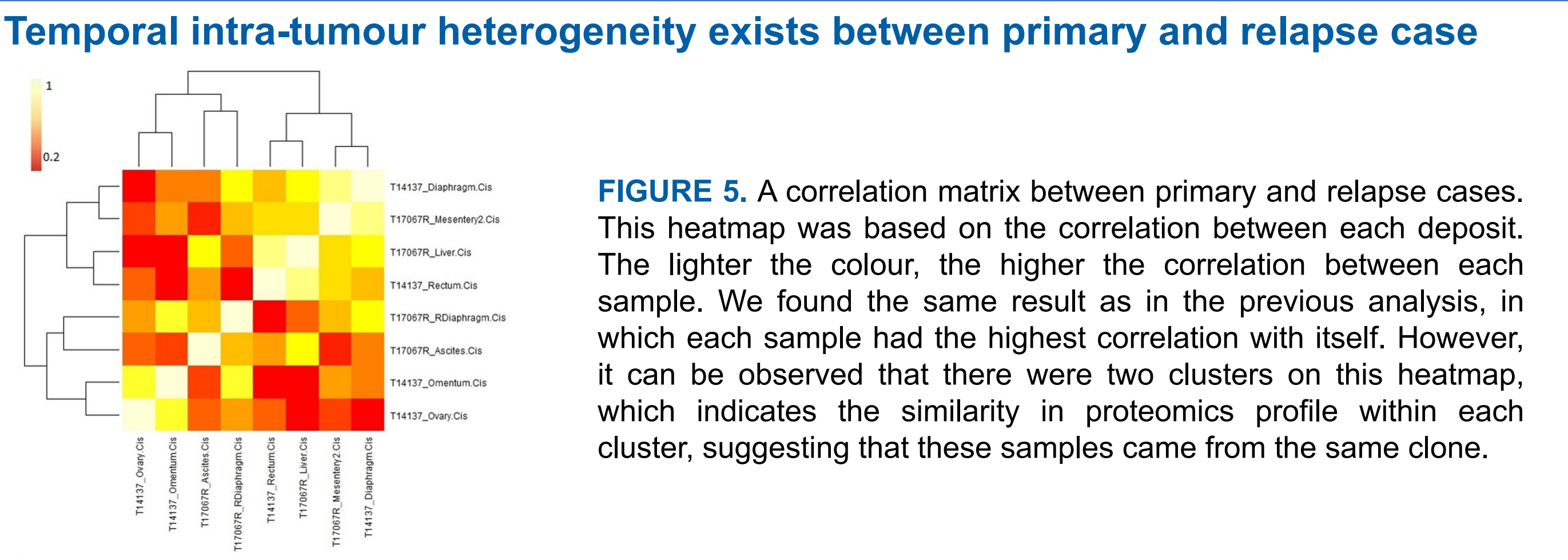
DESIGN AND METHODS

Tumour samples were prospectively collected from chemotherapy-naïve patients with advanced-stage HGSOC undergoing maximal effort primary debulking surgery at Hammersmith Hospital, London. Samples were taken from multiple anatomical sites in each patient and analysed for response to platinum treatment and proteomic signalling, to define heterogeneity between patients and different tumour locations. Primary tumour cells were extracted, cultured short-term *in-vitro* and treated with cisplatin (25µM). Pathway signalling changes following cisplatin treatment were investigated using reverse phase protein array (RPPA). Patients were followed up as standard of care and tumours were collected at relapse when available (Project outline).



RESULTS SUMMARY

- A total of 45 samples (treated and untreated) from 14 patients, including one matched primary/relapse case, were included in this study. Among 300 proteins profiled in the RPPA array, 61 proteins were differentially expressed across all cisplatin-treated and untreated tumour cells.
- In this study, cisplatin treatment activated several pathways that induced apoptosis and cell survival, including AKT, PKC, and MAPKs (JNK and p38 MAPK). Down-regulation of COX IV and Hif-1-alpha, which are involved in survival pathways and have not previously been linked with cellular responses following cisplatin treatment, were also found.
- Vast proteomic intra-tumoral heterogeneity was evident in our cohort, indicating the importance of multi-site sampling for analysis to avoid sampling bias.
- Temporal tumour heterogeneity was present in a matched primary and relapse case. Additionally, high eEF2K and low PR expression were identified as potential biomarkers of poor prognosis.



CONCLUSION

Data from proteomic analysis demonstrates spatial and temporal tumour heterogeneity in advanced HGSOC. Further validation of eEF2K and PR as prognostic biomarkers is warranted.

ACKNOWLEDGEMENT

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