Evolution of cytoreductive surgery

Robert Houstoun of Glasgow had previously been given the erroneous distinction of having been the world’s first ovariotomist based on a case performed by him in 1701 [1–6]. Houstoun’s patient had noted two years of worsening abdominal pain and bloating that had compromised her breathing and led to malnourishment. In his own words: “I found this tumor grown to so monstrous a bulk, that it engrossed the whole left side from the umbilicus to the pubes, and stretched the abdominal muscles to a great degree. It drew toward a point. From being obliged to lie continually on her back, she was grievously excoriated, which added much to her sufferings, which, together with a want of rest and appetite, had greatly emaciated her.”

Houstoun’s description of the operation indicates that he made an incision into the peritoneal cavity and a yellow serum escaped [5]. His next incision exposed the highly colloidal contents, which did not flow but rather protruded. A fir splinter was then introduced and poking around inside, Houstoun ruptured a secondary cyst resulting in free flow of glutinous fluid and an escape of secondary cysts with “pieces of membranes”. By incising such an abnormal ovarian growth instead of tapping it, Houstoun was well ahead of his time, but he never claimed he removed an ovary or an ovarian tumor. Houstoun simply called his case “an account of a dropsy of the left ovary of a woman aged 58, cured by a large incision made in the side of the abdomen”. In fact, Houstoun never claimed that he had performed an oophorectomy, for which two
things were considered to be essential: (1) the tumor should be delivered from the abdomen; (2) its connection with the body should be severed.

William Hunter and his brother John Hunter were born and brought up in the district in which Houstoun’s case occurred and for years lived near the city where it was performed [7–10]. Therefore, they must have known about the case and although they never performed it themselves, they advocated the theory of the performance of the operation through a puncture wound in the abdomen. John Hunter is reported to have said: “I cannot see any reason why, when the disease can be ascertained in an early stage, we should not make an opening into the abdomen and extract the cyst.” A friend of the Hunter brothers, Dr John Bell, also supported the performance of the operation although he is not known to have attempted it himself. Bell taught at Edinburgh University and was a noted Scottish anatomist and surgeon who devoted himself to his professional studies with that enthusiastic ardor so characteristic of genius. Bell’s professional works included Principles of Surgery and the Anatomy of the Human Body and the anatomic drawings are extraordinary for their correctness. Bell’s illustrations are contained at the National Library of Medicine (Figure A1) [11].

Figure A1 Engraving by John Bell (1763–1820). Reproduced with permission from © the National Library of Medicine, 1804. All rights reserved. Courtesy of the US National Library of Medicine [11].
A surgical masterpiece

Ephraim McDowell (1771–1830; Figure A2) was born in Rockbridge County Virginia, one of 11 children born to Samuel and Mary McDowell [8–10,12,13]. The family moved to Kentucky when Samuel was appointed Land Commissioner for the state, ultimately settling in Danville. McDowell traveled to Scotland in 1793 to study medicine at Edinburgh University and although he left without a diploma due to dwindling funds or concerns over the outbreak of war with France, the renowned Edinburgh physician John Bell must have left a great impression on him with his lectures on anatomy. In fact, Bell was said to have “dwelt with particular force and pathos on the organic diseases of the ovaries, speaking of their hopeless character, when left to themselves, and of the possibility, nay practicability, of removing them by operation” as a means of saving a woman’s life.

In December 1809, McDowell travelled 60 miles southwest of Danville to the small community of Motley’s Glen to consult on Mrs Jane Todd Crawford who was believed to be pregnant with twins. Mrs. Crawford, a mother of five in her mid-forties had had an unusually long “pregnancy” and was experiencing abdominal pain (Figure A3) [14]. McDowell examined her and diagnosed her with an ovarian tumor but explained that

Figure A2  Ephraim McDowell (1771–1830), Father of Abdominal Surgery. Reproduced with permission from © the National Library of Medicine, 1800s. All rights reserved. Courtesy of the US National Library of Medicine [12].
no medication could be given to shrink it down. He later wrote: “...only relief you can hope for is an operation that will remove the tumor. But it is only right for me to tell you that I have never removed such a tumor. Nor do I know of any doctor who has... I told the lady I could do her no good. That opening the abdomen to extract the tumor was inevitable death... if she thought herself prepared to die, I would take the lump from her if she could come to Danville.”

Resting her massive abdomen on the pommel of her saddle, Mrs Crawford traveled by horseback to Danville where the operation took place on Sunday, Christmas morning, 1809 in McDowell’s kitchen (Figure A4).

Legend claims a mob waited outside to hang the doctor on the certain death of his patient. By using a left para-median incision, McDowell removed a 22.5 pound ovarian tumor in 25 minutes using a single ligature to secure the blood supply and attachments of the ovary to the uterus [8].

“Having placed her on a table of the ordinary height, I made an incision about three inches from the musculus rectus abdominis, on the left side, continuing the same nine inches in length, parallel with the fibers of the above named muscle, extending into the cavity of the abdomen... The tumor then appeared in full view, but was so large that we could not take it away entire. We put a strong ligature around the fallopian tube near to the uterus; we then cut open the tumor, which was the ovarium
and the fimbrious part of the fallopian tube very much enlarged. We took out fifteen pounds of dirty, gelatinous looking substance. After which we cut through the fallopian tube, and extracted the sack, which weighted seven pounds and one half. As soon as the external opening was made, the intestines rushed out on the table; and so completely was the abdomen filled by the tumor, that they could not be replaced during operation, which was terminated in about twenty-five minutes. We then turned her on her left side, so as to permit the blood to escape after which, we closed the external opening with the interrupted suture, leaving out, at the lower end of the incision, the ligature which surrounded the fallopian tube. Between every two stitches we put a strip of adhesive plaster, which, by keeping the parts in contact, hastened the healing incision. We then applied the usual dressings, put her to bed and prescribed a strict observance of the antiphlogistic regimen."

McDowell visited the patient on the fifth postoperative day and found her up and about, making her bed. She returned home to outlive her surgeon who is said to have never charged her for his services. McDowell would go on to perform the operation a total of twelve times, with a mortality rate of 33%, and in one other case in which he failed to complete the operation due to adhesions.

It is remarkable that McDowell was of a singular mind to undertake these hazardous operations long before the availability of ether, antisepsis
technique, penicillin, and blood banking. Such steadfast determination, innovation, and invigoration has informed those that followed, literally blazing a trail forward at the frontiers of abdominal surgery. The real acceptance of ovariotomy came in the mid-1840s with Atlee’s work in America and with that of Dr Charles Clay who performed the first abdominal hysterectomy across the Atlantic in Manchester, England. This revival coincided with the advent of anesthesia, which eliminated the principal horrors of surgery, namely, the fear and pain. In March 1842, Dr Crawford W Long proved the anesthetic properties of ether, and in October 1846, Warren at the Massachusetts General Hospital again demonstrated these properties and their surgical uses.

Contemplations on an aggressive surgical approach

The next important epoch in the history of ovarian cancer surgery encompasses the 1870s to the 1960s. It is during this period that the dual concepts of exploratory laparotomy and cytoreduction to make chemotherapy more effective were originally proposed. In addition, two seminal manuscripts from the first half of the 20th century note an improved survival in ovarian cancer associated with more aggressive surgery. Finally, the importance of omentectomy and retrograde hysterectomy with concomitant rectosigmoid resection for abdominal spread and fixed pelvic tumors, respectively, are formally described in the medical literature.

Robert Lawson Tait (Figure A5) was born in Edinburgh, Scotland and has occasionally been described as the “Forgotten Gynecologist” [15,16]. He performed his first ovariotomy in 1868 as House Surgeon in Wakefield, Yorkshire. At the age of 25 he moved to Birmingham where he founded the Birmingham and Midland Hospital for Women, which was devoted to “the alleviation of diseases peculiar to women”. He is known for having performed many operations, including several ‘firsts’ such as oophorectomies for sepsis and menstrual problems, the first successful appendectomy and cholecystectomy. In 1873 he performed a laparotomy to remove a full-term, extra-uterine fetus and developed the technique of leaving the placenta in situ to reduce the risk of hemorrhage. The following
year he performed an abdominal subtotal hysterectomy for fibromyoma, and in 1880 he performed the first successful incision into the liver to remove a hydatid cyst. In his records, he describes “Tait’s Operation” for excision of the fallopian tubes and ovaries for pelvic inflammatory disease. In the late 19th century, ectopic pregnancy had an extremely high mortality rate, and one of Tait’s greatest achievements was the development of laparotomy and salpingectomy to remedy the condition. He performed his first operation for a ruptured ectopic pregnancy in 1883; however, the patient died in the post-operative period. Tait continued his work and in over 40 subsequent cases, all but one woman survived.

Tait introduced the concept of exploratory laparotomy in 1879 indicating that many benign ovarian tumors may be mistaken for ovarian cancer [15]. “Tait’s Law” was used to describe his injunction to exploratory surgery: “for my own part, so fearless am I now of abdominal surgery, so splendid have my results in fields of practice which, until three years ago, seemed hopelessly enclosed, that I venture to lay down a surgical law, that in every case of disease in the abdomen or pelvis, in which the health is destroyed or life threatened, and in which the condition is not evidently due to malignant disease, an exploration of the cavity should be made.” In Tait’s era, surgeons did not believe an operation could have a positive impact on patient survival in ovarian cancer, but by the beginning of the 1900s, that dogma had changed.
In 1934, Joe Vincent Meigs suggested that to enhance the effects of postoperative chemotherapy, as much tumor as possible should be removed at the time of surgery for ovarian cancer (Figure A6) [17,18].

In 1935, Frank W Lynch reported on the management of 110 cases of ovarian carcinoma comprised of 95 papillary/adenocarcinomas, five malignant pseudomucinous tumors, one squamous cell carcinoma arising in a dermoid, one dysgerminoma, six granulosa cell tumors, and two Krukenberg tumors, which were considered primary ovarian tumors preoperatively [19]. Lynch noted that 5-year cures (37%) were obtained only when the malignant areas were encapsulated by a cyst wall or when the tumor was of low malignancy. In 1940, Frank A Pemberton reported a series of 149 cases of primary carcinoma of the ovary and introduced the idea of an omentectomy as part of the initial management of ovarian cancer because even when there were no gross metastases, the omentum may be affected subclinically and present as a site of recurrence [20]. The reported 5-year survival was 32%.

In 1968 Equinn William Munnell reported on 235 patients with a 40% 5-year survival treated from 1952–1961 at Columbia-Presbyterian Medical Center [21] and compared their outcomes to two prior series published by Munnell and Taylor from the same institution: (1) 200 cases seen between 1922 and 1943 with a 5-year survival rate of 27.5%; and (2) 148 patients from 1944–1951 for which the cure rate was essentially

Figure A6 Joe Vincent Meigs (1892–1963). Photo by Bachrach. Reproduced with permission from Bachrach, 1955. All rights reserved. Countway Library of Medicine [18].
identical at 28%. In the 1968 report, surgery consisted of total abdominal hysterectomy and bilateral salpingoophorectomy, and with only one exception, all patients had exploratory laparotomy and maximal surgical removal attempted even in advanced cases unless such an attempt threatened to endanger the patient’s life. Maximal surgical effort frequently included partial omentectomy and not infrequently resections of local metastases. Munnell felt that surgery since 1950 had become more extensive and more aggressive and attributed the improvement in survival that was obtained as a result of this approach. In considering omentectomy, Munnell reported that this was not performed in the first series of 200 cases from 1922–1943, three were performed in the 1944–1951 series, and 52 were performed in the 1944–1951 group. Bowel surgery was never performed before 1947 and only five times in addition to pelvic surgery between 1947 and 1951; it was performed 15 times in the 1952–1961 series. He noted that in approximately one-third of the 107 cases with upper abdominal spread, it was possible to perform definitive surgery in which most of the cancer was removed.

Working with Alexander Brunschwig, the architect of total pelvic exenteration for recurrent cervical cancer, Hugh Barber performed this ultra-radical operation on 22 patients with advanced and recurrent ovarian cancer, but the procedures were mutilating with unacceptable postoperative morbidity and mortality rates without attendant cure [22,23]. Christopher N Hudson considered posterior exenteration to be less severe and essentially the same operation performed for primary malignant or intractable inflammatory disease of the rectum, and this led him to consider a radical operation for fixed ovarian tumors confined to the pelvis [24]. The principle is to remove the entire pouch of Douglas as a false capsule to the tumor. The operation can be achieved with minimal damage to adjacent organs by a technique of mobilization of the rectum, which is later allowed to fall back into the hollow of the sacrum after any area adherent to the tumor has been excised by sharp dissection under vision. The plane used in Hudson’s operation lies behind the rectum and in front of the fascia of Waldeyer, and the hysterectomy is performed in retrograde fashion (Figure A7).
If the sigmoid colon and/or portion of the rectum is involved with the tumor and requires resection, re-establishment of colorectal continuity can be accomplished primarily without need for colostomy, and similarly, if one or both ureters are involved and need to be cut, they can be subsequently reimplemented.

**Proof of principle of cytoreduction**
In 1975, 41 years after Meigs’ initial proposition, C Thomas Griffiths published a landmark study that conclusively demonstrated an inverse relationship between residual tumor diameter and patient survival [25] (Figure A8).

**Figure A7** Hudson’s depiction of the retrograde hysterectomy technique. Reproduced with permission from © John Wiley and Sons, *J Obstet Gynaecol Br Commonw*, 1968. All rights reserved. Hudson [24].

**Figure A8** Relationship of survival to size of largest residual metastasis after primary operation for stage III ovarian cancer. Reproduced with permission from © Oxford University Press, *Natl Cancer Inst Monogr*, 1975. All rights reserved. Griffiths [25].
Interestingly enough, the premise for considering the potential impact of reducing intra-abdominal tumor burden was based on the enhanced survival outcome reported by Magrath et al one year earlier in patients with non-Hodgkin lymphoma [26]. Reporting from the National Cancer Institute in Bethesda, Maryland, Magrath et al reported the results of a retrospective study of 68 patients with abdominal Burkitt’s lymphoma seen at the Lymphoma Treatment Centre in Kampala, Uganda [26]. In their series, nine patients had almost complete removal of the tumor, 16 had less than 50% of the tumor removed, and 43 underwent biopsy only. Patients who were amenable to total resection included those with mesenteric, bowel, splenic, and/or ovarian masses, while in those with involvement of the kidney(s) and/or a large part of the liver, as well as those in whom the tumor was arising from retroperitoneal tissues, only partial resection could be achieved. Following postoperative chemotherapy, there was a highly significant difference in the proportion of patients achieving a sustained durable remission (56% versus 11%) and a significant difference in survival (89% versus 45%) between the group having almost complete removal and the partial resection group. This survival effect was observed even when extra-abdominal tumor was present.

The study by Griffiths was a retrospective evaluation of the effect of tumor bulk resection on survival among 102 patients with stage II and stage III ovarian cancer [25]. His analysis demonstrated that when residual disease >1.5 cm in maximum diameter were left in the abdominal cavity, these patients almost invariably were dead within 2 years. When patients were operated on and found to have intra-abdominal carcinomatosis but only miliary seedings, ie, tumor implants <1.5 cm in maximum diameter, in the upper abdomen, they had a 5-year survival of approximately 20%. Griffiths then demonstrated, in a third group of patients, when large volume disease was present in the upper abdomen and he was able to surgically cytoreduce the cancer such that at the end of the operation the residual disease was <1.5 cm in maximum diameter, that they had a prolonged survival with 20% alive at 5 years.

It was this retrospective review by Griffiths that established the concept of aggressive surgery followed by aggressive intensive chemotherapy as
the ideal way to manage advanced stage ovarian cancer. In a follow-up report from 1978, Griffiths and Fuller presented the background and rationale for initiating a program of intensive surgical and chemotherapeutic management using doxorubicin and cyclophosphamide [27]. They clearly described their goal of excising all tumor masses larger than 1.5 cm in diameter and emphasized the necessity of nutritional support. In their opinion the single most important contraindication to maximum cytoreductive surgery is the inability to initiate effective chemotherapy in the postoperative period.

Although there are many series that support the findings of Griffiths, none are randomized controlled trials and therefore may contain selection bias and other types of limitations. The definition of residual disease has also evolved with the Gynecologic Oncology Group (GOG) now using the term ‘optimal cytoreduction’ as leaving residual disease less than 1 cm in maximal tumor diameter. Twenty-first century thought leaders in primary cytoreduction for ovarian cancer argue that optimal surgical approaches should leave the patient with microscopic residual (ie, R_0).

A meta-analysis by Hunter et al appeared in 1992, which evaluated 58 suitable studies that encompassed 6962 patients with advanced ovarian cancer [28]. Among the variables analyzed were the proportion of patients undergoing maximum cytoreductive surgery, use of platinum-containing chemotherapy, dose intensity of chemotherapy, and proportion of patients with stage IV disease. Their analysis indicated that maximum cytoreductive surgery was associated with only a small improvement in median survival time, but that platinum-containing chemotherapy improved median survival significantly (Figure A9).

Building on these important observations, the watershed event arrived in 2002 when the meta-analysis by Bristow et al was published [29]. Eighty-one patient cohorts involving 6885 patients with stage III and IV ovarian carcinoma, all of whom were treated with platinum-based chemotherapy from 1989 through 1998, were studied. Maximal cytoreduction was found to be the most important determinant of survival and this correlation remained significant after controlling for all other variables (eg, proportion of patients with stage IV disease, dose-intensity of the platinum therapy administered, median age, year of publication).
Simple linear regression analysis demonstrated that median survival time increased from 23.0 months in cohorts in which maximal cytoreductive surgery was achieved in ≤25% of patients to 36.8 months in cohorts in which maximal cytoreductive surgery was achieved in more than 75% of patients, an increase of 60%.

The results from Bristow’s meta-analysis instilled confidence among aggressive gynecologic oncologists that they had been on the right track in expanding the frontiers in what could be accomplished surgically in this disease. Over the past decade there has been a steady stream of publications documenting the value of extensive upper abdominal cytoreductive procedures including major hepatectomy, full-thickness diaphragmatic resection, complete parietal and visceral peritonectomy, splenectomy with distal pancreatectomy, and video-assisted thoracoscopic surgery [30–40]. Optimally cytoreduced patients (as well as those left with microscopic residual disease) who receive intraperitoneal plus intravenous chemotherapy have demonstrated significantly increased survival together with descriptive toxicity profiles. More recently, the integration of heated intraperitoneal chemotherapy at the time of maximal cytoreduction has been subject to ongoing investigation.
References


Chemotherapy drugs and regimens

Chemotherapy drugs used for the treatment of ovarian cancer

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<td>Oxaliplatin</td>
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<td>Docetaxel</td>
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<tr>
<td>Nanoparticle albumin-bound paclitaxel</td>
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<td>Gemcitabine</td>
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<td>Trabectedin</td>
<td>DNA backbone cleavage</td>
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<tr>
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<td>Folate antimetabolite that inhibits the enzymes used in purine and pyrimidine synthesis</td>
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<td>Bleomycin</td>
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<td>Vinblastine</td>
<td>Prevents microtubule assembly</td>
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<td>Vincristine</td>
<td>Prevents microtubule assembly</td>
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<td>Capecitabine</td>
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<tr>
<td>Tamoxifen</td>
<td>Competitively binds estrogen receptor</td>
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Table B1 Chemotherapy drugs used in the treatment of ovarian cancer.
Cisplatin

Cisplatin (cis-diamminedichloridoplatinum II, CDDP) is a platinum-containing anti-neoplastic agent that forms crosslinking platinum-DNA adducts, ultimately triggering programmed cell death (apoptosis) (Figure B1). Cisplatin was first described by Peyrone in 1845 and was known for many years as ‘Peyrone’s salt’. In 1865, Rosenberg reported that electrolysis of platinum electrodes generated a soluble platinum complex, which inhibited binary fission in *Escherichia coli*. The bacteria continued to grow as filaments up to 300 times their normal length, although cell division was arrested. The square planar platinum complex was found to be highly effective in forcing filamentous growth of *E. coli* cells and causing regression of sarcomas in rats. Cisplatin was ultimately approved by the US Food and Drug Administration on December 19, 1978 for treatment of testicular and ovarian cancers. The dose-limiting toxicity of cisplatin is nephrotoxicity. The drug is also neurotoxic and emetogenic.

![Figure B1 Mechanism of action of cisplatin. Reproduced with permission from © Nature Publishing Group, 2005. All rights reserved. Wang et al [1].](image-url)
Paclitaxel

The paclitaxel drug development process took over 40 years. The drug was discovered at the Research Triangle Institute in 1967 when Wall and Wani isolated it from the bark of the Pacific Yew tree, *Taxus brevifolia* (Figure B2A). Endophytic fungi in this bark synthesizes paclitaxel, which stabilizes microtubules, interfering with normal breakdown and disassembly of the apparatus during cell division (Figure B2B).

From 1982 to 1994, paclitaxel was the subject of a notable total synthesis by Holton of Florida State University in which he was able to accomplish the complete chemical synthesis of this complex organic molecule from simpler pieces without the aid of biological processes.

Initially, the production of paclitaxel was expensive because it had to be harvested from a scarce resource with 28 kg of crude extract isolated form 1200 kg of bark only yielding 10 g of pure material. Synthetic reproduction of paclitaxel opens the gateway to powerful paclitaxel derivatives not found in nature. The molecule has a tetracyclic core (rings A–D) and an amide tail. Commercially, paclitaxel is known as taxol and in this formulation it is dissolved in Kolliphor EL and ethanol as a delivery agent. The dose-limiting toxicity is myelosuppression. When given with growth factors, peripheral neuropathy becomes dose limiting. Other important adverse events associated with paclitaxel include hypersensitivity and alopecia.

Carboplatin

Carboplatin is a second-generation platinum compound and is comprised of a platinum atom complexed with two ammonia groups. In place of the two chloride ligands, which are the leaving groups of cisplatin, carboplatin has a bidentate dicarboxylate ligand (Figure B3).

It was discovered at Michigan State University in the 1960s and developed at the Institute of Cancer Research in London. Carboplatin is activated intracellularly to form reactive platinum complexes that bind to nucleophilic groups such as the GC-rich sites in DNA. This results in intrastrand and interstrand DNA crosslinks and DNA-protein crosslinks. These effects result in apoptosis and inhibition of cell growth. Carboplatin does not have the nephrotoxic and emetogenic effects of cisplatin. Myelosuppression is dose limiting, with median nadirs occurring...
Figure B2 A, Source of paclitaxel, the Pacific Yew tree; B, mechanism of action of paclitaxel. Reproduced with permission from © Moralea Milne, Gary L Fletcher, 2013. All rights reserved. Milne, Fletcher [2]. Reproduced with permission from © Cold Spring Harbour Press, 2006. All rights reserved. van Amerongen and Berns [3].
at day 21 following treatment. The use of the modified Cockcroft-Gault formula for calculating renal function allows carboplatin to be dosed according to the area under the concentration versus time curve (AUC) (Table B2), thereby predicting platelet nadirs.

**Docetaxel**

Docetaxel is a semi-synthetic, second-generation taxane. Due to the scarcity of paclitaxel, extensive research was carried out leading to the formulation of docetaxel through an esterified product of 10-deacetyl baccatin III, which is extracted from the renewable and readily available European Yew tree *Taxus baccata*. Docetaxel binds to and stabilizes tubulin, inhibiting microtubule disassembly, which results in cell cycle arrest and the G2/M phase and cell death. As with paclitaxel, the dose-limiting toxicity is neutropenia. A fluid retention syndrome and cutaneous toxicities are specific to docetaxel.

**Topotecan**

Topotecan is a water-soluble analogue of the topoisomerase I inhibitor camptothecin. Camptothecin has a planar pentacyclic ring system and is
a natural product extracted from the bark of the *Camptotheca acuminata* tree. Its target, topoisomerase 1, is a nuclear enzyme that relieves torsional strain in DNA by inducing reversible single-strand breaks, allowing the DNA to rotate in front of the advancing replication fork. When topotecan intercalates between DNA bases it binds to the topoisomerase 1-DNA complex and prevents religation of the single-strand breaks, thereby preventing replication. The dose-limiting toxicity of topotecan is leukopenia.

**Pegylated liposomal doxorubicin**

Doxorubicin is an anthracycline antibiotic that intercalates between base pairs in the DNA helix, thereby preventing DNA replication and ultimately inhibiting protein synthesis. Doxorubicin also inhibits topoisomerase II resulting in an increased and stabilized cleavable enzyme–DNA linked complex during DNA replication and subsequently prevents ligation of the nucleotide strand after double-strand breakage. Doxorubicin forms oxygen free radicals resulting in cytotoxicity secondary to lipid peroxidation of cell membrane lipids.

Pegylated liposomal doxorubicin (PLD) is a unique formulation of the anthracycline antibiotic doxorubicin, in which a polyethylene glycol layer surrounds the liposome-encapsulated doxorubicin (Figure B4).
PLD was originally developed to treat Kaposi’s sarcoma – an AIDS-related malignancy that may grow under the skin. The polyethylene glycol coating results in preferential concentration of the drug in the skin, which may result in palmar plantar erythrodysesthesia (PPE or hand-foot syndrome). Pegylation protects the liposomes from detection by the reticuloendothelial system and increases the plasma half-life compared with conventional doxorubicin. The liposomes can extravasate through leaky tumor vasculature promoting targeted drug delivery to the tumor site. Liposome encapsulation and delivery of doxorubicin improves drug penetration into tumors and decreases drug clearance, thereby further increasing the duration of therapeutic effect. The liposomal formulation also modulates toxicity, particularly the cardiotoxic effects observed with anthracyclines. Myocardial damage leading to congestive heart failure may occur as the total cumulative dose of doxorubicin approaches 550 mg/m².
Gemcitabine

Gemcitabine is a nucleoside analogue of deoxycytidine in which two fluorine atoms have been inserted into the deoxyribofuranosyl ring (Figure B5). Intracellularly, gemcitabine undergoes rapid phosphorylation leading to the formation of the active metabolites gemcitabine diphosphate and gemcitabine triphosphate. GDP inhibits ribonucleotide

Figure B5 The mechanism of action of gemcitabine. Gemcitabine is a prodrug that requires cellular uptake and intracellular phosphorylation in order to exert its action which results in DNA masked chain termination. dFdCMP, gemcitabine monophosphate; DCK, deoxycytidine kinase; dFdCDP, gemcitabine diphosphate; dFdCTP, gemcitabine triphosphate; UMP/CMP, nucleoside monophosphate. Reprinted by permission from © Macmillan Publishers Ltd on behalf of Cancer Research UK: British Journal of Cancer (5), copyright (2007). All rights reserved. Ueno et al [5].
reductase, which is responsible for producing the deoxynucleotides required for DNA synthesis and repair. The subsequent decrease in cellular deoxynucleotides favors GTP in its competition for incorporation into DNA. After gemcitabine nucleotide is incorporated on the end of the elongating DNA strand, one more deoxynucleotide is added, and thereafter the DNA polymerases are unable to proceed. This action is termed ‘masked chain termination’ and seems to lock the drug into DNA because proof-reading exonucleases are unable to remove gemcitabine nucleotide from this penultimate position. The unique combination of metabolic properties and mechanistic characteristics suggests that gemcitabine is probably synergistic with other drugs that damage DNA. The dose-limiting toxicity of gemcitabine is hematologic and varies with the administration schedule.

**Pemetrexed**

Pemetrexed is a folate antimetabolite that inhibits thymidylate synthase, dihydrofolate reductase, and glycinamide ribonucleotide formyltransferase to prevent the formation of precursor purine and pyrimidine nucleotides. Originally approved in 2004 for treatment of mesothelioma, pemetrexed has been found to be active in platinum-resistant ovarian cancer for which it has been given an NCCN designation. Dose-limiting toxicity is hematologic and patients receiving pemetrexed therapy are required to be on folic acid and vitamin B₁₂ supplementation.

**Trabectedin**

During the 1950 and 1960s, the National Cancer Institute carried out a wide ranging program of screening plant and marine organism material. Discovered in 1969 to have anticancer activity, trabectedin is a new marine antineoplastic tetrahydroisoquinoline alkaloid isolated from the Caribbean sea squirt *Exteinascidia turbinate* (Figure B6). It is manufactured under total synthesis. It is the first anticancer marine-derived drug to be approved by the European Union and is used for advanced soft tissue sarcoma and, when combined with PLD, for the treatment of recurrent ovarian carcinoma. The chemical structure of the drug is characterized by three fused tetrahydroisoquinolone rings, two of
which (subunits A and B) provide the framework for covalent interaction with the minor groove for the DNA double helix, while the third ring (subunit C) protrudes from the DNA helix allowing for interactions with adjacent nuclear proteins (Figure B7). The chemical interactions induced
by the compound trigger a cascade of events that interfere with several transcription factors, DNA binding proteins, and DNA repair pathways. Unlike most alkylating agents that bind guanine at position N7 or O6 in the main groove of DNA, trabectedin binds to the minor groove along GC rich triplets and alkylates guanine at the N2 position. Covalent binding of trabectedin induces DNA bending towards the main groove and a widening of the DNA minor groove. This interferes with the transcription-coupled nucleotide excision repair machinery to induce lethal DNA strand breaks and block the cell cycle in the G2 phase. Elevation of liver enzymes is a dose-limiting toxicity of trabectedin.

The drugs discussed above as well as additional drugs used in the management of ovarian cancer appear in Tables B2–B6.

Included among these are oxaliplatin and nanoparticle albumin-bound paclitaxel (nab-paclitaxel). Although oxaliplatin is a member of the platinum family, acquired drug resistance to oxaliplatin may occur through different mechanisms than it does to carboplatin or cisplatin, possibly explaining the activity of oxaliplatin among patients previously treated with other platinum agents. With demonstrable activity in colorectal adenocarcinoma, oxaliplatin (combined with capecitabine) has also been used with some success in primary mucinous adenocarcinomas of the ovary, which are often refractory to conventional combinations. Being albumin-bound for delivery, nab-paclitaxel has emerged as an active treatment option for patients with significant hypersensitivity to the vehicle used for paclitaxel. Among the oral chemotherapy formulations in Table B4, low-dose metronomic cyclophosphamide and the pro-drug capecitabine, which is enzymatically converted to 5-fluorouracil, are being studied in combinations with anti-angiogenesis agents for treatment of refractory disease. Finally, although not used for epithelial ovarian cancer, drugs currently (ie, bleomycin) and previously used in the treatment of malignant germ cell tumors of the ovary have been included in Table B6.
The bleomycin-etoposide-cisplatin (BEP) regimen used for malignant germ cell tumors of the ovary.

- **Bleomycin**: Days 1, 8, 15: 30 units. Pulmonary toxicity dose-limiting.
- **Etoposide**: Days 1–5: 100 mg/m². 1.3% risk of secondary acute myeloid leukemia.
- **Cisplatin**: Days 1–5: 20 mg/m².

**Table B6** The bleomycin-etoposide-cisplatin (BEP) regimen used for malignant germ cell tumors of the ovary.

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### Intravenous chemotherapy for platinum-sensitive recurrent disease

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carboplatin + paclitaxel</td>
<td>Day 1: Paclitaxel 175 mg/m² intravenous for 3 hours followed by carboplatin AUC 5–6 intravenous q21 days</td>
</tr>
<tr>
<td>Carboplatin + docetaxel</td>
<td>Day 1: Docetaxel 75 mg/m² intravenous followed by carboplatin AUC 5–6 mg/mL/minute intravenous. Repeat cycles every 21 days for 6–8 cycles</td>
</tr>
<tr>
<td>Carboplatin + gemcitabine</td>
<td>Day 1: Carboplatin AUC 4 intravenous. Days 1, 8: Gemcitabine 1000 mg/m² q21 days</td>
</tr>
<tr>
<td>Carboplatin + PLD</td>
<td>Day 1: Carboplatin AUC 5 plus PLD 30 mg/m² q28 days</td>
</tr>
<tr>
<td>Cisplatin + paclitaxel</td>
<td>Day 1: Paclitaxel 135–175 mg/m² intravenous for 3 hours followed by cisplatin 50–75 mg/m² q21 days</td>
</tr>
<tr>
<td>Cisplatin + gemcitabine</td>
<td>Day 1: Cisplatin 30 mg/m². Days 1, 8: Gemcitabine 600 mg/m² q21 days</td>
</tr>
<tr>
<td>Oxaliplatin + gemcitabine</td>
<td>Day 1: Oxaliplatin 100 mg/m². Days 1, 8: Gemcitabine 1000 mg/m² q21 days</td>
</tr>
<tr>
<td>Trabectedin + PLD</td>
<td>PLD 30 mg/m² followed by 3 hour infusion trabectedin 1.1 mg/m² q21 days</td>
</tr>
</tbody>
</table>

**Table B5** Intravenous chemotherapy regimens for platinum-sensitive recurrent ovarian carcinoma. PLD, pegylated liposomal doxorubicin.

### Oral chemotherapy for platinum-resistant recurrent disease

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etoposide (VP-16)</td>
<td>50–60 m/m² qd x 21 days q28 days</td>
</tr>
<tr>
<td>Metronomic cyclophosphamide</td>
<td>50 mg daily</td>
</tr>
<tr>
<td>Capecitabine</td>
<td>2000 mg/m²/d x 14 days q21 days</td>
</tr>
<tr>
<td>Melphalan</td>
<td>0.2 mg/kg daily x 5 days q28 days</td>
</tr>
<tr>
<td>Hexamethylmelamine</td>
<td>260 mg/m² qd x 14 days q28 days</td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>20 mg twice daily continuously</td>
</tr>
</tbody>
</table>

**Table B4** Oral chemotherapy for platinum-resistant recurrent ovarian carcinoma.

### Intravenous chemotherapy for platinum-resistant recurrent disease

- **Pegylated liposomal doxorubicin**: 40 mg/m² q28 days
- **Topotecan**: 4 mg/m² 30 minutes d1, 8, 15 q28 days
- **nab-Paclitaxel**: Days 1, 8, 15: 100 mg/m² q28 days
- **Pemetrexed**: 900 mg/m² over 10 minutes q21 days

**Table B3** Intravenous chemotherapy for platinum-resistant recurrent ovarian carcinoma.

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**BEP regimen for malignant germ cell tumors of the ovary**

- **Bleomycin**: Days 1, 8, 15: 30 units. Pulmonary toxicity dose-limiting.
- **Etoposide**: Days 1–5: 100 mg/m². 1.3% risk of secondary acute myeloid leukemia.
- **Cisplatin**: Days 1–5: 20 mg/m². –

**Table B6** The bleomycin-etoposide-cisplatin (BEP) regimen used for malignant germ cell tumors of the ovary.
References
Noteworthy clinical trials of historical interest

Griffiths: impact of tumor bulk resection on survival in epithelial ovarian cancer

This trial was discussed in the preceding section on the evolution of the concept of cytoreduction in ovarian carcinoma [1].

‘Early’ ovarian cancer and surgical staging in epithelial ovarian cancer

Prospectively, Young et al systematically restaged 100 patients referred to the Ovarian Cancer Study Group institutions with presumably clinically ‘early’ (ie, International Federation of Gynecology and Obstetrics (FIGO) stage IA–IIB) ovarian carcinoma. The investigators noted that only 25% of the study population had an initial surgical incision that would have allowed complete examination of the pelvis and abdominal cavity. Importantly, 31% were found to have more advanced stage disease upon surgical staging, with 23 (77%) of the 31 ultimately being assigned FIGO stage III (Table C1). Sites of unsuspected disease included the pelvic peritoneum, ascites fluid, diaphragmatic surfaces, and the para-aortic lymph nodes. This study confirmed the need to surgically stage ovarian cancer by using a systematic approach that evaluates all peritoneal surfaces, the omentum, and the pelvic and para-aortic lymph nodes [2].
Gynecologic Oncology Group phase II BEP regimen for malignant germ cell tumors

Using the successful testicular germ cell tumor experience as a template, following complete surgical staging and tumor extraction, Williams et al treated 93 patients with malignant germ cell tumors of the ovary using bleomycin (30 units intravenous weekly) plus etoposide (100 mg/m², days 1–5) and cisplatin (20 mg/m², days 1–5). Cycles were repeated every 21 days for a total of three cycles. At the time of publication, 91 of the patients had remained disease free [3]. The regimen was comparatively more tolerable than the prior germ cell regimen consisting of cisplatin plus vinblastine and bleomycin, although there was one case of acute myelomonocytic leukemia (AML) 22 months after diagnosis attributed to etoposide treatment. The most common genetic change in etoposide-induced AML is translocation at chromosome band 11q23. To this day, the BEP regimen has remained the standard of care for malignant germ cell tumors of the ovary.

References
Appendix D

National and scientific milestones

National and scientific milestones
National Cancer Institute

With passage of the National Cancer Institute (NCI) Act on August 6, 1937, Congress established the NCI as an independent research institute. This was during the second of President Franklin D Roosevelt’s four terms in the White House. During his third term, Congress made the NCI an operating division of the National Institutes of Health by the Public Health Service Act on July 1, 1944. Finally, this Act was amended by Congress with the National Cancer Act of 1971 to broaden the scope and responsibilities of the NCI “in order more effectively to carry out the national effort against cancer.” The NCI coordinates the US National Cancer Program and conducts and supports research, training, health information dissemination, and other activities related to the causes, prevention, diagnosis, and treatment of cancer; the supportive care of cancer patients and their families; and cancer survivorship. As of July 2010, the current director of the NCI is Dr Harold Varmus.

National Cancer Institute – Plant Screening program

In 1955, the NCI set up the Cancer Chemotherapy National Service Center to serve as a public screening center for anticancer activity in compounds submitted by external institutions and companies. In 1960, the NCI commissioned USDA botanists to collect samples from 1000 plant species per year. On August 21, 1962, the botanist Arthur S Barclay collected bark
from a single Pacific Yew tree in a forest north of Packwood, Washington. The material was processed and one of the Taxus samples was found to be cytotoxic in a cellular assay.

**Discovery of the structure of DNA**

1869 was a landmark year in genetic research as it was the year in which the Swiss physiological chemist Johannes Friedrich Miescher (1844–1895) discovered DNA when he identified what he called ‘nuclein’ inside the nuclei of human white blood cells. Following this, in 1919, the Russian biochemist Phoebus Aaron Theodore Levene (1869–1940) who published more than 700 papers on the chemistry of biological molecules, discovered the order of the first main components of a single nucleotide (phosphate-sugar-base) and correctly identified the way RNA and DNA molecules are put together. The Austrian biochemist, Erwin Chargaff (1905–2002), expanded on Levene’s work after reading the famous 1944 paper by Oswald Avery and colleagues at Rockefeller University, which demonstrated that hereditary units, or genes, are composed of DNA. This paper had a profound impact on Chargaff, and inspired him to conduct the work that led to his two major conclusions in 1950. First, he noted that the nucleotide composition of DNA varies among species, and second, that almost all DNA, no matter what organism or tissue type it comes from, maintains certain properties, even as its composition varies. All DNA follows Chargaff’s Rule, which states that the total number of purines in a DNA molecule is equal to the total number of pyrimidines. All of this work set the precedent that allowed the American molecular biologist, geneticist, and zoologist James Dewey Watson (1928– ) and the English molecular biologist, biophysicist, and neuroscientist Francis Harry Compton Crick (1916–2004) to reach their groundbreaking conclusion of 1953 that the DNA molecule exists in the form of a three-dimensional double helix (Figure D1).

Together, Watson and Crick along with the New Zealand-born English physicist and molecular biologist Maurice Hugh Frederick Wilkins (1916–2004), who produced the first clear X-ray images of DNA, were awarded the 1962 Nobel Prize for Physiology or Medicine “for their discoveries...
concerning the molecular structure of nucleic acids and its significance for information transfer in living material.”

The war on cancer
National Cancer Act of 1971
The signing of the National Cancer Act of 1971 on December 23, 1971 by President Richard Nixon marked the beginning of the War on Cancer (Figure D2). This federal law was intended to amend the Public Health Service Act so as to strengthen the National Cancer Institute in order to more effectively carry out the national effort against cancer. Mary Lasker’s devotion to medical research contributed to the passing of the National Cancer Act as for many years as President of the Lasker Foundation, she was instrumental in changing the American Cancer Society to obtain more funding for research and specifically increased federal funding for the National Cancer Institute. Despite significant progress in the treatment of certain forms of cancer such as childhood leukemia, due to a perceived lack of progress, new legislation and new research directions have been aimed at augmenting the original National Cancer Act. Many of these new directions are based on the results of the Human Genome Project and include the Cancer Genome Atlas.
The Human Genome Project

The Human Genome Project is the world’s largest collaborative biological project (Figure D3). The primary goal was to determine the sequence of the human DNA base pairs and to identify and map all of the genes in the human genome. The first official funding originated within the US Department of Energy’s Office of Health and Environmental Research and was in the Reagan Administration’s budget submission to Congress in 1987. The clock for initiation of the Project was set for 1990, with most
of the sequencing performed in universities and research centers in the United States, United Kingdom, China, France, Germany, Japan, and Spain. After 10 years of work costing $3 billion, a working draft of the genome was jointly announced by President Bill Clinton and British Prime Minister Tony Blair on June 26, 2000. An essentially complete genome was announced in April 2003, two years earlier than planned, and in May 2006, the sequence of the last chromosome was published in *Nature*.

**The Cancer Genome Atlas**

Work on the Cancer Genome Atlas commenced in 2005. This project seeks to catalogue genetic mutations responsible for cancer by using genomic sequencing and bioinformatics. In theory, the application of high-throughput genome analysis techniques will allow for a better understanding of the genetic basis of different cancers, which will enhance prevention, diagnostic, and treatment strategies. The Cancer Genome Atlas is jointly supervised by the National Cancer Institute and the National Human Genome Research Institute, and the 3-year pilot project begun in 2006 focused on the characterization of three types of human cancers: gliobastoma multiforme, lung, and ovarian cancer.

**NCI-designated cancer centers**

Of the 68 NCI-designated cancer centers, 27 are cancer centers and 41 are comprehensive cancer centers. An NCI-designated cancer center must demonstrate scientific leadership, resources, and capabilities in laboratory, clinical, or population science, or some combination of these three components. It must also demonstrate reasonable depth and breadth of research in the scientific areas it chooses and transdisciplinary research across these areas. An NCI-designated comprehensive cancer center must demonstrate reasonable depth and breadth of research in each of three main areas: laboratory, clinical, and population-based research as well as substantial transdisciplinary research that bridges these scientific areas. In addition, a comprehensive center must also demonstrate professional and public education and outreach capabilities, including the dissemination of clinical and public health advances in the communities it serves.
NCI’s Cancer Therapy Evaluation Program

The mission of the Cancer Therapy Evaluation Program (CTEP) is to reduce the burden of cancer. CTEP plans, reviews, and coordinates clinical trials for investigational anticancer agents, from the inception of protocols through the preparation and submission of Investigational New Drug Applications (INDs) to the United States Food and Drug Administration (FDA). CTEP also serves as a liaison to the FDA for the extramural clinical research community and industry collaborators. Other CTEP functions include managing, tracking, and reviewing clinical protocols as well as monitoring, planning, and maintaining regulatory compliance of the clinical trials. In addition, CTEP coordinates the distribution of the investigational agents from industry collaborators for use in all NCI-sponsored clinical trials. CTEP attempts to forge broad collaborations within the research community and works extensively with the pharmaceutical and biotechnology industry to effectively develop new cancer treatments. CTEP also seeks to involve outside experts and patients or their advocates in the formulation of research priorities. The contractual framework with CTEP for collaboration exists as a Clinical Trials Agreement (CTA) or a Cooperative Research and Development Agreement (CRADA).

NCI’s Gynecologic Cancer Steering Committee

In May 2006, the Gynecologic Cancer Intergroup transitioned into the Gynecologic Cancer Steering Committee (GCSC). The Steering Committee is composed of cooperative group gynecologic disease committee chairs, Specialized Programs of Research Excellence (SPOREs), R01/P01 investigators, community oncologists, biostatisticians, patient advocates, NCI staff, and three disease-site task forces (ovarian, cervix, and uterine). The GCSC functions to harmonize an efficient, cost-effective, science-driven, and transparent process that will identify and promote the ‘Best Science’ in gynecologic cancer clinical research by addressing the design and prioritization of phase III trials and evaluating randomized phase II studies. As part of its mission, the GCSC is intent on fostering collaboration with international groups and institutions engaged in conducting
trials in gynecologic cancers. As of 2014, the GCSC Co-Chairs are David M Gershenson, MD, Michael J Birrer, MD, PhD, and David Gaffney, MD, PhD.

**NCI’s Ovarian Cancer Task Force**
The Ovarian Cancer Task Force is one of the three disease-site task forces that function as a liaison between investigators developing phase III and randomized phase II trials and the GCSC and CTEP. As of 2014, the Co-Chairs of the Ovarian Cancer Task force are Dr Carol Aghajanian and Dr Kunle Odunsi.

**NCI’s cooperative group merger – NRG Oncology**
As a consequence of an NCI mandate, several cooperative groups have merged into distinct entities. (The mandate did not include the Children’s Oncology Group or the Southwest Oncology Group). The NRG is comprised of the former National Surgical Adjuvant Breast and Bowel Project (NSABP), the Radiation Therapy Oncology Group (RTOG), and the Gynecologic Oncology Group (GOG). The GOG was founded in 1970 by a group of farsighted gynecologic surgeons with a special interest in quality clinical research. They recognized the need for a collaborative research effort, not only among institutions, but also among various disciplines involved in the treatment of women with gynecologic cancers. Prior to that time, the fundamental basis of clinical practice in gynecologic cancer consisted of reports from individual investigators derived largely from case reports and retrospective non-randomized reviews. The GOG was among the first organizations to adopt a multidisciplinary, multi-institutional, prospective approach to the management of gynecologic malignancies. As one of the NCI’s funded cooperative cancer research groups, the GOG designed, conducted, and completed 25 of the 35 phase III randomized clinical trials that have provided the body of evidence-based medicine oncologists use to treat women diagnosed with gynecologic cancer.

Since 1970, the GOG has grown from 11 original member institutions to over 50 principal centers, most of which are academic centers, and over 160 affiliate institutions. The GOG remains a multi-modality group with over 2100 participants, which include gynecologic oncologists, medical oncologists, pathologists, radiation oncologists, nurses, statisticians,
basic scientists, quality of life experts, data managers, and administrative personnel. The GOG is recognized as the leader in the development of new procedures in each of the relevant diagnostic and therapeutic disciplines. As part of NRG, the GOG will continue to run trials through the CTEP mechanism. A new track that permits direct collaboration with industry has been called GOG PARTNERS. Having served three consecutive terms as Group Chair of the GOG, Professor Philip J DiSaia, MD is currently the Presiding Chair of the NRG (Figure D4).

**International Federation of Gynecology and Obstetrics**

The International Federation of Gynecology and Obstetrics (FIGO) was founded on July 26, 1954 in Geneva, Switzerland and has become a worldwide organization that encompasses 125 countries and territories. Its Secretariat is based in London, UK. As of 2012, the President of FIGO is Professor Sir Sabaratnam Arulkumaran. FIGO holds a triennial World Congress, and in the field of gynecologic oncology publishes a Cancer Report (previously named The Annual Report); it also provides FIGO Staging Systems for each of the gynecologic malignancies. The new FIGO staging system for ovarian cancer was implemented on January 1, 2014.

![Figure D4 Professor Philip J DiSaia, Presiding Chair of NRG Oncology.](image-url)
National Comprehensive Cancer Network

The National Comprehensive Cancer Network (NCCN) is an alliance of 23 of the world’s leading cancer centers devoted to patient care, research, and education. Through the leadership and expertise of clinical professionals at NCCN Member Institutions, NCCN develops resources that present valuable information of the numerous stakeholders in the healthcare delivery system. World-renowned experts from NCCN Member Institutions diagnose and treat patients with a broad spectrum of cancers and are recognized for dealing with complex, aggressive, or rare cancers. NCCN Member Institutions pioneered the concept of the multidisciplinary team approach to patient care and conduct innovative research that contributes significantly to understanding, diagnosing, and treating cancer. NCCN programs offer access to expert physicians, superior treatment, and quality and safety initiatives that continuously improve the effectiveness and efficiency of cancer care. The NCCN has produced Guidelines for Treatment for Cancer by Site, for Detection, Prevention, and Risk Reduction, for Supportive Care, for Patients, and in several other important oncologic areas. These may be accessed free of charge at www.nccn.org. NCCN listings of viable therapies based on pivotal clinical trials may occur prior to FDA approval of the drug or regimen under study. Occasionally NCCN Compendium listing will be used by some health maintenance organizations (HMOs) and preferred provider organization (PPOs) to approve the use of an active but as yet unapproved drug for patients covered under their health plans.

United States Food and Drug Administration

Orphan Drug Act

The Orphan Drug Act makes provisions for granting special status to a drug or biological product to treat a rare disease or condition. In theory, orphan drug designation is intended to support the clinical development of new drugs in diseases affecting less than 200,000 people annually in the United States. This route provides the manufacturer with a 7-year market exclusivity on the indication if the agent is approved, during which time no direct generic competition may occur. The FDA may provide technical and financial assistance to expedite and optimize drug
development in some cases. With fewer than 25,000 cases diagnosed annually, ovarian cancer drug discovery falls under the Orphan Drug Act and while NCCN listing as described above can help to make available some drugs to some populations of cancer patients, typically FDA approval is required to make drugs available to patients who depend on public funding (ie, Medicare and Medicaid).

**Drug shortages**

Pegylated liposomal doxorubicin (PLD) has been in short supply in the United States since November 2011 when the FDA intervened at a plant operated by Ben Venue Laboratories in Bedford, Ohio, where equipment had deteriorated to the point that it shed particles into injectable drugs. In October 2011, acknowledging the urgency of the drug shortage crisis (Figure D5), President Barak Obama issued an executive order that instructed the FDA to speed up efforts to get generic drugs approved and on the market. In February 2013, the FDA approved the first generic form of PLD, LIPODOX, made by Sun Pharma Global FZE, a subsidiary of India’s Sun Pharmaceutical Industries Ltd (Mumbai, India).

**Supreme Court ruling on gene patenting**

On June 13, 2013 the Supreme Court ruled that “a naturally occurring DNA segment” (ie, gene) cannot be patented in the case of Association
For Molecular Pathology, et al versus Myriad Genetics, Inc., No. 12-398. This was a unanimous decision by the Supreme Court. In accordance with the viewpoint advocated by the Obama Administration, the Court decided that synthetically generated strands of DNA, called cDNA, are eligible for patent protection. Mary-Claire King, a geneticist from the University of Washington who discovered the breast cancer susceptibility genes stated that “the Supreme Court ruling is splendid for patients, their families, their physicians, scientists, and common sense.”

**Legislative provisions against genetic discrimination**

The Health Insurance Portability and Accountability Act (HIPAA) of 1996 constituted the first federal protection against genetic discrimination in health insurance, by specifically stating that genetic information in the absence of a current diagnosis of illness did not constitute a preexisting condition.

President Bill Clinton next issued Executive Order 13145 to Prohibit Discrimination in Federal Employment Based on Genetic Information in February 2000 – this prohibited agencies employed by the federal government from obtaining genetic information about existing employees and from federal job applicants.

Finally, on May 21, 2008 President George W Bush signed into law the Genetic Information Nondiscrimination Act, which prohibited group health plans from denying coverage to a healthy individual or charging that person higher premiums based solely on a genetic predisposition to developing a disease in the future. This is a key Act because it also prevents employers from using genetic information in making decisions regarding hiring, firing, and promotions.

**Department of Defense Ovarian Cancer Research Program**

The Department of Defense (DoD) Ovarian Cancer Research Program (OCRP) is a Congressionally Directed Medical Research Program (CDMRP) that was established in 1997. The OCRP conducts innovative, multidisciplinary research on early detection, screening, and treatment of ovarian cancer. The OCRP also works to attract new investigators to the field of ovarian cancer research.
Modeled after the successful Breast Cancer Research Program created in 1992, the OCRP has helped advance understanding and treatment of ovarian cancer by supporting research designed to use nanoparticles to deliver diphtheria toxin-encoding DNA to ovarian cancer cells. In addition, the OCRP has funded the discovery that ovarian cancer cells are sensitive to glucose deprivation and resveratrol treatment. Cancer research performed by the DoD has been responsible for fundamentally changing the way cancer research is conducted, and many innovative practices and methods created by CDRMPs have been adopted by the NCI (eg, having cancer patients as consumer reviewers in the proposal review process). On January 13, 2014, Chairmen Mikulski and Rogers put out the Omnibus Appropriations Bill and the Joint Explanatory Statement to the Omnibus for the Department of Defense was released shortly thereafter. In what has been acknowledged as the result of successful lobbying efforts by the Society of Gynecologic Oncology’s Government Relations Committee, for fiscal year 2014, ovarian cancer research has been set at $20 million.

Ovarian Cancer Research Fund
The Ovarian Cancer Research Fund (OCRF), founded in 1994, is the oldest and largest charity in the United States funding ovarian cancer research, and, following the National Cancer Institute and the Department of Defense, ranks third in overall ovarian cancer research funding. The OCRF is funded by individual donors, foundations, and corporate partners. The OCRF has invested over $57 million in ovarian cancer research through 217 grants to investigators at 65 leading medical centers in the United States, with 86% of every dollar raised going to support OCRF programs. For the last two years, the OCRF has received the most applications in the history of the organization. For additional information, including important deadlines, please visit www.ocrf.org.

American Cancer Society
The American Cancer Society (ACS) is a nationwide voluntary health organization dedicated to eliminating cancer. Founded in 1913 as the American Society for the Control of Cancer by 15 prominent physicians
and business leaders in New York City during a time when a cancer diagnosis amounted to near certain death, the founders of the Society knew they had to raise public awareness about cancer if progress was to be possible.

The iconic Sword of Hope symbol, which is part of the ACS logo, resulted from a 1928 nationwide poster contest won by George E Durant of Brooklyn (Figure D6). He selected the sword to express the crusading spirit of the cancer control movement. Today the ACS operates through more than 900 offices throughout the United States. Its home office is located in the American Cancer Society Center in Atlanta, Georgia (www.cancer.org). The ACS publishes Cancer, CA: A Cancer Journal for Clinicians, and Cancer Cytopathology.

**American Society of Clinical Oncology**

Founded in 1964 by Dr Harry Bisel, Dr Jane C Wright, and five other physicians, ASCO today has more than 30,000 members, representing physicians of all oncology subspecialties who care for people with cancer (www.asco.org). Taking place over 5 days with over 35,000 registered attendees, the ASCO Annual Meeting is the largest educational and scientific event in the oncology community. The *Journal of Clinical Oncology* is published three times each month by ASCO and has an impact factor

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![Figure D6 Early logo of the American Cancer Society depicting the iconic sword.](image)
Reproduced with permission from © American Cancer Society, 2014. All rights reserved. American Cancer Society [3].
of 18.038. ASCO’s Conquer Cancer Foundation is a 501(c)(3) charitable organization that supports cancer research in the field of oncology, patient education, and patient advocacy programs. Since the inception of its Grants and Awards Program in 1984, the Conquer Cancer Foundation has funded more than 800 investigators worldwide.

**American Association for Cancer Research**

Founded in 1907 by 11 physicians and scientists, the American Association for Cancer Research (AACR) is the world’s oldest and largest professional association related to cancer research and has more than 33,000 members from 97 countries. With its headquarters based in Philadelphia, the AACR focuses on all aspects of cancer research, including basic, clinical, and translational research into the etiology, prevention, diagnosis, and treatment of cancer (www.aacr.org). The AACR publishes six peer-reviewed journals, including *Cancer Research*, *Clinical Cancer Research*, *Molecular Cancer Therapeutics*, *Molecular Cancer Research*, *Cancer Prevention Research*, and *Cancer Epidemiology, Biomarkers & Prevention*. The AACR Annual Meeting attracts more than 18,000 participants from 74 countries.

**Society of Gynecologic Oncology**

The Society of Gynecologic Oncology (SGO) (formerly Society of Gynecologic Oncologists) is a national society of physicians trained in treating female reproductive cancers. The idea for a national medical association dedicated to the study and treatment of gynecologic cancer originated in February 1968 during a discussion between Dr Hervy E Averette and Dr John J Mikuta at a meeting of the Association of Professors of Gynecology and Obstetrics in New Orleans. Over time, a growing number of physicians signed on to the idea, and the society was formally founded at a meeting held in Key Biscayne, Florida in January 1969 under the chairmanship of Dr George C Lewis, Jr. Headquartered in Chicago, Illinois, the SGO has over 1500 members and is the “leading organization of Gynecologic Oncologists in the United States” (www.sgo.org). The current SGO President, Dr Barbara A Goff, is a Gynecologic Oncologist at the University of Washington. The SGO holds the Annual Meeting on Women’s Cancer, Winter Meetings, and Coding Webinar
Series. In addition, the SGO has a very active Government Relations Committee that has effectively lobbied in Washington, DC on a wide range of issues including physician reimbursement and ovarian cancer research funding. SGO’s Foundation for Gynecologic Oncology (formerly Gynecologic Cancer Foundation) is a 501(c)(3) organization focused on raising money for the needs of SGO members. The Foundation has funded many early SGO investigators who have since gone on to compete successfully for NIH and Department of Defense funding. Dr Beth Y Karlan of Cedars-Sinai is the current Editor-in-Chief of the SGO’s official journal, *Gynecologic Oncology*, and in December 2012 was appointed by President Barack Obama to the National Cancer Advisory Board which advises the National Cancer Institute.

**International Gynecologic Cancer Society**

The International Gynecologic Cancer Society (IGCS) is a not-for-profit independent organization contributing to the prevention, treatment, and study of gynecologic cancer, as well as improvement in the quality of life among women suffering from gynecologic cancer throughout the world. IGCS strives for global representation, reflecting the diverse cultural, economic, and geographic impact of gynecologic cancer. In June 1985 in London, England, a small group of physicians interested in gynecologic cancer met to discuss the concept of a new society of gynecologic oncology feeling that the international exchange of academic information and protocols were lacking. A second meeting was held in conjunction with the FIGO convocation in Berlin during October 1985 and a steering committee consisting of 49 representatives in related disciplines of gynecologic oncology, radiation oncology, medical oncology, and pathology in equal partnership from 20 countries was convened. The formal launch of the IGCS took place in San Francisco during May 1–3, 1986. The IGCS holds biennial meetings all over the world and currently has 1500 members representing more than 75 countries (www.igcs.org). Travel grants and reduced registration fees for the meetings are available for clinicians and scientists from third world countries. The official publication of the IGCS is the *International Journal of Gynecologic Cancer*. 
The current IGCS President is Dr Lynette A Denny from Groote Schuur Hospital in Cape Town, South Africa.

**Ovarian Cancer National Alliance**
The Ovarian Cancer National Alliance (OCNA) educates healthcare professionals and raises public awareness of the risks and symptoms of ovarian cancer (www.ovariancancer.org). The Alliance was founded in 1997 when the leaders of five disparate ovarian cancer organizations met for the first time at the launch of the Department of Defense Ovarian Cancer Research Program and decided to pool their intellect, resources, and energy and come together as the OCNA. The five founding groups were CONVERSATIONS! The International Newsletter for Those Fighting Ovarian Cancer (Texas), the National Ovarian Cancer Coalition (Florida), Ovar’coming (Indiana), the Ovarian Cancer Coalition of Greater Washington (Washington, DC), and SHARE: Self-Help for Women with Breast or Ovarian Cancer (New York). The first board of directors of the OCNA was comprised of women affected by the disease. Today, the Ovarian Cancer National Alliance is the foremost advocate for women with ovarian cancer in the United States. To advance the interests of women with ovarian cancer, the Alliance advocates at a national level for increases in research funding for the development of an early detection test, improved healthcare practices and life-saving treatment protocols. An ovarian cancer survivor since 2002, Diane Rader O’Connor of Vancouver, WA is the current President of the OCNA Board of Directors.

**Ovarian Cancer awareness month**
By way of Presidential Proclamation Ovarian Cancer Awareness month occurred during early September in 2009, 2010, 2011, 2012, and 2013. In 2014 President Barack Obama also proclaimed September as Ovarian Cancer Awareness Month in the United States. The ovarian cancer ribbon color is teal (Figure D7).
Figure D7 The green teal ribbon has been designated the ovarian cancer ribbon.

References
Afterword

On December 19, 2014 the United States Food and Drug Administration (FDA) granted accelerated approval to the poly-ADP ribose polymerase inhibitor (PARPi), olaparib, as a fourth-line therapy for women with BRCA-deficient ovarian carcinoma [1]. Earlier this year on June 25th, the Oncology Drugs Advisory Committee (ODAC) panel members had voted 11 to 2 against regulatory approval of this first-in-class drug as a maintenance therapy for ovarian cancer based on results of a placebo-controlled trial [2,3]. Following the ODAC meeting, AstraZeneca submitted additional data from a single arm, open-label trial demonstrating a 31.1% response rate when olaparib was used in BRCA-positive women who had already received three or more lines of chemotherapy [4]. The ongoing placebo-controlled phase III randomized trial, SOLO 2, is studying olaparib monotherapy in women with recurrent ovarian cancer treated with at least two lines of chemotherapy. Both SOLO 2 and ultimately SOLO 3 are integral to the phase IV commitment following accelerated approval. FDA approval of olaparib was done in conjunction with regulatory approval of a companion diagnostic genetic test (BRACAnalysis CDx™) that will screen serum from ovarian cancer patients for mutations in the BRCA genes (gBRCAm) [1].

One year ago we completed the first draft of this 21st Century Handbook of Clinical Ovarian Cancer and wrote the Forward. A lot happened during 2014 and we’ve been able to cover it all in these pages. We are grateful to Teresa Salazar from Springer US for having reached out to us back in late 2013 to get the pieces in play. We remain indebted to Laura Hajba from Springer Healthcare UK for her editorial skills and tolerance of numerous revisions and expansions of this work during pre-production in order to include the most updated clinically relevant information.

Krish Tewari & Brad Monk
January 15, 2015
Melbourne, Vancouver, Newport Beach, and other various locales

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