Editorial Commentary

Multiomic characterization of high-grade serous ovarian carcinoma: editorial commentary on recent application and consideration for future directions

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Ovarian carcinoma represents a major burden of women's morbidity and mortality. It consists of various histological subtypes and among them, high-grade serous carcinoma (HGSC) is most common in the United States (1). Effective approaches to treat HGSC of the ovary, fallopian tube, and peritoneum remain challenging. Within the last two decades, there has been significant progress in our understanding of the molecular landscape in HGSCs and its precursor lesions, due to genomic changes (e.g., gene sequence changes, copy number variations) as well as transcriptomic or proteomic alterations (1-8). Despite these advancements, direct translation of the results from those studies to benefit women with HGSC awaits to be realized as the 10-year survival rate is less than 15% (3). This has led investigators to incorporate more comprehensive analyses using the data generated from sophisticated techniques in order to better characterize the disease and develop risk strata that are reliable and relevant to clinical application. The report by Hollis and colleagues is a timely one aiming at better understanding clinical phenotypes, progression, and survival patterns among HGSC molecular subtypes (9). Through a multiomic approach, they identified protein markers, compared transcriptomic subtype profiles, and studied homologous recombination repair (HRR) pathway-related mutations and copy number changes to determine if molecular characters can distinguish different clinical subtypes of HGSC.

There are several implications from integrated omic studies including this new report. They validate the importance of genomic instability in HGSC initiation and progression, promise clinically meaningful molecular classifications, and emphasize the emerging roles of tumor microenvironment with specific focus on tumor immunogenicity in HGSC development and response to treatment. However, there are several challenges ahead in applying the results of multiomic biomarker studies to clinical practice.

This report integrates an HRR-centric algorithm that classifies HGSC tumors according to prognosis. The authors compare overall survival (OS) of patients with tumors of the following features: mutation in *BRCA1* (*BRCA1*m), *BRCA2* (*BRCA2*m), amplification of *CCNE1* (*CCNE1*g), mRNA overexpression of genes located in chromosome 11q13.5 (region harboring *EMSY*, termed *EMSY*-overxp in this study) and HRR wildtype (HRRwt) (9). As expected, the *BRCA2*m group had the best OS while CCNE1g and HRRwt groups had the worst OS (9). Interestingly, the authors found a survival advantage in groups without

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*BRCA1/2*m, but with mRNA transcript overexpression of EMSY in chromosome 11q13.5 (9). *EMSY* encodes a protein that binds and inactivates BRCA2 proteins (10,11). It is intuitive that EMSY may likely function to contribute to HRR deficiency but whether EMSY is over-expressed in HGSC tissue at the protein level is certainly unclear. In fact, chromosome 11q13.5 harbors several other genes of which *Rsf*-1, just adjacent to *EMSY*, has been reported to be amplified and overexpressed at the protein levels in chromosome 11q13.5 amplified HGSCs and their precursor lesions, serous tubal intraepithelial carcinomas (12). Rsf-1 protein is involved in ISWI chromatin remodeling and Rsf-1 amplification was associated with shorter OS compared to those without (12).

The results from this report support an association between HRR genotype and immune-rich phenotype on a basis of transcription analysis. Although similar findings have been previously reported, the authors provide more details on such correlation. HGSCs with either *BRCA2*m or *BRCA1*m were associated with the Tothill C2 and immunoreactive The Cancer Genome Atlas (TCGA) subtypes (9). These authors also find three canonical pathways (i.e., polo-like kinase, BRCA1-mediated DNA response, and G2/M DNA damage checkpoints) are highly associated with and may contribute to the high levels of chromosomal disruption in HGSC (13). Another major finding from this study is that the results show immune cell infiltration burden as a prognosis marker. The authors find that higher proportion of $CD3^+$ tumor infiltrating lymphocytes (TILs) were associated with prolonged survival and better response to chemotherapy, and this correlated with genomic variants *BRCA1/2*m as well as with the Tothill and TCGA transcriptomic subtypes, C2 and IMR, respectively (9). Although understanding the TME as it relates to the immunogenicity of HGSC is encouraging, application of these concepts clinically has been challenging since their response rates to immunotherapies have been modest (14,15). In the study, over half of the HGSC tumors were HRRwt (57%), with or without *CCNE1*g (9). The authors' HRR-centric algorithm confirms that both HRRwt and *CCNE1*g are associated with worse OS and response to chemotherapy when compared to the HRR-deficient cases (9). Notably, the anti-angiogenic agent bevacizumab confers the most progression-free survival (PFS) benefit to HRRwt patients as well as those that would be trascriptomically classified as PRO or C5 subtype, corresponding to the TCGA and Tothill subtypes, respectively (9). Taken together, there seems to be reliable, clinically translatable knowledge gained when the status of the HRR pathway (or related genes) in HGSC tumors is discerned.

The paper also concludes that use of immunohistochemistry can provide reliable and specific (2,16,17) approach to help outcome prediction. In this report, the authors find that loss of RB engendered significantly better OS and more favorable response to chemotherapy, and that it was especially prevalent in HRR-deficient variants of HGSC (9). Additionally, this report now classifies PTEN-loss and RB-loss as non-mutually exclusive, with a co-occurrence rate of more than 20% (9). Whether the co-loss of both tumor suppressors is associated with any clinical sign awaits further study in a large HGSC cohort. A long-standing challenge in applying immunostaining in clinical setting is the concern of the specificity and sustainable source of the antibody, interpretation of the staining pattern, the intra-tumoral heterogeneity and, most importantly, whether a single or a small set of staining markers whould have the power for clinical correlation when tested in a large independent cohort.

We propose that future success in the application of multiomic characterization of HGSC will depend on several factors, many of which rely on a reproducible and facile workflow to diagnose and characterize varying clinical profiles. DNA and protein are considered relatively stable markers and are easier to reproduce (18). However, compared to DNA and protein, RNA expression has historically been considered a less stable marker due to biodegradation by RNase, an enzyme highly present in the everyday environment (18). Additionally, formalin-fixed paraffin embedded (FFPE) specimens, when compared to fresh frozen tissue, are associated with fragmented and chemically modified nucleic acids, which can potentially add challenges and introduce bias when assaying RNA, if fresh frozen tissue isn't available (19). And, while more sophisticated transcriptomic analysis platforms have been increasingly available, the overall cost and turnaround time have limited our broader clinical use (20). This calls for improvements in technique, which may include having less coverage and more shallow reads to broaden throughput and surveillance of the transcriptome (20). This approach could potentially lower costs and increase accessibility. Integration of reliable and affordable transcriptome profiling combined with profiling known stable markers (DNA and protein) has potential for robust combinational approach to predicting HGSC prognosis and treatment response.

We would be remiss to mention the implications of

a more granular precision medicine without also taking into consideration the potential effects of next-generation "-omic" profiling on disparate populations, especially those which are historically underserved. Studies have shown that adherence to the National Comprehensive Cancer Network (NCCN) treatment guidelines is a key determinant to survival disparities seen in minority populations (21). In fact, there were no differences in survival based on race or socioeconomic status after controlling for adherence to NCCN treatment guidelines (22). What this tells us is that guideline adherence differences between specific populations will undoubtedly perturb their access to multiomic diagnostics. Additional considerations include biases in big data, with scoring systems at risk of introducing new forms of discrimination, most of which are attributable to human bias (23). The populations from which samples are taken, inappropriate length of surveyed time, and neglect of relevant variables within the diagnostic algorithm can be sources of bias. Historically, differential access to skilled technology became the impetus for the "Digital Divide," whereby social status (age, gender, race, income, and level of education) directly determines one's likelihood of access (24). To ensure an equitable distribution of multiomic profiling opportunities for all patients, in addition to public health initiatives, we encourage continued diversity, equity, and inclusion (DEI) initiatives across institutions to increase awareness. Furthermore, we encourage patient recruitment of diverse populations, implementation of mandated data sharing, and intentional consideration of heterogenous populations in the design of technology and data management.

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Footnote

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