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HIGHLIGHTS

- The use of chemoresponse assay to inform treatment decisions in recurrent ovarian cancer has the potential to be cost-effective.
- The use of the chemoresponse assay has the potential to be cost-effective in both platinum sensitive and platinum-resistant patients.

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ABSTRACT

Objective. Clinical validation of a chemoresponse assay was recently published, demonstrating a significant increase in overall survival in recurrent ovarian cancer patients treated with therapies to which their tumor was sensitive in the assay. The current study investigates the cost effectiveness of using the assay at the time of ovarian cancer recurrence from the payer's perspective.

Methods. Using a Markov state transition model, patient characteristics and survival data from the recent clinical study, the cumulative costs over the study horizon (71 months) for both the baseline (no assay) and intervention (assay consistent, hypothetical) cohorts were evaluated.

Results. The assay consistent cohort had an incremental cost effectiveness ratio (ICER) of $6206 per life year saved (LYS), as compared to the baseline cohort. Cost-effectiveness was further demonstrated in platinum-sensitive and platinum-resistant populations treated with assay-sensitive therapies, with ICERs of $2773 per LYS and $2736 per LYS, respectively.

Conclusions. The use of a chemoresponse assay to inform treatment decisions in recurrent ovarian cancer patients has the potential to be cost-effective in both platinum-sensitive and platinum-resistant patients.

Introduction

Over 70% of newly diagnosed cases of epithelial ovarian cancer (EOC) present at an advanced stage (stages III–IV), which accounts for the poor prognosis. Advanced stage EOC patients have a median survival of 44 months and a five year survival of 35% to 38% [1–3]. In the United States, the standard of care treatment for patients with advanced stage EOC is cytoreductive surgery, followed by postoperative platinum-based chemotherapy [4]. Despite complete clinical remission in 80% to 90% of patients undergoing the standard of care first-line treatment, 70% to 90% of them relapse, and the majority who relapse experience multiple recurrences that can often be induced into remission by further surgery and chemotherapy [5].

While treatment guidelines for the primary occurrence of advanced stage EOC recommend numerous platinum-based combination therapies, an even greater number of treatment regimens are recommended for recurrent disease. Currently, nearly 10 different platinum-based therapies are recommended for treatment of patients with platinum sensitive (PS) recurrent disease (experiencing recurrence greater than 6 months following first-line treatment), and over 20 different therapies

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(mostly single agents) are recommended for treatment of patients with platinum resistant (PR) recurrent disease (experiencing recurrence within 6 months following first-line treatment) [6], with little to no guidance on how to select among the options. Thus, in the absence of specific directives beyond the primary setting, treatment choices for recurrent EOC patients are made empirically [7].

Despite historical debate regarding their clinical use, chemoresponse assays are a promising method for evaluating individual patient response to a variety of chemotherapy regimens and are gaining clinical validity. A previous economic analysis showed cost savings in a hypothetical cohort of patients treated with assay sensitive therapies [8], and recent multi-site clinical studies reported an association between survival and treatment with assay-sensitive therapies in advanced EOC, thus warranting an economic analysis of this assay based on patient clinical outcomes. A study of 276 women with stage III–IV primary ovarian, fallopian or peritoneal cancer established that the chemoresponse assay result for carboplatin was the only covariate that could identify patients who are platinum resistant (PR) prior to first-line treatment with a platinum-based regimen. Patients with a resistant assay to carboplatin experienced disease progression at almost twice the rate of those who were non-resistant [9]. Additionally, a prospective, non-interventional study evaluated the use of the chemoresponse assay in 262 recurrent or persistent EOC patients. Patients empirically treated with assay-sensitive therapies (physicians were blinded to assay results at the time of treatment selection) experienced significantly improved outcomes over those treated with assay-resistant therapies — a 50% improvement in progression-free survival (PFS) and a 14 month improvement in median overall survival (OS) [10]. Further analysis of this cohort suggests that the chemoresponse assay may be a predictive marker, capable of discerning response to specific treatments [11]. Clinical utility of the assay was also demonstrated in a comparative study wherein the OS of assay-informed primary EOC patients [12] was compared to non-assay-informed (control) patients, collated from four large clinical studies [1–3,13]. Despite moderately worse prognostic clinical factors, patients in the assay-informed arm experienced a 10% improvement in median OS, as compared to the control arm. Furthermore, the median OS in patients treated with assay-sensitive therapies was 65% longer (72 vs. 44 months) than that in the control arm [14].

Based on these observations, the current analysis sought to investigate the relative cost effectiveness of an assay-informed second line treatment regimen relative to assay-uninformed, empiric standard of care, assuming the payer's perspective. Using a Markov state transition model and integrating patient characteristics and clinical outcomes from a recent clinical study, the cost effectiveness of the assay will be evaluated for recurrent ovarian cancer patients, as well as subsets of platinum sensitive and platinum resistant patients.

Methods

Model

This analysis compares two hypothetical cohorts of patients with recurrent EOC who have undergone a secondary surgery or paracentesis, based on the distribution of patients by their assay outcome, as reported in a recent clinical study [10]. In the baseline cohort, patients were assigned to second line treatments using standard clinical practices, without consideration of chemoresponse assay results. The comparator cohort is assay consistent, meaning that the chemoresponse assay was employed (and yielded successful results) and patients were treated with sensitive second line therapies identified by the assay. In the referenced study, 28% of the patients received an on-study treatment that was also a sensitive (S) treatment per the chemoresponse assay (Table 1, row 1) [10]. Patients were also tallied by assay results to therapies other than the on-study treatment and by their platinum sensitivity status (Table 1, row 2). Fifty-four percent of the patients had at least one S treatment identified by the assay and could have received an S treatment in this study; this distribution was used to define the assay consistent cohort.

Using the survival outcomes reported in the referenced study [10], as well as the distributions given in Table 1, a Markov state transition model was built with the following three states: State 1: Remission 2, State 2: Recurrence 2 & Other and State 3: Death (Fig. 1). State 2 encompasses all events from the onset of a second recurrence and preceding death. The cycle length in the model was set at one month and the time horizon at 71 months; the maximum duration of follow-up in Rutherford et al. OS was defined as the length of time from the start of recurrence chemotherapy until death or last contact (for censored patients) [10]. The mean OS was estimated as the area under the estimated cohort survival curve up to 71 months.

To estimate p_{11}, p_{21} and p_{31} (Fig. 1), a marginal Cox proportional hazard regression [15] was used to model the time from remission to disease progression and from remission to death vs. platinum sensitivity status and the assay results. To estimate p_{22} and p_{32}, a conditional proportional hazard regression for recurrent events [16] was used to model the time from disease progression to death. The output from both models is reported in Table 2. These two survival regressions provide probability estimates for the Markov transition matrices in each of the four possible patient groups of platinum sensitivity and assay outcome. Using the weights in Table 1, the weighted sum of the four transition matrices makes up the final transition matrix in each cohort. Details on the computation of the cohort transition probabilities are provided in the Supplementary materials.

The Markov transition model enables survival estimates in each cohort, over the study horizon. Furthermore, this model is used to estimate the average cost per patient in each cohort over the entire time horizon.

Costs

The major costs associated with the treatment of recurrent EOC and considered for this analysis were divided into five categories: cost of the chemoresponse assay, cost of surgery, cost of chemotherapy, cost of adverse events and toxicities, and cost of end of life care. The main source for the cost data in this analysis was the published peer-reviewed literature, although costs of chemotherapy and paracentesis reflect current Medicare pricing. It was assumed that both arms incur the same cost per surgery, end of life care and treatment of toxicities, although the published cost data are more applicable to the baseline cohort, as opposed to the assay consistent cohort. This is a conservative strategy favoring the baseline cohort, since it is unlikely that the prevalence and cost per treatment for toxicity, surgery and end of life care are higher in the assay consistent group. Additionally, all cost figures related to

Table 1
Classification of study patients by platinum sensitivity and assay result (N = 262) [10].

	Platinum sensitive[a] and assay sensitive[b]	Platinum sensitive[a] and assay resistant[c]	Platinum resistant[a] and assay sensitive[b]	Platinum resistant[a] and assay resistant[c]
Actual clinical assignment during blinding	17%	38%	11%	34%
Potential clinical assignment	32%	23%	22%	23%

[a] Platinum sensitivity was the result observed clinically, prior to the beginning of the study.
[b] A patient was classified as "assay sensitive" if at least one therapy tested by the assay had an S result.
[c] A patient was classified as "assay resistant" if all therapies tested by the assay has either an IS or an R result.

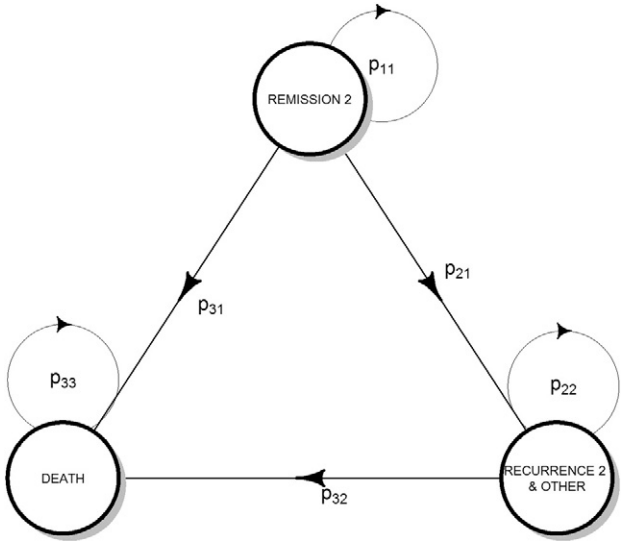

Fig. 1. A three state Markov transition model for recurrent EOC. The three states are State 1: Remission 2 (immediately following a second line treatment at the time of the first recurrence), State 2: Recurrence 2 & Other (all events from the onset of a second recurrence and preceding death) and State 3: Death.

services (surgery, hospitalization for toxicities and end of life care) were adjusted for inflation.

Cost of the chemoresponse assay

The cost of the chemoresponse assay is incurred only by the patients in the assay consistent cohort. Patients in this cohort are assumed to have their tumors evaluated prior to the beginning of second line of therapy (i.e. at the time of the first recurrence). The average cost of the assay (ChemoFx®, Helomics™ Corporation, Pittsburgh, PA) is $434.65 per therapy tested. On average, 10 therapies are tested per tumor, at a cost of $4346.50, which is the cost figure included in this analysis.

Cost of surgery

To reflect the clinical cohort [10], 93% of patients in each of the baseline and assay consistent cohorts were assumed to have undergone a secondary cytoreductive surgery, while 7% in each cohort were assumed to have undergone paracentesis. Both surgery and paracentesis were clinically indicated, and excess tissue or fluid was available for use in the chemoresponse assay; no additional procedures were required to fulfill tissue requirements for the assay. The cost of surgery, inclusive of hospital and physician charges incurred during the surgical hospitalization, ranged from $21,914 to $33,678 in 2009, depending on the complexity of the surgery [17]. The midrange of this interval ($27,796) was used in the current model, adjusted for inflation to 2013 dollars ($30,182). Using current Medicare pricing, the cost of paracentesis ranges from $193.08 to $597.48, depending upon the use of imaging as well as the facility in which the procedure takes place [18]. The average price among the various options was used in the current model ($395.96).

Cost of chemotherapy

All patients in the current model were treated with a second line therapy at the time of the first recurrence. The costs associated with 6 cycles of each chemotherapy regimen, as well as the associated administration costs (in the physician office setting), were estimated using current Medicare physician fee schedule for administration payments and drug pricing database for chemotherapy agents [19,20]. Doses were calculated assuming a body surface area of 1.8 m^2, serum creatinine of 0.9 mg/dL, weight of 170 lb, height of 62 in., and age of 63 years. To estimate the cost of the second line chemotherapy in the baseline cohort, the distribution of administered therapies in the referenced cohort [10] and the costs calculated for the baseline cohort were used (Supplementary Table S1). Thus, the average cost of six cycles of salvage chemotherapy in the baseline cohort was estimated at $7990 in current dollars. The cost of the second line chemotherapy in the assay consistent cohort was estimated by the average cost of all therapies in the highest category of assay sensitivity for each patient; this cost was $4957 in current dollars.

Cost of major adverse events and toxicities

Neutropenia and anemia are two major hematologic adverse events (AEs) related to chemotherapy in EOC. Among the platinum-based therapies, the incidence of grade 3/4 anemia is 1% for carboplatin and 11% for cisplatin, while for the other therapies the incidence ranges from 5% for pegylated liposomal doxorubicin (PLD) to 28% for topotecan [21]. Neutropenia is common with nonplatinum therapies and occurs in 12% of patients administered PLD, 45% of patients administered etoposide and 77% of patients administered topotecan [21]. The current analysis assumes a conservative 5% rate of grade 4 anemia in both cohorts associated with second line chemotherapy and a 3% rate of grade 4 neutropenia. The cost of hospitalization for grade 4 neutropenia and anemia was estimated at $9500 and $3500, respectively, assuming $8000 for the cost of hospitalization for diagnosis and $25,000 for the cost of hospitalization and subsequent death, while an additional 5% are hospitalized for other reasons [22]. Since these cost figures were reported for the year 2013, they have not been further adjusted.

Cost of end of life care

The average cost per patient within 60 days of end of life (EOL) differs dramatically based on the length of time spent in hospice [23]. In a group of patients from 1999 to 2003, the average cost per patient for spending 10 to 60 days in hospice was $15,164. In contrast, the average cost per patient for the same healthcare resources for patients spending 10 days or less in hospice was $59,319 [23]. Based on Medicare records, the percentage of advanced stage ovarian cancer patients receiving hospice care was 74.9% in 2005, of which 26.2% spent seven days or less in hospice [24]. This analysis uses an EOL care rate of 74.9% and conservatively assumes that 26.2% of these patients spend 10 days or less in hospice and incur an average EOL cost of $75,102 per patient in 2013. For the patients spending 10 to 60 days in hospice, an average cost of $19,198 per patient will be assumed.

Table 2
Cox proportional hazard regressions to model the time from remission to disease progression or to death, as compared to platinum sensitivity status and assay results.

Covariates	Marginal model		Conditional model	
	HR (n = 262)	p-Value	HR (n = 262)	p-Value
Platinum sensitivity status (PS vs. PR)	0.60	<0.0001	0.68	0.0001
Chemoresponse assay result (S vs. IS or R)	0.66	0.0052	0.65	0.0003
Event stratum[a]	0.09	<0.0001	0.71	0.0011

[a] In the marginal model, "Event stratum" was a categorical variable denoting two possible events for each patient: disease progression and death since remission. In the conditional model, "Event stratum" was a categorical variable denoting two conditional events for each patient: disease progression since remission and death since disease progression.

Cost-effectiveness and sensitivity analysis

The relative cost effectiveness of the intervention is expressed by the incremental cost effectiveness ratio per life-year saved (ICER/LYS), which is the ratio of the difference in the average costs per patient to the difference in the mean overall survivals. The standard threshold for a healthcare intervention to be deemed cost-effective is an expenditure of between $50,000 and $100,000 per additional year of life saved [25]. Keeping the costs for surgery, individual chemotherapies, EOL care and AE treatment constant between both cohorts, the model results are affected only by the cost of chemoresponse assay and survival outcomes. First, the results are presented in the reference cost effectiveness model (Table 3). To account for the uncertainty in the HR estimates associated with the assay and its impact on the ICER/LYS, the range in the ICER/LYS was estimated by independently sampling 1000 times from each of the two 95% CI of the HRs for the assay. Several stratified analyses for the reference model are also reported. To assess the sensitivity of the model due to the cost of chemotherapy, the scenario when the oncologist chooses the least expensive treatment within the highest category of sensitivity for each patient in the assay consistent cohort was also investigated.

Results

The Markov model median OS and mean OS in the baseline cohort were estimated at 25 and 29.8 months, respectively. By comparison, the median OS and mean OS in the referenced clinical study were 26.5 and 31 months, respectively [10]. In the assay consistent cohort, the Markov model median OS was 28 months and the mean OS was 32.3 months. The modeled average costs per patient in the baseline and assay consistent cohorts were $39,610 and $40,903, respectively. The reference model yielded an ICER of $6206 per LYS for the study horizon (Table 3). When narrowing the comparison to the subgroup of platinum sensitive and assay sensitive patients, the ICER is $2773 per LYS, while in the platinum resistant and assay sensitive patients, the ICER is $2736 per LYS (Table 3). When choosing the least expensive therapy within the patient's highest category of sensitivity, the average cost of six cycles of chemotherapy becomes $1759 in the assay consistent cohort. Introducing this change alone in the model makes the chemoresponse assay a dominant intervention (Supplementary Table S2). The model is sensitive to the cost of chemotherapy, but the upper bound of this source of sensitivity has been tested by assuming the same unit cost of therapy for both cohorts in the reference model (Supplementary Table S1 and Table 3). Despite this conservative assumption, the intervention remains cost effective at the lower $50,000 threshold.

Discussion

Treatment decisions for patients with recurrent EOC are largely guided by response to previous therapy, incident and anticipated toxicity, performance status and disease distribution. However, among any individual cohort, the specific chemotherapy choice is largely empiric, reflecting numerous acceptable regimens. Currently, the most utilized clinical covariate in making individualized treatment decisions is treatment free interval, which informs the use of platinum-based therapy in platinum sensitive patients. However, as with most clinical covariates, its accuracy is not absolute, and additional measures of patient response may be beneficial in further personalizing treatment strategies. Despite several clinical drug trials that have sought to identify preferable treatments, no clear standard of care has emerged, further demonstrating the need for decision support tools in this population where multiple rounds of treatment (due to multiple recurrences) are commonplace.

The current study employs a Markov model to hypothetically compare the cost of treatment decisions that adhere to chemoresponse assay results at the time of second line therapy in patients with recurrent EOC with those that are made empirically, in the absence of chemoresponse testing. Typically, a healthcare intervention, such as a chemoresponse assay, is considered to be cost effective if the comprehensive cost of its use is less than $100,000 per additional life year saved [25]. In the current study, use of and adherence to chemoresponse assay results yield an ICER of $6206 per additional life year saved, suggesting that the assay intervention is cost-effective even at a conservative $50,000 threshold. Furthermore, in analyses of patients with an assay-sensitive result for at least one therapy, the ICER dropped to $2773 per LYS in PS patients and to $2736 per LYS in PR patients, where the need for decision support tools is greater due to poorer prognosis. While the current study examines cost effectiveness in the recurrent EOC setting, future studies are planned which will evaluate the cost effectiveness of this chemoresponse assay across the entire treatment duration of patients with advanced EOC, accounting for its influence in both the primary and recurrent settings.

Although the baseline cohort was designed to mimic a patient cohort [10], and in many respects this goal was met (e.g. the model-based median OS in the baseline cohort was comparable to the median OS observed clinically), the assay consistent cohort is hypothetical, with no equivalent observed patient group for comparison. The survival outcome in the assay consistent cohort was modeled based on the observed survival difference between the patients treated with assay S and R therapies [10] and a hypothetical reassignment of all patients to be treated with an assay S therapy, consistent with the assay results for each patient. The model then assumed that the empirical assignment to treatment (baseline cohort) (Table 1, row 1) and the assay consistent reassignment (assay consistent cohort) could be generalized at the population level. Additionally, the model assumed that the observed survival difference between patients treated with assay S and assay R treatments may be generalized to the greater population.

Since physicians were blinded to assay results in the baseline cohort, there is no concern of bias in the empirical treatment assignments in that cohort (i.e. bias toward 'guessing' the assay assignment). Consequently, the treatment assignments in the assay consistent cohort were independent of those made empirically in the baseline cohort. However, in this analysis, one potential source of bias is inclusion of

Table 3
Results for the reference cost effectiveness model. The range in the ICER/LYS was estimated by independently sampling 1000 times from each of the two 95% CI of the HRs for the assay.

		Baseline cohort	Assay consistent cohort	ICER/LYS (range)
Full cohort	Average cost per patient	$39,610	$40,903	
	Median overall survival	25 months	28 months	$6206
	Mean overall survival	29.8 months	32.3 months	($4578–$10,208)
Platinum sensitive, assay sensitive subgroup	Average cost per patient	$39,514	$40,762	
	Median overall survival	35 months	43 months	$2773
	Mean overall survival	38 months	43.4 months	($1535–$5982)
Platinum resistant, assay sensitive subgroup	Average cost per patient	$39,638	$40,892	
	Median overall survival	23 months	28 months	$2736
	Mean overall survival	26.8 months	32.3 months	($1407–$6720)

subjects who exhibit assay S to all tested treatments as well as those who exhibit assay R to all tested treatments. In the referent clinical cohort only 10% of patients were sensitive to all single agent treatments and 8% were resistant to all [10]. To date, there is no established methodological framework in place for conducting efficient randomized clinical trials for multi-treatment markers such as this chemoresponse assay. This is a new frontier in the biostatistics and marker validation fields that is currently being explored [26,27].

In this study, all unit costs were held constant between the baseline and assay consistent cohorts, with the exception of the cost of the assay in the assay consistent group. The current analysis reveals that the chemoresponse assay may impact the cost of treatment in several ways. Given the association between treatment with an assay S therapy and prolonged OS [10], the assay may reduce or delay the cost of certain treatment aspects, as is the case with EOL care costs. The assay may also optimize the cost of treatment by allowing the physician to not only select an effective therapy, but also select a less expensive chemotherapy among those that are identified as S, with the potential for the assay intervention to be cost-saving (Supplementary Table S2). Of note, doxorubicin, the most expensive chemotherapy included in this analysis, was administered 20% of the time in the baseline cohort while the assay indicated it as effective only 8% of the time in the assay consistent cohort (data not shown). Although not captured in this analysis, the use of a chemoresponse assay in making treatment decisions may potentially reduce toxicities and their associated costs, as well as improve the patients' overall quality of life, by reducing the number of ineffective treatment rounds. The cost effectiveness of the assay may be further enhanced when accounting for these differences. However, the current study assumes identical toxicity profiles across both cohorts, but a change in the therapy distribution could entail a favorable change in the toxicity and AE profiles (type, frequency) toward those patients treated with effective agents, thereby avoiding toxicities, costs, and further compromised quality of life associated with ineffective treatments. Despite these limitations, this analysis was able to estimate an upper bound in the ICER/LYS that still qualifies the intervention as cost-effective.

Given the potential impact on OS and resulting cost-effectiveness in both PS and PR patients, a chemoresponse assay should be considered when developing personalized treatment plans for patients with recurrent EOC.

Conflict of interest statement

Some authors (VP, MJG, SLB) are paid employees of Helomics™ Corporation, which sponsored this work. Other authors received compensation from Helomics™ Corporation for participation in a clinical study (MAP, TJR) and as a member of their speakers' bureau (TCK). The remaining authors (JLK, JKC, RLC) report no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ygyno.2014.11.019.

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