MyChoice® CDx Plus

HRD Companion Diagnostic Test

Clinical summary

Systematic analysis of HRD testing in ovarian cancer – development of recommendations for optimal assay performance

Romey et al., Modern Pathology 2024

Introduction

Homologous recombination deficiency (HRD) testing is an important element of personalized treatment planning for patients with ovarian cancer. The optimal tissue requirements for these complex molecular assays are however not well-defined, leading to a significant number of unsuccessful assays and suboptimal diagnoses.

Study Objectives

To analyse tumor and tissue parameters for HRD analysis in a large cohort of real-world cancer samples and develop recommendations for selection of tissue samples to maximize the success rate of HRD analyses.

Methods

2654 FFPE tumor samples (sent to the institute from October 2020 to September 2022) were analysed by the Institute of Pathology of the Philipps-University Marburg for HRD using the Myriad MyChoice CDx Plus assay.

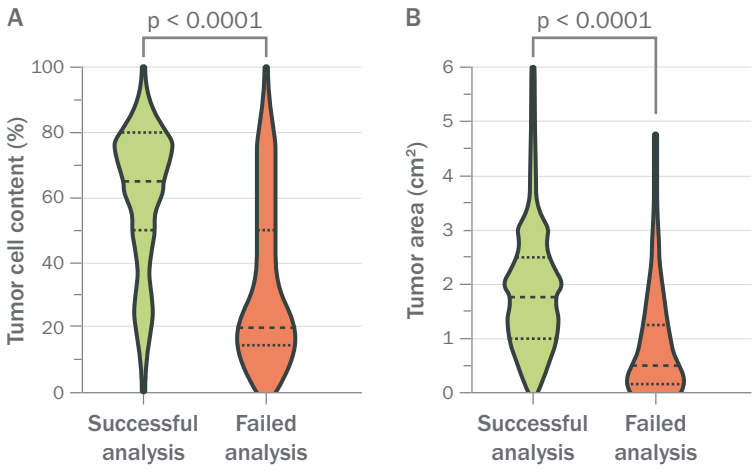
- Molecular profiling was performed by Next-Generation Sequencing (NGS) to analyze mutations in *BRCA1*, *BRCA2*, and 13 additional HRR genes.
- The genomic instability score (GIS) was determined by combining loss of heterozygosity (LOH), telomeric allelic imbalance (TAI), and large-scale state transition (LST) analyses.
- To be considered successfully analyzed, samples had to either yield a valid GIS result and/or harbor a clinically significant mutation in either *BRCA1* or *BRCA2*.

Results

- 2396 (90.3%) were successfully tested

Tumor and tissue analysis

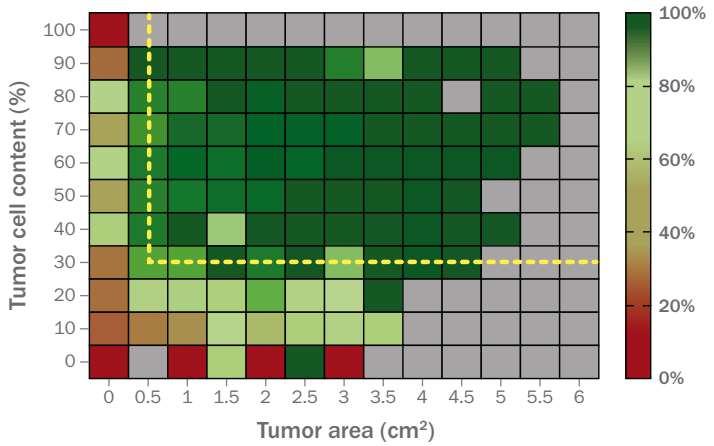
- Tumor samples that passed analysis on average showed significantly higher tumor cell content ($p < 0.0001$, **Fig. A**) and tumor area ($p < 0.0001$, **Fig B**) than those that failed analysis.



Myriad genetics®

- Assay success rates strongly increased when tumor cell content and tumor area values reached specific thresholds (tumor cell content >0.25-0.35; tumor area >0.25-0.75 cm^2).
- When these conditions were met, at least 85% of analyses were successful, with most combinations showing success rates of >95% (**Fig. E**).

E



Heat map showing impact of tumor cell content and area on assay success.
Heat map gradient shows ratio of passed samples from 0% (dark red) to 100% (dark green).
Yellow dotted line shows recommended cutoff for optimal assay success chance, grey areas indicate parameter combinations not found inside the cohort.

To allow for the best possible chance of analysis success, the authors propose:

- tumor cell content ≥30%
- tumor area ≥0.5 cm^2

The HRD success rate for tumor samples that fulfilled both conditions was 98%.

Tumor histology

- 85.1% of samples analyzed were high-grade serous ovarian carcinoma (HGSOC)
- HGSOC samples had the highest pass rate (92.2%) while all other ovarian cancer subtypes had <80% pass rate

HRD and BRCA mutational status

- 41.1% (984/2396) of samples were HRD positive
- 15.2% harbored a *BRCA1* or *BRCA2* mutation*
- *BRCA1/2*-mutated samples exhibited significantly higher GIS values than those with wild-type *BRCA1/2*-status

* The frequency of *BRCA1/2* mutations in this cohort was about half the rate presented in the PAOLA-1 cohort. The difference may have resulted from some cancer centers' germline testing beforehand, and only sending tumor samples for HRD testing where a wild type germline *BRCA1/2* status was reported.

Conclusions

The study provides important recommendations for tissue selection for HRD testing in ovarian cancer:

- If multiple tumor samples are available for HRD testing, selecting those that possess at least 30% tumor cell content, and a tumor area of ≥0.5 cm^2 is recommended.

HGSOC tumors recorded the highest chance to achieve a conclusive result on GIS and thus, HRD status.

These recommendations, which could lead to a testing success rate of up to 98%, will likely have a significant impact on personalized therapeutic strategies for this aggressive tumor type.