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Review

Drug repurposing in gynaecological cancers: Proven drugs for new challenges

Amani Alghalayini [a,*], Farhana A. Sarker [a], Kristie-Ann Dickson [a], Nikola A. Bowden [b], Deborah J. Marsh [a]

[a] Translational Oncology Group, School of Life Sciences, Faculty of Science, University of Technology Sydney, Ultimo, NSW 2007, Australia
[b] School of Medicine and Public Health, University of Newcastle, Newcastle, NSW 2289, Australia

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ABSTRACT

Gynaecological malignancies, including cervical, endometrial, ovarian, vaginal and vulval cancers, pose therapeutic challenges that contribute to this group being the third most frequent cause of cancer-related deaths globally in women. While advances have been made in both screening for cervical cancer and immunisation against human papillomavirus strains in some countries, other gynaecological cancers have not seen improvements in early screening and prevention strategies. Drugs inhibiting poly (ADP-ribose) polymerase (PARP) have been incorporated into the clinical management of homologous recombination-deficient ovarian cancers, including as maintenance therapies post-surgery; however, these constitute only around half of all ovarian cancers. Developing new therapeutic options for all gynaecological malignancies, including those that demonstrate innate or acquired resistance to standard-of-care chemotherapeutic regimens, remains a challenge. Drug repurposing, defined as the repositioning of drugs that have been approved for the treatment of specific indications to treat other conditions, demonstrates strong potential for the clinical management of gynaecological malignancies. This review highlights diverse drug repurposing approaches applied to gynaecological cancers. Examples include computational methods such as disease and drug signature matching, network or pathway mapping, genetic association studies, drug similarity networks, molecular docking, machine learning, and serendipitous clinical observations. High-throughput compound library and drug-based phenotypic screening also contribute to candidate identification. Repurposed drugs with established safety and pharmacological profiles can accelerate therapeutic discovery; however, some regulatory and industry barriers remain. Coupled with advanced patient-centred technologies, 3D tumoroids, tumour-on-a-chip, and microfluidic systems, drug repurposing strategies promise to advance personalised medicine and improve survival outcomes for women with gynaecological malignancies.

1. Introduction

Gynaecological malignancies represent a significant health challenge and are the third most common cause of cancer-related mortality amongst women worldwide [1]. These cancers include cervical, endometrial (corpus uteri), ovarian, vulval and vaginal cancers [2]. According to the 2022 GLOBOCAN report, over 1.4 million cases of gynaecological cancers were diagnosed globally, with more than 600,000 deaths attributed to cervical, endometrial, and ovarian cancers [3]. Cervical cancer remains the fourth most commonly diagnosed cancer in women worldwide and the third leading cause of cancer-related mortality, claiming approximately 348,000 lives in 2022 [3]. Endometrial and ovarian cancers are similarly challenging, with an estimated 98,000 and 207,000 global deaths, respectively, in the same year [3]. Although less common, the incidence of vaginal and vulval cancers is increasing among younger women in several high-income countries, primarily due to the rising prevalence of persistent high-risk human papillomavirus (HPV) infections [4]. Despite advances in prevention and screening, including vaccination for cervical cancer, high mortality rates persist for other gynaecological cancers due to the lack of effective early detection methods and treatment options [5]. While improvements in surgical techniques, chemotherapy, targeted therapies, and immunotherapies have enhanced survival outcomes, effective treatments for advanced-stage gynaecological cancers remain limited. This

* Corresponding author.
E-mail address: amani.alghalayini@uts.edu.au (A. Alghalayini).

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underscores the urgent need for innovative therapeutic strategies to overcome drug resistance and improve both progression-free and overall survival.

The advent of precision medicine has reshaped cancer treatment paradigms [6]. Unlike traditional one-size-fits-all approaches, precision medicine focuses on tailoring therapies based on the specific molecular and genetic profile of a patient's tumour [5]. In gynaecological cancers, particularly ovarian and endometrial cancers, genomics and molecular profiling have revealed critical insights into tumour biology [7]. For example, the discovery of germline *BRCA1/2* mutations in ovarian cancer has led to the application of targeted therapies such as poly (ADP-ribose) polymerase (PARP) inhibitors, including olaparib (Lynparza™), niraparib (Zejula™), and rucaparib (Rubraca™), exploiting deficiencies in homologous recombination DNA repair [8]. Similarly, the frequent dysregulation of the PI3K/AKT/mTOR signalling pathway in ovarian and endometrial cancers presents an opportunity for employing existing pathway inhibitors [9]. Everolimus (Afinitor™), an mTOR inhibitor approved for renal cell carcinoma, is being explored for its potential in treating gynaecological cancers with PI3K/AKT/mTOR pathway dysregulation [10]. Moreover, the identification of genetic changes causing deficiency in the mismatch repair pathway (dMMR) and microsatellite instability in endometrial cancer has led to the consideration of immune checkpoint inhibitors, highlighting how molecular profiling can guide treatment decisions [11]. Research into the tumour microenvironment (TME) has also uncovered immune cell populations and extracellular matrix (ECM) components as promising therapeutic targets in cancer treatment [12]. These molecular insights not only inform the development of new therapies but also pave the way for rational drug repurposing in gynaecological cancers.

Drug repurposing, leveraging existing drugs for new indications outside the scope of the original medical indication (often referred to as drug repositioning, reprofiling, or re-tasking), offers a promising avenue to enhance treatment outcomes for gynaecological cancers [13,14]. Ongoing advances in drug repurposing and genomic technologies are catalysing the integration of precision medicine into the management of gynaecological cancers. While standard-of-care chemotherapy remains the cornerstone of treatment for many patients, the management of recurrent or resistant disease often involves an empirical trial-and-error approach to identify effective therapies. Precision medicine offers a paradigm shift by enabling tailored, biomarker-driven therapeutic strategies that transcend the limitations of empirical treatment selection, minimise adverse effects, and ultimately improve patient survival and outcomes [15]. This approach aims to deliver the right treatment to the right patient at the right time, ultimately leading to more personalised and effective care. Accelerating the identification and development of repurposed drugs can provide more accessible therapies for patients with gynaecological cancers, addressing treatment gaps and improving prognoses. By avoiding many of the time-consuming and costly development stages of traditional drug discovery, which typically takes 10–15 years and costs between 1 and 1.5 USD billion, drug repurposing offers a faster and more cost-effective alternative (Fig. 1) [16,17]. Additionally, repurposed drugs come with well-characterised pharmacological and safety profiles, which significantly reduce the risk of failure in clinical trials. Currently, only 10 % of drug candidates advance to phase I clinical trials, with a mere 1 in 30,000 compounds achieving regulatory approval [18]. However, the global pharmacopeia already includes over 4700 approved drugs, offering a vast repository for repurposing efforts [19,20].

Drug repurposing, while historically driven by serendipitous discoveries, is fundamentally predicated on the polypharmacological principle that many drugs act beyond their originally intended targets [24]. This intrinsic promiscuity of pharmaceuticals enhances the probability of identifying novel therapeutic applications through either previously unrecognised off-target activities or newly recognised

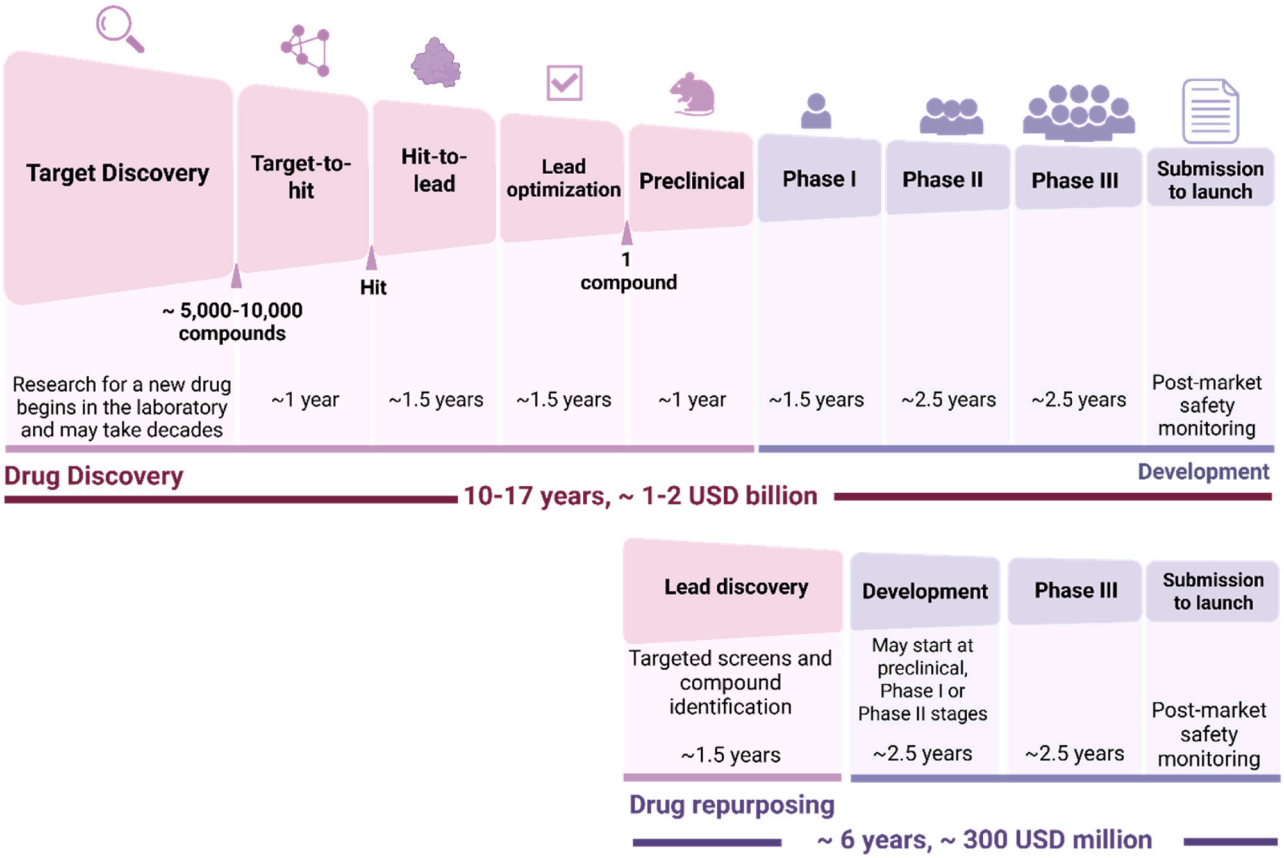


Fig. 1. Timeline and cost comparison between traditional drug development and drug repurposing. Data compiled from [21–23]. Created using Biorender.

on-target effects. This approach has already led to success in oncology, with several non-cancer drugs being repurposed to target tumour-specific pathways and combat resistance mechanisms [25]. Successful examples of drug repurposing include chlorambucil (Leukeran™) and thalidomide (Thalomid™) [26]. Chlorambucil, initially developed as an alkylating agent derived from mustard gas, was later found to be effective as a treatment for leukemias [27]. Thalidomide, despite its tragic history of causing birth defects, has been successfully repurposed to treat conditions such as leprosy and multiple myeloma [28]. These examples illustrate the transformative potential of drug repurposing in addressing unmet therapeutic needs.

This review aims to explore the role of drug repurposing in meeting the therapeutic challenges of gynaecological cancers. This review will discuss preclinical and clinical hurdles in drug repurposing and the limitations that must be overcome. Key repurposed drugs and their mechanisms of action will be highlighted, along with their clinical relevance and potential to address the unique challenges of gynaecological cancers. Additionally, it will examine the methodologies employed to identify drugs with the potential to be repurposed, including *in silico*, *in vitro*, and *in vivo* approaches. Finally, it will emphasise emerging technologies, including patient-derived models, which are poised to revolutionise drug repurposing by enabling personalised and effective cancer therapies. By shedding light on these advances, this review aims to underscore the transformative potential of drug repurposing in improving outcomes for patients with gynaecological cancers.

2. Advantages of drug repurposing approaches to treat gynaecological cancers: emphasising the 3Rs principle

Drug repurposing offers several advantages in addressing the challenges faced in treating gynaecological cancers. One of the significant benefits of drug repurposing is its ability to save time and reduce costs by utilising existing compounds with established safety profiles. However, it also presents an opportunity to shift the paradigm of preclinical research by moving away from traditional animal models and embracing alternatives that adhere to the 3Rs principle of Replacement, Reduction, and Refinement. This framework aims to minimise the use of animals in scientific research while improving the quality and translational value of preclinical findings [29].

While repurposed drugs have historically advanced to clinical trials following successful *in vivo* validation, recent regulatory developments and technological innovations are gradually reshaping this requirement. For instance, the U.S. Food and Drug Administration (FDA) has announced a plan to phase out mandatory animal testing for monoclonal antibodies and other drugs within the next five years, reflecting a broader commitment to replacing animal models with scientifically validated alternatives [30]. Reasons that further testing of repurposed drugs in animal models may be redundant include when comprehensive human safety and toxicity data already exist, and when *in vivo* models fail to accurately recapitulate the human disease poised to potentially benefit from a repurposed drug, with poor predictive value limiting ultimate clinical benefit. In this evolving research and therapeutic landscape, *in vivo* studies may still be relevant in situations where systemic toxicity cannot yet be fully captured through *in vitro* or computational methods [31–33]. Clinically informed analyses, such as patient case reports and real-world data, are expected to increasingly generate hypotheses for drug repurposing without additional *in vivo* studies into the future [34].

As repurposing of approved drugs involves compounds that have already undergone Phase I clinical trials to confirm safety in humans, the focus can shift to utilising more human-relevant models that are ethically sound and scientifically rigorous. Some alternative *in vitro* models, including tumour spheroids and organoids, as well as microfluidic platforms facilitating tumour-on-a-chip models, are moving towards effectively replicating the human TME [35]. These models can provide valuable insights into drug efficacy and toxicity without the ethical and scientific concerns associated with animal testing. Cultures of human tumoroids, for example, have gained significant traction in cancer research as they closely mimic the structural and functional aspects of human tumours, offering a more accurate prediction of drug responses compared to traditional 2D cell culture systems [36]. Additionally, lab-on-a-chip technologies enable the simulation of dynamic tumour environments, including fluid flow, which allows for high-throughput screening (HTS) of repurposed drugs with fewer ethical concerns [37]. For instance, the Mimetas OrganoPlate® platform supports 3D organ models under perfusion conditions, allowing more accurate assessment of drug efficacy and toxicity compared to traditional static models [38]. These advances facilitate the efficient testing of large numbers of compounds that can potentially be repurposed, thereby accelerating the identification of effective treatments for gynaecological cancers. By transitioning to advanced, non-animal testing methods, drug repurposing not only enhances the speed and cost-effectiveness of cancer drug discovery but also fosters a more ethical and scientifically relevant approach to preclinical research.

3. Drugs identified with the potential to be repurposed to treat gynaecological cancers

This section highlights examples of repurposed drugs, their mechanisms of action, and their potential to improve outcomes in gynaecological cancer treatment.

3.1. Ovarian cancer

Ovarian cancer comprises a group of distinct histopathological subtypes, each with unique molecular features, clinical behaviours, and treatment responses. Subtypes such as high-grade serous ovarian cancer (HGSOC), ovarian clear cell carcinoma (OCCC), endometrioid ovarian carcinoma (EnOC), mucinous ovarian carcinoma (MOC), and low-grade serous ovarian carcinoma (LGSOC) exhibit distinct genetic alterations and therapeutic vulnerabilities. This heterogeneity contributes to the overall poor prognosis of ovarian cancer and highlights the limitations of a one-size-fits-all treatment approach [39]. Approved therapies for ovarian cancer typically involve a combination of surgery, chemotherapy, targeted therapies, and, in some cases, immunotherapy. Chemotherapy, consisting of platinum-based agents like carboplatin (Paraplatin™), is used in conjunction with taxanes such as paclitaxel (Taxol™) or docetaxel (Taxotere™) as a first-line treatment [40]. Targeted therapies include anti-angiogenic agents like bevacizumab (Avastin™) that target vascular endothelial growth factor (VEGF), inhibiting the formation of new blood vessels in tumours, and PARP inhibitors such as olaparib, niraparib, and rucaparib, which are effective for patients with *BRCA* mutations or epigenetic silencing of genes involved in homologous recombination repair [41]. Hormonal therapies, such as tamoxifen (Nolvadex™) or aromatase inhibitors, are occasionally used in hormone receptor-positive disease [42]. Immunotherapies, including checkpoint inhibitors like pembrolizumab (Keytruda™), show emerging promise, especially in subtypes characterised by dMMR [43]. Additionally, hyperthermic intraperitoneal chemotherapy, delivering heated chemotherapy directly into the abdominal cavity during surgery, is sometimes employed to eliminate residual disease [44]. These therapies are often combined and tailored to the specific type of ovarian cancer and the genetic profile of the patient. Below is an overview of several repurposed drugs currently being investigated in clinical and preclinical studies for their potential in treating ovarian cancer, with an emphasis on their mechanisms of action.

3.1.1. Clinically approved drugs under investigation for repurposing for ovarian cancer

Several clinically approved drugs are currently being investigated for

repurposing as potential treatments for ovarian cancer (Table 1). For example, ketorolac (Toradol™), a non-steroidal anti-inflammatory drug (NSAID), was originally developed for pain management [45]. However, recent evidence suggests that its S-enantiomer selectively inhibits key cancer cell signalling and metastasis regulators Rac1 and Cdc42 GTPases. Given this, ketorolac is currently being evaluated in a clinical trial (NCT02470299) to assess its potential to improve survival outcomes in post-operative patients with HGSOC and OCCC [46]. Similarly, the antifungal agent itraconazole (Sporanox™) was repurposed based on findings that it inhibits Hedgehog signalling and angiogenesis in melanoma, two processes critical to tumour progression and chemoresistance [47]. Preclinical and early-phase clinical studies (NCT03081702) suggest that itraconazole may enhance chemotherapy responses in platinum-resistant HGSOC, LGSOC, and, more recently, in OCCC, possibly exerting antitumour effects via lysosomal dysfunction [48].

Atovaquone (Mepron™), an antiprotozoal agent that inhibits mitochondrial respiration, was selected for potential repurposing to treat ovarian cancer based on its ability to inhibit pro-proliferative transcription factor Signal Transducer and Activator of Transcription 3 (STAT3) [49], and is currently under investigation in a Phase II trial (NCT05998135) for platinum-resistant ovarian cancer [50,51]. Metformin (Glucophage™), a first-line treatment for type 2 diabetes, approved by the FDA in 1994, emerged from epidemiological observations linking its use to reduced cancer incidence. A meta-analysis of 13 studies of diabetic patients revealed that treatment with metformin was associated with a 24 % reduced risk of ovarian cancer incidence and a 45 % decrease in ovarian cancer-associated mortality compared to those patients who did not take this drug [52]. Mechanistic studies subsequently demonstrated that metformin activates AMP-activated protein kinase (AMPK), which can inhibit cancer cell proliferation by disrupting metabolic pathways critical for tumour growth (Fig. 2). Clinical trials are now evaluating metformin's potential to modulate the TME in HGSOC by analysing changes in immune cell infiltration, angiogenesis, and stromal cell activity, aiming to enhance anti-tumour immune responses and improve therapeutic outcomes [53–56].

In addition, several approved drugs are being investigated for label expansion, the regulatory approval of an already approved drug for a new indication, as potential treatments for ovarian cancer (Table 2). Trastuzumab deruxtecan (Enhertu®), a HER2-targeting antibody-drug conjugate (ADC) approved for metastatic breast, gastric, and non-small cell lung cancers, is being explored in ovarian cancer, endometrial and cervical cancer, with a Phase II trial (NCT04482309) evaluating its activity and safety in HER2-expressing tumours [57]. Similarly, Disitamab Vedotin (Aidixi®), another HER2-targeting ADC, is being investigated for label expansion in HER2-expressing ovarian and endometrial cancers in a Phase II basket study (NCT06003231) [58]. Palbociclib (Ibrance®), a CDK4/6 inhibitor, combined with letrozole (Femara®), an aromatase inhibitor, has shown encouraging activity in recurrent ER/PR-positive ovarian cancers, with a Phase II trial (NCT03936270) reporting meaningful clinical benefit and an acceptable safety profile [59]. Lenvatinib (Lenvima®), a multi-kinase inhibitor, combined with pembrolizumab and paclitaxel, has demonstrated promising activity in recurrent ovarian and endometrial cancers, achieving a 43 % response rate with manageable toxicity in a Phase II trial (NCT04781088) [60]. Ruxolitinib (Jakafi®), a JAK1/2 inhibitor, is being explored in combination with standard chemotherapy for ovarian, fallopian tube, or primary peritoneal cancer, showing preliminary safety and encouraging activity in a Phase I/II trial (NCT02713386) [61].

3.1.2. *Preclinical evidence for drug repurposing in ovarian cancer*

3.1.2.1. Antiviral drugs. Antiviral drugs are emerging as promising candidates for repurposing in ovarian cancer treatment, offering an innovative approach to combat this highly aggressive malignancy (Table 3). Although originally developed to target viral infections, several antivirals have demonstrated anticancer properties through mechanisms that interfere with tumour cell survival, proliferation, and metastasis. Nelfinavir (Viracept™), an HIV protease inhibitor approved by the FDA for the treatment of HIV/AIDS in 1997, has demonstrated potential to target key oncogenic signalling pathways [62]. The analyses showed activation of the PI3K/AKT signalling pathway and induction of endoplasmic reticulum (ER) stress, both of which are critical to cancer cell survival. Nelfinavir targets AKT within the PI3K/AKT/mTOR pathway and has been shown to suppress tumour growth and enhance sensitivity to chemotherapy and radiotherapy in HGSOC models. This includes both carboplatin-sensitive and carboplatin-resistant cell lines [63,64]. Ritonavir (Norvir™) is another HIV protease inhibitor approved by the FDA in 1996 for the treatment of HIV/AIDS [65]. Beyond its antiviral use, ritonavir also shows anticancer effects. It impairs proteasome function and modulates key oncogenic pathways, including AKT and the retinoblastoma protein (RB) [66]. Preclinical studies in ovarian cancer models show that ritonavir induces apoptosis and cell cycle arrest, with enhanced cytotoxicity observed when combined with AKT suppression using agents including the pharmacological inhibitor LY294002 or synthetic siRNA, suggesting potential for synergistic therapies targeting AKT signalling [67]. Ribavirin (Copegus™), an antiviral originally approved by the FDA in 1998 for the treatment of hepatitis C, has been shown to inhibit RNA metabolism, inflammatory signalling, and cellular stress response pathways [68,69]. Jin and colleagues demonstrated that ribavirin targets eIF4E and suppresses the AKT/mTOR and eIF4E/p70S6K signalling pathways in ovarian cancer cells. Their study, conducted in cisplatin-resistant HGSOC cell lines, showed that ribavirin significantly inhibited cell proliferation and enhanced cytotoxicity when combined with cisplatin [70]. Efavirenz (Sustiva™), an antiretroviral drug approved by the FDA in 1998 for the treatment of HIV-1 infection, was identified as a potential PARP inhibitor. It showed significant cytotoxic effects in both homologous recombination-deficient (HRD) and homologous recombination-proficient (HRP) HGSOC cell lines [71].

3.1.2.2. Anthelmintic and antimalarial drugs. Anthelmintic and antimalarial drugs are being explored for repurposing in ovarian cancer due to their ability to target key molecular pathways involved in cancer cell metabolism and survival. Ivermectin (Stromectol™) is an antiparasitic agent approved by the FDA in 1978 for the treatment of parasitic infections [72–74]. It induces G2/M phase arrest, caspase-dependent apoptosis, and enhances cisplatin sensitivity in ovarian cancer xenograft mouse models, via inhibition of Akt/mTOR signalling and the lncRNA-EIF4A3 (long coding RNA-Eukaryotic translation initiation factor 4 A isoform 3) axis, which is implicated in many cancer signalling processes [75,76]. Mebendazole (Vermox™) is an anthelmintic approved by the FDA in 1974 for the treatment of helminth infections [77]. It disrupts microtubule dynamics, induces apoptosis, and inhibits tumour growth both *in vitro* and *in vivo*. Its p53-independent action synergises with PRIMA-1MET (APR-246™), a small molecule that reactivates mutant p53 tumour suppressor protein, supporting its therapeutic potential in ovarian cancer [78]. Chloroquine (Resochin™), an antimalarial agent approved by the FDA in 1949 for malaria treatment, was identified for potential repurposing by way of its known ability to inhibit autophagy by preventing the fusion of autophagosomes and lysosomes, a critical survival mechanism in cancer [79]. Preclinical studies demonstrated that chloroquine enhances cisplatin's cytotoxicity by promoting apoptosis, DNA damage, and cell cycle arrest, particularly in drug-resistant EOC [80].

3.1.2.3. Alcohol antagonist drugs. Disulfiram (Antabuse™), an FDA-approved drug since 1951 for the treatment of alcohol dependency, has been repurposed for ovarian cancer treatment based on its ability to inhibit aldehyde dehydrogenase (ALDH) and proteasome activity [81]. Caminear and colleagues showed that disulfiram more effectively targets chemoresistant, tumour-initiating EOC cells, compared to selective

Table 1
List of repurposed drugs undergoing or completed clinical trials for gynaecological cancer indications.

Drug	Mechanism of Action	Current Approval	Current Regulatory Approval	Approval year	Repurposed Indication	Mechanism of action (repurposed indication)	Clinical Trial Phase (status)	Official Title of Study	NCT Identifier
Arsenic Trioxide	Proteasome Inhibitor	Acute promyelocytic leukemia	FDA, TGA	2000	Ovarian cancer, endometrial Cancer	Inhibition of cell proliferation via targeting of structural mutant p53	Not Applicable (unknown, last reported: recruiting)	A Clinical Trial to Evaluate the Efficacy, Safety, and Tolerability of Arsenic Trioxide for Injection in Patients with Recurrent and Metastatic Ovarian Cancer and Endometrial Cancer with P53 Mutation	NCT04489706
					Stage IVB or recurrent cervical carcinoma	Radiosensitising agent	Phase II (completed)	A Phase II Study of Arsenic Trioxide (NSC #706363) in Patients with Advanced Cervical Carcinoma	NCT00005999
Atovaquone	Inhibits mitochondrial electron transport and pyrimidine synthesis	Antiprotozoal agent for Pneumocystis carinii pneumonia	FDA, TGA	2000	Ovarian cancer	STAT3 inhibition	Phase II (recruiting)	Phase II Clinical Trial Repurposing Atovaquone for the Treatment of Platinum-Resistant Ovarian Cancer	NCT05998135
Bortezomib	Proteasome inhibitor blocks protein degradation, induces apoptosis	Multiple myeloma and mantle cell lymphoma	FDA	2003	Cervical cancer	Modulation of NF-kB activity, a radiosensitising agent	Phase I (completed)	A Phase I Open-labelled, Dose-escalation, Safety Study of the Combination of Velcade and Chemoradiation for the Treatment of Cancer Patients	NCT00329589
Cidofovir	Antiviral agent, inhibits viral DNA polymerase	Cytomegalovirus (CMV)	FDA	1996	Cervical cancer	Radiosensitisation of HPV-positive cancer cells; modulation of the expression of viral oncoproteins by an antiviral agent	Phase I (completed)	Modulation of the Expression of Papillomavirus (HPV) Oncoproteins to Major the Radiosensitivity: Phase I Trial Combining an Antiviral Agent VISTIDE and Radiochemotherapy in Cervical Cancers	NCT00811408
					Stage IB, stage II, stage III, or stage IVA cervical cancer	Targeting the expression of mRNA codons in HPV oncoproteins E6 and E7, radiosensitiser	Phase I (unknown, last reported: recruiting)	Modulating the Expression of Oncoproteins of Papillomavirus (HPV) to Increase Radiosensitivity: a Phase I Study of Antiviral Agent Cidofovir and Chemoradiotherapy in Cervical Cancers	NCT00811408
Gemcitabine	Deoxycytidine analogue, inhibits DNA synthesis by incorporating into DNA and inhibiting DNA polymerase	Ovarian cancer, breast cancer, non-small cell lung cancer, and pancreatic cancer	FDA, TGA, EMA	1996	Vulvar cancer	Increase efficacy of cisplatin therapy, a radiosensitising agent, cytotoxic	Phase II (unknown, last reported: active, not recruiting)	A Phase II Trial Evaluating Cisplatin (NSC #119875) and Gemcitabine (NSC #613327) Concurrent with Intensity-Modulated Radiation Therapy (IMRT) in the Treatment of Locally Advanced Squamous Cell Carcinoma of the Vulva (NCT #01595061)	NCT01595061
Itraconazole	Cytochrome P450-dependent Synthesis of ergosterol in fungal cell membranes	Antifungal for blastomycosis, histoplasmosis, and aspergillosis	FDA	1980	Platinum-resistant epithelial ovarian cancer	Lysosomal dysfunction (via lysosomal compartments, the trans-Golgi network and late endosomes/ lysosomes)	Phase I/II (completed	A Phase I/II Trial Investigating the Tolerability, Toxicity and Efficacy of Hydroxychloroquine and Itraconazole in Patients with Advanced Platinum-resistant Epithelial Ovarian Cancer (EOC) (HYDRA-1 Study)	NCT03081702
Ketorolac	Blocking cyclooxygenase (COX enzymes), Rac1 and Cdc42 GTPases (R-enantiomer)	Severe pain management (NSAID)	FDA, TGA	1992	Ovarian cancer	Inhibitor of Rac1 and Cdc42 GTPases	Not Applicable (completed)	A Randomised Placebo-controlled Evaluation of GTPase Inhibition by Post-operative Intravenous Ketorolac in Ovarian Cancer Patients	NCT02470299
Metformin	Anti-hyperglycaemic agent decreases hepatic glucose production, decreases	Type 2 diabetes mellitus	FDA, TGA	1995	Advanced stage HGSOC	Modulation of AMPK signalling	Phase 0 (completed)	IMPACT: A Phase 0 Randomised Window-of-Opportunity Study of Novel and Repurposed Therapeutic Agents in Women Triaged to Primary	NCT03378297

(*continued on next page*)

Table 1 (*continued*)

Drug	Mechanism of Action	Current Approval	Current Regulatory Approval	Approval year	Repurposed Indication	Mechanism of action (repurposed indication)	Clinical Trial Phase (status)	Official Title of Study	NCT Identifier
	intestinal absorption of glucose, and improves insulin sensitivity							Surgery for Advanced Epithelial Ovarian Cancer in Stages IIIa - IV.	
					Advanced stage ovarian cancers (Epithelial Ovarian, Fallopian Tube or Primary Peritoneal Carcinoma)	Possible synergism to standard-of-care chemotherapies (carboplatin, paclitaxel	Phase II (unknown, last reported: recruiting)	A Phase II, Open-Label, Non-Randomised, Pilot Study of Paclitaxel, Carboplatin and Oral Metformin for Patients Newly Diagnosed with Stage II-IV Epithelial Ovarian, Fallopian Tube or Primary Peritoneal Carcinoma	NCT02437812
					Advanced-stage ovarian cancers	Modulation of AMPK signalling; possible sensitising to standard-of-care chemotherapies (carboplatin, paclitaxel and docetaxel)	Phase II (active, not recruiting)	A Randomised Placebo Controlled Phase II Trial of Metformin in Conjunction with Chemotherapy Followed by Metformin Maintenance Therapy in Advanced Stage Ovarian, Fallopian Tube and Primary Peritoneal Cancer	NCT02122185
					Advanced-stage ovarian cancers	Targeting of ALDH-positive cancer stem cells (CSCs); alteration of DNA methylation in CSCs, inhibition of CSC-driven chemoresistance	Phase II (completed)	A Phase II Evaluation of Metformin, Targeting Cancer Stem Cells for the Prevention of Relapse in Patients with Stage IIC/III/IV Ovarian, Fallopian Tube, and Primary Peritoneal Cancer	NCT01579812

FDA: U.S. Food and Drug Administration, EMA: European Medicines Agency, and TGA: Therapeutic Goods Administration of Australia.
(Note: This table represents selected examples and is not an exhaustive list)

ALDH1A1 inhibitors, due to its broader activity spectrum [82]. Tang and colleagues further demonstrated that disulfiram synergises with PARP inhibitors by possibly enhancing PARP1-trapping and thus inducing DNA damage via impaired repair mechanisms, highlighting its potential to improve therapeutic efficacy in ovarian cancer [83].

3.1.2.4. Cholesterol-lowering drugs - statins. Statins, originally developed to manage hypercholesterolemia and reduce cardiovascular risk, have gained attention in oncology for their potential to exploit metabolic dependencies in cancer cells. Simvastatin (Zocor™), a lipid-lowering agent approved by the FDA in 1991 for the treatment of hypercholesterolemia and cardiovascular risk reduction, targets 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase, the rate-limiting enzyme in the mevalonate pathway [84]. Beyond its cardiovascular use, simvastatin has demonstrated therapeutic potential in OCCC. Simvastatin suppresses tumour growth by inhibiting Rho GTPase and PI3K/AKT signalling pathways that are critical for proliferation and survival. It also enhances the efficacy of chemotherapeutics such as cisplatin. In OCCC models, simvastatin reduced c-MYC expression, inhibiting CDK signalling and cell proliferation as well as inducing both apoptosis and autophagy. Simvastatin showed greater efficacy in OCCC cell lines than in HGSOC lines, supporting its potential utility as a repurposed therapeutic specifically for OCCC [85].

3.1.2.5. Herbal-derived compounds. Natural products have long served as a rich source for drug discovery, with increasing interest in repurposing phytochemicals for cancer therapy due to their diverse bioactive properties. One such compound is piperlongumine, an alkaloid derived from the plant *Piper longum (long pepper)*, traditionally used in Ayurvedic medicine. Piperlongumine has shown potent anticancer effects in preclinical ovarian cancer models by inducing apoptosis, causing G2/M cell cycle arrest, and increasing reactive oxygen species (ROS) via the inhibition of survivin, an anti-apoptotic protein [86]. Furthermore, when combined with the standard chemotherapeutic agent paclitaxel, piperlongumine exhibited synergistic antiproliferative effects, highlighting their potential as a complementary therapy to enhance existing ovarian cancer treatments [86]. Curcumin is approved in certain countries, including Australia, China, Canada, and Germany, for indications related to inflammation. It is a polyphenol extracted from the rhizome of *Curcuma longa* (turmeric), that is itself a herbal compound widely studied for repurposing in ovarian cancer therapy. Traditionally used in Ayurvedic and Chinese medicine, curcumin exhibits anti-inflammatory and antioxidant properties. In preclinical EOC models, curcumin has been shown to inhibit cell proliferation, induce apoptosis, and suppress metastasis through modulation of multiple signalling pathways, including NF-κB, PI3K/AKT, and STAT3. Additionally, curcumin has been reported to enhance the sensitivity of ovarian cancer cells to platinum-based chemotherapy [87].

3.2. Endometrial (uterine) Cancer

Endometrial (uterine) cancer is typically managed with a combination of surgery, radiation, chemotherapy, and targeted therapies, depending on tumour stage and grade [88]. Standard chemotherapy regimens include carboplatin and paclitaxel for advanced or recurrent cases, with doxorubicin and cisplatin as second-line options [89]. Hormone therapies, such as medroxyprogesterone acetate (Depo-Provera™) or megestrol acetate (Megace® ES™), are considered for low-grade tumours, particularly in patients desiring fertility preservation or those unfit for surgery [90]. Several drugs originally developed for other indications are now being investigated, both preclinically and clinically, for repurposing in endometrial cancer treatment.

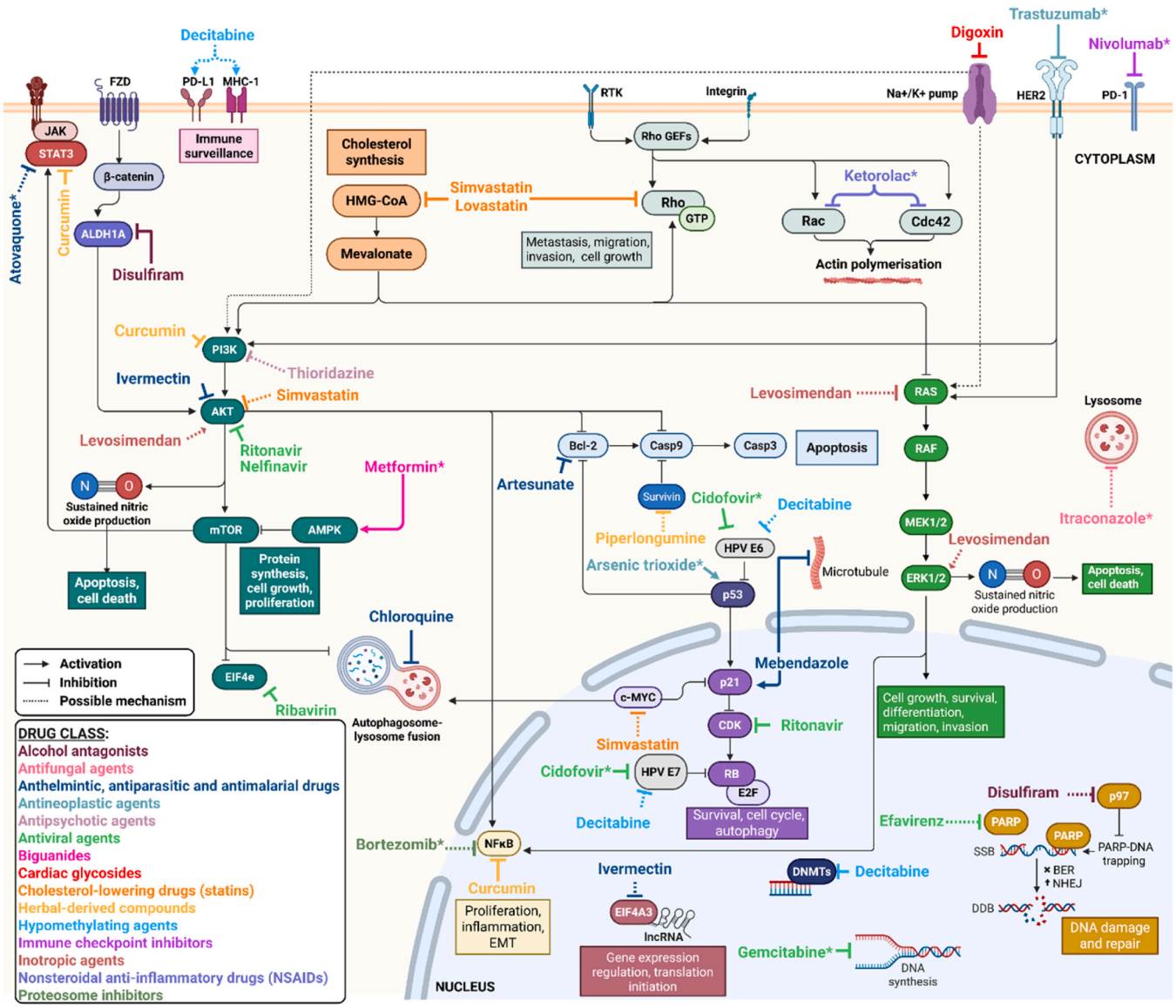


Fig. 2. Repurposed drug candidates targeting signalling pathways in gynaecological malignancies. This schematic highlights key signalling pathways and molecular mechanisms implicated in gynaecological cancers. It illustrates how approved drugs, originally developed for other indications, may modulate these pathways, offering new therapeutic opportunities through drug repurposing. Bold lines indicate direct mechanisms of action, while dotted lines represent possible emerging mechanisms. Repurposed drug candidates are currently being evaluated preclinically and/or clinically for use in gynaecological cancers. Drugs marked with an asterisk (*) are currently in clinical trial(s). Drugs are colour-coded by class as indicated in the key. Created using BioRender.

3.2.1. Clinically approved drugs under investigation for repurposing to treat endometrial cancer

Arsenic trioxide (Trisenox™), originally FDA-approved in 2000 to treat acute promyelocytic leukemia (APL), has emerged as a repurposing candidate for solid tumours, including endometrial cancer (Table 1) [91]. Its anticancer effects stem from the induction of apoptosis, ROS generation, anti-angiogenesis, and disruption of oncogenic signalling pathways [92]. It is particularly promising in tumours harbouring a *TP53* mutation that alters the structure of the p53 protein, such as missense mutations. Arsenic trioxide has been shown to bind mutant p53 and restore tumour-suppressive functions in patient-derived xenograft models of serous endometrial cancer [93]. While clinical evidence remains limited, ongoing trials support further evaluation of arsenic trioxide in recurrent or treatment-resistant endometrial cancer [91,94,95]. Interestingly, case control studies of Alendronate (Fosamax™), a bisphosphonate approved by the FDA in 1995 for the treatment and prevention of osteoporosis, suggest that long-term use of alendronate, particularly in combination with statins, may reduce the risk of endometrial cancer [96–98].

Also, multiple approved agents are being explored for label expansion in endometrial cancer (Table2). Trastuzumab (Herceptin™), an anti-HER2 monoclonal antibody originally approved by the FDA in 1998 for the treatment of HER2-positive breast cancer, is under investigation for repurposing in endometrial cancer [99]. A Phase II clinical trial (NCT00006089) assessed the efficacy and safety of trastuzumab in patients with advanced or recurrent HER2-positive endometrial cancer. Preclinical studies and early-phase trials suggest that trastuzumab may suppress tumour proliferation and improve outcomes in patients with HER2-positive endometrial cancer [100,101]. Letrozole and abemaciclib (Verzenio™), FDA-approved in 1997, a selective CDK4/6 inhibitor, has shown promising activity in estrogen receptor-positive disease, achieving a 30 % objective response rate in recurrent ER-positive endometrial and LGSOC in a Phase II, two-stage study (NCT03675893), with durable responses across molecular subgroups [102]. Nab-sirolimus (nab®), an FDA-approved mTOR inhibitor in 2021, combined with letrozole, is being investigated for label expansion

Table 2
List of repurposed drugs Under Investigation for Label Expansion in gynaecological cancer.

Drug	Mechanism of Action	Current Approval	Current Regulatory Approval	Approval year	Repurposed Indication	Mechanism of action (repurposed indication)	Clinical Trial Phase (status)	Official Title of Study	NCT Identifier
Trastuzumab	Anti-HER2 monoclonal antibody inhibits tumour cell proliferation	HER2-positive breast cancer	FDA, TGA, EMA	1998	Stage III, Stage IV, or Recurrent Endometrial Cancer	Targeted anti-proliferative for HER2-positive cells	Phase II (completed)	A Phase II Evaluation of Trastuzumab (MoAb HER2) in Patients with Advanced, Recurrent or Persistent Endometrial Carcinoma with or Without Prior Chemotherapy	NCT00006089
Trastuzumab deruxtecan	HER2-targeting Antibody-drug conjugate (ADC)	HER2-positive breast, gastric, and Non-small cell lung cancer	FDA, TGA, EMA	2019	Endometrial cancer, Cervical cancer, Ovarian cancer	HER2-targeted cytotoxicity	Phase II	A Phase 2, Multicenter, Open-label Study to Evaluate the Efficacy and Safety of Trastuzumab Deruxtecan (T-DXd, DS-8201a) for the Treatment of Selected HER2 Expressing Tumours (DESTINY-PanTumor02)	NCT04482309
Nivolumab	PD-1 immune checkpoint inhibitor	Melanoma, lung cancer	FDA, TGA, EMA	2014	Cervical cancer, Vaginal and Vulvar cancer	Modulation of immune activation/inhibitory molecules of virus-specific T cells	Phase I/II (completed)	Non-Comparative, Open-Label, Multiple Cohort, Phase 1/2 Study of Nivolumab Monotherapy and Nivolumab Combination Therapy in Subjects with Virus-Positive and Virus-Negative Solid Tumours	NCT02488759
Disitamab Vedotin	HER2-targeting ADC	HER2-positive gastric cancer	NMPA	2025	Ovarian, endometrial cancer	HER2-targeted cytotoxicity	Phase II	A Phase 2 Basket Study of Disitamab Vedotin in Adult Subjects with Previously Treated, Locally-Advanced Unresectable or Metastatic Solid Tumours That Express HER2	NCT06003231
Palbociclib and Letrozole	CDK4/6 inhibitor, aromatase inhibitor	Metastatic ER/PR-positive/HER2-negative breast cancer	FDA, TGA, EMA	2015 and 1997	Recurrent ER/PR-positive endometrioid and high-grade serous ovarian cancers	Cell cycle inhibition	Phase II (completed)	Palbociclib Plus Letrozole Treatment After Progression to Second-Line Chemotherapy for Women With ER/PR-positive Ovarian Cancer	NCT03936270
Lenvatinib, Pembrolizumab and Paclitaxel	Multi-kinase inhibitor, PD-1 inhibitor, chemotherapy	Thyroid cancer, Renal cell carcinoma, Melanoma, Non-small cell lung cancer	FDA, EMA	2015 and 2014	Recurrent ovarian, fallopian tube and endometrial cancer, Primary peritoneal cancer	Anti-angiogenic, immunotherapy and cytotoxic	Phase II	Phase II Study with Safety Lead-In of Lenvatinib, Pembrolizumab, and Weekly Paclitaxel for Recurrent Endometrial, Epithelial Ovarian, Fallopian Tube and Primary Peritoneal Cancer	NCT04781088
Ruxolitinib	JAK1/2 inhibitor	Myelofibrosis, polycythemia vera	FDA, TGA, EMA	2011	Ovarian, fallopian tube, primary peritoneal cancer	JAK/STAT inhibition and cytotoxic	Phase I/II (completed)	A Phase I/II Study of Ruxolitinib With Front-Line Neoadjuvant and Post-Surgical Therapy in Patients with Advanced Epithelial Ovarian, Fallopian Tube or Primary Peritoneal Cancer	NCT02713386
Letrozole and Abemaciclib	Aromatase inhibitor, CDK4/6 inhibitor	ER-positive breast cancer	FDA, TGA, EMA	1997 and 2021	Recurrent ER-positive endometrial cancer and low-grade serous ovarian cancer	Cell cycle inhibition	Phase II	RESOLVE: letRozole abEmaciclib combinationS in endOmetriaL and oVarian cancEr: A Multi-Cohort Phase 2 Study of Letrozole/Abemaciclib Alone and in Combination with Metformin, Zotatifin and Gedatolisib	NCT03675893
Nab-sirolimus and Letrozole	mTOR inhibitor, aromatase inhibitor	Malignant Perivascular Epithelioid Cell Tumour	FDA	2021 and 1997	Advanced or recurrent endometrioid endometrial cancer	mTOR inhibition and endocrine therapy	Phase II	A Phase 2 Multi-centre Open-label Trial of Nab-Sirolimus in Combination with Letrozole in Advanced or Recurrent Endometrioid Endometrial Cancer	NCT05997017
Temsirolimus	mTOR inhibitor	Renal cell carcinoma	FDA, EMA	2007	Recurrent or metastatic ovarian and endometrial carcinoma	mTOR inhibition	Phase II (completed)	Efficacy, Tolerability and Safety of Temsirolimus in Women with Platinum-refractory Ovarian Carcinoma or Advanced Endometrial Carcinoma	NCT01460979

(*continued on next page*)

Table 2 (*continued*)

Drug	Mechanism of Action	Current Approval	Current Regulatory Approval	Approval year	Repurposed Indication	Mechanism of action (repurposed indication)	Clinical Trial Phase (status)	Official Title of Study	NCT Identifier
Pembrolizumab with or without Bevacizumab	PD-1 inhibitor, anti-VEGF	Melanoma, Non-small cell lung cancer	FDA, TGA	2014 and 2004	Advanced or recurrent cervical cancer	Immune checkpoint blockade	Phase III (completed)	A Phase 3 Randomised, Double-Blind, Placebo-Controlled Trial of Pembrolizumab (MK-3475) Plus Chemotherapy Versus Chemotherapy Plus Placebo for the First-Line Treatment of Persistent, Recurrent, or Metastatic Cervical Cancer (KEYNOTE-826)	NCT03635567
Cemiplimab	PD-1 inhibitor	Cutaneous squamous cell carcinoma	FDA, TGA, EMA	2018	Recurrent cervical cancer	Immune checkpoint blockade	Phase III (completed)	An Open-Label, Randomised, Phase 3 Clinical Trial of REGN2810 Versus Investigator's Choice of Chemotherapy in Recurrent or Metastatic Cervical Carcinoma	NCT03257267
Nivolumab	PD-1 inhibitor	Melanoma, NSCLC	FDA	2014	Vulvar, vaginal, cervical cancers	Immune checkpoint blockade	Phase I/II (completed)	Non-Comparative, Open-Label, Multiple Cohort, Phase 1/2 Study of Nivolumab Monotherapy and Nivolumab Combination Therapy in Subjects with Virus-Positive and Virus-Negative Solid Tumours	NCT02488759
Pembrolizumab	PD-1 inhibitor	Melanoma, Non-small cell lung cancer	FDA, TGA, EMA	2014	Vulvar cancer (neoadjuvant and radiotherapy combination)	Immune checkpoint blockade	Phase I/II	Neo-adjuvant Pembrolizumab in Vulvar Squamous Cell Carcinoma: A Clinical Proof-of-concept Study	NCT05761132
							Phase II	A Phase 2 Study of Combined Chemo-immunotherapy With Cisplatin-pembrolizumab and Radiation for Unresectable Vulvar Squamous Cell Carcinoma	NCT04430699

FDA: U.S. Food and Drug Administration, EMA: European Medicines Agency, TGA: Therapeutic Goods Administration of Australia, and NMPA: China's National Medical Products Administration.
(Note**:** This table represents selected examples and is not an exhaustive list)

Table 3
Repurposed approved drugs in preclinical models of ovarian cancer.

Drug name	Mechanism of action	Current indication	Mechanism of action in repurposed indication	Preclinical findings	Regulatory Approval	Approval year	References
Antiviral drugs							
Efavirenz	Antiretroviral drug, inhibits HIV-1 reverse transcriptase enzyme	HIV/AIDS	Broad-spectrum PARP-enzyme inhibition	Cytotoxic effects in HRD and HRP HGSOC cell lines	FDA	1998	[71]
Nelfinavir	HIV protease inhibitor	HIV/AIDS	Inhibits AKT; induces ER stress	Suppress tumour growth, enhance sensitivity to chemotherapy, and radiosensitise carboplatin-sensitive and carboplatin-resistant HGSOC cell lines.	FDA, EMA	1997	[62–65]
Ribavirin	Inhibits RNA metabolism and stress response	Hepatitis C	Suppresses eIF4E signalling, modulating the AKT/mTOR pathway	Inhibits cell proliferation and enhances cytotoxicity when combined with cisplatin in cisplatin-resistant HGSOC cell lines	FDA	1998	[68–71]
Ritonavir	HIV protease inhibitor	HIV/AIDS	Inhibits AKT signalling pathways, modulates RB signalling (via inhibition of CDK) to induce cell cycle arrest	Induces apoptosis and cell cycle arrest in ovarian cancer cell lines, with enhanced cytotoxicity when used in combination with AKT inhibitors.	FDA	1996	[65–67]
Anthelmintic, antiparasitic and antimalarial drugs							
Chloroquine	Inhibits polymerisation of heme in *Plasmodium* acid vesicles	Antimalarial treatment	Inhibits autophagy; induces cell cycle arrest	Enhances cisplatin-induced apoptosis in drug-resistant EOC via the inhibition of cytoprotective autophagy.	FDA	1949	[79,80]
Ivermectin	Binding to glutamate-gated chloride ion channels. Gamma-aminobutyric acid (GABA) receptor inhibitor	Parasitic infections	Induces G2/M arrest, inhibition of Akt/mTOR signalling. Mediates binding of lncRNA to EIF4A3.	Induces caspase-dependent apoptosis, sensitises to cisplatin; linked to improved survival outcomes in ovarian cancer xenograft mouse models.	FDA	1978	[72–76]
Mebendazole	Interferes with helminth cellular tubulin formation	Helminth infections	Disrupts tubulin polymerisation, tumour suppressor function via the induction of p21 expression (inhibiting CDKs)	Induces apoptosis and inhibits tumour growth *in vitro* and *in vivo*. Synergistic with PRIMA-1MET (a small molecule that restores mutant p53 to wild-type).	FDA	1974	[77,78]
Alcohol antagonist drugs							
Disulfiram	ALDH inhibitor, proteasome inhibitor, GABA agonist	Alcohol dependency	ALDH inhibitor, induces sensitisation to PARPi via possible inhibition of p97 to prolong PARP1 DNA trapping	Targets chemoresistant, tumour-initiating EOC cells. Synergises with PARPi to enhance DNA damage	FDA	1951	[81–83]
Cholesterol-lowering drugs - statins							
Simvastatin	HMG-CoA reductase inhibitor	Hypercholesterolemia prevention	Disrupts mevalonate pathway; Rho GTPase inhibitor; modulates PI3K/AKT signalling; inhibits c-MYC	Anti-proliferative, induces autophagy and apoptosis, inhibits migration in OCCC cell lines, and increases sensitivity to standard-of-care chemotherapies.	FDA	1991	[84,85]
Herbal-derived compounds							
Curcumin	Anti-inflammatory and antioxidant	Ayurvedic medicine, traditional Chinese medicine	Modulation of cancer signalling pathways NF-κB, PI3K/AKT, STAT3	Inhibit proliferation and migration, induce apoptosis, and enhance the sensitivity of ovarian cancer cells to platinum-based chemotherapy.	TGA	2018	[87]
Piperlongumine	Cytotoxic, antiangiogenic, antimetastatic, anticoagulant, antinociceptive, antidepressant, antibacterial, antifungal	Ayurvedic medicine	Induces oxidative stress and apoptosis (via inhibition of Survivin), modulates cancer signalling pathways.	Induces apoptosis, causing G2/M cell cycle arrest, and increasing reactive oxygen species (ROS) in triple-negative breast cancer cell lines. Increases sensitivity to ovarian cancer standard-of-care chemotherapy, paclitaxel.	N/A	N/A	[86]

FDA: U.S. Food and Drug Administration, EMA: European Medicines Agency, and TGA: Therapeutic Goods Administration of Australia.

in advanced or recurrent endometrioid endometrial cancer in a Phase II trial (NCT05997017) [103]. Temsirolimus (Torisel®), another FDA mTOR inhibitor approved in 2007, was evaluated in women with recurrent or metastatic ovarian and endometrial carcinoma in a Phase II study (NCT01460979) [104].

3.2.2. Preclinical evidence for drug repurposing in endometrial cancer

Lovastatin (Mevacor™), a statin approved by the FDA in 1987 for treating hypercholesterolemia, inhibits HMG-CoA reductase, thereby disrupting cholesterol biosynthesis and tumour metabolism. It has demonstrated anti-proliferative and pro-apoptotic effects in endometrial cancer cell lines, indicating both therapeutic and preventive potential in high-risk populations, such as women with obesity, metabolic syndrome, or hormone-related risk factors [105–107]. Digoxin (Lanoxin™), a cardiac glycoside, inhibits Na^+/K^+-ATPase, disrupting cellular signalling pathways involved in tumour cell survival. Preclinical studies have shown its potential efficacy against dedifferentiated endometrial carcinoma, highlighting its promise as a therapeutic agent for aggressive tumour subtypes [108].

3.3. Cervical cancer

Cervical cancer, primarily caused by persistent infection with high-risk types of HPV, has benefited from significant advancements such as the implementation of screening methods like the Cervical Screening Test (or Papanicolaou '*Pap*' test) and HPV testing [109]. These screening techniques enable early detection, which improves the effectiveness of treatments such as surgery, chemotherapy, and radiation therapy. Treatment options vary depending on the cancer stage. For localised tumours, surgery (such as trachelectomy, salpingectomy or hysterectomy) is often performed, while more advanced stages often require surgery followed by combined radiation therapy and chemotherapy [110]. Recently, immunotherapies, including checkpoint inhibitors targeting programmed cell death protein-1 (PD-1) and cytotoxic T-lymphocyte-associated protein-4 (CTLA-4) pathways, have shown significant promise in advanced cervical cancer. By blocking these inhibitory pathways, agents such as ipilimumab (Yervoy™) (anti--CTLA-4) can restore T-cell activity, enhancing the immune system's ability to recognise and destroy HPV-associated tumour cells [111]. Ongoing research is focused on developing more targeted therapies to improve treatment outcomes, particularly for women with advanced or recurrent cervical cancer. Drug repurposing has emerged as a promising approach, offering the potential for new therapies that could improve outcomes, particularly in cases resistant to standard treatment [112].

3.3.1. Clinically approved drugs under investigation for repurposing for cervical cancer

Bortezomib (Velcade™) is a proteasome inhibitor approved by the FDA in 2003 for the treatment of multiple myeloma and mantle cell lymphoma (Table 1) [113]. A Phase I clinical trial (NCT00329589) is currently investigating the maximum tolerated dose and safety profile of bortezomib when administered in combination with chemoradiation in patients with cervical cancer, evaluating changes in the expression of pro-inflammatory and pro-proliferative NF-κB (Nuclear factor kappa-light-chain-enhancer of activated B cells) [114]. Similarly, arsenic trioxide, a proteasome inhibitor approved by the FDA in 2000 for APL, has shown promising activity in cervical cancer through mechanisms including induction of apoptosis, disruption of mitochondrial membrane potential, generation of ROS and targeting of the structural mutant of p53 [115]. A Phase II clinical trial (NCT00005999) evaluated the safety and radiosensitising potential of arsenic trioxide in combination with cisplatin and radiation in patients with advanced-stage cervical cancer. However, detailed results from this study have not yet been published [116]. Cidofovir (Vistide™), an antiviral agent approved by the FDA in 1996 for the treatment of cytomegalovirus (CMV) retinitis in immunocompromised patients, inhibits viral DNA polymerase and incorporates it into cellular DNA, causing DNA damage and anti-proliferative effects. Studies have demonstrated activity of cidofovir against both HPV-positive and HPV-negative cervical carcinoma, as well as head and neck squamous cell carcinoma [117,118]. In clinical trials that were prematurely discontinued, primarily due to insufficient patient enrolment (NCT02515877, NCT00811408), cidofovir achieved a complete response in 8 of 9 patients, with 2-year and 4-year overall survival rates of 93 % and 84 %, respectively, and a 2-year progression-free survival of approximately 76 % [119].

Multiple approved therapies are currently under evaluation for label expansion in cervical cancer (Table 2). Pembrolizumab, in combination with standard of care chemotherapy, with or without bevacizumab, is being evaluated in advanced or recurrent cervical cancer in the Phase III KEYNOTE-826 trial (NCT03635567) [120]. Cemiplimab (Libtayo®), a PD-1 immune checkpoint inhibitor, is being assessed in the Phase III EMPOWER-Cervical trial (NCT03257267), where it demonstrated a survival benefit over chemotherapy in patients with recurrent disease following first-line platinum therapy, with a safety profile consistent with prior studies [121].

3.3.2. Preclinical evidence for drug repurposing in cervical cancer

Levosimendan (Simdax™) was initially approved by the European Medicines Agency (EMA) in 2000 as a calcium sensitiser and inotropic agent for the management of acute heart failure [122]. Experimental screening in cervical cancer cell lines has demonstrated its antineoplastic effects, including inducing cell-cycle arrest at the G1 and G2/M phases, increasing the sub-G1 hypodiploid population, and inhibiting cell migration and invasion [123]. It was proposed that these antineoplastic effects were achieved through the activation of nitric oxide (NO) production via AKT, ERK and MAPK signalling pathways, which at sustained levels can inhibit cell proliferation and induce apoptosis [123,124]. Its growth-inhibitory effect was most potent in the HPV-negative cervical cancer cell line, although its antimetastatic activity was modest compared to cisplatin [123]. Artesunate (Malartin™) is a semi-synthetic derivative of artemisinin and an established antimalarial drug approved by the FDA in 2020 [125]. It has demonstrated anticancer potential by inducing oxidative stress, inhibiting cell proliferation, and promoting apoptosis in SiHa cervical cancer cells. Artesunate inhibits cell growth in a dose-dependent manner, modulating Bcl2 family proteins, increasing ROS, and decreasing mitochondrial membrane potential [126].

Thioridazine (Mellaril™) is an antipsychotic drug approved by the FDA in 1959 for schizophrenia and other psychoses. It targets cancer stem cells and induces apoptosis in cervical cancer cells. Thioridazine regulates cell cycle proteins and inhibits the PI3K/AKT/mTOR/p70S6K pathway. Additionally, dopamine D2 receptor (DRD2) expression is elevated in cervical cancer tissues, and thioridazine inhibits tumour growth by downregulating DRD2 expression, thereby inducing apoptosis and necrosis. However, thioridazine was withdrawn from clinical use in 2005 due to its association with life-threatening cardiac arrhythmias [127,128]. Decitabine (Dacogen™), a hypomethylating agent approved by the FDA in 2006 for myelodysplastic syndromes and acute myeloid leukemia (AML), reactivates silenced tumour suppressor genes through the inhibition of DNA methyltransferases [129]. In cervical cancer models, decitabine has been shown to reduce cell viability, induce G2/M cell cycle arrest, and enhance immune responses by upregulating MHC class I and PD-L1 expression, ultimately increasing chemosensitivity [130,131]. In HPV-positive cervical cancers, Decitabine depletes viral oncoproteins E6 and E7, restoring the tumour-suppressive activity of p53 and RB [132].

3.4. Vulvar cancer

Vulvar cancer is the fourth most common gynaecological malignancy, with squamous cell carcinoma (SCC) as the predominant histological subtype. Less common subtypes include melanoma, sarcoma, and

basal cell carcinoma [133]. Although it primarily affects post-menopausal women, incidence is rising among younger populations due to infection with high-risk HPV types, particularly HPV-16 and HPV-18 [134]. Vulvar cancer can be broadly classified into HPV-associated and HPV-independent subtypes, each with distinct molecular drivers [135]. HPV-positive tumours are characterised by E6 and E7 oncoproteins, which inactivate tumour suppressors p53 and RB, whereas HPV-negative tumours are frequently linked to *TP53* mutations and chronic inflammation [136]. While treatment guidelines remain undefined for advanced disease, platinum-based chemotherapy is standard for metastatic or unresectable tumours. Immunotherapies like pembrolizumab and anti-angiogenic agents such as bevacizumab are sometimes used off-label in select patients, typically those with platinum-resistant disease, high PD-L1 expression, MSI-H, or high tumour mutational burden, or when no other treatment options are available, even though these drugs are not formally approved for these specific indications. In the post-platinum setting, immune checkpoint inhibitors and EGFR-targeting agents may offer therapeutic benefit [137]. Drug repurposing represents a promising avenue for expanding treatment options for this rare cancer type.

3.4.1. Clinically approved drugs under investigation for repurposing to treat vulvar cancer

Gemcitabine (Gemzar™), a deoxycytidine analogue initially developed as an antiviral agent, was approved by the FDA in 1996 for the treatment of pancreatic cancer and has since been utilised for various other solid tumours, including ovarian cancer (Table 1). Emerging evidence supports its potential for repurposing in vulvar cancer. In a Phase II clinical trial (NCT01595061), the combination of gemcitabine, cisplatin, and intensity-modulated radiotherapy significantly improved pathological complete response rates in patients with locally advanced, unresectable vulvar squamous cell carcinoma [138].

Salinomycin (Coxistac™), a polyether antibiotic and ionophore, was originally approved by the FDA in 2009 as an anti-coccidial veterinary antibiotic, primarily for use in poultry. Although not approved for human therapeutic use, salinomycin was granted Orphan Drug Designation by the FDA for the treatment of lung cancer, including small-cell lung cancer, due to its promising anticancer activity demonstrated in preclinical studies. These effects are attributed primarily to its ability to target cancer stem cells and induce apoptosis. Importantly, in advanced vulvar cancer, a clinical pilot study (not an official clinical trial) involving systemic administration of salinomycin showed tumour regression, partial clinical responses, and a reduction in serum squamous cell carcinoma markers [139].

Several approved therapies are being explored for potential label expansion in vulvar cancer (Table 2). Nivolumab (Opdivo™), a PD-1 immune checkpoint inhibitor approved by the FDA in 2014 for melanoma and non-small cell lung cancer, has also shown potential in gynaecological malignancies. In the Phase I/II CheckMate 358 trial (NCT02488759), nivolumab achieved a 20 % objective response rate in patients with recurrent or metastatic cervical, vaginal, or vulvar cancers [140]. Pembrolizumab is being investigated as a neoadjuvant therapy in the APOLLO study (NCT05761132) [141] and in combination with radiotherapy, with or without cisplatin, in a Phase I/II trial (NCT04430699) [142].

3.4.2. Preclinical evidence for drug repurposing in vulvar cancer

Metformin has demonstrated antiproliferative activity in vulvar carcinoma models, paralleling its investigation in ovarian cancer clinical trials as a potential adjunct therapy [143]. Its anti-cancer mechanism is primarily attributed to the activation of AMPK and the subsequent inhibition of the mTOR signalling pathway, which is commonly dysregulated in HPV-associated malignancies. In preclinical studies of vulvar cancer, metformin not only suppressed cell proliferation but also enhanced radiosensitivity, supporting its potential role as a radiosensitizer in combination treatment regimens [144].

4. Drug repurposing approaches

The accurate identification of a repurposing candidate for a specific disease indication is a pivotal first step in the drug repurposing process, establishing the foundation for downstream success. A variety of complementary approaches have emerged to support repurposing efforts, ranging from computational predictions and experimental screening to analyses of real-world clinical and epidemiological data. These methods differ in scope, complexity, and data requirements, yet all aim to systematically uncover previously unrecognised drug-disease associations. Drug repurposing efforts often integrate multiple strategies, such as combining clinical insights with computational modelling or validating predictions through laboratory assays, highlighting the multidisciplinary and collaborative nature of modern repurposing frameworks (Fig. 3). The subsequent sections delve into these methodologies, emphasising their relevance in identifying novel therapies for gynaecological cancers.

4.1. Computational screening approaches

4.1.1. Signature matching screens

Signature matching aims to uncover potential therapeutic targets by comparing the ‘disease signature’, the gene expression profile of a disease, with ‘drug signatures’, the gene expression changes induced by drugs. These signatures can be derived from diverse data types, including transcriptomic, proteomic and metabolomic, chemical structure, and adverse event profiles [145]. By aligning these profiles, this approach can predict compounds capable of reversing disease-associated dysregulation and restoring a healthy molecular state. For example, a study on endometrial cancer has reported a dual-arm transcriptomic signature-matching approach to identify potential repurposing for approved drugs by comparing transcriptomic data from metastatic and non-metastatic endometrial cancer patients [146]. By combining signature matching via the Connectivity Map (CMap) (a computational method that determines whether a predefined set of genes shows statistically significant differences between two biological states) and pathway analysis using Pathifier (Bioconductor; a tool that quantifies pathway-level disruptions in gene expression data) (Table 4), this study identified 18 overlapping drug candidates. Among these, five clinically approved drugs, pictilisib, selumetinib (Koselugo™), alisertib, dactinomycin (Cosmegen™), and palbociclib (Ibrance™), demonstrated high potential for repurposing in endometrial cancer. Notably, pictilisib, a PI3K/AKT/mTOR pathway inhibitor, emerged as a particularly promising candidate due to its prior efficacy in other cancers and potential applicability in gynaecological cancers [147, 148]. Selumetinib, a selective MEK1/2 inhibitor, has also shown potential in endometrial cancer. A phase II clinical trial evaluating its efficacy in patients with recurrent or persistent disease found it tolerable, though it did not meet all pre-specified criteria as a monotherapy [149].

In another study, Irham and colleagues identified promising drug candidates for endometrial cancer by integrating genomic data from cBioPortal (an open-access platform that provides large-scale cancer genomics data, including mutations and gene expression profiles) with drug-target associations from DrugBank and CMap analysis [150]. They first identified significantly altered genes in endometrial cancer and then matched these genes to known drug targets using DrugBank. CMap analysis was subsequently used to evaluate how well drug-induced gene expression profiles could reverse the cancer-specific gene expression signatures. Through this integrative approach, bosutinib (Bosulif™), a selective dual inhibitor of Src and ABL tyrosine kinases; acitretin (Neotigason™), a second-generation retinoid; and nilutamide (Nilandron™), a non-steroidal anti-androgen, were highlighted as high-scoring alternatives to standard chemotherapies such as paclitaxel [150]. Similarly, Zou and colleagues employed gene set enrichment analysis (GSEA) of CMap data to identify novel candidates for EOC [151].

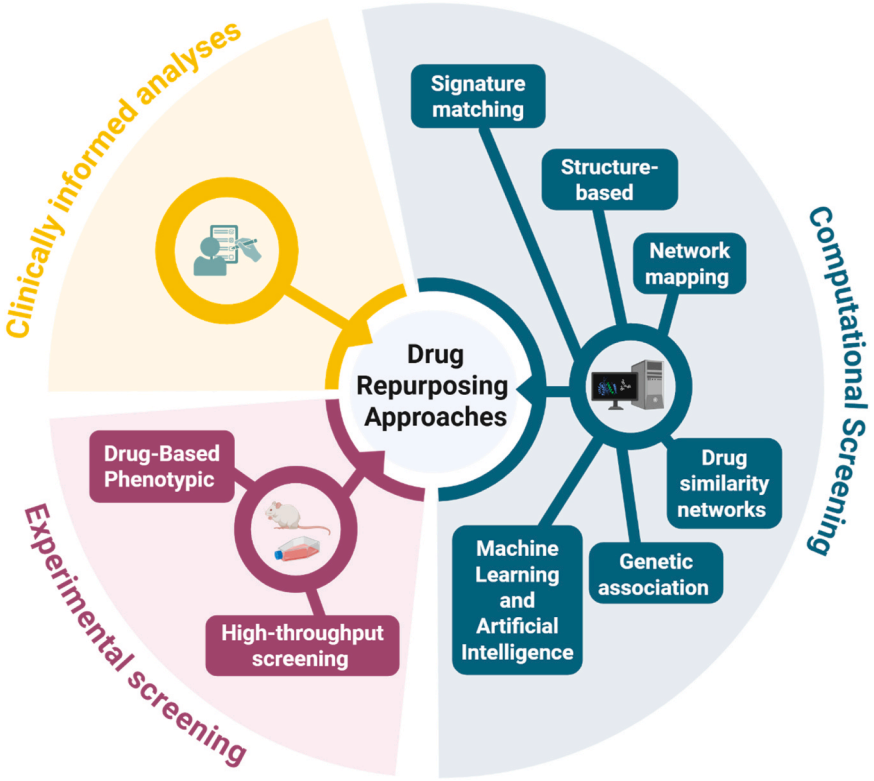


Fig. 3. Overview of screening approaches for identifying drugs with the potential to be repurposed. Approaches are broadly grouped into three categories: Computational screening, which includes in silico methods such as signature matching, structure-based modelling, network mapping, machine learning, and genetic association studies; Experimental screening, which involves drug-based phenotypic assays and high-throughput screening platforms; and Clinically informed analysis, which encompasses serendipitous clinical insights and case reports. These complementary strategies collectively support the identification and prioritisation of candidate drugs for new therapeutic indications. Created using Biorender.

Table 4
Examples of computational screening approaches and tools used for drug repurposing in gynaecological cancers.

Approach	Tool/Platform	Description	Identified Drug(s)	Cancer Type	Reference
Signature matching	Connectivity Map (CMap)	Matches drug and disease gene expression signatures to identify compounds that reverse disease states	Pictilisib, selumetinib	Endometrial cancer	[146]
	Pathifier	Measures pathway deregulation scores across gene expression datasets	Pictilisib, selumetinib, alisertib, dactinomycin, and palbociclib	Endometrial cancer	[146–149]
	cBioPortal and DrugBank	Extracts gene-drug target relationships integrated with gene expression data.	Bosutinib, acitretin, nilutamide	Endometrial cancer	[150,151]
Structure-based docking	Molecular docking and molecular dynamics simulations	Simulates binding interactions between small molecules and protein targets	Valganciclovir, cytarabine	Cervical cancer	[152]
	Molecular dynamics simulations	Assesses interaction stability between ligand and target proteins over time	Venetoclax	Cervical cancer	[153]
	Pharmacophore modelling and molecular docking	Identifies spatial arrangements of features essential for drug-target interactions	Lanreotide	Endometrial cancer	[154]
Network mapping	Cytoscape	Visualises and analyses complex interaction networks	Piperlongumine and chrysin	Cervical cancer	[159]
	STRING	Integrates experimental and predicted PPI networks	Belinostat, vorinostat; bumetanide, ibuprofen, panobinostat	Cervical cancer	[160]
	GeneMANIA	Expands networks using co-expression and functional genomics	Reteplase, alteplase, gliclazide	Endometrial cancer	[161]
Drug similarity networks	DrugPredict	Calculates drug-disease profile similarity using the Jaccard coefficient	Celecoxib, nimesulide, indomethacin	High-grade serous ovarian cancer (HGSOC)	[166]
Genetic association	GPS-Net	Links SNPs or gene variants with diseases and drug responses	Ouabain, niclosamide	Ovarian serous cystadenocarcinoma	[171]

4.1.2. Structure-based screens

Structure-based or molecular docking techniques are useful to predict binding affinities and specificity of interactions between compounds and target proteins, thus providing a mechanistic framework for identifying repurposed drug candidates. Virtual screening of large compound libraries against specific protein targets allows the ranking of drugs by predicted efficacy, streamlining the prioritisation of candidates that inhibit key cancer pathways. For instance, Kumar and colleagues employed a combined approach integrating structure-based pharmacophore modelling, virtual screening, molecular docking, and molecular

dynamics simulations, to identify valganciclovir (Valcyte™), an antiviral prodrug, and cytarabine (Cytosar-U™), a cytosine analogue chemotherapy agent, FDA-approved inhibitors of the E6 protein, a critical driver of HPV-associated cervical cancer [152].

Poleboyina and colleagues identified degarelix (Firmagon™), goserelin (Zoladex™), triptorelin pamoate (Trelstar™), and venetoclax (Vencleata™) as high-affinity binders to nitric oxide synthase 2a (NOS2), which is often linked to poor prognosis in cervical cancer [153]. They employed molecular docking to predict the initial binding poses and affinities of these compounds to NOS2, followed by molecular dynamics simulations to assess the stability and dynamics of the drug-protein interactions over time. Molecular dynamics simulations provide a detailed understanding of how these molecules behave in a simulated physiological environment, accounting for the flexibility and movement of both the protein and ligand. Among the candidates, venetoclax was identified as a promising selective inhibitor of inducible NOS, demonstrating favourable binding interactions with the potential to mitigate cervical cancer progression. Another study by Mahema and colleagues used gene expression analysis to identify intercellular adhesion molecule 1 (ICAM-1) as a shared target in endometriosis and endometrial cancer [154]. Integrating pharmacophore modelling and molecular docking of 421 anticancer drugs, they highlighted lanreotide (Somatuline® Depot), a synthetic somatostatin analog, as a potential drug target for both endometriosis and endometrial cancer, pending experimental validation.

4.1.3. Network mapping

Network or pathway mapping approaches provide a systems-level framework for interrogating molecular interactions by representing genes, proteins, and drugs as nodes connected by edges denoting physical or functional associations, and then integrating drug-target relationships to identify prospective drug targets [155]. By pinpointing highly connected "hub" proteins or critical oncogenic pathways, network mapping can prioritise drugs that target nodes with the greatest potential to disrupt oncogenic signalling and regulatory circuits [156–158]. Several computational tools facilitate this strategy. Cytoscape, for example, supports the visualisation and analysis of complex molecular networks and enables the integration of diverse datasets, including gene expression, mutation profiles, and drug-target annotations, thereby identifying drugs that modulate key dysregulated nodes in cancer-related networks [159]. STRING provides a foundational map of protein-protein interactions, derived from both experimental data and predictive modelling, onto which drug targets can be overlaid using curated sources such as DrugBank [160]. GeneMANIA extends these networks by incorporating additional data types, such as co-expression, co-localisation, and genetic interactions, revealing indirect or secondary drug effects and helping to uncover multi-target therapeutic strategies [161].

Using this approach, Faheem and colleagues developed a network-based drug repurposing strategy that involved constructing the HPV-induced cervical cancer protein interaction network (HPV2C) alongside modelling a drug-target interaction network. This led to the identification of 13 novel drug combinations targeting pathways associated with HPV-induced cervical cancer, underscoring the effectiveness of this strategy in discovering viable therapeutic candidates for cervical cancer [162]. Belinostat (Beleodaq™) and vorinostat (Zolinza™) pan-histone deacetylase (pan-HDAC) inhibitors were identified among the drug combinations that have shown effectiveness against HPV-18, and their combination has proven beneficial in treating virus-related cancers such as cervical cancer [163]. In another study, Faheem and colleagues applied a similar network-based approach to identify potential immune checkpoint inhibitors for endometrial cancer [164]. The authors constructed a network of proteins that interact with endometrial cancer-related immune checkpoint proteins, revealing 115 distinct drug-associated pathways, and identified 16 FDA-approved drugs with potential for repurposing as immune checkpoint inhibitors. The predicted pathways showed that 15 of these drugs could be grouped into two major pathway categories, comprising 17 immune pathways and 98 metabolic pathways. A subsequent drug-drug correlation analysis, which assessed the similarity in drug activity and their impact on shared pathways within the network, provided insights into potentially beneficial combinations, presenting new opportunities for the rapid repurposing of FDA-approved medications into clinical trials for endometrial cancer. Literature-based validation confirmed that 3 of the 16 identified drugs, specifically bumetanide (Bumex™), a diuretic medication; ibuprofen (Advil™), an NSAID; and panobinostat (Farydak™), a pan-HDAC inhibitor, have already been investigated in endometrial cancer and demonstrated inhibitory potential. Additionally, other drugs, including belinostat, dexibuprofen (Seractil™), the active enantiomer of ibuprofen, NSAID, artenimol, an antimalarial, fostamatinib (Tavalisse™), a spleen tyrosine kinase inhibitor, and elexacaftor, a cystic fibrosis transmembrane conductance regulator, were noted to exhibit immunomodulatory properties, supporting their relevance as repurposing candidates for immune checkpoint inhibition in endometrial cancer.

4.1.4. Drug similarity networks

Drug similarity networks connect compounds based on shared characteristics, including molecular structure, mechanisms of action, and/or clinical outcomes. By identifying drugs with similarities to established cancer therapeutics that are approved for unrelated conditions, this approach enables efficient identification of drugs with the potential to be repurposed. Such network-based methods offer a strategic way to prioritise drugs that may exhibit analogous therapeutic effects to existing cancer treatments, thereby accelerating the discovery of potential anticancer agents [165]. An example of such an approach is the DrugPredict system, a comprehensive computational platform tailored for drug repurposing applications in HGSOC [166]. DrugPredict integrates disease-specific molecular signatures, such as gene expression or mutational profiles derived from HGSOC datasets, with drug-associated phenotype profiles, which describe the biological impact of various compounds. By calculating the degree of similarity between HGSOC and drug profiles using the Jaccard coefficient, the system quantifies the overlap of molecular features between disease and drug effects [167]. Differentially expressed genes from HGSOC were identified through The Cancer Genome Atlas (TCGA) and mapped to their mouse homologs to create a mutational phenotype profile. Similarly, drug-associated genes from the Comparative Toxicogenomics Database (CTD) were mapped to create drug-specific profiles. Using this method, DrugPredict ranked FDA-approved drugs based on their potential efficacy in targeting HGSOC pathways. Top candidates, including celecoxib (Celebrex™) and nimesulide (NSAID) (approved in specific countries, including China, Russia, and Switzerland), were validated in HGSOC cell lines, demonstrating significant anti-tumour effects by reducing cell viability and inducing apoptosis in both platinum-sensitive and resistant cells. Using these strategies, the NSAID indomethacin was identified as a promising drug with the potential to be repurposed as a chemotherapy for treating platinum-resistant HGSOC [166].

4.1.5. Genetic association

Genetic association studies involve identifying correlations between specific genetic variations and traits or diseases, offering valuable insights into the genetic foundations of complex conditions. By leveraging advanced methodologies such as Genome-Wide Association Studies (GWAS) and resources like TCGA, researchers can analyse mutation patterns and correlate them with drug sensitivity profiles. This approach deepens our understanding of disease mechanisms and informs the development of targeted treatment strategies, which can play a key role in drug repurposing efforts [168,169]. For instance, integrating GWAS data with epigenomic profiling and promoter capture HiC maps (high-throughput chromosome conformation capture) has led to the identification of candidate risk genes in hormone-dependent cancers,

including breast, endometrial, ovarian, and prostate cancers [170]. Some of these genes encode proteins that are already known drug targets, suggesting that drugs developed for one disease could be repurposed to treat other hormonally driven malignancies, such as ovarian and endometrial cancers. Cheng and colleagues employed advanced DNA and RNA sequencing techniques to identify novel therapeutic targets, facilitating drug repurposing for various diseases, including ovarian cancer [170]. By tailoring their approach to the specific molecular characteristics of individual disease modules, they were able to uncover previously unconsidered therapeutic options. Notably, the use of the Genome-Wide Positioning Systems Network (GPS-Net) demonstrated substantial success in predicting drug responses across a large cohort of approximately 5000 cancer patients from diverse cancer types, including lung adenocarcinoma, breast cancer, ovarian cancer, colorectal cancer, and melanoma. By identifying which existing drugs could effectively target the molecular profiles of these cancers, this study opened the door to repurposing 140 FDA-approved drugs for new cancer indications. One notable finding was the identification of niclosamide (Niclocide™), an anti-parasitic drug, as a promising candidate for the treatment of ovarian serous cystadenocarcinoma by modulating key tumour progression pathways [171].

4.1.6. Machine learning and artificial intelligence

Machine learning, artificial intelligence, and deep learning employ computational algorithms to analyse large datasets and identify patterns, facilitating predictions based on data, without the need for manually programmed instructions for each specific task. These methodologies enhance literature searches, leverage electronic health records, and improve computational approaches for analysing drug-target interactions. Consequently, they are integral to various stages of drug discovery and development, including initiatives aimed at repurposing drugs for cancer therapies [172,173]. Deep learning models, such as convolutional neural networks (CNNs), which are designed to automatically detect and extract hierarchical patterns from data, have been effectively used to predict drug efficacy. CNNs, originally developed for image recognition tasks, have been adapted to analyse complex biomedical datasets. By integrating multi-omics data, including genomics, proteomics, and metabolomics, CNNs help identify candidate drugs that may overcome chemotherapy resistance in cancers such as ovarian cancer. Zhang and colleagues employed deep learning to enhance predictive, preventive, and personalised medicine for ovarian cancer by identifying drug resistance characteristics at the single-cell level [174]. Using the Knowledge-enhanced artificial neural network (KAN) architecture, a model that integrates prior biological knowledge with neural network learning, they developed a classifier that stratifies patients into four subtypes with varying drug sensitivities and immune profiles, allowing for more tailored treatment strategies and accurate prognosis predictions based on these resistance traits. Supervised learning methods such as support vector machines and random forests are increasingly used to classify drug responses based on molecular signatures in cancers, facilitating more personalised treatment approaches [175,176]. These machine-learning techniques process gene expression data to uncover patterns associated with drug efficacy, providing valuable insights into potential repurposed therapies [177]. Additionally, graph-based machine learning models are improving drug-target interaction predictions by analysing structural and interaction data, helping to identify drugs that might have as yet unrecognised therapeutic potential [178]. Overall, these AI-driven approaches are accelerating the drug repurposing process, uncovering viable treatment options faster than traditional discovery methods.

4.2. Experimental screening approaches (in vitro/in vivo)

4.2.1. High-throughput screening (HTS)

HTS enables the systematic evaluation of large-scale compound libraries against defined biological targets by integrating automation, miniaturised assays and advanced data analysis [179]. This approach significantly increases efficiency and throughput, making HTS a powerful tool in early-phase drug discovery [180]. A recent study used HTS to evaluate 3436 compounds in 12 patient-derived LGSOC cell lines and one normal ovarian cell line to identify potential therapeutic options specifically for LGSOC. This approach led to the discovery of 60 high-confidence and 19 moderate-confidence compounds showing selective toxicity against cancer cells. Importantly, the study highlighted both established drug targets, such as the mTOR/PI3K/AKT pathway, and novel targets, including EGFR and MDM2-p53 inhibitors, suggesting new avenues for LGSOC therapy. Kumar and colleagues developed patient-derived three-dimensional (3D) spheroid models of dedifferentiated endometrial carcinoma to conduct HTS, identifying cardiac glycosides, particularly digoxin and digitoxin (Crystodigin™), as effective candidates [181]. Their findings demonstrated that digoxin significantly suppressed dedifferentiated endometrial carcinoma (DDEC) tumour growth *in vivo* at clinically relevant serum concentrations, suggesting its potential as a systemic therapy for SWI/SNF (SWItch/Sucrose Non-Fermentable)-inactivated DDEC and possibly other similar tumour types.

4.2.2. Drug-based phenotypic screening

Drug-based phenotypic screening involves observing the effects of drugs on whole organisms or cancer cells without prior knowledge of their molecular targets [182]. This approach is valuable in cancer research as it helps identify drugs that impact disease features, such as cell proliferation, migration, and apoptosis, even without understanding the underlying mechanisms [183]. Chen and colleagues used drug-based phenotypic screening on patient-derived organoids to assess drug sensitivities across various ovarian cancer subtypes, including HGSOC, MOC, OCCC, and endometrial cancer [184]. This approach enabled *ex vivo* assessment of drug response, revealing subtype-specific sensitivities and supporting both drug repurposing and personalised treatment strategies for ovarian and related cancers.

4.3. Clinically informed analyses

Clinically informed analyses, including patient case reports and real-world treatment data, can uncover unexpected therapeutic benefits of existing drugs, offering a cost-effective, hypothesis-generating strategy grounded in clinical reality that complements target-driven methods [185]. Unlike traditional preclinical or target-based drug discovery approaches, which often rely on *in vitro* models and mechanistic screening, clinical observation-based approaches identify new therapeutic opportunities by recognising patterns of improved outcomes in patients receiving drugs for unrelated conditions [186]. For instance, metformin, an anti-diabetic medication that targets mTOR and HER2 kinase pathways, has demonstrated anti-proliferative and pro-apoptotic effects. Subsequent studies have associated metformin use with improved survival outcomes in gynaecological cancers, including endometrial, ovarian, and cervical cancers [187]. Similarly, the anti-malarial agent artemisinin has shown promising anticancer activity in cervical cancer. Clinical observations have reported tumour regression and enhanced treatment responses in patients who received artemisinin while being treated for malaria [188,189]. A case study demonstrated the potential of ibrutinib (Imbruvica™), a Bruton's tyrosine kinase (BTK) inhibitor, for drug repurposing in solid tumours [190]. A patient with chronic lymphocytic leukemia and recurrent LGSOC experienced normalisation of CA-125 levels during ibrutinib treatment. Upon discontinuation, CA-125 levels increased, suggesting a possible therapeutic effect of ibrutinib on LGSOC.

5. Clinical challenges and limitations of drug repurposing in gynaecological cancers

Despite the promise of drug repurposing as a lower-risk strategy for

identifying alternative therapies for gynaecological cancers, several clinical challenges and limitations hinder its widespread adoption. These challenges range from regulatory hurdles and trial design complexities to pharmaceutical industry barriers and difficulties in patient selection. Overcoming these obstacles is crucial to accelerating the clinical translation of repurposed drugs for gynaecological malignancies.

5.1. Regulatory hurdles

A significant barrier to drug repurposing is the complexity of regulatory frameworks, which are primarily designed for the approval of novel therapeutics. In the United States, repurposed drugs can be submitted through the 505(b)(2) pathway, codified under the Hatch-Waxman Amendments of 1984 and further supported by the FDA Modernisation Act of 1997. This pathway facilitates a more efficient approval process by allowing partial reliance on existing safety and efficacy data [191]. Since its introduction, the 505(b)(2) pathway has grown in use and now accounts for approximately twice the number of drug approvals seen via the traditional 505(b)(1) route. By allowing reliance on existing safety and efficacy data, it reduces the need for extensive new studies, lowering costs and shortening timelines [33,192]. To qualify, applicants must demonstrate a novel administration route or disease indication distinct from the drug's original approval [191]. Alternatively, EMA regulates repurposed drugs under Article 10 of Directive 2001/83/EC, introduced in 2001, which does not permit reliance on non-proprietary studies, necessitating additional tailored investigations [193]. The Therapeutic Goods Administration (TGA) in Australia adopts similar principles to the FDA's 505(b)(2) pathway, permitting drug developers to submit applications that rely on existing clinical data from previously approved drugs. Additionally, the TGA's Medicines Repurposing Program (MRP), introduced in 2024, provides a pathway for registering off-label medicines that offer significant public health benefits, thereby improving access and addressing unmet clinical needs [194].

5.2. Trial design issues

Trial design issues are a significant challenge in drug repurposing. Although repurposed drugs often have established safety profiles, demonstrating efficacy for new indications requires tailored clinical trials. These trials must address specific mechanisms of action, disease models, dosing regimens, and patient populations distinct from the original use. Additionally, trial endpoints may need to reflect goals such as survival benefit, progression-free survival, or symptom control, which vary by disease [195]. Regulatory agencies may demand more stringent evidence for repurposed drugs, requiring tailored trial designs, biomarker studies, and patient stratification [196]. Despite the potential for faster approval due to existing safety data, the need for specialised trials remains a considerable challenge [169]. In gynaecological cancers, rare subtypes and heterogeneous patient populations complicate recruitment, further delaying clinical translation [197,198]. Overcoming these challenges requires collaboration between academia, industry, and regulatory bodies to develop efficient trial designs that facilitate the timely integration of repurposed drugs into clinical practice for gynaecological cancers.

5.3. Pharmaceutical industry barriers

Pharmaceutical industry barriers pose significant challenges to the successful repurposing of drugs for gynaecological cancers. One of the most pressing obstacles is the lack of financial incentives. Unlike novel therapeutics, which benefit from patent protection and exclusive market rights, repurposed drugs are typically off-patent, offering limited commercial profitability. The absence of market exclusivity reduces the potential return on investment, making drug repurposing less appealing to pharmaceutical companies [13,199]. Furthermore, repurposing existing drugs for new indications demands substantial investment in clinical trials. While repurposed drugs may present a faster regulatory pathway due to established safety profiles, the requirement for specialised trials to demonstrate efficacy in the new clinical context remains a considerable financial burden [200]. Moreover, the lack of collaboration and knowledge-sharing between academic researchers, industry, and regulatory agencies further complicates the repurposing process. While promising drug candidates may be identified within academic settings, the translation of these findings into clinical applications is hindered by gaps in infrastructure and strategic partnerships [195,200]. Additionally, synergistic drug combinations that could offer enhanced therapeutic benefits face challenges when the drugs are sourced from different pharmaceutical companies. Intellectual property rights and commercial interests may prevent collaborative efforts, limiting the potential for combination therapies that could be more effective than single-drug treatments. These barriers further complicate the development of more effective treatment options for gynaecological cancers [201].

6. Conclusion and future directions

Drug repurposing presents a highly promising strategy to meet the urgent therapeutic needs of gynaecological cancers. By utilising existing drugs with known safety profiles, this approach can significantly accelerate the development of effective treatments, offering a faster and more cost-efficient alternative to traditional drug discovery pipelines. Repurposing also aligns well with the principles of precision medicine, allowing therapies to be tailored to individual patients based on the genetic and molecular characteristics of their tumours. However, several challenges hinder the broader clinical application of drug repurposing. The inherent heterogeneity of gynaecological cancers and the frequent difficulty of early diagnosis complicate patient stratification and treatment response prediction. To overcome this issue, the development of advanced non-animal models, such as patient-derived organoids, tumour-on-a-chip systems, and other microfluidic platforms, not only aligns with the 3Rs principle but also facilitates personalised therapy development through integration with biomarker discovery. Designing appropriate clinical trials for repurposed drugs also remains complex, as these trials must consider new mechanisms of action, novel indications, and distinct patient populations.

Looking ahead, emerging technologies, including artificial intelligence, machine learning, and HTS, are poised to transform drug repurposing by enabling the rapid and systematic identification of candidate compounds. Future clinical trials built around molecularly defined patient cohorts will also advance these repurposing efforts and ensure their successful translation into clinical practice. In conclusion, the application of drug repurposing, driven by technological innovation, molecular profiling, and collaborative research, has the potential to reshape the therapeutic landscape of gynaecological cancers. As the field advances and existing challenges are progressively addressed, drug repurposing is expected to become a cornerstone of modern oncology, offering timely, cost-effective, and personalised treatment options for women affected by these diseases.

Abbreviations

3Rs: Replacement, Reduction, and Refinement
ADC: Antibody-drug conjugate
AKT: Protein Kinase B
ALDH1A: Aldehyde Dehydrogenase 1 Family Member A1
AML: Acute Myeloid Leukemia
AMPK: AMP-Activated Protein Kinase
APL: Acute Promyelocytic Leukemia
Bcl2: B-Cell Lymphoma 2
BER: Base Excision Repair

BTK: Bruton's Tyrosine Kinase
Casp3: Caspase 3
Casp9: Caspase 9
CDK: Cyclin-Dependent Kinase
Cdc42: Cell Division Cycle 42
CNN: Convolutional Neural Network
CMV: Cytomegalovirus
CTD: Comparative Toxicogenomics Database
CTLA-4: Cytotoxic T-Lymphocyte-Associated Protein 4
CMap: Connectivity Map
c-MYC: MYC Proto-Oncogene
DDEC: Dedifferentiated Endometrial Carcinoma
DDB: Damage-Specific DNA Binding Protein
dMMR: mismatch repair pathway
DNA: Deoxyribonucleic Acid
DNMTs: DNA Methyltransferases
DRD2: Dopamine D2 Receptor
DSB: Double-Strand Break
eIF4E: Eukaryotic Translation Initiation Factor 4E
EIF3A: Eukaryotic Translation Initiation Factor 3 Subunit A
ECM: Extracellular Matrix
EGFR: Epidermal Growth Factor Receptor
EMA: European Medicines Agency
E2F: E2 Promoter-Binding Factor
ERK1/2: Extracellular signal-regulated kinases 1 and 2
FDA: Food and Drug Administration (USA)
G1: Gap 1 Phase
G2/M: Gap 2 / Mitosis Phase
GPS-Net: Genome-Wide Positioning Systems Network
GSEA: Gene Set Enrichment Analysis
GTP: Guanosine Triphosphate
GWAS: Genome-Wide Association Studies
HER2: Human Epidermal Growth Factor Receptor 2
HGSOC: High-Grade Serous Ovarian Cancer
HIV: Human Immunodeficiency Virus
HMG-CoA: 3-Hydroxy-3-Methylglutaryl-Coenzyme A
HPV: Human Papillomavirus
HTS: High-Throughput Screening
ICAM-1: Intercellular Adhesion Molecule 1
JAK: Janus Kinase
KAN: Knowledge-Enhanced Artificial Neural Network
LGSOC: Low-Grade Serous Ovarian Cancer
lncRNA: Long Non-Coding RNA
MEK1/2: Mitogen-Activated Protein Kinase Kinase 1/2
MHC: Major Histocompatibility Complex
MLK1/2: Mixed Lineage Kinase 1 and 2
MOC: Mucinous Ovarian Carcinoma
MRP: Medicines Repurposing Program
mTOR: Mammalian/Mechanistic Target of Rapamycin
MSI-H: Microsatellite Instability-High
Na^+/K^+-ATPase: Sodium-Potassium Adenosine Triphosphatase
NF-κB: Nuclear Factor Kappa-Light-Chain-Enhancer of Activated B Cells
NHEJ: Non-Homologous End Joining
NO donors: Nitric Oxide Donors
NSAID: Non-Steroidal Anti-Inflammatory Drug
OCCC: Ovarian Clear Cell Carcinoma
PARP: Poly (ADP-ribose) Polymerase
p21: Cyclin-Dependent Kinase Inhibitor 1 (CDKN1A)
p53: Tumour protein p53
PD-1: Programmed Cell Death Protein 1
PD-L1: Programmed Death-Ligand 1
PI3K: Phosphoinositide 3-Kinase
RAS: Rat Sarcoma virus oncogene
RAF: Rapidly Accelerated Fibrosarcoma Kinase
RB: Retinoblastoma Protein
RNA: Ribonucleic Acid
Rho: Ras Homolog
Rho GEFs: Rho Guanine Nucleotide Exchange Factors
ROS: Reactive Oxygen Species
RTK: Receptor Tyrosine Kinase
SCC: Squamous Cell Carcinoma
SSB: Single-Strand Break
STAT3: Signal Transducer and Activator of Transcription 3
SWI/SNF: SWItch/Sucrose Non-Fermentable (Chromatin Remodelling Complex)
TGA: Therapeutic Goods Administration (Australia)
TCGA: The Cancer Genome Atlas
TME: Tumour Microenvironment
TP53: Tumour Protein p53
VEGF: Vascular Endothelial Growth Factor

Authors' contributions

A.A. conceptualised the review, collected the data, and wrote the various drafts of the manuscript, including the construction of tables and figures. F.A.S. prepared and edited figures and tables, and contributed to manuscript editing. K.A.D. and N.A.B. contributed to manuscript editing. D.J.M. supervised the overall direction of the project and edited all versions of the manuscript. All authors read and approved the final manuscript.

CRediT authorship contribution statement

Amani Alghalayini: Writing – review & editing, Writing – original draft, Visualization, Validation, Resources, Project administration, Investigation, Conceptualization. **Farhana A Sarker:** Writing – review & editing, Visualization. **Kristie-Ann Dickson:** Writing – review & editing. **Nikola A Bowden:** Writing – review & editing. **Deborah J Marsh:** Writing – review & editing, Supervision, Project administration, Investigation, Funding acquisition, Conceptualization.

Consent for publication

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No data was used for the research described in the article.

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