

# Ovarian cancer

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## Abstract

Epithelial ovarian cancer (EOC) describes a group of diseases characterized by differing pathogeneses, molecular profiles, histologies and prognoses. The low incidence of each distinct histological type of EOC poses challenges for obtaining an accurate diagnosis, robust evidence to guide management, and a mechanistic understanding to ensure availability of effective therapies. Most EOCs, including high-grade serous ovarian cancer, predominantly originate from the fimbriated ends of the fallopian tube, whereas low-grade serous, clear cell, endometrioid and mucinous EOCs are thought to originate from other tissues. Despite recognized genetic susceptibilities for the disease, no effective screening is available and late-stage diagnosis remains common. Known genetic susceptibilities are addressed by risk reduction surgery including removal of both fallopian tubes and both ovaries. Management is predominantly based on adequate surgery and chemotherapy with carboplatin and paclitaxel, with the addition of anti-angiogenic therapy as indicated. The incorporation of poly(ADP-ribose) polymerase inhibitors into first-line therapy has considerably altered outcomes in some women with EOC who have defective homologous recombination DNA repair, including in those with *BRCA1* and/or *BRCA2* mutations. Other molecular characteristics are important in distinct types of EOC, but the use of matched targeted therapies remains under investigation, as does the role of immunotherapy for EOC, for which trial data have been disappointing to date. Translationally enriched clinical trials will be important to further explore and validate accurate biomarkers to better guide clinical care.

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## Introduction

Epithelial ovarian cancer (EOC), which is characterized by its epithelial cell origin, and similarities in morphological appearance and clinical approaches, is not a single entity but includes malignancies with distinct molecular profiles and mechanisms, histologies and prognoses. Each distinct histological type of EOC is rare<sup>1</sup>, necessitating optimization of research and clinical trial design to support focused management guidelines by EOC type.

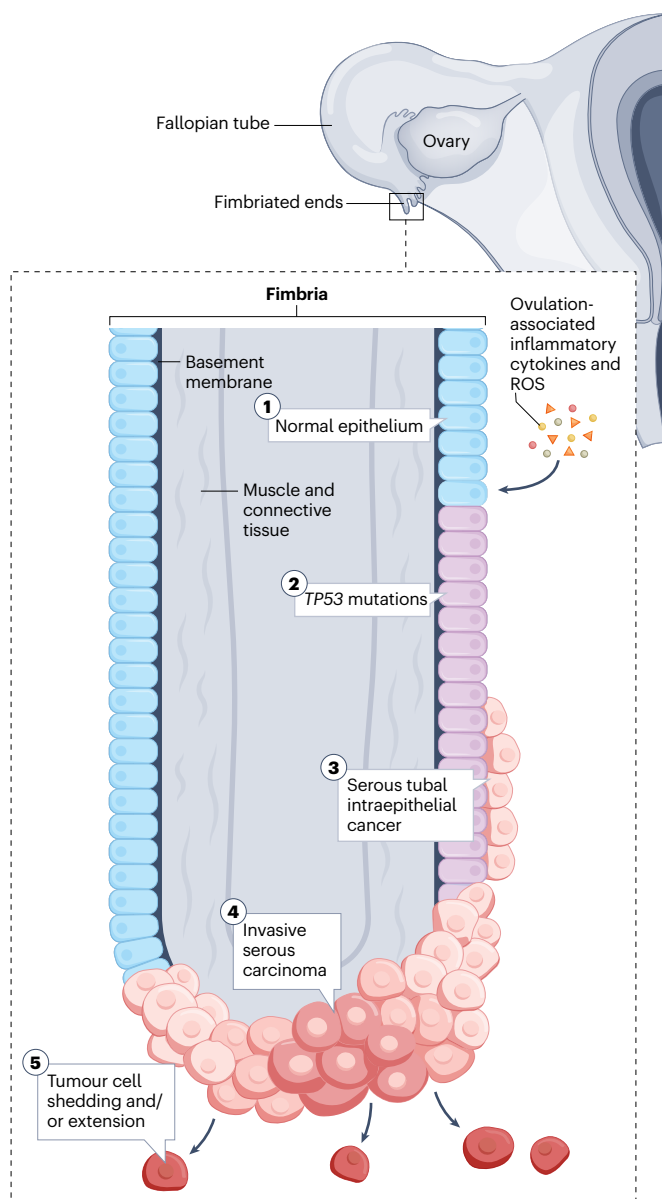
Around 85% of EOC are high-grade serous ovarian cancer (HGSOC), high-grade endometrioid ovarian carcinoma and high-grade serous fallopian tube cancer (HGSFT), which are collectively called HGSOE in this Primer<sup>2</sup>. The fimbriated ends of the fallopian tube are recognized as the origin of intraepithelial malignancy that progresses to HGSOC<sup>3</sup> (Fig. 1). Early dissemination and late-stage presentation are due to tumour cell shedding into the abdominal cavity (Fig. 2). This shedding or transformation of peritoneal cells into Müllerian-type

structures can account for primary peritoneal cancer<sup>4</sup>. Primary peritoneal cancer is also included in the broad HGSOE category, as all these malignancy types have overlapping biology, cell of origin, molecular and metastatic mechanisms, treatment recommendations and patient outcomes.

In this Primer, we discuss diagnostic approaches for EOC, the challenges of screening and prevention and the main aspects of management. We also provide insights for the less common types of EOC: low-grade serous ovarian cancer (LGSOC), clear cell ovarian cancer (CCOC) and mucinous ovarian cancer (MOC). All EOC are managed based on the extent of disease using combined surgicopathological criteria according to the International Federation of Gynaecology and Obstetrics (FIGO) guidelines and TNM staging<sup>2,5</sup>. It is recommended that most patients receive primary debulking surgery (PDS) followed by adjuvant chemotherapy with a platinum-based and a taxane-based agent. For patients in whom PDS is not feasible at first diagnosis, including those with more advanced disease and associated morbidity, neoadjuvant chemotherapy (NACT) is recommended<sup>6</sup>. Maintenance therapy has emerged as an important consideration<sup>7–9</sup>.

Landmark advances in the past 5 years have included phase III clinical trial evidence supporting the clinical utility of poly(ADP-ribose) polymerase inhibitor (PARPi) (such as olaparib) therapy and recognition of the long-term risks of PARPi therapy, which inform how, when and for whom PARPi should best be used. We further also discuss the importance of symptom management, survivorship and quality of life (QOL), especially in the maintenance setting, and the strikingly improved outcomes in selected subsets of women with HGSOC. Unfortunately, most patients with HGSOC experience recurrence of their cancer and die of the disease. We summarize current knowledge of the process of disease progression and development of platinum-resistant ovarian cancer (PROC). PROC is defined as disease progression within 6 months of completion of primary platinum-based chemotherapy (a platinum agent, either alone or usually in combination with a taxane, such as paclitaxel); by contrast, platinum-sensitive ovarian cancer is defined as disease that progresses after 6 months of completion of primary platinum-based chemotherapy, and refractory disease is defined as disease that progresses during primary treatment<sup>10</sup>. We also highlight relevant differences for the less common types of EOC, emerging changes in EOC management and the direction of future clinical trials.

The following extremely rare EOC types, unless indicated, are not addressed in depth in this Primer, as we focus on providing broad standard of care (SOC) approaches to EOC management: mesonephric-like carcinoma of the ovary (frequency <1%)<sup>11</sup>, small cell carcinoma of the ovary–hypercalcaemic type (<0.1%)<sup>12</sup>, and squamous cell carcinoma of the ovary, which is usually derived from a transformed teratoma<sup>13</sup>. In addition, non-epithelial ovarian cancers, such as germ cell tumours and sex cord stromal tumours, granulosa cell tumour and Sertoli–Leydig cell tumours<sup>14</sup>, which account for ~10% of all ovarian cancers, are not discussed.



**Fig. 1 | Origin of intraepithelial ovarian malignancy and disseminated epithelial ovarian cancer.** The ovaries are small organs in proximity to the fimbriated ends of the fallopian tubes. The most prevalent type of epithelial ovarian cancer is high-grade serous ovarian cancer originating from the fimbriated ends. The fallopian tube epithelium is composed of a single layer of ciliated and secretory epithelial cells that are exposed to ovulation-associated inflammatory cytokines and reactive oxygen species (ROS). Evaluation of tubal cells shows early acquisition of *TP53* mutation, prior to detectable malignant and premalignant (serous tubal intraepithelial cancer) lesions. Steps 1–5 demonstrate the progression from premalignancy to invasive and shedding disease.

## Epidemiology

### Incidence, prevalence and survival

EOC is the eighth most common cancer affecting women worldwide, accounting for almost 325,000 new cases and >206,000 deaths in 2022 (ref. 15). In a 2021 Global Burden of Disease Study analysis, the total incidence of ovarian cancer was 0.2 million (95% uncertainty interval 0.2–0.3) and total deaths were 0.1 million (95% uncertainty interval 0.1–0.2), both of which had increased by >80% from 1990 (ref. 16). The incidence in individuals aged ≤39 years had also increased between 1990 and 2021. In the 2023 US cancer statistics analysis, the 5-year survival rate for stage I EOC was >90%, whereas the overall 5-year survival rate was only 50% owing to advanced stage presentation and a low cure rate<sup>17</sup>. The likelihood of recurrence and death from disease is higher in patients diagnosed with advanced-stage ovarian cancer (70–80%) than in those with an early-stage diagnosis (~25%)<sup>18</sup>.

Globally, ovarian cancer incidence and mortality are projected to rise sharply in low-income and middle-income regions, such as Africa, South Asia, Southeast Asia and Latin America, where limited diagnostic and treatment infrastructure contributes to high mortality-to-incidence ratios and growing disability-adjusted life years (DALY) (Box 1). Incidence, prevalence and DALY rates are also increasing among younger women, particularly in South Asia, the Caribbean and western sub-Saharan Africa, reflecting shifting reproductive patterns and metabolic risk factors in these populations<sup>19–25</sup>.

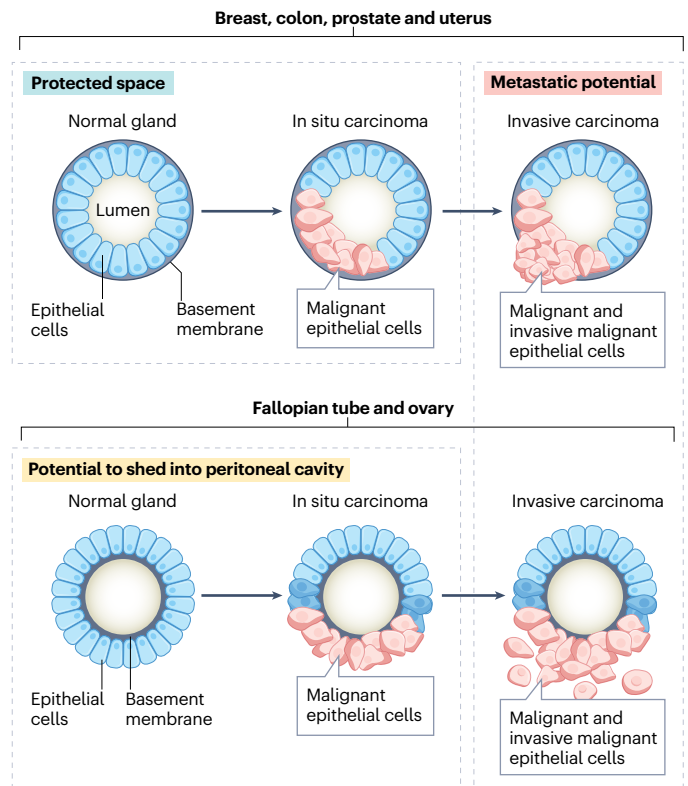
HGSOC incidence has been highest in high-income countries of northern Europe and North America. However, the rates in eastern Europe and parts of Asia have risen, particularly in women <50 years of age<sup>26</sup>. The reported declining incidence of EOC observed in high-income countries<sup>27</sup> may be a classification artefact, in part due to the recognition that EOC originates from the fallopian tube fimbriae<sup>28</sup>, leading to recoding of HGSOC as HGSFT. HGSOC accounts for ~68% of EOC including ovarian carcinosarcoma (OCS) (<5%) on the same epithelial spectrum (Table 1). The next most common type is CCOC (~10%), followed by low-grade endometrioid ovarian cancer (LGEIOC) (~10%), LGSOC (3%) and MOC (4%)<sup>29–32</sup>.

The relative frequencies of EOC types vary across geographical regions and ethnicities. CCOC accounts for 5–12% of EOC in North America and western countries, but has a prevalence of 25–30% in Japan and East Asia, for reasons that are unclear<sup>33–35</sup>. Of note, CCOC is genomically more similar to endometrial clear cell carcinoma, both being considered endometriosis-associated diseases, than to clear cell renal cell carcinoma, which has a distinct molecular profile<sup>36</sup>.

### Risk factors

Advanced age, nulliparity, a germline pathogenic variant in a recognized ovarian cancer susceptibility gene or a family history of ovarian cancer are established risk factors. By contrast, oral contraceptive use, parity or risk-reducing surgery are protective<sup>37,38</sup>. Most risk factors are not modifiable, contributing to the challenges of ovarian cancer prevention. In addition, the strengths of associations of ovarian cancer risk factors are heterogeneous and differ across EOC types. Broadly, the median age range at diagnosis of HGSOC is 62–64 years, with presentation one to two decades earlier in individuals with germline *BRCA1* mutations or one decade earlier in individuals with *BRCA2* mutations<sup>39</sup>.

Germline pathogenic variant alleles in *BRCA1* and *BRCA2* (*BRCA1/2*), which lead to impairment in homologous recombination DNA repair (HR), are the most common risk factors for EOC<sup>40</sup>. They lead to the development of HGSOC, and account for up to 75% of familial



**Fig. 2 | Ovaries and fallopian tubes are ‘inside-out’ organs: distinctive dissemination of epithelial ovarian cancer.** The epithelial cell layer of the fallopian tube and the ovary rest on top of the basement membrane and are, therefore, exposed to the abdominopelvic cavity. This is in contrast, or seemingly ‘inside-out’, to the common epithelial structure in normal and malignant but non-invasive breast, prostate, endometrial and colon organization, where the basement membrane creates an anatomical barrier that (malignant) cells must traverse. This arrangement facilitates early and potentially rapid tumour cell dissemination by shedding, consistent with the predominantly late-stage presentation of high-grade serous ovarian cancer with tumour seeding to the abdomen, on the serosal surfaces of the liver and bowel, and on the peritoneum.

EOC risk<sup>41,42</sup>. The cumulative ovarian cancer risk to age 80 years is ~44% (95% CI 36–53%) in those with *BRCA1* mutations and ~17% (95% CI 11–25%) in those with *BRCA2* mutations<sup>43</sup>. Germline pathogenic variants in *BRCA1/2* occur in up to 17% of individuals with HGSOC, and variants in other genes with related effects occur in an additional 6% of those with HGSOC, irrespective of family history<sup>40,41</sup>. Mutations in genes involved in DNA mismatch repair account for ≤5% of familial EOC risk through individuals with Lynch syndrome, presenting predominantly with CCOC and LGEIOC<sup>44–46</sup>. Higher parity, age at menopause and endometriosis are also associated with CCOC and LGEIOC<sup>47</sup>. The recognition of the role of different risk factors within EOC types has important potential implications for preventive measures.

### Mechanisms/pathophysiology

#### HGSOC

Pathological, epidemiological, molecular, genetic and mouse model studies have shown that the likely progenitors of most, if not all, HGSOCs are the secretory epithelial cells of the distal fallopian tube.

## Box 1 | Global health issues for ovarian cancer

### Major global health issues

**Disparities in disease burden.** Incidence and mortality are rising sharply in Africa, Southeast Asia, South Asia, western sub-Saharan Africa and Latin America. Mortality and morbidity are complicated by limited healthcare infrastructure, poor awareness and sociodemographic disadvantages<sup>19–21</sup>.

**Access to care.** Survival is considerably lower in regions with lower sociodemographic index due to limited access to advanced diagnostic tools, treatments and cancer management systems. Disparities affecting minority groups are also found within high-income countries<sup>22</sup>.

**Economic impact.** Annual global costs exceed US\$70 billion, including productivity losses and care-giver time, with 2.5 million working days lost every year<sup>23</sup>.

**Lack of a reliable screening test.** Epithelial ovarian cancer symptoms are non-specific and screening options are ineffective, leading to diagnosis at advanced stages in >75% of patients. There is a pressing need for improved early or population-level detection strategies<sup>24</sup>.

**Rising younger patient burden.** Although predominantly affecting older women, incidence and prevalence among young women

are increasing, especially in developing regions. This results in a considerable increase in disability-adjusted life years, with effects on fertility and psychosocial health<sup>22</sup>.

**Biological and lifestyle risk factors.** *BRCA1/2* mutations, reproductive factors (declining global fertility), high fasting plasma glucose, obesity and environmental exposures (for example, to asbestos) contribute to increasing risk<sup>25</sup>.

### Recommendations endorsed by leading global health authorities

- Strengthening health systems to enable equitable access to diagnostic and therapeutic resources.
- Investing in public health education, awareness campaigns and tailored interventions for high-risk populations.
- Expanding research into screening modalities and targeted therapies.
- Addressing socioeconomic and care-giver impacts through policy reform and workforce support.

Without substantial global action, annual cases and deaths will continue to rise, particularly affecting vulnerable populations, families and communities worldwide, escalating human and financial tolls.

Evaluation of these tubal cells shows early acquisition of *TP53* mutation before the development of detectable malignant and premalignant (serous tubal intraepithelial cancer (STIC)) lesions<sup>28,48</sup> (Fig. 1). However, some HGSOCs seem to arise without fallopian tube involvement and, therefore, precursor cells in the ovary cannot be ruled out<sup>3,49,50</sup>. Primary peritoneal cancer, identified in the absence of ovaries and fallopian tubes or detectable disease in the ovaries or fallopian tubes, is molecularly and histologically identical to HGSOCs and probably develops owing to shedding of malignant cells into the local microenvironment from early fallopian tubal lesions (Fig. 2).

DNA damage and deficiencies in its repair are essential in HGSOC oncogenesis and response to treatment<sup>51</sup>. The most common causes of loss of HR function are germline and/or somatic mutations in *BRCA1/2*. Dysfunction of p53 activity by pathogenic mutation in *TP53* (96.7% of HGSOC) is a molecular driver and obligate early event in HGSOC development, leading to impaired DNA repair, cell cycle regulation and tumour cell surveillance<sup>48</sup>. The remaining few cases of HGSOC have an alternative alteration in the p53 pathway, such as *MDM2* or *MDM4* amplification<sup>48</sup>. *BRCA1/2* loss, either before (germline) or possibly after (somatic) a *TP53* aberration, disables HR and near-universal *TP53* mutations disable the p53 damage response checkpoint. Cells with these aberrations survive with unrepaired double-strand breaks, accumulate chromosomal rearrangements and progress from STIC and STIC precursor lesions (p53 signatures) to invasive ovarian carcinoma<sup>52</sup>. Most additional molecular changes occur downstream of these early genomic instability events.

About half of HGSOCs have loss of HR function, including by homozygous loss of function of an HR gene, and harbour a HR deficiency (HRD) genomic signature<sup>51,53</sup>. In up to 17% of HGSOC, this involves a germline mutation in *BRCA1/2* (ref. 41). The HRD phenotype

has been described across all high-grade EOC types with the exception of MOC<sup>41,53</sup>. The most common cause of HRD is a pathogenic (Table 2) germline alteration, which requires additional loss of the second allele, or a somatic alteration, which requires two somatic alteration events for homozygous loss of function<sup>51</sup>. HRD is characterized by a high degree of genomic instability, as well as increased sensitivity to DNA-damaging agents including platinum-based agents and PARPi<sup>54</sup>. HRD-negative HGSOC are functionally HR proficient (HRP).

The proportion of tumours with pathogenic variants of HR genes in other EOC types vary: ~33% of OCS, ~26% of CCOC and <1% of MOC<sup>32,41,42</sup>. Compared with serous EOC, for which *BRCA1/2* variants account for 79% of HRDR gene mutations, non-serous EOC has a much wider distribution of mutations in non-*BRCA* HRDR genes, accounting for a total of 56% of tumours<sup>41</sup>. Up to 15% of non-serous EOC are mismatch repair deficient or are microsatellite instability high, which is due to germline mutation in 4.5% tumours<sup>46</sup>.

Amplification of *CCNE1*, as well as other mechanisms of cyclin E protein upregulation, increases replication stress and is another well-described molecular aberration that is detected in ~20% of HGSOC at diagnosis. It is associated with increased chemotherapy resistance, can increase with the development of resistance to platinum-based agents, and has an HRP phenotype<sup>46,55,56</sup>. *CCNE1* alteration is a dynamic event but can be found de novo at diagnosis. Initial presence and/or acquisition of *CCNE1* upregulation are negative prognostic signs<sup>57</sup>.

### Rare EOC

Both CCOC and LGenOC can arise from endometriosis. *ARID1A* loss-of-function mutations are highly enriched in endometriosis-associated ovarian cancers, occurring in 40–70% of CCOC and 30–40% of LGenOC.

In both histotypes, identical *ARID1A* mutations and loss of ARID1A protein expression are seen in the carcinoma and in contiguous atypical endometriosis but not in distant benign endometriosis, supporting ARID1A inactivation as an early molecular event that links endometriosis to malignant transformation<sup>58</sup>. Both endometriosis-associated CCOC and LGenOC tend to present at a younger age, with smaller, more often unilateral tumours and earlier FIGO stage, whereas non-endometriosis-associated counterparts are more frequently advanced stage, bilateral and associated with ascites at diagnosis. Molecularly, endometriosis-associated tumours are more likely to show canonical endometriosis-linked alterations, such as *ARID1A* and *PIK3CA* mutations, and continuity with atypical endometriosis. By contrast, non-associated CCOC and LGenOC less often show a visible endometriotic precursor, and may have a somewhat different mutation spectrum and microenvironment, although survival differences between the groups are modest or inconsistent across studies<sup>59</sup>. Around half of CCOC have identifiable transition zones from endometriosis into an invasive clear cell component of the ovarian carcinoma<sup>60–62</sup> (Table 1).

Furthermore, the state of the cell of origin may differ between the two types, with secretory-phase endometrium giving rise to CCOC and proliferative-phase endometrium to LGenOC<sup>63</sup>. In CCOC, somatic pathogenic *ARID1A* variants have been identified in endometriosis proximate to the malignancy, supporting *ARID1A* mutation as a molecular driver event<sup>32,33</sup>. Although endometriosis may be associated with only a small fraction of CCOC, nearly half of CCOC have an association with endometriosis<sup>64</sup>. Almost all CCOC show upregulation of hepatocyte nuclear factor 1b (*HNF1B*) and oxidative stress-related genes<sup>34</sup>, as well as somatic pathogenic variants of *ARID1A*, *PIK3CA* and *TERT*<sup>65</sup>. Individuals with CCOC with *TP53* mutations, a rare subset, are more likely to present at an advanced stage, have no antecedent history of endometriosis, and have a worse prognosis compared with the CCOC with *ARID1A* mutations<sup>65</sup>. LGenOC may be synchronous with a low-grade endometrioid endometrial carcinoma<sup>66</sup>. LGenOC has a high frequency of somatic pathogenic variants of *CTNNB1*, *PIK3CA*, *PTEN*, *ARID1A* and *KRAS*, and is obligatory wild-type *TP53* (refs. 33,67).

LGSOC accounts for 3% of EOC and is histologically, molecularly, and clinically distinct from HGSOC<sup>68</sup>. LGSOC may be found in a continuum with serous borderline tumour (also known as low malignant potential tumour). *TP53* and *BRCA1/2* pathogenic variants and HRD are extremely rare events in LGSOC<sup>68</sup>. It is molecularly characterized by oestrogen and progesterone receptor positivity and functionality, and aberrations in the mitogen-activated protein kinase (MAPK) pathway<sup>69</sup>. These include pathogenic variants in *KRAS* (19–55%), *NRAS* (25%) and *BRAF* (5%)<sup>32,68</sup>. Mutations in *BRAF* especially are found more commonly in serous borderline tumours and are associated with decreased progression to invasive disease and an excellent cure rate with surgery<sup>70</sup>, LGSOC with *KRAS* mutations has a better prognosis than wild-type *KRAS* LGSOC, and have been associated with sensitivity to platinum-based agents and improved overall survival<sup>71</sup>.

MOC is a heterogeneous tumour type derived from mucin-secreting cells. It is critical to distinguish MOC from mucinous carcinomas metastatic to the ovary (Krukenberg and Krukenberg-like tumours), as treatment and outcome differ between these tumour types<sup>72,73</sup>. MOC has frequent alterations in *KRAS*, *NRAS*, *TP53* and *BRAF*, and low frequency, but notable, *ERBB2* amplification. Pathogenic *KRAS* variants and *HER2* amplification tend to be mutually exclusive<sup>72–76</sup>.

OCS, on the HGSOC continuum, is an aggressive epithelial tumour with biphasic histology containing both epithelial (carcinomatous) and metaplastic mesenchymal (sarcomatous metaplasia)<sup>77</sup>. Recurrent

pathogenic variants seen in OCS are similar to those in HGSOC (*TP53* and *PIK3CA*) with amplifications in *MYC*, *ERBB2*, *CNNE1* and *MDM2* (refs. 78,79). OCS can have pathogenic variants in *BRCA1* (8–17%) or *BRCA2* (0–10%)<sup>78</sup>. The genomics of the carcinomatous and sarcomatous components are identical and, overall, represent a more mesenchymal (basal) end of the HGSOC spectrum<sup>77</sup>.

## Tumour microenvironment

The microenvironment of EOC is important in the patterns of progression and metastatic spread. The ovary is a permissive environment for growth of malignant cells originating from the fallopian tube by local extension or by shedding into the abdominopelvic cavity<sup>80,81</sup> (Fig. 2). Similarly, the omentum, which is a fatty and highly vascularized tissue, is an optimal environment for EOC growth<sup>82</sup>. Interactions of the tumour and these environments lead to the induction of blood and lymph vessel formation and vessel leakiness. Key cytokines involved in this process include tumour-produced VEGF and IL-6, both of which drive vascularization, induce ascites formation and promote immune senescence<sup>83,84</sup>.

The constitution of the immune tumour microenvironment is prognostic in EOC<sup>85</sup>. High levels of CD8<sup>+</sup> tumour-infiltrating lymphocytes correlate with improved survival, whereas the presence of regulatory T cells, some myeloid subsets and downregulation of specific major histocompatibility complexes correlate with reduced survival<sup>86</sup>. The lack of efficacy of immune checkpoint inhibitors in HGSOC suggests that the immune tumour microenvironment requires further study.

## Diagnosis, screening and prevention

### Clinical presentation and diagnosis

Women with EOC most commonly present with non-specific, generalized and progressive symptoms, including abdominal distension,

**Table 1 | Molecular characteristics of different epithelial ovarian cancer types**

EOC type	Per cent of total EOC	Molecular characteristics	Other notes
High-grade serous <sup>a</sup>	~68	<i>TP53</i> <sup>mut</sup> , genomic instability, PAX8 <sup>+</sup> , WT1 <sup>+</sup>	Precursor: serous tubal intraepithelial carcinoma
Low-grade serous	3	<i>KRAS</i> <sup>mut</sup> , <i>BRAF</i> <sup>mut</sup> , PAX8 <sup>+</sup>	Mutations in <i>BRAF</i> more common in serous borderline tumour
Clear cell	10	<i>ARID1A</i> <sup>mut</sup> , <i>PIK3CA</i> <sup>mut</sup> , <i>PIK3CA</i> <sup>amp</sup>	Up to half have prior endometriosis (more likely to be <i>ARID1A</i> <sup>mut</sup> )
High-grade endometrioid	<1	<i>TP53</i> <sup>mut</sup>	Recategorized within high-grade serous ovarian cancer
Low-grade endometrioid	~10	<i>ARID1A</i> <sup>mut</sup> , <i>PTEN</i> LOH <sup>a</sup> , <i>PIK3CA</i> <sup>mut</sup> , <i>CTNNB1</i> <sup>amp</sup>	Endometrioid ovarian borderline tumour frequency of mutations similar to invasive, 15–30% associated with endometriosis
Mucinous	4	8–10% <i>TP53</i> <sup>mut</sup>	Intestinal type only; if advanced, look for gastrointestinal and appendiceal primary tumour

A further 3% of other exceedingly rare types of epithelial ovarian cancer (EOC) are not included<sup>29–31</sup>. amp, amplification; LOH, loss of heterozygosity; mut, mutant. <sup>a</sup>Including ovarian carcinosarcoma (5% of EOC).

**Table 2 | DNA repair genes associated with epithelial ovarian cancer**

Genes	Germline pathogenic variant frequency (%)		Somatic pathogenic variant frequency (%)	
	HGSOC	NSOC	HGSOC	NSOC
<b>DNA repair by homologous recombination</b>				
<i>BRCA1, BRCA2</i>	15–20	7	5–7	6
<i>RAD51C, RAD51D, PALB2, BRIP1</i>	6	8	<2	7
<b>DNA mismatch repair</b>				
<i>MLH1, MSH2, MSH6, PMS2</i>	<1	5	<1	10

HGSOC, high-grade serous ovarian cancer; NSOC, non-serous ovarian cancer.

early satiety, pain, fatigue, loss of appetite, bowel or bladder dysfunction and/or shortness of breath. Patients are often tested and/or treated for other diagnoses, including common gastrointestinal complaints, delaying a definitive diagnosis. A symptom index<sup>87</sup> may prompt early investigation towards an ovarian cancer diagnosis, which can include assessment of the (non-specific) tumour marker CA125 and imaging, such as pelvic ultrasonography, CT or MRI<sup>88</sup>.

Serum CA125 levels are not validated for screening or diagnosis. They are less reliable in premenopausal women and those with early-stage EOC or non-serous ovarian cancer. Levels may rise with peritoneal irritation due to ascites and carcinomatosis, or infection, inflammation and non-malignant entities, such as endometriosis, adenomyosis, benign ovarian cysts, uterine fibroids, pelvic inflammatory disease, pregnancy, menstruation, liver cirrhosis and heart failure<sup>89</sup>. Scoring systems for screening (improvement in survival) or diagnosis (adequate specificity) based on a combination of CA125 levels, transvaginal ultrasonography findings and menopausal status have been tested, but none has been proven effective; however, in some jurisdictions, they may be used to differentiate a benign ovarian mass from a suspected malignancy<sup>90</sup>. Serum levels of carcinoembryonic antigen (CEA) and CA19-9 may be abnormal at diagnosis of MOC, and assessment of  $\beta$ -human chorionic gonadotropin, lactate dehydrogenase and  $\alpha$ -fetoprotein may be helpful in the differential diagnosis of ovarian germ cell tumours. A CA125 to CEA ratio greater than 25 can support EOC as the primary diagnosis, in the absence of level I evidence, in under-resourced regions where time and distance prohibit immediate tissue evaluation, especially when a patient presents with emergent need for intervention<sup>90</sup>. Differential diagnoses may vary with geographic location and comorbidities, and range from other infectious or inflammatory entities to other malignancies (Box 2). Diagnosing ovarian cancer during pregnancy is difficult because pregnancy-related symptoms, physiological changes in tumour markers, imaging limitations due to fetal safety, and the rarity and heterogeneity of tumours, all obscure or delay recognition of malignancy<sup>91,92</sup>.

Standard imaging with CT of the thorax, abdomen and pelvis using oral and intravenous contrast agent is SOC to evaluate disease distribution<sup>31,90</sup>. Chest radiography and detailed ultrasonography can be used where advanced imaging is not available, and MRI is suitable in patients with an iodine allergy. Imaging is important in all stages to guide staging and planning of treatment (neoadjuvant versus surgical intervention). Imaging techniques that are not validated for diagnosis or monitoring of EOC, but may be recommended by guidelines include diffusion-weighted CT or MRI and fluorodeoxyglucose PET. Some molecular and immunohistochemistry markers can discriminate EOC types (Table 1). WT1 and PAX8 are markers of a Müllerian and a fallopian

tube origin, respectively, and are elevated in HGSOC, with PAX8 also elevated in LGSOC<sup>32,50</sup>.

### Pathological staging

EOC are staged using combined surgicopathological criteria according to the 2014 International FIGO guidelines<sup>2</sup>. An update of these guidelines in 2021 refined the classification of metastasis to retroperitoneal lymph nodes and microscopic peritoneal involvement<sup>5</sup>. Staging requires a tissue pathological diagnosis (needle biopsy or surgical biopsy preferred to cytology of fluid) and surgical or imaging documentation of the extent of disease dissemination<sup>2</sup>. Histological and, if no safe alternative, cytological diagnosis, should be performed by a specialized gynaecological pathologist. Stage I EOC are confined to one ovary (IA) or both ovaries (IB), or have physiological or iatrogenic rupture, disease on the ovary surface, or malignant washings upon surgical entry (IC). Stage II EOC extends into pelvic structures, specifically to uterus and/or fallopian tubes and/or ovaries (IIA), or to other pelvic intraperitoneal tissues (including bladder, rectum or pelvic peritoneum) (IIB). Stage III EOC has spread into the abdominal cavity above the pelvis: positive retroperitoneal lymph nodes only but no intraperitoneal spread (IIIA); macroscopic peritoneal metastasis beyond the pelvis visible to the surgeon, measuring  $\leq 2$  cm in greatest dimension, with or without retroperitoneal lymph node involvement (IIIB); and macroscopic peritoneal disease  $> 2$  cm (with or without nodal involvement (IIIC)). Stage IV disease includes extra-abdominal disease and visceral metastases. Locoregional spread due to shedding into the abdominal cavity onto serosal surfaces, omentum and mesentery, and stasis within obstructed draining lymphatics, are more common than visceral parenchymal metastases, even in patients presenting at an advanced disease stage<sup>93</sup>.

### Molecular diagnostics

It is strongly recommended that all newly diagnosed HGSOC undergo tumour mutational analysis. Molecular information is increasingly

## Box 2 | Differential diagnosis of pelvic mass and symptoms associated with ovarian cancer<sup>204</sup>

- Endometrioma
- Benign tubo-ovarian mass, benign cysts or hydrosalpinx
- Borderline (low malignant potential) ovarian masses
- Subserosal fibroids
- Trophoblastic disease (gestational or non-gestational)
- Pregnancy
- Perimenopausal symptoms
- Polycystic ovary syndrome
- Ovarian hyperstimulation syndrome
- Hormonal intake, including hormone replacement therapy
- Inflammatory bowel disease
- Constipation
- Reflux and gastric ulcer or acidity
- Tubo-ovarian abscess or pelvic inflammatory disease
- Abdominal tuberculosis
- Secondary metastases to ovary from other sites (Krukenberg or Krukenberg-like tumour)

For further information, see ref. 204.

**Table 3 | Outcomes of randomized ovarian cancer screening trials for an average-risk population**

Trial	Screening modality (n)	Key results	
		Stage	EOC mortality
SCSOCS <sup>102</sup>	Combined annual serum CA125 measurement and TUS versus control (82,487)	Stage I EOC frequency no statistically significant increase between screening and control arms (63% versus 38%; $P=0.23$ )	No stage shift or mortality benefit
PLCO <sup>101</sup>	Combined annual serum CA125 measurement (6 years) and TUS (4 years) versus control (78,215)	Stage III–IV EOC frequency similar in the screening and control arms (77% versus 78%)	No stage shift or mortality benefit; specifically, 3.1 deaths per 10,000 person-years in the screening arm versus 2.6 deaths per 10,000 person-years in the control arm
UKCTOCS <sup>99</sup>	Annual multimodal longitudinal serum CA125 measurement (ROCA) with TUS and repeat CA125 measurement as a second-line test versus annual TUS as first-line and second-line tests versus control (202,638)	Multimodal screening versus no screening stage IV EOC incidence 24.5% decreased and stage I EOC incidence 47% increased; TUS versus no screening: no difference	Stage shift but no mortality benefit; specifically, multimodal screening versus no screening ( $P=0.58$ ) or TUS versus no screening ( $P=0.36$ )

EOC, epithelial ovarian cancer; PLCO, the Prostate, Lung, Colorectal and Ovarian Cancer Screening Randomized Controlled Trial; ROCA, Risk of ovarian cancer algorithm; SCSOCS, Shizuoka Cohort Study of Ovarian Cancer Screening; TUS, transvaginal ultrasonography; UKCTOCS, UK Collaborative Trial of Ovarian Cancer Screening Trial.

important in treatment planning<sup>42</sup>, especially if a family member is a carrier of a pathological germline variant in *BRCA1/2* or a Lynch syndrome mismatch repair gene. Molecular tumour testing of HGSOE can affect downstream treatment decisions, such as the incorporation of PARPi into maintenance therapy<sup>54</sup>. A component of mutational analysis is generation of information that can identify HRD status, also a treatment discriminant. Only two HRD assays have been prospectively validated for use in treatment decision-making<sup>51</sup>. Many tests developed in academic and industry settings have also been used, most of which have not been cross-validated against an approved test. A cross-analysis of several commercial HRD assays showed poor overall concordance across assays, raising the concern and challenge for uniform validated HRD testing<sup>94</sup>. Current HRD tests detect extant static levels of genomic scarring, represented by a genomic instability score (for example, calculated as the sum of loss of heterozygosity, large-scale state transition and telomere allele imbalance in one test)<sup>42,51,95</sup>. A pretreatment biopsy HRD result will not represent real-time HRD potential at later lines of treatment as the cancer may have become functionally HRP under treatment pressure and cancer evolution.

In some jurisdictions, testing may be warranted for *KRAS* mutations in LGSOC for consideration of RAF inhibitor combination therapy<sup>96</sup>, and for folate receptor- $\alpha$  expression in HGSOE for consideration of mirvetuximab soravtansine, the first antibody–drug conjugate (ADC) approved for the treatment of ovarian cancer<sup>97,98</sup>.

### Screening and prevention

There are no validated ovarian cancer screening modalities, and screening is not recommended for women at an average population risk of ovarian cancer. Two large negative randomized controlled trials have been reported. The UK Collaborative Trial on Ovarian Cancer Screening (UKCTOCS)<sup>99</sup> used annual and longitudinal serum CA125 measurement, with repeat CA125 measurement and transvaginal ultrasonography (multimodal screening) as second-line tests. The Prostate Lung Colorectal Ovarian (PLCO) cancer screening trial<sup>100</sup> used annual serum CA125 measurement with a single cut-off value and transvaginal ultrasonography<sup>101–103</sup> (Table 3). Both studies focused on the general risk population. Neither of these studies showed an overall survival benefit. Some earlier detection and downstaging of EOC was demonstrated with the multimodal screening in the UKCTOCS study, without effects on mortality<sup>99</sup>. Similarly, the Shizuoka Cohort Study of Ovarian Cancer Screening (SCSOCS) used annual CA125 measurement plus transvaginal

ultrasonography screening in low-risk postmenopausal women. Screening increased detection of earlier-stage disease and enabled a higher rate of complete cytoreduction, but the trial did not demonstrate a statistically significant reduction in ovarian cancer mortality<sup>102</sup>. Potential harms of screening include false-positive results leading to unnecessary surgical procedures. The risk becomes acceptable only if a screening programme achieves very high specificity (around 99.6% with sensitivity  $\geq 75\%$ , giving a positive predictive value of  $\geq 10\%$ ) and has proven mortality benefit in randomized trials; without this, too many women with false-positive tests undergo unnecessary surgery, as seen in the PLCO and UKCTOCS trials, and screening should not be implemented as a population-level public health measure<sup>24</sup>.

Multimodal screening has also been investigated in women deemed at high risk of EOC, including predominantly those with germline *BRCA1/2* mutations. Studies reported to date were non-randomized and unable to examine effects on survival. EOC prevention is essential in women at high risk of the disease. Efforts currently focus on identification of these women through genetic testing, with cascade testing of relatives, so that preventive measures can be offered. Risk-reducing salpingectomy (RRS) or salpingo-oophorectomy decreases lifetime EOC risk in germline *BRCA1/2* carriers by up to 97%<sup>104,105</sup>, and is recommended for those with a  $>4$ –5% lifetime risk of EOC. The use of RRS in this setting is based on the preference to avoid premature menopause in young women (if safe to do so) and the identification of the fallopian tubes as the source of HGSOE, with the finding of serous tubal carcinoma in situ lesions in 4–7% of women at high risk of disease<sup>106</sup> and in 0.4% of the general population<sup>107</sup>. The Sectioning and Extensively Examining the Fimbria (SEE-FIM) protocol is the validated diagnostic pathology standard<sup>108</sup>. The long-term protection provided by RRS has not yet been determined.

Early RRS with delayed oophorectomy in women at high risk of EOC is under investigation (NCT04294927, NCT04251052)<sup>109,110</sup>. Opportunistic bilateral salpingectomy, at the time of an abdominal surgical procedure, is an attractive risk reduction strategy for women at average risk. One population-based retrospective cohort study from British Columbia, Canada, found no HGSOE cancers in 25,889 women undergoing opportunistic RRS compared with 15 HGSOE cancers in 32,080 observed women; the follow-up duration was relatively short: RRS 3.2 years (1.6–5.1 years), control group 7.3 years (4.6–8.7 years)<sup>111</sup>. Prospective studies of opportunistic RRS are required to establish the effect size of EOC risk reduction and mortality.

In the National Comprehensive Cancer Network guidelines, an important addition to prevention strategies has been the genetic screening of all those with EOC (including fallopian tube cancer or primary peritoneal cancer) at any age for mutations in *BRCA1*, *BRCA2* and other relevant high-to-intermediate penetrance genes (such as *RADSIC*, *RAD51D*, *BRIPI* and mismatch repair genes for Lynch syndrome), irrespective of family history<sup>112,113</sup>. The ESMO guidelines exclude purely MOC<sup>114,115</sup>. Family members found to carry a pathogenic variant can be offered cancer prevention strategies<sup>31,116</sup>.

## Management

### Initial management including surgery

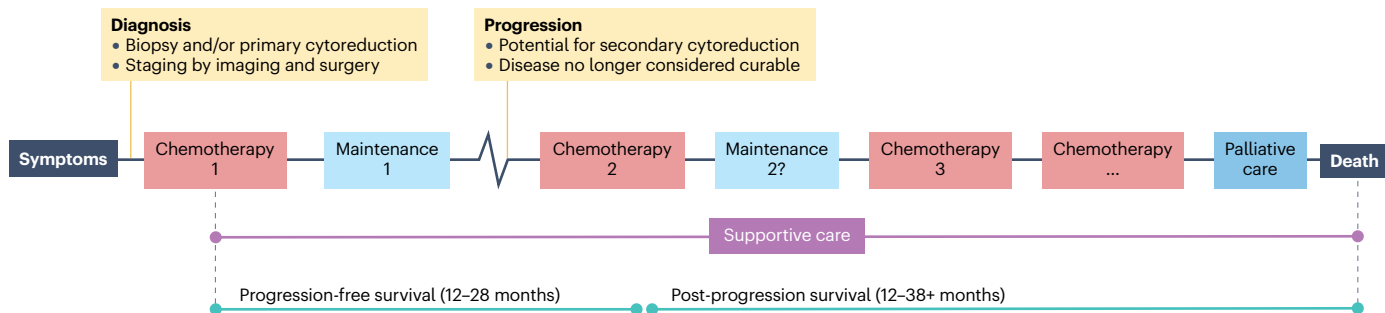
Treatment starts with pathological diagnosis, which is often a component of PDS (Fig. 3). Surgical resection is the most accessible intervention worldwide, and sometimes the only intervention available in under-resourced regions. Improving access to good quality gynaecological oncological surgical care is an important global goal<sup>90</sup>. The ability to cytoreduce to no visible residual disease (also called R0 resection) is affected by surgeon expertise, perioperative and postoperative support, extent of surgical exploration and resection, disease biology and patient preference (Table 3). Surgical intent for this intervention ranges from least invasive (obtaining a diagnostic tissue or fluid sample) to optimal R0 resection. Trial findings underscore the importance of patient selection rather than presumption of benefit for initial surgical plans if full treatment resources are available<sup>117</sup>. Similarly, the role of palliative surgery or limited bowel resection to ameliorate end organ damage is indicated on a case-by-case basis and, if feasible, via multidisciplinary team discussion. Consideration of survivorship starts at diagnosis and continues throughout the patient journey.

Documentation of presumptive early-stage disease can lead directly to surgery if a perioperative frozen section is available to confirm the diagnosis. Alternatively, assessment of early-stage disease can be initiated with a limited tissue sampling for diagnosis followed by completion staging and debulking surgery if malignancy is confirmed. Completion surgery is crucial in determining the type of adjuvant treatment. Systematic pelvic and para-aortic node dissection, peritoneal biopsies and omentectomy can up-stage an apparent stage I cancer to stage III in up to 30% of patients, with implications for both treatment and prognosis<sup>118,119</sup>. Fertility-sparing surgery may be considered in borderline cancer or unilateral invasive disease (stage IA)<sup>119</sup>, and options can be discussed on an individual basis for staging and treatment purposes, followed by completion surgery after completion of childbearing.

The goal of debulking surgery for treatment of advanced EOC is to remove all visible disease. This can be performed either before starting chemotherapy as PDS or after three or four cycles of NACT, when it is called interval debulking surgery (IDS)<sup>120</sup>. The surgery includes removal of as much ovarian cancer as possible and can include bowel resection, splenectomy and/or other visceral resection depending on resource availability, surgical team experience and the medical status of the patient. Bowel resection may be amenable to end-to-end anastomosis or require a temporary or permanent ostomy. Observational and clinical studies have demonstrated that extent of residual EOC after PDS or IDS is one of the strongest independent prognostic factors for survival<sup>121</sup> (Table 4). Maximum survival benefit is obtained with a R0 resection, with survival decrement associated with the extent of residual disease<sup>122</sup>. Consultation with a gynaecological oncologist and allied surgical specialities enables optimal decision-making, incorporating medical oncology input and patient preference.

**Neoadjuvant chemotherapy with IDS.** NACT with IDS was developed for advanced-stage EOC presentation if R0 or minimal residual disease outcomes are not anticipated with PDS. NACT plus IDS was non-inferior to PDS with adjuvant chemotherapy in several trials as discussed in detail in the referenced guidelines<sup>6,123</sup>. PDS remains the gold standard, when the surgical team has determined that complete visible debulking is feasible. The presence of carcinomatosis, extensive ascites (for example, estimated at >500 ml) and/or bulky disease not likely to be resectable to R0 status are now considered relative contraindications for PDS<sup>6,124</sup>. IDS would be preferred over PDS in the presence of extra-abdominal disease or poor performance status<sup>6</sup>. The use of checklists, such as the European Society of Gynaecological Oncology quality indicators and criteria for resectability, are recommended<sup>124</sup> (Box 3). Current guidelines indicate that IDS should be considered after three or four cycles of NACT and followed by completion of three or four further chemotherapy cycles<sup>6</sup>. Diagnostic biopsy followed by NACT is also recommended if a multidisciplinary surgical team capable of achieving optimal cytoreduction is not available. Resource-adapted guidelines for referral and management of newly diagnosed EOC have addressed these issues in their recommendations<sup>90</sup>.

**Hyperthermic intraperitoneal chemotherapy.** Controversy surrounds the use of hyperthermic intraperitoneal intraoperative chemotherapy (HIPEC), despite studies demonstrating overall survival benefit<sup>125</sup>. Concerns raised include lack of controls to determine



**Fig. 3 | Timeline of epithelial ovarian cancer therapy.** A hypothetical patient journey from diagnosis to death from epithelial ovarian cancer involves various interventions, such as imaging, primary debulking and diagnostic surgery for diagnostic confirmation and staging, adjuvant (or neoadjuvant) therapy, maintenance therapy, the potential for interval unmaintained remission, and

subsequent first and later progression of disease with appropriate treatment interventions. Survival after disease progression has improved markedly in EOC, and patients with recurrent disease may have numerous different treatment regimens before a move to palliative and hospice care. Supportive care should be ongoing from the time of diagnosis.

whether benefit is accrued due to the hyperthermia, drug dose intensity and/or intraperitoneal treatment location<sup>126</sup>. Furthermore, the timing of HIPEC (at PDS versus IDS versus debulking at progression) and the chemotherapy agents used all differ between trials. Despite being discussed in several guidelines<sup>6,115,127</sup>, HIPEC is not recognized as a SOC approach in many countries, especially as it is a very resource-intensive intervention.

## Systemic treatment of newly diagnosed EOC

The SOC for newly diagnosed EOC, across most resourced regions, is either PDS with SOC adjuvant chemotherapy or NACT plus IDS (Fig. 3). The worldwide standard minimum treatment is either carboplatin or cisplatin given every 3 weeks for six cycles, with jurisdictional differences in practice. Direction is provided using the most generally supported practices. The optimal treatment is carboplatin with paclitaxel given every 3 weeks for six cycles<sup>95</sup> (Table 4). Weekly carboplatin plus paclitaxel chemotherapy may be considered for patients with a poor performance status and/or impaired kidney function<sup>95</sup>. Addition of anti-VEGF therapy (for example, bevacizumab) to primary chemotherapy and for a further 15 cycles of maintenance chemotherapy is recommended for patients with advanced EOC who have ascites, bulky disease and/or parenchymal disease, based on preplanned subset analyses of progression-free survival (PFS) and overall survival<sup>95,128–130</sup>. Maintenance anti-VEGF therapy for 15 cycles is now standard, given no benefit of extension to 30 cycles in one randomized study<sup>7</sup>.

The role of intraperitoneal chemotherapy in EOC remains controversial, with data from the past decade showing no superiority of this approach in the target population comprising patients with newly diagnosed stage II–III EOC in whom the disease has been optimally cytoreduced to  $\leq 1$  cm (ideally no visible) residual disease, and who have good performance status, limited adhesions and adequate organ function<sup>131</sup>. It is unclear whether the previously described superiority of intraperitoneal therapy compared with intravenous therapy was due to the agent used, agent dose intensity, and/or location and frequency of administration. The most recent studies of intraperitoneal chemotherapy did not demonstrate PFS superiority over SOC intravenous treatment with carboplatin plus paclitaxel plus bevacizumab<sup>132,133</sup>. The role of weekly (dose-dense) paclitaxel administration also remains unclear. The initial study, performed in Japan, showed remarkable benefit. In this trial from 2023, investigating intraperitoneal versus intravenous 3-weekly carboplatin plus weekly administration of paclitaxel, in predominantly Japanese patients, an improvement in PFS was observed in the intraperitoneal administration group<sup>134</sup>. However, this intraperitoneal regimen was not superior to SOC therapy in a predominantly European population<sup>135</sup>, suggesting that the likely explanation may be pharmacogenomic differences between ethnic groups<sup>5</sup>.

**Maintenance therapy.** PARPi administration is a validated maintenance-of-benefit treatment given after successful first-line surgery and platinum-based chemotherapy with the aim of prolonging the duration of response and delaying recurrence in patients with advanced stage HGSOE (Fig. 4). No data exist for use of PARPi in stage I or II EOC or rare EOC histologies. The use of switch maintenance therapy, defined as the introduction of a new therapy for the maintenance phase of treatment, in selected patient groups is supported by four randomized controlled trials<sup>136–142</sup>. Biallelic *BRCA1/2* loss of function due to germline or somatic events is associated with the most consistent and strongest susceptibility of EOC to both platinum-based and PARPi treatment. Similar results have been

**Table 4 | Common chemotherapy regimens used in the treatment of epithelial ovarian cancer**

Regimens per EOC stage	Reference clinical trials
<b>First-line neoadjuvant and adjuvant chemotherapy</b>	
C (AUC 5–6) and P (175 mg/m <sup>2</sup> ) every 3 weeks for six cycles (CP) $\pm$ B maintenance $\pm$ PARPi maintenance	Vergote et al. <sup>130</sup> , GOG 218 (ref. 128), ICON7 (ref. 129)
C (AUC 5–6) every 3 weeks and P (80 mg/m <sup>2</sup> ) weekly on days 1, 8 and 15 every 3 weeks for six cycles $\pm$ B maintenance (see below)	JGOG 3016 (ref. 188), ICON 8B <sup>189</sup> , GOG 262 (ref. 190)
C (AUC 6) and docetaxel (75 mg/m <sup>2</sup> ) every 3 weeks for six cycles	SCOTROC <sup>191</sup>
C AUC 5 and PLD 30 mg/m <sup>2</sup> every 3 weeks for six cycles	MITO-2 (ref. 146)
C (AUC 2) and P (60 mg/m <sup>2</sup> ) weekly on days 1, 8 and 15 every 3 weeks for six cycles	MITO-7 (ref. 192)
P (135 mg/m <sup>2</sup> ) every 3 weeks and i.p. CDDP (100 mg/m <sup>2</sup> on day 2) every 3 weeks and i.p. P (60 mg/m <sup>2</sup> on day 8) every 3 weeks for six cycles	GOG 172 (ref. 193)
P (80 mg/m <sup>2</sup> ) weekly on days 1, 8 and 15 and i.p. C (AUC 6) on day 1 every 3 weeks for six cycles	IPOCC <sup>134</sup>
<b>First-line maintenance therapy</b>	
B 7.5 mg/kg up to 12 cycles (after concurrent chemotherapy with B)	ICON7 (ref. 129)
B 15 mg/kg up to 15 cycles (after concurrent chemotherapy with B)	GOG218 (ref. 128)
Olaparib 300 mg twice daily for 24 months + B 15 mg/kg 3 weekly for up to 15 months with olaparib	PAOLA-1 (ref. 139)
Olaparib 300 mg twice daily for 24 months	SOLO1 (ref. 194)
Niraparib 200 mg to 300 mg once daily for 36 months	PRIMA <sup>140</sup> and PRIME <sup>195</sup>
Rucaparib 600 mg twice daily for 24 months	ATHENA MONO <sup>142</sup>
<b>Treatment of recurrent platinum-sensitive EOC</b>	
CP every 3 weeks $\pm$ B	GOG213 (ref. 158)
C (AUC 5) and PLD (30 mg/m <sup>2</sup> ) every 4 weeks $\pm$ B	CALYPSO <sup>196</sup> , AGO-OVAR 2.21/ENGOT-ov 18 (ref. 156)
C (AUC 4 every 3 weeks) and gemcitabine (1,000 mg/m <sup>2</sup> on days 1 and 8 every 3 weeks) $\pm$ B	OCEANS <sup>197</sup> , AGO-OVAR 2.21/ENGOT-ov 18 (ref. 156)
Platinum-based chemotherapy followed by PARPi maintenance therapy until progression or unacceptable toxicity: olaparib 300 mg twice daily, rucaparib 600 mg twice daily, niraparib 200–300 mg twice daily	Study 19 (ref. 198), SOLO2 (ref. 199), ARIEL 3 (ref. 200), NOVA <sup>201</sup>
<b>Treatment of recurrent platinum-resistant or refractory EOC</b>	
Weekly P 80 mg/m <sup>2</sup> i.v. on days 1, 8, 15 and 22 every 4 weeks $\pm$ B 10 mg/kg every 2 weeks	AURELIA <sup>149</sup>
Topotecan 4 mg/m <sup>2</sup> per week on days 1, 8 and 15 on a 28-day cycle $\pm$ B 10 mg/kg every 2 weeks; or 1.25 mg/m <sup>2</sup> per day on days 1 to 5 on a 21-day cycle $\pm$ B 15 mg/kg every 3 weeks	AURELIA <sup>149</sup>
PLD 40–50 mg/m <sup>2</sup> every 4 weeks $\pm$ B 10 mg/kg every 2 weeks	Mutch et al. <sup>202</sup> , AURELIA <sup>149</sup>
Gemcitabine 1,000 mg/m <sup>2</sup> on days 1 and 8 every 3 weeks	Mutch et al. <sup>202</sup>
Mirvetuximab soravtansine in FR $\alpha$ -positive ovarian cancer, i.v. 6 mg/kg of adjusted ideal body weight every 3 weeks	Moore et al. <sup>203</sup>

AUC, area under the curve; B, bevacizumab/anti-VEGF; C, carboplatin; CDDP, cisplatin; CP, carboplatin paclitaxel; EOC, epithelial ovarian cancer; FR $\alpha$ , folate receptor- $\alpha$ ; i.p., intraperitoneal; i.v., intravenous; P, paclitaxel; PARPi, PARP inhibitor; PLD, pegylated liposomal doxorubicin.

### Box 3 | Optimal surgical staging and debulking and related scores

#### Optimal primary debulking surgical requirements

- En bloc resection of ovaries, tubes and uterus
- Omentectomy
- Removal of ascites
- Lymph node sampling for optimal staging or debulking of enlarged lymph nodes
- Assessment of serosal surfaces with (blind) biopsies
- Removal of all visible disease (RO)
- Bowel resection if necessary and feasible (appendectomy for mucinous ovarian cancer or if abnormal macroscopically)

#### AGO score for selection for secondary cytoreduction<sup>154</sup>

- Performance status 0
- Complete resection during initial surgery
- Ascites  $\leq$ 500 ml

#### iMODEL weighted score $\leq$ 4.7 for optimal cytoreduction<sup>155</sup>

- Stage I–II versus III–IV
- Residual disease after primary debulking surgery RO versus other
- Platinum-free interval  $\geq$ 16 months versus  $<$ 16 months
- Eastern Oncology Cooperative Group performance status 0–1 versus 2–3
- CA125 at recurrence  $\leq$ 105 U/ml versus  $>$ 105 U/ml
- Ascites at recurrence absent versus present
- AGO, Arbeitsgemeinschaft Gynaekologische Onkologie.

observed in smaller studies in patients with less common germline *RADS1C*, *RADS1D* or *PALB2* pathogenic variants<sup>143,144</sup>. PARPi is approved for use in patients who have either germline or somatic *BRCA1/2* mutations or a HRD signature, ideally by approved and/or validated tests, and at least a partial response to first-line platinum-based therapy. Similar criteria have been used for patients who receive anti-VEGF therapy with their first-line chemotherapy, in which case an anti-VEGF therapy for 15 cycles can be administered with concomitant olaparib for 2 years as a maintenance option<sup>138,139</sup>. The SOLO1 trial, a study of olaparib maintenance in patients with germline or somatic *BRCA1/2* mutations, demonstrated a statistically significant delay in disease recurrence for several years: the median PFS was 56.0 months (95% CI 41.9 months to not reached) with olaparib versus 13.8 months (95% CI 11.1–18.2 months) with placebo (HR 0.33 months, 95% CI 0.25–0.43 months)<sup>136</sup>. A non-significant but clinically important overall survival benefit was also observed at 7 years, with 67.0% of patients receiving olaparib versus 46.5% of patients receiving placebo being alive, and 45.3% versus 20.6%, respectively, being alive without a first subsequent treatment (overall survival HR 0.55, 95% CI 0.40–0.76;  $P = 0.0004$  ( $P < 0.0001$  required to declare statistical significance))<sup>137</sup>. Benefit is less striking but still statistically and clinically significant for patients with HRD-positive tumours who respond to platinum-based treatment. Little benefit is observed in those with HGSOE without *BRCA1/2* mutations and/or HRD, despite responsiveness to platinum-based agents, and most guidelines do not recommend PARPi maintenance in this setting<sup>123</sup>. No benefit of immune checkpoint therapy alone or in combination has been found in patients with EOC<sup>145</sup>.

#### Recurrent EOC

Platinum-free interval, the time between end of primary and start of secondary platinum-based therapy owing to disease progression, is a continuous variable. Disease progression within 6 months of completion of primary platinum-based chemotherapy has guided the definition of platinum resistance since publication of the seminal trial on secondary platinum-based treatment in 1991 (ref. 10). This definition creates three subsets of patients in relation to platinum-based treatment: those with refractory disease, defined as progression during primary treatment; those with platinum-resistant recurrent disease (PRROC), defined as progression within 6 months of completion of the most recent treatment; and those with platinum-sensitive recurrent disease (PSROC), defined as progression later than 6 months of completion of the most recent treatment (Figs. 4 and 5). Treatment of recurrent EOC is guided by this platinum sensitivity status. The modalities used in SOC for recurrent EOC continue to be surgery in selected patients and chemotherapy<sup>6</sup>. Radiotherapy is used for emergent disease amenable to focal palliation<sup>127</sup>. Hormonal therapy may be considered for LGSOC<sup>114,127</sup>, and immune checkpoint inhibitor therapy only in rare patients with disease with a mismatch repair deficiency<sup>114,127</sup>.

Other chemotherapeutic agents, including pegylated liposomal doxorubicin, gemcitabine and topotecan<sup>7,146–149</sup> (Table 4), are commonly used alone or in combination with platinum-based agents for second-line treatment in PSROC. These drugs function as DNA-damaging agents and may have some cross resistance with platinum-based agents<sup>150</sup>. Single-agent use is recommended in PRROC, although combinations with bevacizumab are in use.

**Platinum-sensitive recurrent disease.** Secondary cytoreduction in PSROC recurrence has been examined in three trials. The AGO DESKTOP III trial showed benefits of surgery in both PFS and overall survival<sup>151</sup>. The trial had stringent selection criteria including limited and fully resected tumour volume at primary diagnosis, limited tumour volume at recurrence, ascites volume  $<$ 500 ml and no carcinomatosis, and PSROC (Box 3). The less stringent, but still highly selective, SOC-1 trial, showed a PFS advantage with no overall survival benefit<sup>152</sup>. The GOG-0213 trial was the trial with selection criteria closest to real-world experience. The trial showed an overall survival detriment that was not statistically significant in patients undergoing surgery (HR 1.29, 95% CI 0.97–1.72;  $P = 0.08$ )<sup>153</sup>. Thus, careful patient selection is required when considering secondary cytoreduction, with surgery performed only in those patients in whom complete resection of all visible disease is considered technically feasible<sup>6,154,155</sup>.

Platinum-based therapy in combination with a second cytotoxic agents (doublet therapy) is the cornerstone of standard systemic treatment of PSROC<sup>147,156</sup> instead of, or after, surgery, with the consideration of added maintenance therapy. Data demonstrate value for carboplatin in combination with pegylated liposomal doxorubicin (CALYPSO trial)<sup>115,116</sup>, 3-weekly paclitaxel (ICON4 and GOG-0213 trials)<sup>157,158</sup> or gemcitabine (OCEANS trial)<sup>148</sup>, with further benefit from the addition of bevacizumab administered during chemotherapy and continued as maintenance therapy<sup>148,158</sup>. Patients who have received bevacizumab in their first-line therapy may continue to benefit from bevacizumab in subsequent doublet regimens.

Several randomized trials have investigated a switch to PARPi maintenance therapy in patients with PSROC who are PARPi-naïve and attained at least a partial response following at four or more cycles of platinum-based therapy<sup>95</sup>. The benefit of PARPi until progression or unacceptable toxic effects was identified for all three available PARPi

(olaparib, niraparib and rucaparib), with the greatest benefit in patients with germline or somatic *BRCA1/2* mutations and, to a lesser extent, in those with HRD<sup>95</sup>. No benefit was seen in patients with HRP disease or without *BRCA1/2* mutations. PARPi maintenance monotherapy may also be considered for patients with PARPi-naïve PSROC that has a pathogenic variant in *RAD51C*, *RAD51D* or *PALB2*, and has responded to platinum-based therapy in the recurrent setting<sup>95</sup>. Treatment with PARPi should be based on the individual patient and provider assessment of risks, benefits, preferences and emerging data of collateral resistance to DNA-damaging therapies<sup>8,9</sup>. Approval was withdrawn for PARPi treatment after the second disease recurrence owing to a negative effect on overall survival<sup>8</sup>.

Existing data do not support rechallenge with PARPi in patients who received first-line PARPi maintenance therapy; the OReO study demonstrated a non-clinically significant 1.5-month benefit for the re-use of PARPi<sup>159</sup>. There are no studies examining anti-VEGF plus PARPi combinations for maintenance in those with PSROC. Of note, an increased and persistent risk of myelodysplastic syndrome and acute myelogenous leukaemia was observed in studies of second-line maintenance PARPi<sup>160</sup>. Such increased risk was not observed in studies of first-line maintenance PARPi with a follow-up period of  $\geq 5$  years<sup>137,161</sup>.

**Platinum-resistant disease.** SOC for patients unable to tolerate platinum-based agents or who have PRROC generally includes single-agent chemotherapy with or without bevacizumab, and supportive care options<sup>95,162</sup>. The prognosis for these patients is poor, with a median overall survival of  $< 12$  months. Thus, palliation of symptoms and maintenance of QOL are the primary focus of treatment in this context<sup>162</sup>. The AURELIA study demonstrated some benefit of the addition of bevacizumab to single-agent chemotherapy in patients with PRROC, although most of these patients were bevacizumab-naïve. A subset analysis showed that the bulk of the benefit occurred in the subgroup of patients receiving weekly paclitaxel with bevacizumab compared with weekly paclitaxel alone (PFS 10.4 versus 3.9 months; HR 0.46)<sup>149,162,163</sup>. In 2024, the anti-folate receptor ADC mirvetuximab soravtansine was approved by the FDA for use in patients with PRROC. This agent has toxic effects for which mitigation approaches are necessary<sup>164</sup>, but was the first therapy to provide a clinically meaningful improvement in overall survival in patients with PRROC<sup>97,98</sup>.

### Differential treatment of rare EOC

Rare EOCs include LGenOC, LGSOC, CCOC and MOC. Treatment directions for rare EOCs are generally extrapolated from data from clinical trials, despite these trials recruiting predominantly patients with HGSOC. PDS with a goal of achieving full cytoreduction remains a key recommendation for the initial treatment of rare EOCs. Appendectomy is SOC at debulking for all patients, especially those with mucinous histology to distinguish MOC from metastatic disease from the appendix or other organs<sup>72</sup>. Platinum-based adjuvant chemotherapy is generally considered as a SOC therapy for extensive disease, although some EOC types (CCOC, LGSOC and MOC) have reduced depth and duration of response compared with HGSOC<sup>114</sup>. LGSOC and LGenOC are also responsive to hormonal therapies, and aromatase inhibitor therapy, such as tamoxifen or letrozole, may often be used as first-line maintenance therapy in patients with stage II, III or IV disease on the basis of retrospective registry data<sup>32,69</sup>. Optimal first-line and maintenance therapy for CCOC, MOC and rarer histologies requires further study (Fig. 3).

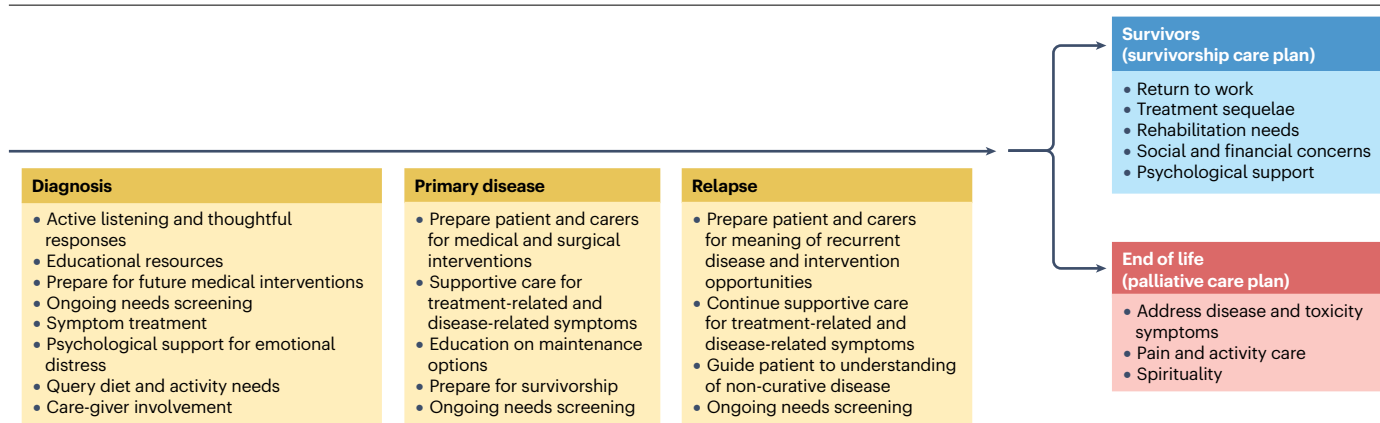
LGSOC is a distinct molecular entity of EOC and around 50% of patients with LGSOC have aberrations in genes activating the MAPK

pathway. Of note, a *KRAS* pathogenic variant does not portend a poor prognosis in LGSOC as it does in other cancers<sup>69,165</sup>. PFS was improved in patients with recurrent LGSOC who received the MEK inhibitor (MEKi) trametinib compared with the SOC choices tamoxifen, letrozole or single-agent chemotherapy (HR 0.48, 95% CI 0.36–0.64;  $P < 0.0001$ )<sup>32,69</sup>. The PFS with tamoxifen was extremely poor and may have biased the outcome of the control arm of this study. A similar study of the MEKi binimetinib versus single-agent chemotherapy, not including the two hormonal interventions, was determined to be futile at its first interim analysis<sup>166</sup>. Trends in both studies showed a more favourable outcome in patients with LGSOC with pathogenic variants in the MAPK pathway<sup>69,165</sup>. The combination of the RAF and MEK inhibitor avutemetinib plus the focal-adhesion kinase inhibitor defactinib had a good safety profile and promising efficacy in a phase II study<sup>96</sup>. It received accelerated FDA approval for *KRAS*-mutated, recurrent LGSOC in May 2025 (ref. 167). The confirmatory phase III trial is ongoing (NCT06072781)<sup>168</sup>.

The similarities between MOC and gastrointestinal tumours have led to chemotherapy regimen considerations based on fluorouracil and

	Low-grade serous ovarian cancer	Clear cell or low-grade endometrioid ovarian cancer	High-grade serous ovarian cancer	Mucinous ovarian cancer
Neoadjuvant and/or adjuvant	Carboplatin and/or paclitaxel $\pm$ anti-VEGF mAb			Surgery followed by carboplatin and/or paclitaxel or by FOLFOX or FOLFIRI <sup>a</sup>
Maintenance	Letrozole <sup>a</sup>	anti-VEGF mAb or PARPi or anti-VEGF mAb + PARPi <sup>b</sup>		
Platinum-sensitive recurrent disease		Platinum-doublet $\pm$ anti-VEGF mAb		
Platinum-resistant recurrent disease		Single-agent chemotherapy <sup>c</sup> $\pm$ anti-VEGF mAb or mirvetuximab soravtansine		
Recurrent, not otherwise specified	Avutemetinib and/or defactinib (consider trametinib)			Gastrointestinal tumour or epithelial ovarian cancer regimens <sup>a</sup>

**Fig. 4 | Treatment matrix by epithelial ovarian cancer type.** Use of all regimens depends on licensing and availability in a given jurisdiction. FOLFIRI, 5-fluorouracil, leucovorin and irinotecan; FOLFOX, 5-fluorouracil, leucovorin and oxaliplatin; mAb, monoclonal antibody; VEGF, vascular endothelial growth factor. <sup>a</sup>No prospective randomized data. <sup>b</sup>Poly(ADP-ribose) polymerase inhibitor (PARPi) use for selected populations. <sup>c</sup>Single-agent chemotherapy such as weekly paclitaxel, topotecan or pegylated liposomal doxorubicin.



**Fig. 5 | Supportive care needs during the patient journey.** Epithelial ovarian cancer affects health-related quality of life during all stages and treatment trajectories of the disease.

oxaliplatin, without evidence supporting this approach. The GOG-0241 trial, which was to test that question, closed early due to poor accrual, and only 18 of 40 patients with tumour available for pathology review had MOC<sup>72,73,169</sup>. MOCs frequently have molecular alterations, making targeted therapies an area for future study<sup>74,75</sup>.

## Quality of life

EOC remains a considerable health challenge that affects not only survival but also health-related QOL (HRQOL), during all stages and treatment trajectories of the disease (Fig. 5). Focus on the physical, emotional and social well-being of patients, as well as shared decision-making, remains an important component of good medical care<sup>170</sup>. Understanding and supporting the patient's perspective, needs and cancer experience should be a standard element of care<sup>170-172</sup>. Attention to monitoring and addressing symptoms has been shown to improve quality of care, HRQOL and survival<sup>170,173-175</sup>. Formal measurement of HRQOL is an important consideration for inclusion in definitive clinical trials, and advances including digitalization of tools and application of artificial intelligence for analysis have been initiated<sup>176</sup>. Focus on elements that affect individual patient HRQOL is an obligation of the treatment team.

Patients report physical and emotional symptom burdens during and after treatments<sup>21</sup>. These symptoms, often underestimated, negatively affect HRQOL<sup>170,177</sup>. Distress and disease-related symptoms are the two major effects identified at diagnosis. Surgery leads to short-term declines in HRQOL due to postoperative recovery with bowel disorders and residual pain<sup>178,179</sup>. Presence of ascites and related risk or presence of incomplete or complete bowel obstruction can cause pain, swelling, early satiety, shortness of breath due to inability of the diaphragm to extend fully, and extrinsic bowel compression by carcinomatosis<sup>180</sup>. Initiation of NACT chemotherapy with anti-VEGF therapy (such as bevacizumab or biosimilars) can provide comfort and clinical benefit. Chemotherapy regimens have varied adverse events, many of which may persist after therapy and/or maintenance treatment are discontinued. Haematological bone marrow suppression is a common adverse event with most SOC agents, such as carboplatin or cisplatin, paclitaxel and PARPi, and selected patients may benefit from the use of granulocyte colony-stimulating factor and erythropoietin or transfusion<sup>181</sup>. Adverse effects, such as neuropathy, digestive disorders

and psychosocial symptoms (including anxiety, fatigue and sleep disorders) are common and may persist<sup>182,183</sup>. Balancing the benefit of prolonged treatment and/or maintenance also requires consideration of time without deterioration of HRQOL, a variable now being addressed in clinical trials. As the disease progresses, adverse effects of treatment and disease that reduce HRQOL also become a negative prognostic factors. Symptoms also may persist during treatments and disease-free intervals, affecting HRQOL of survivors.

Data from other cancers show that early introduction of supportive and palliative care can improve HRQOL<sup>184</sup>. Attention to health and psychosocial details at all points along the disease journey can make living with EOC more tolerable for the patient and her family or care-givers. Critical interventions to ameliorate disease-specific toxic effects, treatment-related toxicities, social stresses (such as financial toxicity) and the effects of those events on the patient and her family or care-givers must be considered. Some of these actions include early or even anticipatory introduction of central venous access, prescription of anti-emetic and anti-hypertensive medicines, and psychological and social support. The effects of continuous maintenance treatments and use of agents with long half-lives that cause low-grade but persistent toxicity must also be considered. In addition to physical effects, the persistent sense of being unwell can impact the emotional strength and stability of the patients. Efforts should include focus on survivorship needs for patients with EOC throughout their journey.

## Outlook

### Knowledge gaps

Linking basic, translational and clinical research findings is fundamental and accelerates the entry of advances into clinical practice. For example, clinical trial participation of patients with EOC and collection of biospecimens, such as tumour, blood, cell-free DNA and others, for prospectively defined or future unspecified use are paramount to creating the scaffolding to address outstanding gaps in knowledge. Harmonized biospecimen collection and storage strategies and harmonized minimum data collection facilitate collaboration across groups and across clinical trials. The design of translationally rich clinical trials, including adaptive and other innovative trial designs, should be encouraged to improve clinical trial interpretation and the ability to address future questions using the trial outcome data and associated biospecimens.

Regulatory encouragement of industry collaboration can open access to large numbers of trials and patient materials and data.

Validated, truly predictive, biomarkers of treatment benefit and resistance, as well as early detection tools, are needed to reverse the continued late diagnosis of EOC and high mortality among patients with the disease. Genomic analyses have led to new standards in treatment, including the need for EOC type-specific trials, and the use of PARPi maintenance treatment for selected patients with tumours that have germline or somatic *BRCA1/2* mutations or HRD. A less costly, quicker and more readily available approach to molecular testing than current techniques is needed to optimize access also in lower-resourced regions. Sub-setting of disease groups based on genomic results could identify molecular subsets at diagnosis allowing triage of patients to more directed SOC or targeted clinical trials.

The availability of molecular targeted analyses and treatments has uncovered new mechanisms of treatment resistance, providing avenues for further research into overcoming therapeutic resistance. The development of collateral chemotherapy resistance to platinum agents, emanating from PARPi resistance, has been observed in several phase III trials<sup>9,185</sup>. This has led to the characterization of a patient population at risk of developing ‘platinum-sensitive, PARPi-resistant’ disease for which benchmarks and opportunities need to be defined; this is a crucial biomarker and treatment challenge.

ADCs are a unique type of agent with an antibody-targeting moiety linked to a cytotoxic payload; different types of linkers, the degree of antibody loading (amount of toxin per antibody) and the type of payload all contribute to the agent effect; optimizing and identifying new ADC components are all active areas of research<sup>186</sup>. Some ADCs, such as folate receptor-based ADCs and selected HER2-targeted ADCs, seem to require a minimum target expression to be effective. New data in breast cancer suggest that back-to-back use of ADCs with the same payload may attenuate their benefit<sup>186</sup>.

Improvement in primary evaluation and treatment of EOC has translated to reduced morbidity and extended survival. Prospective evaluation of new surgical techniques may advance progress. These include the use of minimally invasive (laparoscopic and/or robotic) surgery after NACT in those with an impressive response to therapy; surgical advances to minimize morbidity from peritonectomy, bowel surgery and stoma formation; and optimizing techniques to achieve a more targeted or selective approach for debulking or precision surgery.

## Research priorities

New diagnostic tests for EOC screening strategies are under development, including new DNA methylation biomarkers and circulating tumour DNA as analytes, as well as multicancer early detection biomarker tools<sup>187</sup>. The validation of prognostic and predictive biomarkers for therapies, streamlined to conserve scarce biopsy tissue, should be a priority. For HRD assessment, real-time functional biomarkers that directly reflect DNA repair (for example, RAD51 focus assays using recently acquired tumour tissue, and indirect assays reflecting PARPi susceptibility) are needed. Improved understanding of the immune microenvironment and other predictive biomarkers of immunotherapy will be essential in designing and delivering effective immunotherapy for ovarian cancer. Pharmacogenomic population analysis could provide insights on the, sometimes, extreme adverse drug reactions with some therapies, which severely limit therapeutic application. EOC subtype-specific trials will continue to be important to optimize care for those with non-HGSOC for whom specific trials and disease-specific data are currently limited.

The future challenge will continue to be our incomplete understanding of EOC and how that directs design and optimization of biomarkers and clinical trial design. Improving treatment dose and duration optimization and diagnostic and treatment access in resource-restricted settings must be addressed. Focusing on timely publication of translational analyses of clinical trials will speed understanding of new therapies in differing ovarian cancer contexts, improving outcomes for women with EOC.

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## Author contributions

Introduction (C.L.S. and E.C.K.); Epidemiology (S.B., C.L.S. and E.C.K.); Mechanisms/pathophysiology (S.B., J.-M.L., D.S.T., C.L.S. and E.C.K.); Diagnosis, screening and prevention (A.M., S.B., C.L.S. and E.C.K.); Management (A.M., D.S.T., J.-M.L., C.L.S. and E.C.K.); Quality of life (F.J., C.L.S. and E.C.K.); Outlook (C.L.S. and E.C.K.); overview of the Primer (C.L.S. and E.C.K.).

## Competing interests

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