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The rise of genomic profiling in ovarian cancer

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Abstract

Introduction—Next-generation sequencing and advances in ‘omics technology have rapidly increased our understanding of the molecular landscape of epithelial ovarian cancers.

Areas covered—Once characterized only by histologic appearance and clinical behavior, we now understand many of the molecular phenotypes that underlie the different ovarian cancer subtypes. While the current approach to treatment involves standard cytotoxic therapies after cytoreductive surgery for all ovarian cancers regardless of histologic or molecular characteristics, focus has shifted beyond a ‘one size fits all’ approach to ovarian cancer.

Expert commentary—Genomic profiling offers potentially ‘actionable’ opportunities for development of targeted therapies and a more individualized approach to treatment with concomitant improved outcomes and decreased toxicity.

Keywords

genomic profiling; ovarian cancer; targeted therapy; precision medicine

1.0 Introduction

The standard approach to treatment of the ovarian cancer patient continues to evolve. Within the past decade, our knowledge of this deadly disease has advanced in diagnostic imaging, treatment with platinum based and taxane combination chemotherapy [1–3] and aggressive cytoreduction [4] to no gross residual disease [5]. Technological advances, coupled with a better understanding of tumor biology, has piqued gynecologic oncologists’ interest toward more personalized therapy. The practice of precision medicine requires tailoring a specific

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Declaration of Interest

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treatment for a particular cancer type at a precise time point. Over the past decade in the treatment of malignancies, the paradigm of cancer treatment across many tumor lineages has shifted from the empiric use of cytotoxic therapies to genotype-directed therapy using targeted agents as well as to the implementation of immuno-oncology agents. In general, ovarian cancer therapy has lagged in this process.

Oncology is an ideal medical field for the development of targeted or precision medicine [6–9]. Like the genomic studies that have occurred in ovarian cancer, more recent trends have been to categorize oncology patients by their tumors' genetic alterations rather than by the primary site of origin [10, 11]. The primary goal of molecular targeted therapy is to match patients with a specific therapy, based on their molecular aberrations, to increase the likelihood of a response and impact survival. This is also expected to decrease toxicity. Rather than take a blanket approach to therapy by treating all ovarian cancers with standard of care chemotherapy with a platinum and taxane after cytoreduction, this type of therapy would identify genomic alterations that were specific to the tissue removed by biopsy or surgery and integrate this information with other aspects of the patients tumor such as histology and spread [12, 13].

This step toward individualization of cancer therapies has been fueled by technological advances of high throughput molecular, proteomic, metabolomics and genomic techniques [14]. Next-generation sequencing has made genomic profiling of solid malignancies possible through whole-genome, exome, target sequencing of DNA as well as transcriptome sequencing of fresh, frozen, and fixed tumor samples widely accessible in all models of clinical practice [10, 15, 16]. Not only has the cost of performing these assays continued to decrease but they are now applicable to smaller tumors and also to more challenging conditions such as formalin fixed paraffin embedded samples. The advent of sequencing of circulating DNA including exosomal DNA offers the potential to bypass the need to obtain tumor tissue for analysis, making the ability to assess the tumor at the time of therapy or even during therapy more practical. How to best incorporate genomic profiling into our clinical practice and make informed treatment decisions that impact outcomes for women with ovarian cancer remains unknown [17] but is rapidly evolving. Mining the pre-existing genomic data that we have previously collected is associated with past and current challenges. However, we must also anticipate the future and how we navigate the inherent heterogeneity, relative lack of driver mutations, genomic instability, propensity for clonal evolution over time, and resistance that develops to chemo- and targeted therapies of ovarian cancers.

1.1 Genomic profiling of ovarian cancer

Previous clinicopathologic and molecular studies of epithelial ovarian cancer have classified tumors into two broad categories [18]: type I (low grade serous, mucinous, endometrioid, clear cell cancers, and Brenner tumors) and type II (high grade serous, high grade endometrioid, malignant mixed mesodermal tumors, and undifferentiated carcinomas) (Table 1) [19–21]. Type I tumors are characterized by specific mutations in KRAS, regulators of the mitogen-activated protein kinase (MAPK) pathway such as BRAF, receptor tyrosine kinases such as ERBB2, and PI3K abnormalities such as loss of function mutations

in PTEN [20, 22]. Mutation of KRAS in type I ovarian cancers has been characterized as a “driver” mutation, and is thought to play a crucial role in tumorigenesis as well as disease progression and likely responsiveness to therapy. These molecular events confer an addiction of the tumor cell to a particular molecular pathway with specific dependencies despite other existing “passenger” alterations. High grade serous ovarian cancers frequently contain TP53 mutations and alterations of BRCA1/2 and associated homologous recombination (HR) genes either by mutation, promoter methylation, or loss of heterozygosity [23]. These mutations can be either germline contributing to cancer predisposition syndromes, or somatic. More recently, individual centers, genomic consortiums and initiatives such as The Cancer Genome Atlas (TCGA) and International Cancer Genomics Consortium have completed large scale studies of multiple tumor types to better understand and characterize alterations within pathways involved in the development of solid malignancies [24, 25]. These genomic studies have included glioblastoma, colon, ovarian, breast, lung, and uterine cancers.

TCGA evaluated 489 high grade serous ovarian cancers and identified four subtypes based on their molecular signatures: immunoreactive; differentiated; proliferative; and mesenchymal [26, 27]. However, these subsets appear to represent “gradients” rather than discrete tumor subtypes or cell of origin. Significant findings from this analysis included almost universal TP53 mutations as well as frequent germline or somatic mutations in BRCA1 and/or BRCA2 and other related HR DNA repair genes. Tumors that lacked a TP53 mutation within this TCGA analysis have recently been re-reviewed, and 93% of the tumors were either not a pure high grade serous ovarian carcinoma or represented a pathologic diagnosis other than a high grade serous ovarian carcinoma. This suggests that lack of TP53 molecular alterations within a tumor are inconsistent with the high grade serous ovarian cancer diagnosis, and an alternative diagnosis should be sought [28]. Also noted from the TCGA was overall lack of genomic stability, lack of driver mutations, and high frequency of loss-of-function events. These loss-of-functions events are related to abnormal homologous recombination, through dysfunction of proteins in the homologous recombination pathway or silencing of BRCA1 through methylation. Recurrent somatic mutations were identified in NF1, RB1, and CDK12, albeit at relatively low frequencies. These results largely recapitulated findings from our group on 235 ovarian cancers [29].

Another large scale analysis of germline mutations and tumor suppressor genes in 360 women with ovarian, peritoneal or fallopian tube cancers revealed that 24% carried loss-of-function mutations: 18% in BRCA1 or BRCA2 and 6% in other DNA repair genes BARD1, BRIP1, CHEK2, MRE11A, MSH6, NBN, PALB2, RAD50, RAD51C, or TP53. Six of these genes had not previously been implicated in inherited ovarian carcinoma [30]. Other profiling studies have reclassified ovarian carcinomas based on profiling characteristics. Tothill and colleagues performed microarray gene expression profiling on 285 serous and endometrioid tumors and identified six molecular subtypes, one of which was a high grade serous subtype reflecting mesenchymal features, and was characterized by N-cadherin and P-cadherin and low expression of CA125 and MUC1 [31]. Overall, this study demonstrated similar subtypes to the TCGA study with additional subtypes encompassing tumor types not included in the TCGA analysis. Although a less frequent histology pathologically, molecular profiles of characterized clear cell carcinoma and low grade endometrioid cancers were

marked by somatic mutations in ARID1A, which encodes AF250a, a key component of the SWI–SNF chromatin remodeling complex [32, 33]. ARID1A performs a key function in DNA damage repair and gets recruited to DNA double strand breaks via its interactions with ATR, an upstream DNA damage checkpoint kinase, and enables sustained DNA damage signaling. The use of poly-ADP ribose polymerase (PARP) and EZH2 methyltransferase inhibitors in patients with ARID1A-mutant tumors may provide a potential therapeutic strategy, which has been demonstrated in pre-clinical models [34, 35]. ARID1A mutant tumors have also been demonstrated to be sensitive to EZH2 inhibitors offering an additional therapeutic opportunity for exploration.

Additionally, a small number of treated tumors have been profiled in the recurrent setting. Profiling tumors refractory to platinum-based therapy has identified amplification of 19q12, which contains cyclin E (CCNE1) in 15% of high grade serous cancers [36, 37]. CCNE1 has been identified as an amplified oncogene in high grade serous ovarian cancers and is strongly associated with treatment resistance to platinum-based chemotherapy [36, 37]. Knockdown of cyclin E resulted in G1/S phase arrest, reduced cell viability and apoptosis only in amplification-carrying cells [38]. Mucinous carcinomas, which typically do not respond to current platinum-based and taxane chemotherapy, have been noted to exhibit amplification of HER2 in 18.2% of mucinous carcinomas and 18.8% of mucinous borderline ovarian tumors [39].

Predictive biomarkers, descriptors that identify selective susceptibility to an intervention, have also emerged from big data profiling studies. Predictive biomarkers predict how a patient will respond to a particular intervention or the differential outcomes of two or more interventions, including toxicity. Recently, TP53 alterations have been found to predict sensitivity to VEGF/VEGFR inhibitors in clinic [40]. Prognostic biomarkers are those that characterize the outcome, such as survival or the probability of recurrence after adjuvant chemotherapy. Examples of prognostic biomarkers in ovarian cancer include CA125 [41] (post-operative levels of CA125 greater than 35 units/mL are independent prognostic factors for survival), EphA2 [42] (overexpression is associated with poor prognosis), and Dicer and Drosha mRNA levels (decreased Dicer expression correlates significantly with worse overall survival) [43]. Additionally, biomarker expression rates between subtypes have been evaluated by protein expression. For example, WT1, more frequently expressed in high grade serous carcinoma [44], and eight other markers including, CDKN2A, DKK1, HNF1B, MDM2, PGR, TFF3, TP53, VIM, can be used to predict one of five transcriptional subtypes in a retrospective cohort [45].

1.2 Heterogeneity and driver mutations in ovarian cancer

As with all therapies, intratumoral heterogeneity and how this contributes to ability of the tumor to overcome even the most precisely matched therapy will require further investigation. Conventional histopathology has shown that marked phenotypic heterogeneity is characteristic of some ovarian cancers. Primary and matched metastatic tumors have distinct phylogenetic branching patterns to suggest evolution of tumor clones through acquisition of additional mutations that underlie further tumor progression [46–48]. Mutational signatures from metastatic sites reflect subclones and populations that existed in

the primary tumor, and some clones may acquire certain mutations that target metastases to specific organs [47, 48]. Finally, through further acquisition of passenger alterations, novel phenotypes may be created through these acquired genetic interactions. While these processes have been studied in multiple tumor lineages, their role in the resistance of ovarian cancers to therapy is less well characterized and requires further investigation. It is through this acquired resistance, that mixed responses to therapies may be seen [49]. Indeed, companion biomarkers that have been developed in parallel may become less reliable or useful in this situation. While initial cytoreduction offers the most tumor material from the primary and multiple metastatic sites, biopsy of a single site of metastatic disease at the time of recurrence will likely underestimate how the genomic tumor landscape has changed. Although protocols with targeted agents often delineate specifically where and when to re-biopsy, the necessity, whether or not tumoral evolution and heterogeneity is captured by a single point in time biopsy, and ethical considerations about acquisition of tissue without direct therapeutic benefit, must all be considered. Indeed, these concerns are fueling the development of analysis of circulating and exosomal DNA as surrogates for the tumor heterogeneity across multiple metastatic sites.

Recent historical success stories highlight therapies that match genetically defined tumor subtypes to improve treatment response and patient survival. Amplification of ERBB2/HER2 in breast cancer is successfully targeted by trastuzumab, a humanized monoclonal anti-HER2 antibody [50]. Imatinib, a tyrosine kinase inhibitor targets BCR-ABL, which is a constitutively activated tyrosine kinase that causes chronic myeloid leukemia (CML) [51]. In patients with non-small cell lung cancer, who received treatment with gefitinib and erlotinib, have enhanced susceptibility to these inhibitors only if their tumor harbors a specific epidermal growth factor receptor (EGFR) mutation [52]. Treatment of metastatic melanoma with vemurafenib in patients with tumors that carry the BRAF^{V600E} mutation resulted in complete or partial tumor regression in the majority of patients [53], however as with most targeted therapies, these responses are transient. Recurrent translocations, such as those in non-small cell lung cancer including the EML4 anaplastic lymphoma kinase (ALK) rearrangement and c-ros oncogene 1 (ROS1) fusions, have been found to be targetable by an ALK/ROS1 inhibitor, crizotinib, and result in tumor shrinkage or stable disease [54, 55]. Also, treatment with vismodegib (a hedgehog pathway inhibitor) in patients with medulloblastoma or basal cell carcinomas (with a loss of function mutation in PTCH1) resulted in tumor regression and symptom regression [56, 57]. Identification of mutations have also identified and predicted those patients who will not respond to therapy. For example, the presence of RAS mutations in colorectal cancer is associated with decreased overall survival with panitumumab and chemotherapy [58]. Identification of these predictors can avoid treatment of patients who would not benefit, sparing them untoward toxicities and adverse events. However, high grade serous ovarian cancer does not offer opportunities for therapy with these agents due to the lack of recurrent mutations. A number of small molecules designed to normalize p53 function are in trial such as APR-246 and COTI-2, however, these trials are still at an early phase. Unfortunately, the mutations that occur in other types of ovarian cancer are not yet currently therapeutically targetable although ongoing studies are place to determine whether RAS and ARID1A mutant tumors can be targeted.

Not all molecular events that function as driver mutations in one cancer may do so in another cancer, and vice versa. In fact, specific alterations may engender different responses such as treatment of HER2-amplified breast and gastric cancer [50, 59] showing benefit to HER2 inhibitors but a lack of benefit for the same inhibitors in ovarian and uterine cancers [60, 61]. Indeed, colorectal carcinomas harboring the specific BRAF^{V600E} mutation have been noted to have poor response rate to vemurafenib as compared to melanoma [62]. The success of imatinib in CML and vemurafenib in patients with tumors that carry the BRAF^{V600E} mutation in melanoma reflects the reliance of these tumors on driver mutations [63] as well as a lack of bypass mechanisms in these lineages. However, advanced ovarian cancer and other solid malignancies have at least 30 to 60 mutated genes, but only 2 to 8 driver mutations [64]. This complexity, crosstalk between pathways, and feedback loops often yield unpredictable effects to therapy, and clinicians must realize the limitation of prescribing a targeted agent to match merely one mutation [65].

Microarray based gene expression studies have retrospectively demonstrated that ovarian cancer represents both a clinically diverse and molecularly heterogeneous cancer. These microarray based technologies permit analysis of thousands of transcripts in parallel, which allows for further classification into subgroups [66, 67]. Over the past ten years, prognostic and predictive molecular classifications have emerged, and their clinical impact remains promising, yet uncertain.

Early generation gene expression studies focused on identification of relevant genes that could serve as predictors of prognosis but lacked validation and were largely retrospective [68–71]. A systematic validation of gene expression based prognostic models published between 2007 and 2012 [72] identified 14 prognostic models for late stage ovarian cancer. These were validated in ten previously published data sets and showed a large range of accuracy. The top ranked including the TCGA consortium [26], the signature published by Yoshihara et al. [73]; and one by Bonome et al [74]. More recent technology including Illumina targeted RNA sequencing assays, NanoString assays, and transcriptome sequencing (RNAseq) have been used, but requires further validation [75, 76]. Use of next generation sequencing has highlighted several important areas that require further research including mutation reversions and upregulation of genes encoding multi-drug resistant proteins. These findings suggest that multiple serial samples must be obtained to best understand the changes that occur within a tumor as it progresses and develops resistance. However, the heterogeneity that exists within patient's tumor may provide only a single snapshot in time of the biology within a tumor. Cancer represents an evolutionary process, making prediction of which driver mutations to target difficult. Attempts to trace the genetic alterations through stepwise processes has been difficult in ovarian cancer, and current molecular profiling often fails to address the high level of heterogeneity and chromosomal instability that contribute to ovarian cancer pathogenesis and evolution [77].

The clinical impact of the chromosomal instability in high grade serous ovarian carcinomas remains largely unknown. Several recent studies have addressed this issue [23, 78]. Using the 455 genomic profiles from ovarian cancer from TCGA, Cope and colleagues used a chromosomal disruption index to summarize the extent of copy number aberrations across the genome. A multivariate survival analysis showed that a higher chromosomal disruption

index was associated with worse survival and expression of several genes was highly correlated a higher index.

Efforts from the multiple cancer genome sequence projects have challenged the preexisting framework of the current somatic gene mutation theory of cancer [79]. Chromosomal changes impact the genomic system to a greater extent than individual gene mutations. The heterogeneity seen within tumors is due to massive chromosomal instability, but one unifying theory to explain this mechanism has yet to be elucidated. Heterogeneous cancer types like ovarian cancer represent an evolutionary process and the identification of driver mutations limits practical application [80, 81]. This genomic chaos represents one new proposed mechanism for the development of drug resistance [82, 83] and includes chromothripsis, which describes a cellular catastrophe [84].

1.3 PARP and PARP inhibitors

Genomic profiling has yet to identify any approved molecular targets for ovarian cancer patients with the exception of germline and likely somatic BRCA1 and BRCA2 mutations [85]. Given that germline mutations in BRCA1 and BRCA2 account for approximately 15% of ovarian carcinomas, including women without a family history, the Society of Gynecologic Oncology recommended in a clinical practice statement: “Women diagnosed with epithelial ovarian, tubal, and peritoneal cancers should receive genetic counseling and be offered genetic testing, even in the absence of a family history [86–88].”

BRCA1/2 mutations function as both a predictive and prognostic biomarker. In general, patients with a BRCA mutation have more platinum sensitive disease and longer overall survival. The homologous recombination pathway, where BRCA1/2 are key components, is complex, and approximately half of all high grade serous ovarian cancers have some abnormality within this pathway [30, 89, 90]. Homologous recombination is the dominant DNA repair pathway for double strand DNA breaks, but when BRCA1/2 are mutated or otherwise dysfunctional, the base excision repair single strand DNA break pathway and the double stranded DNA repair nonhomologous end joining pathway are activated [91–93]. The rate limiting step within the base excision repair pathway is activation of PARP, which binds to the DNA and provides a structural change, which then activates subsequent repair proteins. This explains the success of PARP inhibitors and higher activity in BRCA mutated patients with ovarian cancer. PARP also functions to trigger apoptosis when it is inhibited through the low fidelity nonhomologous end joining repair pathways by creating more errors that are unable to be ultimately repaired [92]. The mechanism and success of PARP inhibitors in BRCA mutant tumors does not solely rest in their ability to block repair of single stranded DNA breaks. PARP trapping is the ability of PARP inhibitors to trap the PARP1 and PARP2 enzymes at the site of damaged DNA. This PARP-DNA complex is more cytotoxic than the unrepaired single strand breaks, which suggest that PARP inhibitors also act as a poison by trapping the PARP enzyme onto the DNA, which interferes with DNA replication. The available PARP inhibitors vary in their trapping abilities [94].

Olaparib was the first PARP inhibitor to be approved for use in recurrent ovarian cancer in patients (who had received three prior chemotherapy regimens) with BRCA1/2 mutations (Figure 1) [95, 96]. These data result from a phase II study of 298 patients that had germline

mutations and had progressed after three lines of therapy. Tumor response rates were 31% and 54.6% of patients were progression free after six months of treatment. Median overall survival was 16 months [96]. The European Medicines Agency (EMA) has approved olaparib be used as a monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed BRCA-mutated (germline and/or somatic) high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who have responded (complete response or partial response) to platinum-based chemotherapy [97, 98]. Veliparib, another PARP inhibitor has also been evaluated in women with germline BRCA mutations and recurrent ovarian cancer. The proportion of patients who responded was 26% overall, and 20% and 35% for platinum-resistant and platinum-sensitive patients, respectively. Overall, the therapy was well tolerated with only one grade 4 event (thrombocytopenia), and median progression free survival was 8.18 months [99].

The ARIEL2 trial sought to prospectively identify patients with non-germline BRCA1 or BRCA2 mutations who may have a homologous recombination deficiency by using a next-generation sequencing assay and analysis algorithm to predict rucaparib sensitivity by detecting tumor BRCA status and whether there is a high genomic loss of heterozygosity representing a DNA “scar” reflecting prior loss of HR repair. The association of loss of heterozygosity with defects in HR is based on a prior observation from our group [100]. Interim analysis for the first 61 patients were reported, and three subgroups were analyzed and included those with a BRCA1/2 mutation, a BRCA wild type with high LOH, and BRCA wild type with low LOH with objective response rates of 70%, 48%, and 8%, respectively [101].

The only effective biomarker-directed therapy in ovarian cancer consists of PARP inhibitors. However, resistance arises readily resulting in generally short term responses. Multiple resistance mechanisms to PARP inhibitors in ovarian cancer patients have been identified [76, 102]. The mechanisms of resistance include secondary mutations in the BRCA2 gene itself [103, 104] or loss of Tp53bp1 expression, a non-homologous end-joining factor [105, 106] amongst others. The mechanism of resistance induced by loss of Tp53bp1 was suggested to be deletion of Tp53bp1 promoting the processing of broken DNA ends to produce recombinogenic single stranded DNA that is competent for homologous recombination. Pharmacological effects also play a role in resistance to PARP inhibitors, such as increased expression of ATP-binding cassette transporters [107]. Increased expression leads to reduced drug efficacy by enhancing the intracellular to extracellular translocation of PARP inhibitors. The level of PARP protein may also influence resistance to PARP inhibitors through the differential trapping of PARP1 and PARP2 enzymes at the site of DNA damage. The different PARP inhibitors vary in their PARP trapping activity. An enhanced PARP1 trapping ability with greater amounts of the trapped PARP1-DNA complex leads to enhanced cytotoxicity. PARP1 loss of function mutants have been found to be more resistant to olaparib, suggesting that the PARP1 protein is necessary for olaparib-induced lethality [108, 109].

Resistance to other targeted therapies has been documented with EGFR^{T790M} in gefitinib- and erlotinib-resistant lung cancers [110] and ALK^{L1196M} in crizotinib-resistant ALK-rearranged lung cancer [111]. These newly found mutations, whether they are selected by

the therapy or arise de novo, can affect the success of the targeted therapy by directly altering the target or through conformational changes of the targeted kinase. It remains unknown if these types of resistance mechanisms can be reliably predicted and if secondary resistance from a clonal selection process can be overcome.

1.4 Other possible targets and “actionable” mutations

An alteration can be considered “actionable” when identified through genomic testing if a drug can be used to target that particular alteration. Although results vary widely depending on the tissue type, 39–83% of patients with cancer are predicted to have a mutation for which matched therapy exists [112, 113]. Within ovarian cancer, rational combinations of therapy for typically chemoresistant forms of epithelial cancer can be conceived, and some of which have been previously evaluated in clinical trials (Figure 2 and Table 2).

Low grade serous ovarian cancer is characterized by MAPK pathway mutations, which makes selumetinib, an inhibitor of MEK1/2, an informed targeted agent. In an early phase II trial of 52 patients with this therapy, 15% had objective responses reported, with one complete response and seven partial responses [114]. This led to the development of several randomized phase III trials to evaluate MEK inhibition compared to standard of care. Hormonal therapy and treatment of recurrent low grade serous ovarian cancer patients with agents including aromatase inhibitors, tamoxifen, and leuprolide acetate has also been evaluated. Estrogen and progesterone receptor expression can be assessed on paraffin-embedded sections of tumor and immunohistochemically analyzed. Gershenson et al. reported an experience with 64 women with recurrent low grade ovarian carcinoma treated with hormonal therapy, and the overall response rate was 9% with a stable disease rate of 61%. Median progression free survival was 7.4 months. Those patients whose tumors expressed estrogen and progesterone receptors had a longer median time to progression of 8.9 months than those whose tumors expressed the estrogen receptor and no progesterone receptor (6.2 months) [115].

Clear cell carcinoma, characterized by ARID1A mutations, has also been noted to be driven by hypoxia, similar to clear cell cancer of the kidney. Compared to high grade serous carcinomas, clear cell carcinomas have overexpression of the IL6-STAT3-HIF (interleukin 6-signal transducer and activator of transcription 3-hypoxia induced factor) pathway, suggesting that SRC family kinase inhibitors such as dasatinib or by other small molecules that target this pathway, may be effective [116]. Other ovarian cancers that have an ARID1A mutation such as low grade endometrioid ovarian cancers may benefit from treatment with a PARP inhibitor due to the role ARID1A plays in the DNA damage repair pathway [34] or as noted above to EZH2 inhibitors.

The phosphatidylinositol-3-kinase (PI3K) pathway is among one of the most commonly altered pathways in solid malignancies [117], especially ovarian cancer [118], which affects cell metabolism and survival [119]. Multiple pre-clinical studies have investigated direct inhibition of PI3K and mTOR in high grade serous, clear cell and mucinous ovarian carcinomas [120–123]. Various pathway inhibitors have been developed including PI3K, AKT, mTOR, and dual mTOR/PI3K inhibitors. A phase I trial involving an AKT inhibitor, perifosine and docetaxel has been completed in platinum resistant recurrent ovarian cancer

patients that demonstrated acceptable safety and one patient with a partial response and four patients with stable disease [124]. A phase II trial GOG 170-1 has evaluated temsirolimus as a monotherapy in patients with recurrent ovarian cancer and reported a progression free survival of 3.1 months with a partial response rate of 9.3% [125]. Other phase II trials have evaluated the use of mTOR inhibitors and temsirolimus in combination with chemotherapy in the front line setting in patients with clear cell carcinoma. In this study, the combination of carboplatin and paclitaxel with temsirolimus was well tolerated, but when compared to historical controls, this regimen did not statistically increase progression free survival at 12 months [126]. Overall PI3K pathway targeted agents have been disappointing as monotherapy potentially due to lack of a therapeutic index. Combination therapy such as with PARP inhibitors has demonstrated intriguing activity in ovarian cancer and is the target of multiple clinical trials including ones at our center.

Small cell carcinoma of the ovary, hypercalcemic type (SCCOHT), a highly aggressive undifferentiated ovarian cancer, has been characterized by a deleterious germline or somatic inactivating mutations in the SWI/SNF chromatin-remodeling gene in SMARCA4 (aka BRG1), which encodes the BRG1 protein [127–129]. Subsequent studies have suggested that loss of SMARCA4 and SMARCA2 protein expression is both sensitive and specific for SCCOHT [127, 130]. Identification of this variant through profiling and genetic testing could help improve the dismal prognosis of SCCOHT patients. Interestingly, mutations in SMARCA4 can also signal sensitivity to PARP inhibitors similar to ARID1A. This opportunity is being explored in early clinical trials in other tumor lineages.

Trastuzumab, pertuzumab (a recombinant, humanized monoclonal antibody directed against HER2 that inhibits ligand-activated heterodimerization with other HER receptors), and lapatinib (a small molecular dual tyrosine kinase inhibitor of HER2 and EGFR), are a potential treatment options for women with mucinous ovarian carcinoma when the tumor has HER2 amplification and overexpression. However, multiple trials evaluated the role of HER2-direct therapies in ovarian cancer have shown modest (or no) response and lack of relationships between tumor expression of HER2, clinical response or survival benefit [131–134]. Due to the relative rarity of mucinous tumors compared to other histologic subtypes, accrual to a trial with mucinous tumors only would be difficult. Poor response rates have been attributed to intratumoral heterogeneity, alternative signaling and survival pathways, and immune function [135–137].

2.0 Guidelines and recommendations

In March 2014, the Society of Gynecologic Oncology issued a “Clinical Practice Statement: Next Generation Cancer Gene Panels versus Gene by Gene Testing.” This statement cautions providers to consider both the limitations and advantages offered by cancer gene panels (and not germline testing for BRCA mutational status). Panels offer decreased cost, improved efficiency of testing, but the major drawback is the increased complexity of results. A primary concern is how to act on results of uncertain clinical significance, when a variant is identified and the impact on downstream function is unknown. At this time, the practice statement urges clinical management should not be dictated by uncertain variants in BRCA1/2 and other DNA repair genes, rather family history should guide current

recommendations. Referrals to genetic counselors or other knowledgeable medical professionals should be used to help counsel patients on the acquisition of these tests or their interpretation [138].

The National Comprehensive Cancer Network does not address the use of genomic profiling in patients with ovarian cancer in its most recent version (1.2016) [139]. Although the American Society of Clinical Oncology (ASCO) has published guidelines on biomarkers and mutational testing of breast, colorectal, and lung cancers, none currently exist for ovarian cancer [139]. The Gynecologic Cancer InterGroup (GCIG) convened in 2010 and issued a consensus statement [140] on clinical trials in ovarian cancer, recommending collection of biological specimens to clarify the role of genomic aberrations in response to therapy. The European Society for Medical Oncology indicates in their 2013 guidelines for newly diagnosed and recurrent epithelial ovarian cancer that more research is needed to identify molecular markers which could lead to advances in personalized medicine [141].

A number of commercially available tests have become available to physicians and patients in recent years, and the list of available tests continues to grow. Among these, Caris Life Sciences® offers Caris Molecular Intelligence®, which includes multiple testing technologies including immunohistochemistry, chromogenic in situ hybridization, fluorescence in situ hybridization, 46- and 592-gene next-generation sequencing, sanger sequencing, pyro Sequencing and fragment analysis [142]. FoundationOne from Foundation Medicine also offers a genomic profile on solid and liquid tumors using next-generation sequencing, which has been validated [143]. The Clarity Foundation offers a “tumor blueprint” to ovarian cancer patients, which measures a panel of protein biomarkers in over 300 genes [144]. Myriad Genetics as well as other companies offer comprehensive analysis of the spectrum of cancer predisposition genes that are likely to represent markers of sensitivity to PARP inhibitor.

3.0 Conclusion

The genomic architecture of ovarian cancer is heterogenous and complex. Our understanding of this genomically unstable disease has rapidly increased with comprehensive genomic profiling using next-generation sequencing. At this juncture, we continue to acquire more data to identify alterations within a tumor that could potentially be targeted with novel therapeutics to offer hope when current cytotoxic regimens fall short. Within the next decade, we predict that cancer therapy will begin to shift away from empiric chemotherapy in a one-sized fits all approach to treatment. Rather, we will begin to test agents less traditional clinical trial designs and approach treatment from a molecular phenotype as opposed to the tissue of origin. These opportunities will not only apply to targeted therapy but to immuno-oncology agents as well as rational combinations of the two. Importantly, the true utility of targeted and immunotherapy will only be realized in complex diseases such as ovarian cancer through the identification and implementation of rational combination therapies. It is unlikely that monotherapy approaches will demonstrate marked activity in complex epithelial cancers such as ovarian cancer that demonstrate a paucity of molecular drivers. Our current armamentarium of targeted therapies falls short, but with the

possibilities of druggable targets, we will continue to accelerate development of therapeutics to offer more than hope to patients with ovarian cancer.

4.0 Expert commentary

Traditional clinical trials are giving way to newer trial designs, such as basket trials. Basket trials are designed to assess efficacy of a single drug in patients with various types of malignancies that contain a single genomic alteration. They are independent of histology and biomarker selected and driven, which is based on the hypothesis that biomarkers predict respond to targeted therapies across a variety of cancer types [156]. The National Cancer Institute's (NCI) Molecular Analysis for Therapy Choice (MATCH) trial is an ongoing clinical trial that includes patients with any solid tumor or lymphoma that have a targetable genomic aberration. Patients are matched in a series of single arm Phase II studies with a targeted agent without regard to the cancer's tissue of origin. This basket trial enables more efficient testing of potential targets [152]. Consideration to other trial types should be given including "window-of-opportunity" trials. In this trial design, women with newly diagnosed ovarian cancer (as confirmed by pathologic biopsy), would receive a study drug for one to two weeks between the time of biopsy and surgical resection. This allows for evaluation of the targets modulated by the study drug after a given period of exposure time and determine if additional modifications to clinical development should be considered. Additionally, pharmacokinetic assessments can be made on post-resection samples. Alternatively, if the woman received neoadjuvant therapy instead of upfront surgical resection, the biological agent can be added along with traditional chemotherapy for a longer period of time prior to surgery. One of the primary reasons alternative clinical trial designs must be considered is that traditional ways of evaluating response through Response Evaluation Criteria in Solid Tumors (RECIST) criteria, invalid conclusions may be reached about the potential benefit of an investigational agent. Pre-surgical studies such as these may further expedite approval of these agents because they shed light on the biologic effect of the drug early in the development, rather than waiting for the results of Phase II and III studies. Furthermore, they contribute to the validation of markers that will help clinicians identify which patients will best benefit from this type of therapy.

In ovarian cancer patients whose tumors possess actionable mutations, most are not treated on clinical trials with investigational agents. However, clinical trials are frequently open in only a subset of institutions, which limits the diffusion of these therapies, even if they appear to be efficacious. Whether or not insurance carriers will provide coverage to routine profiling of tumors and treatment with an agent off trial if an actionable target is uncovered, remains to be seen. Larger ethical questions of who should be tested and treated, when profiling should occur, and how cost influences these treatment decisions will need to be answered. Other ethical considerations to be addressed will include the possibility that a germline sequence variant is uncovered during a comprehensive genomic profile. How will this information be disseminated to patients and their families?

5.0 Five-year view

The modern clinician faces an emerging problem: how to utilize the sequencing data to select the best therapy for their patient with recurrent ovarian cancer. At the time of this review, targeted, biomarker direct therapy for the treatment of ovarian cancer, with the exception of PARP inhibitors, remains investigational. While most actionable alterations will continue to be treated on protocol, the emergence of multi-disciplinary tumor boards and changes in the way we design clinical trial are among trends in the near future.

The use of genomic profiling to inform therapeutic decisions is currently being undertaken in gynecologic and ovarian cancers through the creation of institutional molecular tumor boards. Another institutional experience with a formalized precision medicine program was published from the University of Oklahoma Health Sciences Center and 62 women were profiled with FoundationOne testing (31 of which were ovarian cancer tumors). Molecular profiling resulted in identification of only a few actionable mutations and so far, only four patients have had therapies matched to their actionable mutations [145].

Several studies have been published that suggest improved clinical benefit in patients with advanced cancer (including lung and breast cancer and melanoma) who received genomically targeted therapy in clinical trials over those patients who do not [146–149]. In 2007, the Initiative for Molecular Profiling and Advanced Cancer Therapy was launched for patients who were referred to the Phase I Program at The University of Texas MD Anderson Cancer Center (Houston, TX). This project sought to use specific targeted therapies to treat patients whose tumors contained targetable alterations on phase I trials. Previous studies found longer time to treatment failure in patients who received matched therapy, high overall response rates, and longer survival [150]. A validation analysis was performed confirming previous observations that in the matched therapy group, a two-month landmark analysis demonstrated that responders have longer survival and progression free survival [151]. However, few of the tumors in these studies were ovarian cancers due to the paucity of actionable mutations and the lack of access to PARP inhibitors for BRCA1/2 mutations during these trials.

Personalized and precision medicine will continue to impact the cancer treatment of patients over the next five years. A meta-analysis of 570 phase II studies (including 32,149 patients) of single agents over three years compared arms of personalized treatment strategies versus no personalization. A personalized strategy was an independent predictor of better outcomes and fewer deaths related to toxicities. Non-personalized targeted therapies had worse outcomes than standard chemotherapy [9]. Several worldwide randomized clinical trials are currently ongoing, including MATCH, I-SPY 2, and PROSPECT [152–154]. These trials are using genomic information to inform treatment decisions in addition to the feasibility and clinical utility of these tests. ASCO has also begun recruiting patients to the Targeted Agent and Profiling Utilization Registry (TAPUR) study, which is a non-randomized clinical trial evaluating the efficacy and safety of targeted therapies prescribed to patients whose tumors have an actionable variant. The primary endpoint for the study is objective response rate or stable disease at 16 weeks, but other endpoints include progression free survival, overall survival, time on treatment, and adverse events [142]. It is important to note that the only

randomized phase II trial to date, SHIVA, failed to demonstrate a benefit for targeted therapy [155]. There are many potential reasons for this failure, however, it does supply a cautionary note.

6.0 Key issues

1. Tumors are undergoing reclassification from site of origin to their genetic criteria.
2. Genomic profiling should not guide decision making for therapy unless a patient is identified to have a BRCA1 or BRCA2 mutation or has enrolled on a clinical trial.
3. Not all somatic or germline mutations are druggable or actionable.
4. Companion biomarkers that predict whether a patient will respond to a current therapy should be developed in parallel with targeted agents.
5. The primary goal of molecular targeted therapy is to match tumors from patients that harbor specific alterations with a matched therapy to induce a response and impact survival.
6. Other types of clinical trial designs, such as basket trials, are designed to assess efficacy of a single drug in patients with various types of malignancies that contain a single genomic alteration.
7. Not all molecular events that function as driver mutations in one cancer may do so in another cancer, and vice versa. In fact, specific alterations in one type of cancer may have opposite behavior in another cancer type and may affect treatment.
8. Predictive biomarkers predict how a patient will respond to a particular intervention, while prognostic biomarkers are those that characterize the outcome, such as survival.

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Reference annotations

* Of interest

** Of considerable interest

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Figure 1.

In normal cells with intact BRCA, PARP functions to repair DNA normally. Treatment with PARP inhibitors inhibits a cell's ability to repair its DNA and leads to cell death. There are multiple mechanisms of PARP inhibitor resistance.

Figure 2.

Precision medicine or targeted therapies are treatments aimed at specific genes, proteins, or receptors on the tumor cell or within the microenvironment.

Table 1

Molecular characteristics of type 1 and 2 ovarian cancer neoplasms.

	Histology	Molecular characteristic
Type 2	High grade serous	TP53 mutation BRCA1/2 HRD WT1 KRAS mutation PIK3CA amplification
	High grade endometrioid	PIK3CA mutation TP53 mutation WT1
Type 1	Low grade serous	KRAS mutation BRAF mutation ER+/PR+ EGFR amplification PIK3CA amplification/mutation PTEN mutation
	Low grade endometrioid	CTTNB1 mutation PTEN mutation PIK3CA mutation ARID1A mutation BRAF mutation
	Clear cell	IL6/JAK2/STAT3 pathway ARID1A mutation PTEN mutation or LOH PIK3CA amplification/mutation EGFR amplification /mutation
	Mucinous	KRAS mutation BRAF mutation HER2 amplification

Table 2

Clinical trials evaluating molecular therapeutics in ovarian cancer patients.

Actionable Target	Therapeutic	Response Rate	Reference	Ongoing Trials
RAS/RAF/MEK	Selumetinib	15%	[114]	NCT00551070
BRCA1/2	Olaparib	18–44%	[96, 97, 157–164]	NCT02571725 NCT02282020 NCT02476968 NCT02340611 NCT01623349 NCT02477644 NCT02484404 NCT02345265 NCT02446600 NCT02502266 NCT02121990 NCT02418624 NCT02485990
	Niraparib	40%	[165]	NCT02354131 NCT02655016 NCT02354586 NCT02657889
	Rucaparib	2%	[166]	NCT01482715
	Veliparib	0–35%	[99, 167–169]	NCT02470585 NCT01749397
EGFR	Gefitinib	4–90%	[170–173]	NCT00317772
	Erlotinib	6–23.1%	[174–179]	
	Cetuximab	4%	[180, 181]	
ER/PR	Anastrozole	9–22%	[115, 182]	NCT02476955 NCT02188550 NCT02584465 NCT02285179
	Tamoxifen			
	Leuprolide acetate			
HER2	Trastuzumab		[60]	
	Pertuzumab	74%	[131]	
	Lapatinib		[134, 183]	NCT02342587
PTEN/PI3K/AKT/mTOR	Perifosine	5%	[124]	
	Temsirolimus	9%	[125]	
	MKC-1		[184]	
SRC	Dasatinib		[180, 185]	NCT02059265
	Saracatinib	53%	[186, 187]	
TP53	MK 1775		[188]	NCT02101775
VEGFR	Bevacizumab	15.9–78.5%	[189–196]	NCT02354131 NCT02393898 NCT01802749 NCT01735071 NCT02606305 NCT02659384 NCT02839707 NCT02641639
	Aflibercept	10–54%	[197, 198]	

Actionable Target	Therapeutic	Response Rate	Reference	Ongoing Trials
	Cediranib	26–44%	[161, 199–201]	NCT02340611 NCT02484404 NCT02345265 NCT02446600 NCT02502266
	Sorafenib	4.7–69%	[202–209]	
	Sunitinib	3.3–16.7%	[210–212]	NCT00979992 NCT01824615
	Pazopanib	18%	[213–215]	NCT01238770 NCT01262014 NCT01402271 NCT01402271 NCT01600573 NCT01610206 NCT02055690 NCT02383251