***Chen 2018***

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|---|---|
| **Patient Sampling** | **Country**<br>China<br>**Study design**<br>Cohort study<br>**Population (n)**<br>103<br>**Inclusion criteria**<br>All patients were diagnostically confirmed with epithelial ovarian cancer (EOC) through pathological examination, received no radiotherapy or chemotherapy before surgery, and underwent 6 courses of platinum- containing chemotherapy after the operation.<br>**Exclusion criteria**<br>N/R<br>**Participants included (n)**<br>103 |
| **Patient characteristics and setting** | **Age range**<br>20 to 76 years (mean 42.6±10.5)<br>**Smoking status**<br>N/R<br>**Stage of primary tumour**<br>N/R<br>**Chemotherapy/radiotherapy before therapy?**<br>No<br>**Recurrences (n)**<br>52<br>**Site of recurrences**<br>N/R<br>**Setting**<br>Hospital |
| **Index tests** | **Index tests**<br>human epididymis protein 4 (HE4)<br>**HE4 technique**<br>Enzyme-linked immunosorbent assay (ELISA)<br>**HE4 threshold**<br>70 pmol/L |
| **Target condition and reference standard(s)** | **Target condition**<br>Recurrence of ovarian cancer following surgery and underwent 6 courses of platinum-containing chemotherapy.<br>**Reference standards**<br>Gynecological examination, abdominopelvic ultrasound and computed tomography (CT) or magnetic resonance imaging (MRI) in the abdominopelvic cavity |
| **Flow and timing** | **Follow-up schedule** |

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|---|---|
| | One hundred and three patients with EOC who were admitted to our hospital between January 2013 and January 2014.Follow-up was terminated when recurrence appeared or patient's death, or at the end point of this study (January 2017).<br>**Timing**<br>3 mL of fasting venous blood was additionally collected at the 1st, 3rd, 6th, 12th, 18th, 24th and 36th months after surgery. |
| **Notes** | |

Patient Selection

| **A. Risk of Bias** | |
|---|---|
| Was a consecutive or random sample of patients enrolled? | Unclear |
| Was a case-control design avoided? | Yes |
| Did the study avoid inappropriate exclusions? | Yes |
| **Could the selection of patients have introduced bias?** | Unclear risk |

| **B. Concerns regarding applicability** | |
|---|---|
| **Are there concerns that the included patients and setting do not match the review question?** | Low concern |

Index Test All

tests

| **A. Risk of Bias** | |
|---|---|
| Were the index test results interpreted without knowledge of the results of the reference standard? | Unclear |
| If a threshold was used, was it pre-specified? | Yes |
| **Could the conduct or interpretation of the index test have introduced bias?** | Unclear risk |

| **B. Concerns regarding applicability** | |
|---|---|
| **Are there concerns that the index test, its conduct, or interpretation differ from the review question?** | Low concern |

Reference Standard

| **A. Risk of Bias** | |
|---|---|
| Is the reference standards likely to correctly classify the target condition? | Unclear |
| Were the reference standard results interpreted without knowledge of the results of the index tests? | Unclear |

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|---|---|
| **Could the reference standard, its conduct, or its interpretation have introduced bias?** | Unclear risk |

| **B. Concerns regarding applicability** | |
|---|---|
| **Are there concerns that the target condition as defined by the reference standard does not match the question?** | Low concern |

Flow and Timing

| **A. Risk of Bias** | |
|---|---|
| Was there an appropriate interval between index test and reference standard? | Unclear |
| Did all patients receive the same reference standard? | Unclear |
| Were all patients included in the analysis? | Yes |
| **Could the patient flow have introduced bias?** | Unclear risk |

Notes

| **Notes** |
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***Innao 2016***

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|---|---|
| **Patient Sampling** | **Country** Thailand<br>**Study design**<br>Cohort study<br>**Dates of data collection**<br>N/R **Population**<br>**(n)** 47<br>**Inclusion criteria**<br>Every case of patients who were proved that being an epithelial ovarian cancer. They had been complete treatment by surgery and adjuvant chemotherapy six cycles. Also, they must make consent to participate in the study.<br>**Exclusion criteria**<br>The patients who had been diagnosed that being an epithelial ovarian cancer but refused to participate in the study.<br>**Participants included (n)**<br>47 |
| **Patient characteristics and setting** | **Age range**<br>31 to 80 years<br>**Smoking status** N/R<br>**Stage of primary tumour**<br>FIGO stage III-IV<br>**Perioperative investigations done to ensure no residual disease**<br>N/R **Chemotherapy/radiotherapy?**<br>Chemotherapy<br>**Recurrences (n)**<br>23<br>**Site of recurrences**<br>N/R<br>**Setting**<br>Hospital |
| **Index tests** | **HE4 timing**<br>Every three months until the end of the research<br>**HE4 technique**<br>N/R<br>**HE4 threshold**<br>Two fold from post-operative biomarker<br>**Definition of positive**<br>Above the theshold |

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|---|---|
| | **Which HE4 value (s) used?**<br>N/R |
| **Target condition and reference standard(s)** | **Follow-up schedule**<br>The patients were followed up every month after completion of chemotherapy courses with physical examination, X-rays, CT scan or MRI. HE4 and CA125 were monitored every three months until the end of the research.<br>**Reference standard**<br>Routine physical examination, chest or abdominal X- rays, CT scan or MRI (chest, abdomen or pelvic cavity) |
| **Flow and timing** | **Timing of HE4 vs reference standard (days)**<br>per protocol |
| **Notes** | |

Patient Selection

| **A. Risk of Bias** | |
|---|---|
| Was a consecutive or random sample of patients enrolled? | Unclear |
| Was a case-control design avoided? | Yes |
| Did the study avoid inappropriate exclusions? | No |
| **Could the selection of patients have introduced bias?** | High risk |

| **B. Concerns regarding applicability** | |
|---|---|
| **Are there concerns that the included patients and setting do not match the review question?** | Low concern |

Index Test All tests

| **A. Risk of Bias** | |
|---|---|
| Were the index test results interpreted without knowledge of the results of the reference standard? | Yes |
| If a threshold was used, was it pre-specified? | Yes |
| **Could the conduct or interpretation of the index test have introduced bias?** | Low risk |

| **B. Concerns regarding applicability** | |
|---|---|
| **Are there concerns that the index test, its conduct, or interpretation differ from the review question?** | Low concern |

Reference Standard

| **A. Risk of Bias** |
|---|

| | |
|---|---|
| Is the reference standards likely to correctly classify the target condition? | Yes |
| Were the reference standard results interpreted without knowledge of the results of the index tests? | Yes |
| **Could the reference standard, its conduct, or its interpretation have introduced bias?** | Low risk |

| **B. Concerns regarding applicability** | |
|---|---|
| **Are there concerns that the target condition as defined by the reference standard does not match the question?** | Low concern |

Flow and Timing

| **A. Risk of Bias** | |
|---|---|
| Was there an appropriate interval between index test and reference standard? | Yes |
| Did all patients receive the same reference standard? | Yes |
| Were all patients included in the analysis? | Yes |
| **Could the patient flow have introduced bias?** | Low risk |

Notes

| **Notes** |
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***Manganaro 2013***

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|---|---|
| **Patient Sampling** | **Country**<br>Italy<br>**Study design**<br>Cross-sectional study **Dates of data collection** N/R<br>**Population (n)**<br>21<br>**Inclusion criteria**<br>Patients with epithelial ovarian cancer who show clinical remission after surgery and undergo adjuvant chemotherapy.<br>**Exclusion criteria**<br>N/R<br>**Participants included (n)**<br>21 |
| **Patient characteristics and setting** | **Age range**<br>43 to 85 years<br>**Smoking status** N/R<br>**Stage of primary tumour**<br>FIGO stage III-IV<br>**Perioperative investigations done to ensure no residual disease**<br>N/R **Chemotherapy/radiotherapy?**<br>Chemotherapy<br>**Recurrences (n)**<br>9<br>**Site of recurrences**<br>N/R<br>**Setting**<br>Hospital |
| **Index tests** | **HE4 timing**<br>1-3 months from surgery, 4-6 months from surgery, 7-10 months from surgery.<br>**HE4 technique**<br>HE4 EIA assay (Fujirebio Diagnostics)<br>**HE4 threshold**<br>150 pmol/l<br>**Definition of positive**<br>Absolute concentrations of HE4 are above the threshold<br>**Which HE4 value (s) used?**<br>N/R |

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|---|---|
| **Target condition and reference standard(s)** | **Follow-up schedule**<br>Each patient contributed 3 serum samples drawn at 3- month intervals as follows: time interval I (1-3 months from surgery), time interval II (4-6 months from surgery), time interval III (7-10 months from surgery). |
| **Flow and timing** | **Timing of HE4 (days)**<br>per protocol |
| **Notes** | |

Patient Selection

| **A. Risk of Bias** | |
|---|---|
| Was a consecutive or random sample of patients enrolled? | Unclear |
| Was a case-control design avoided? | Yes |
| Did the study avoid inappropriate exclusions? | Yes |
| **Could the selection of patients have introduced bias?** | Unclear risk |

| **B. Concerns regarding applicability** | |
|---|---|
| **Are there concerns that the included patients and setting do not match the review question?** | Low concern |

Index Test All tests

| **A. Risk of Bias** | |
|---|---|
| Were the index test results interpreted without knowledge of the results of the reference standard? | Unclear |
| If a threshold was used, was it pre-specified? | Yes |
| **Could the conduct or interpretation of the index test have introduced bias?** | Unclear risk |

| **B. Concerns regarding applicability** | |
|---|---|
| **Are there concerns that the index test, its conduct, or interpretation differ from the review question?** | Low concern |

Reference Standard

| **A. Risk of Bias** | |
|---|---|
| Is the reference standards likely to correctly classify the target condition? | Unclear |
| Were the reference standard results interpreted without knowledge of the results of the index tests? | Unclear |
| **Could the reference standard, its conduct, or its interpretation have introduced bias?** | Unclear risk |

| B. Concerns regarding applicability | |
|---|---|
| **Are there concerns that the target condition as defined by the reference standard does not match the question?** | Low concern |

Flow and Timing

| A. Risk of Bias | |
|---|---|
| Was there an appropriate interval between index test and reference standard? | Unclear |
| Did all patients receive the same reference standard? | Yes |
| Were all patients included in the analysis? | Yes |
| **Could the patient flow have introduced bias?** | Unclear risk |

Notes

| Notes |
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*Nassir 2015*

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|---|---|
| **Patient Sampling** | **Country**<br>Germany **Study design**<br>Cross-sectional study **Dates of data collection** N/R<br>**Population (n)**<br>38<br>**Inclusion criteria**<br>Epithelial ovarian cancer patients with platinum-based second-line chemotherapy.<br>**Exclusion criteria**<br>N/R<br>**Participants included (n)**<br>38 |
| **Patient characteristics and setting** | **Age range**<br>N/R<br>**Smoking status**<br>N/R<br>**Stage of primary tumour**<br>N/R<br>**Perioperative investigations done to ensure no residual disease**<br>N/R **Chemotherapy/radiotherapy?**<br>Second-line chemotherapy<br>**Recurrences (n)**<br>15<br>**Site of recurrences**<br>N/R<br>**Setting**<br>Hospital |
| **Index tests** | **HE4 timing**<br>Six months after the end of last platinum-based second- line chemotherapy cycle<br>**HE4 technique**<br>HE4 EIA assay (Fujirebio Diagnostics AB, Gothenburg, Sweden)<br>**HE4 threshold**<br>50 pM<br>**Definition of positive**<br>Above the threshold<br>**Which HE4 value (s) used?**<br>N/R |

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|---|---|
| **Target condition and reference standard(s)** | **Follow-up schedule**<br>Six months after the end of last platinum-based first-line chemotherapy cycle<br>**Reference standard**<br>Response Evaluation Criteria In SolidTumours (RECIST) criteria or according to CA125 variations (GCIG-criteria) |
| **Flow and timing** | **Timing of HE4 vs reference standard (days)**<br>per protocol |
| **Notes** | |

Patient Selection

| **A. Risk of Bias** | |
|---|---|
| Was a consecutive or random sample of patients enrolled? | No |
| Was a case-control design avoided? | Yes |
| Did the study avoid inappropriate exclusions? | Yes |
| **Could the selection of patients have introduced bias?** | High risk |

| **B. Concerns regarding applicability** | |
|---|---|
| **Are there concerns that the included patients and setting do not match the review question?** | Low concern |

Index Test All tests

| **A. Risk of Bias** | |
|---|---|
| Were the index test results interpreted without knowledge of the results of the reference standard? | Unclear |
| If a threshold was used, was it pre-specified? | No |
| **Could the conduct or interpretation of the index test have introduced bias?** | High risk |

| **B. Concerns regarding applicability** | |
|---|---|
| **Are there concerns that the index test, its conduct, or interpretation differ from the review question?** | Low concern |

Reference Standard

| **A. Risk of Bias** | |
|---|---|
| Is the reference standards likely to correctly classify the target condition? | Yes |
| Were the reference standard results interpreted without knowledge of the results of the index tests? | Unclear |

| | |
|---|---|
| **Could the reference standard, its conduct, or its interpretation have introduced bias?** | Unclear risk |

| **B. Concerns regarding applicability** | |
|---|---|
| **Are there concerns that the target condition as defined by the reference standard does not match the question?** | Low concern |

Flow and Timing

| **A. Risk of Bias** | |
|---|---|
| Was there an appropriate interval between index test and reference standard? | Unclear |
| Did all patients receive the same reference standard? | Yes |
| Were all patients included in the analysis? | Yes |
| **Could the patient flow have introduced bias?** | Unclear risk |

Notes

| **Notes** |
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***Plotti 2012***

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|---|---|
| **Patient Sampling** | **Country**<br>Italy<br>**Study design**<br>Case-control<br>**Dates of data collection**<br>N/R **Population**<br>**(n)** 34<br>**Inclusion criteria**<br>(1) aged between 18 and 80 years; (2) Eastern Cooperative Oncology Group performance status 0-2 according to World Health Organization criteria; (3) informed consent obtained from the patients.<br>**Exclusion criteria**<br>(1) abnormal cardiac, hematological, renal, respiratory, and/or hepatic functions; and (2) presence of a secondary malignancy.<br>**Participants included (n)**<br>34 |
| **Patient characteristics and setting** | **Age range**<br>38 to 67 years<br>**Smoking status** N/R<br>**Stage of primary tumour**<br>FIGO stage I-III<br>**Perioperative investigations done to ensure no residual disease**<br>N/R<br>**Chemotherapy/radiotherapy?**<br>Twenty-nine patients (85 %) previously underwent primary cytoreduction followed by adjuvant platinum- based chemotherapy, five patients (11.8 %) received neoadjuvant chemotherapy before first debulking surgery followed by adjuvant platinum-based chemotherapy, and two patients (15 %) underwent primary cytoreduction without adjuvant chemotherapy. **Recurrences (n)**<br>34<br>**Site of recurrences**<br>Pelvis in 15 patients, lymph nodes in 10 patients, liver and/or spleen in 9 patients.<br>**Setting**<br>Hospital |
| **Index tests** | **HE4 timing**<br>The day before secondary surgery |

| | |
|---|---|
| | **HE4 technique**<br>HE4 EIA assay (Fujirebio Diagnostics)<br>**HE4 threshold**<br>70 pmol/L<br>**Definition of positive**<br>Above the threshold<br>**Which HE4 value (s) used?**<br>The day before secondary surgery |
| **Target condition and reference standard(s)** | **Follow-up schedule**<br>N/R<br>**Reference standard**<br>Radiologic imaging(CT, MRI, and/or Positron EmissionTomography (PET/CT)), histologically confirmation |
| **Flow and timing** | **Timing of HE4 vs reference standard (days)**<br>per protocol |
| **Notes** | |

Patient Selection

| **A. Risk of Bias** | |
|---|---|
| Was a consecutive or random sample of patients enrolled? | Unclear |
| Was a case-control design avoided? | No |
| Did the study avoid inappropriate exclusions? | Yes |
| **Could the selection of patients have introduced bias?** | High risk |

| **B. Concerns regarding applicability** | |
|---|---|
| **Are there concerns that the included patients and setting do not match the review question?** | High concern |

Index Test All tests

| **A. Risk of Bias** | |
|---|---|
| Were the index test results interpreted without knowledge of the results of the reference standard? | No |
| If a threshold was used, was it pre-specified? | Yes |
| **Could the conduct or interpretation of the index test have introduced bias?** | High risk |

| **B. Concerns regarding applicability** | |
|---|---|
| **Are there concerns that the index test, its conduct, or interpretation differ from the review question?** | High concern |

Reference Standard

| **A. Risk of Bias** | |
|---|---|
| Is the reference standards likely to correctly classify the target condition? | Yes |
| Were the reference standard results interpreted without knowledge of the results of the index tests? | Yes |
| **Could the reference standard, its conduct, or its interpretation have introduced bias?** | Low risk |

| **B. Concerns regarding applicability** | |
|---|---|
| **Are there concerns that the target condition as defined by the reference standard does not match the question?** | High concern |

Flow and Timing

| **A. Risk of Bias** | |
|---|---|
| Was there an appropriate interval between index test and reference standard? | Yes |
| Did all patients receive the same reference standard? | Unclear |
| Were all patients included in the analysis? | Yes |
| **Could the patient flow have introduced bias?** | Unclear risk |

Notes

| **Notes** |
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***Steffensen 2016***

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|---|---|
| **Patient Sampling** | **Country** Sweden<br>**Study design**<br>Cohort study<br>**Dates of data collection**<br>N/R **Population**<br>**(n)** 88<br>**Inclusion criteria**<br>The current study included patients with ovarian cancer who had completed first-lineombination chemotherapy. Patients with a serum sample drawn at the end of chemotherapy and ≥2 post-chemotherapy blood samples were included in the study.<br>**Exclusion criteria**<br>N/R.<br>**Participants included (n)**<br>88 |
| **Patient characteristics and setting** | **Age range**<br>28 to 77 years (Median 64)<br>**Smoking status**<br>N/R<br>**Stage of primary tumour**<br>FIGO stage I-IV<br>**Perioperative investigations done to ensure no residual disease**<br>N/R **Chemotherapy/radiotherapy?**<br>Chemotherapy<br>**Recurrences (n)**<br>55<br>**Site of recurrences**<br>N/R<br>**Setting**<br>Hospital |
| **Index tests** | **HE4 timing**<br>Peripheral venous blood samples drawn at the end of chemotherapy and at every scheduled follow-up visit. **HE4 technique**<br>HE4 EIA kit (Fujirebio, Diagnostics AB)<br>**HE4 threshold**<br>41 pmol/l<br>**Definition of positive**<br>Above the threshold<br>**Which HE4 value (s) used?** |

| | |
|---|---|
| | N/R |
| **Target condition and reference standard(s)** | **Follow-up schedule**<br>Every 3 months for the first two years, every 6 months for the third year, and once a year for the fourth and fifth years.<br>**Reference standard**<br>Gynecological Cancer Intergroup CA125 criteria and/or radiological confirmation |
| **Flow and timing** | **Timing of HE4 vs reference standard (days)**<br>per protocol |
| **Notes** | |

Patient Selection

| **A. Risk of Bias** | |
|---|---|
| Was a consecutive or random sample of patients enrolled? | Yes |
| Was a case-control design avoided? | Yes |
| Did the study avoid inappropriate exclusions? | Yes |
| **Could the selection of patients have introduced bias?** | Low risk |

| **B. Concerns regarding applicability** | |
|---|---|
| **Are there concerns that the included patients and setting do not match the review question?** | Low concern |

Index Test All
tests

| **A. Risk of Bias** | |
|---|---|
| Were the index test results interpreted without knowledge of the results of the reference standard? | Yes |
| If a threshold was used, was it pre-specified? | No |
| **Could the conduct or interpretation of the index test have introduced bias?** | High risk |

| **B. Concerns regarding applicability** | |
|---|---|
| **Are there concerns that the index test, its conduct, or interpretation differ from the review question?** | Low concern |

Reference Standard

| **A. Risk of Bias** | |
|---|---|
| Is the reference standards likely to correctly classify the target condition? | Yes |
| Were the reference standard results interpreted without knowledge of the results of the index tests? | Yes |

| | |
|---|---|
| **Could the reference standard, its conduct, or its interpretation have introduced bias?** | Low risk |

| **B. Concerns regarding applicability** | |
|---|---|
| **Are there concerns that the target condition as defined by the reference standard does not match the question?** | Low concern |

Flow and Timing

| **A. Risk of Bias** | |
|---|---|
| Was there an appropriate interval between index test and reference standard? | Yes |
| Did all patients receive the same reference standard? | Yes |
| Were all patients included in the analysis? | Yes |
| **Could the patient flow have introduced bias?** | Low risk |

Notes

| **Notes** |
|---|