Prognosticating gestational trophoblastic neoplasia: from FIGO 2000 to future models

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Summary

The FIGO 2000 Prognostic Scoring System is a global standard for prognostication in patients with gestational trophoblastic neoplasia (GTN). However, the system has not been updated in over 20 years, and in clinical practice it has several critical limitations, including inadequate assessment of single-agent chemotherapy resistance and overuse in unsuitable clinical scenarios. This review critically examines these shortcomings and summarizes recent efforts to refine the system. After identifying its limitations, we propose novel refinements: instead of relying on a single system to address multiple clinical objectives, we advocate for specialized scoring models, each tailored to a specific clinical goal. This approach simplifies and enhances the effectiveness of prognostic assessments. Additionally, biological and genetic markers must be integrated into these models to improve accuracy. Looking ahead, we emphasize the need for advanced technologies and multicentre collaboration to build more personalized and adaptive GTN management frameworks, ultimately improving clinical practice and outcomes.

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Keywords: FIGO 2000; Gestational trophoblastic neoplasia; Prediction; Prognostication; Resistance

Introduction

Gestational trophoblastic neoplasia (GTN) describes a spectrum of rare gynaecological malignancies originating from gestational trophoblastic cells. GTNs can be categorized into four main histopathological subtypes: invasive mole (IM), choriocarcinoma, placental site trophoblastic tumour (PSTT), and epithelioid trophoblastic tumour (ETT).[1] Over 90% of patients achieve complete remission with effective chemotherapy regimens and standardized comprehensive management strategies. Human chorionic gonadotropin (hCG), a specific biomarker for GTN, is crucial for early detection and monitoring treatment efficacy. However, individual responses to treatment are heterogeneous, mandating standardized and accurate prognostic tools.

This need for prognostication led to the development of the International Federation of Gynaecology and Obstetrics (FIGO) 2000 Prognostic Scoring System for GTN (hereafter referred to as **FIGO 2000**). The FIGO 2000 system, recognized globally, sets the standard for evaluating the prognosis and clinical status of patients with GTN, particularly those with invasive mole and choriocarcinoma (the unique clinicopathological characteristics of PSTT and ETT mean that the FIGO system is not applicable to these subtypes).[1–5] FIGO 2000 categorises GTN patients based on pre-chemotherapy scores: 0–6 indicates a "low risk" of single-agent chemotherapy resistance, leading to treatment with methotrexate (MTX) or actinomycin-D (Act-D), while scores of 7 or higher indicate "high risk," necessitating multi-agent chemotherapy (Table 1). The 2015 update introduced an ultra-high-risk category, enhancing the system's prognostic accuracy by aligning scores more closely with outcomes.[6]

Methods

Search strategy and selection criteria

Data contributing to the section "Insights and challenges to refining FIGO 2000" were identified by searching the PubMed and Web of Science databases from January 1, 2017 to February 1, 2024 using the following search terms: in PubMed, "gestational trophoblastic neoplasia [Title]" AND ("prognostic system [Title/Abstract]" OR "scoring system [Title/Abstract]" OR "risk factor [Title/Abstract]") and "model

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Risk factor	0	1	2	4
Age	<40 years	≥40 years	–	–
Antecedent pregnancy	Mole	Abortion	Term	–
Interval from index pregnancy (months)	<4	4–6	7–12	>12
Pre-treatment serum hCG (IU/L)	$<10^3$	10^3–10^4	10^4–10^5	$>10^5$
Largest tumour size (including uterus)	<3 cm	3–4 cm	≥5 cm	
Site of metastases	Lung	Spleen, kidney	Gastrointestinal	Liver, brain
Number of metastases	0	1–4	5–8	>8
Previous failed chemotherapy	No	–	Single-agent	Multiple-agent

Note: Total scores of 0–6 indicate low risk, 7 or higher indicate high risk. An 'ultra-high-risk' category was introduced in the 2015 FIGO GTN updates guidelines for scores ≥13 or extensive metastasis.

Table 1: **The FIGO 2000 prognostic scoring system.**

[Title/Abstract]"; and in Web of Science: TI=(gestational trophoblastic neoplasia) AND (TS=(prognostic system) OR TS=(scoring system) OR TS=(risk factor)) AND TS=(model). Finally, seven studies were included in the review.

The inclusion criteria were: (i) retrospective or prospective studies; (ii) focus on prognostic scoring, chemotherapy resistance, or treatment evaluation in GTN; (iii) propose a new model; and (iv) sample size >100 cases. Abstracts, conference reports, and grey literature were excluded unless directly related to previously published peer-reviewed work. 2017 was selected as the start date because the most recent influential review on FIGO prognostic scoring by Parker et al. was published in 2017.

Role of funding source

The funding sources had no role in the study design; writing the report; nor the decision to submit the article for publication.

Current limitations of FIGO 2000: evaluating its evidence base

FIGO 2000 was pivotal in standardizing prognostic evaluations of patients with GTN. GTN prognostic scoring evolved over the decades from initial rudimentary classifications to the sophisticated and standardized system we now recognize as FIGO 2000.[7–14] FIGO 2000, finalized in 1999, was based on numerous retrospective clinical studies of diverse patient cohorts across the world.[15–19] Nevertheless, despite inclusion in the scoring system, the methodologies and conclusions from these studies were inconsistent.

Notably, the methodologies used in the studies underpinning FIGO 2000 were extremely diverse, with varied inclusion criteria such as presence of metastasis, consistency of chemotherapy regimens, and prior chemotherapy exposure. Inclusion criteria did not consistently specify whether PSTT or ETT were excluded, and the studies spanned several decades, adding further heterogeneity in treatment. For example, Lurain et al. analysed drug resistance in 139 patients with metastatic lesions from 1969 to 1988, without restricting to single- or multi-agent therapy. Kim et al. examined 165 patients treated with the EMA/CO (etoposide, methotrexate, actinomycin-D, cyclophosphamide, vincristine) regimen from 1982 to 1995, concentrating on factors associated with deaths.[18] These variable study designs and objectives underscore the complexity of creating a unified prognostic system without introducing biases.

Moreover, the conclusions of retrospective studies were highly heterogenous. While many studies defined chemotherapy resistance as their primary endpoint, others, like Kim et al., prioritized survival,[18] with these differences in outcome definitions complicating direct comparisons. Therefore, the evidence base for FIGO 2000 is characterized by relatively poor-quality evidence and limited reproducibility, relying instead on the clinical experience and insights of ISSTD members rather than empirical data.[3]

The inclusion of treatment modalities other than single-agent chemotherapy calls the reliability of FIGO 2000 for assessing single-agent chemotherapy success rates into question. There is therefore a need for a more evidence-based, universally applicable, and reproducible prognostic framework to enhance treatment outcomes and consistency in GTN management.

Re-examining prognostic risk factors in FIGO 2000 beyond established parameters

For contemporary use, there is growing interest in re-examining the risk factors included in FIGO 2000, particularly those that have an uncertain impact on outcomes. The evidence consistently links chemotherapy resistance to pre-treatment hCG levels, antecedent pregnancy, and maximal tumour diameter. However, the prognostic relevance of age is still debated.[20–23]

Recent studies have revisited factors previously overlooked within FIGO 2000, not least the significance of pulmonary metastasis and the characteristics of uterine lesions.[24–27] In 2015, Vree et al. were among the

first to suggest a prognostic role for pulmonary metastasis in GTN, comparing outcomes in a cohort of 72 GTN patients with pulmonary metastasis against 362 without, noting a markedly higher recurrence rate in the former group (16.7% vs. 2.2%, $p < 0.0001$).[24] Frijstein et al. analysed outcomes after single-agent therapy in 65 GTN patients with pulmonary metastasis and 975 without, identifying increased MTX resistance (60% vs. 38.9%, $p = 0.001$) and a higher recurrence rate (9.2% vs. 2.7%, $p = 0.012$) in patients with metastasis.[25] However, these analyses predominantly used chest X-rays to diagnose pulmonary metastasis, which might fail to detect small nodules or accurately determine nodule size. A more recent 2022 study using CT to detect metastases reported that nodules ≥1.8 cm were significant predictors of resistance to multi-agent chemotherapy and recurrence, thus highlighting the prognostic value of detailed pulmonary nodule characterization for prognostication.[27]

In terms of uterine lesions, Epstein et al. demonstrated that large uterine GTN lesions (≥4 cm) were significantly associated with increased MTX resistance (73% vs. 17%, $p = 0.008$).[28] These associations between pulmonary and uterine lesions and GTN resistance underscore the importance of comprehensive radiological assessment prior to chemotherapy and the need to include radiological factors in prognostic systems.

Revisiting weight assignments for risk factors in FIGO 2000

In FIGO 2000, each prognostic risk factor is assigned 0, 1, 2, or 4 points, but the rationale behind these weightings is opaque. For example, 1 point is assigned to diverse factors including age ≥40 years, a termination of pregnancy as the antecedent pregnancy, pre-treatment hCG levels of 1000–10,000 IU/L, or a four- to six-month interval from the index pregnancy (Table 1). It is therefore important to consider whether these diverse factors contribute equally to resistance or affect survival outcomes, for which there is little empirical support. Risk factor weights are ideally determined based on large, homogeneous patient cohorts using odds ratios (ORs) from multivariate logistic regression. New models, ideally, should undergo both internal and external validation.[29] However, the studies foundational to FIGO 2000 had variable inclusion criteria, chemotherapy protocols, and primary outcomes, making it challenging to establish objective prognostic scoring standards.

Furthermore, metastases outside the reproductive and pulmonary systems are of uncertain prognostic significance. Notably, a 2020 study from China on 53 GTN patients with metastases to the urinary system reported an 80% efficacy rate (24/30) for first-line multi-agent chemotherapy using the floxuridine, actinomycin D, etoposide, and vincristine (FAEV) regimen.[30] In instances of GTN metastasis to the brain, combining first-line multi-agent chemotherapy (either FAEV or EMA/CO) with intrathecal MTX yielded efficacy rates of 72–80% and five-year survival rates of 71–85%.[31–34] These findings underscore the need to re-evaluate the distinct prognostic significance of different sites of metastasis.

Some criteria within FIGO 2000, especially counting metastases, are notably ambiguous. The current guidelines suggest only including lung nodules visible on X-rays in the metastasis count,[23] but chest CT can reveal micro-metastases, resulting in differences in prognostic scores based on the imaging technique employed. Minor lung nodules identified by X-ray were though to have a negligible impact on prognosis,[35,36] but recent research suggests that any lung metastases are of prognostic importance in patients with GTN.[24,25,27] The significance and definition of metastasis counts within the scoring system must therefore be reassessed.

Finally, FIGO 2000 may overestimate scores due to significant associations between certain factors. For example, patients whose antecedent pregnancy was full-term (2 points) are often diagnosed with choriocarcinoma, which is typically associated with a longer interval from the index pregnancy, often seven months (2 points) or even over a year (4 points). Given that choriocarcinoma is essentially high-risk disease, the need to differentiate between several high-risk indicators to advocate for multi-agent chemotherapy seems superfluous. Neglecting the interrelationships between risk factors could misjudge the severity of the patient's condition.

Refining definitions for low-risk groups in FIGO 2000

The FIGO 2021 guidelines (based on FIGO 2000) propose different treatment strategies depending on risk group, recommending single-agent chemotherapy, such as MTX or Act-D, for patients with low-risk GTN and multi-agent chemotherapy for those at high risk. Efficacies of MTX and Act-D vary in low-risk patients due to different administration methods. A 2021 meta-analysis demonstrated that remission rates with Act-D were significantly higher than with MTX in low-risk patients (81.2% [259/319] vs. 66.1% [199/301], OR 2.17), and also that the side-effect profiles for each drug were different.[37] Notably, pulse Act-D may be a more patient-friendly option, particularly for those who cannot attend daily for MTX therapy. Guided by FIGO, primary remission rates are good, certain groups require prognostic/predictive refinement, especially those scoring 5–6 or assigned high scores. Furthermore, 20–35% of patients in the low-risk group develop resistance to first-line chemotherapy, increasing to >60% in those with scores of 5–6 and 80% in those scoring 6 points.[38–40]

A 2022 Chinese study revealed that 75.9% of GTN patients with FIGO scores of 5–6 developed resistance following first-line single-agent therapy, while only

15.2% of those receiving initial multi-agent chemotherapy showed resistance.[41] Another Chinese study of 135 patients receiving single-agent Act-D indicated that patients with FIGO scores of 5–6 had a 15.2-times greater risk of developing resistance to single-agent chemotherapy than those with FIGO scores of 0–4 ($p = 0.002$).[42] The optimal treatment protocol for patients scoring 5–6 clearly needs reconsidering. 2018 FIGO GTN guidelines introduced a stratified treatment scheme for the low-risk group, favouring multi-agent chemotherapy for those scoring 5–6.[43] The 2021 update further highlighted the scoring system's inadequacies for patients with these scores or those diagnosed with choriocarcinoma, emphasizing the increased resistance rates associated with single-agent therapy and suggesting a lower threshold for multi-agent chemotherapy.[1]

Addressing these issues, a 2021 multicentre cohort study[40] proposed customizing the choice of single- and multi-agent chemotherapy for patients scoring 5–6 based on specific clinical indicators. The study reported that "choriocarcinoma pathology" and "extragenital system metastasis" were critical predictors of chemotherapy resistance in this group. The authors recommended multi-agent chemotherapy for patients lacking these risk factors but with hCG levels ≥410,000 IU/L; for those with one risk factor and hCG levels ≥150,000 IU/L; and for patients with both factors, advising an immediate switch to multi-agent therapy.[40] This approach effectively amends the original scoring system, indicating that the binary stratification into low and high risk requires further nuanced discussion and exploration.

Evaluating the 'ultra-high-risk' category in FIGO 2000

The introduction of an "ultra-high-risk" category[1,44] in FIGO 2000 was a significant development that addressed the precise classification of patients with FIGO scores ≥12 or those with extensive metastasis. A pivotal 2016 retrospective analysis by Bolze et al. reported a notable five-year mortality rate of 38.4% in 29 patients with scores ≥13 compared with a 4.9% mortality rate in high-risk patients with scores of 7–12.[45] A subsequent study of 143 patients in China reported a significantly lower five-year overall survival rate of 67.9% for individuals scoring ≥12. Critical prognostic factors identified through this study included a history of non-molar pregnancy, presence of brain metastasis, previous chemotherapy failures, and a history of surgery.[46]

While the ultra-high-risk category attempts to refine prognostic accuracy by closely monitoring disease progression and forecasting outcomes, it also presents the FIGO system with the considerable challenge of precisely predicting treatment responses, recurrence rates, or mortality within a comprehensive scoring framework.

Shortcomings in recurrence risk assessment within FIGO 2000

Recent studies have revealed notable deficiencies in FIGO 2000's ability to accurately evaluate recurrence risk. Powles et al. reported that the time span from pregnancy termination to starting chemotherapy was a significant adverse predictor of recurrence or mortality in high-risk GTN patients.[47] Further scrutiny of relapse in a Chinese cohort indicated that patients experiencing an interval of over one year after treatment faced a 6.6-times relapse risk compared with those within a 12-month interval ($p < 0.001$). This research also highlighted a previously unrecognized risk factor, namely a period from treatment onset to the normalization of β-hCG levels of >14 weeks, which was associated with a 2.2-times risk of relapse compared with patients normalizing within 14 weeks ($p = 0.030$).[48] Additionally, a recent investigation on lung metastasis by the same team discovered that patients with lung nodules >1.8 cm were at significantly increased risk of relapse (OR 5.137, $p = 0.045$).[27] Despite the critical nature of these risk factors, they still do not feature in the current prognostic scoring systems, underscoring a crucial area for possible improvement.

Insights and challenges to refining FIGO 2000

Since 2017, research on prognostic scoring systems for GTN has predominantly relied on single-centre, retrospective data,[20,21,40,49–52] with a focus on refining and enhancing FIGO 2000. These efforts have led to the introduction of new scoring factors and the identification of prognostic indicators particularly relevant to resistance against first-line chemotherapy in both univariable and multivariable analyses. These studies, together with the unique aspects of the revised prognostic models, are summarized in Table 2.

In this research landscape, studies from China[21,50] and the UK[20] have shared the goal of developing new models by refining FIGO 2000. However, variability in patient inclusion criteria and treatment strategies across centres has probably contributed to differences in regression analysis outcomes, with the interval from pregnancy termination to the start of treatment consistently identified as predictive of resistance, emphasizing the heterogeneity of patient cohorts. Reliance on FIGO 2000 as the evaluative benchmark presumes its accuracy, which might detract from the clinical utility of these new models. Qin et al. introduced an innovative model to predict drug resistance that incorporated uterine artery time-averaged mean velocity (*UtA-TAmean*) with prognostic scores, which underwent training and external validation.[49]

Braga et al.'s multicentre cohort study focused on patients with FIGO scores of 5–6. Through regression analysis, they established the comparative prognostic value of choriocarcinoma and metastasis using three distinct hCG cutoff values to assess the likelihood of

Study 1	Inclusion criteria and cases	Primary treatment	Methodology	Risk/prognostic factors considered	Notes
Jiang et al. 2017 [21]	1420 cases (PUMCH, 2002-2013) Low risk: 917 High risk: 503	Single-agent chemotherapy (MTX or Act-D): FIGO score ⩽4 Multi-agent chemotherapy (FAV, FAEV or EMA/CO): FIGO score>4 or choriocarcinoma	**Primary outcome**: CR or resistance to primary treatment **Study objectives**: To simplify FIGO prognostic system **Data analysis**: Univariate and multivariate logistic regression analysis	1) Antecedent pregnancy (mole, term) 2) Interval (7-12 months, >12months) 3) Number of metastasis (>8) 4) Prior failure of chemotherapy	1) Factors such as hCG and the maximum diameter of the tumour were not significant in the logistic regression, which is a divergence from other studies 2) The heterogeneity in treatment plans, leading to different interventions, makes it inappropriate to conduct a joint logistic regression analysis on patients receiving different chemotherapy regimens

Score	0	1	2	3	4
Antecedent pregnancy	Mole		Abortion, term		
Interval (months)	<6		7~12		>12
Number of metastases	0-8				>8
Metastasis sites	None or vaginal/pelvic	Only lung		Lung + other	
Prior chemotherapy failure			Single-agent	Multi-agent	

Comments：The regression results and HR values simplified the original prognostic scoring system，New low-risk group: ⩽5 points ，New high-risk group: ⩾6 points

Study 2	Inclusion criteria and cases	Primary treatment	Methodology	Risk/prognostic factors considered	Notes
Eysbouts et al. 2017 [20]	813 cases (Charing Cross Hospital, 2003-2012) Low risk: 725 cases High risk: 88 cases	Single-agent chemotherapy (MTX): low risk Multi-agent chemotherapy (EMA/CO): high risk	**Primary outcome**: Resistance to first-line single-agent chemotherapy **Objective**: To simplify the FIGO 2000 system **Data Analysis**: Univariate, multivariate logistic regression and Wald logistic regression analysis were performed. The FIGO 2000 was used as the gold standard to assess how many patients from the original low-risk group moved into the high-risk one	1) Interval (>7 months) 2) Pretreatment hCG (>10000 IU/L) 3) Maximum tumour size (>5 cm)	1) The regression analysis did not consider the site of metastasis and history of chemotherapy failure as risk factors, as those patients directly underwent multi-agent chemotherapy 2) The sole purpose of this study was to simplify the original FIGO 2000 system, without making any corrections to the shortcomings of the original prognostic scoring system

Original FIGO	AUC	True-positive	True-negative	False-positive	False-negative	Sensitivity	Specificity	Identical classification
Model3	1	722	73	1	0	1	0.99	99.90%
Age								
Antecedent pregnancy								
Internal								
Pretreatment serum hCG								
Number of metastases	Risk classification according to FIGO 2000 was considered the 'gold standard'							

Comments：This study constructed three new models. It is believed that simplified Model3 is most in line with the original FIGO 2000, with only one person needing to be transferred from the low-risk group to the high-risk group

(Table 2 continues on next page)

resistance to single-agent therapy in this intermediate-risk subgroup.[40] This approach avoided direct comparison with FIGO 2000, potentially improving prognostic scoring. The PREDICT-GTN1 study of 4191 patients developed six new prognostic models using logistic regression and machine learning, which were then benchmarked against the original scoring system,[51] but these models were not statistically superior to FIGO. In the follow-on PREDICT-GTN2 study, which used the original cohort as the training set and 144 newly admitted patients as the validation set, the same team developed three bivariate models based on hCG values, concluding that simplified models could sufficiently replace FIGO 2000.[52] Nevertheless, predicting resistance to multi-agent therapy is still an unresolved challenge. These studies highlight the complexities of proposing updates within the established framework of FIGO 2000, particularly when evaluating the efficacy of single-agent therapy using new models for patients who have transitioned to multi-agent chemotherapy.

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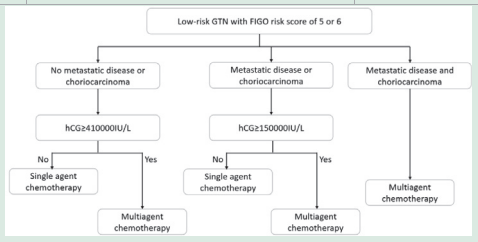
Study 3	Inclusion criteria and cases	Primary treatment	Methodology	Risk/prognostic factors considered	Notes
Braga et al. 2021 [40]	Patients scoring 5-6: 431 cases (Charing Cross Hospital, UK; Rio de Janeiro Trophoblastic Disease Centre, Brazil; New England Trophoblastic Disease Centre, 1964-2018)	Single-agent chemotherapy (MTX): 351 cases Multi-agent chemotherapy (EMA/CO): 80 cases	**Primary outcome**: Resistance to first-line chemotherapy **Objective**: To optimize the treatment decision-making for patients with FIGO scores of 5-6 **Data Analysis**: Univariate and nested multivariate logistic regression analyses were used to construct the model; under the risk factor grouping, bootstrap resampling was used to determine the hCG value with an 80% positive predictive value for hCG	1) Choriocarcinoma 2) Pretreatment hCG 3) Metastatic disease	1) The treatment options for patients with FIGO scores of 5-6 were judiciously determined through a process of risk factor stratification and hCG stratification, providing a logical framework for decision-making 2) The study does not explicitly elucidate whether the pathological diagnosis of "choriocarcinoma" bears any correlation to the non-molar pregnancy
					
	Comments: "Choriocarcinoma" and "metastatic disease" were treated as binary variables, and both were discussed as risk factors, resulting in three risk groups with 0, 1, and 2 risk factors respectively. Different hCG cut-off values were used for each risk group				

Study 4	Inclusion criteria and cases	Primary treatment	Methodology	Risk/prognostic factors considered	Characteristics of the new model	Notes
Qin et al. 2021 [49]	Patients whose first-line therapy was single-agent MTX:147 cases (the Women's Hospital, Zhejiang University School of Medicine, China, 2012-2018)	Single-agent chemotherapy: MTX training set: 110 cases (myometrial invasion, 81.8%; 90/110 and without myometrial invasion 18.2%; 20/110). Validation set: 37 cases	**Primary outcome**: Resistance to first-line chemotherapy **Objective**: To construct a new prognostic model incorporating ultrasonographic features **Data analysis**: For the training set, univariate and multivariate logistic regression analyses were conducted on cases with myometrial lesions to construct the predictive model. Cross-validation was performed on the training set, while internal validation was carried out on the validation set	1) FIGO score 2) Uterine artery time-averaged mean velocity (*UtA-TAmean*) cm/s	The model, incorporating only two factors, is represented by the equation: ***y=−2.95332+0.41696×FIGO score+0.03551×UtA-TAmean***. The AUC is 0.757, with an optimal cut-off of 0.5062, yielding a sensitivity of 45.2% and a specificity of 96.6%. Upon validation with a subset of 33 cases exhibiting myometrial lesions, all four patients exceeding the cut-off value demonstrated resistance to MTX, resulting in a sensitivity of 30.8% and a specificity of 100%	1) Only one ultrasonographic feature, *UtA-TAmean*, was utilized in the study. However, this feature is replicable and readily obtainable in clinical practice 2) Further external validation is still required

(Table 2 continues on next page)

Future directions for refining FIGO 2000 for GTN: developing multifaceted models for diverse clinical outcomes

Tasked with guiding treatment decisions for a wide spectrum of clinical scenarios, the current FIGO system lacks the robust evidence base needed to achieve these multiple clinical aims. To address this, it may be beneficial to apply knowledge from scoring systems used for other diseases, such as rheumatoid arthritis, to develop a diversified scoring system that can predict a range of

(Continued from previous page)

Study 5	Inclusion criteria and cases	Primary treatment	Methodology	Risk/prognostic factors considered	Notes
Weng et al. 2022 [50]	578 cases (the Women's Hospital, Zhejiang University School of Medicine, China, 2000-2018) Low risk: 475 cases High risk: 103 cases	Single-agent regimens (5-d MTX, 8-d MTX, weekly MTX; 5-d Act-D; 8-d 5-FU): for low-risk patients Multi-agent regimens (EMA/CO, EMA/EP, TP/TE): for high-risk patients	**Primary outcome**: Resistance to first-line single-agent chemotherapy **Objective**: To simplify the FIGO 2000 system **Data analysis:** Several new models were constructed through univariate and multivariate logistic regression analyses. The FIGO 2000 was used as the gold standard to evaluate the consistency between the new model and the old scoring system	1) Antecedent pregnancy (term) 2) Interval (>12 months) 3) Pretreatment hCG (>10000IU/L)	1) The diversity in treatment plans led to different interventions, making it inappropriate to conduct a logistic regression analysis on populations with different chemotherapy regimens 2) This study did not demonstrate that the new simplified model had superior efficacy to the FIGO 2000 , thus diminishing the significance of simplifying the model construction

Model	Risk Factor	Predictive Positive	Predictive Negative	Positive Predictive Value	Negative Predictive Value	Sensitivity	Specificity	Accuracy
Model 2	Interval; Pretreatment serum hCG	168	271	0.196	0.952	0.717	0.656	0.663
Model 4	Interval; Pretreatment serum hCG; Largest tumour size; Antecedent pregnancy	174	265	0.201	0.958	0.761	0.646	0.658
Model 6	Age; Interval; Pretreatment serum hCG; Largest tumour size; Number of metastases; Antecedent pregnancy	152	287	0.217	0.955	0.717	0.697	0.699
Original FIGO 2000		0	439	0	0.985	0	1	0.895

Comments：Pretreatment hCG and interval were indispensable prognostic risk factors for first-line chemotherapy. Among the six simplified new models, the model that includes the aforementioned two factors clearly had the stronger predictive performance

(Table 2 continues on next page)

clinical outcomes.[53,54] A set of tools, rather than one tool, could address specific clinical questions to improve outcomes and prevent overtreatment or undertreatment. By adopting separate systems for diagnosis, disease activity assessment, remission, and prognosis, such a framework could allow for a more nuanced and personalized assessment and prediction of outcomes for patients under different treatment pathways, thereby enhancing clinical decision-making and hopefully improving outcomes. We propose that the four main goals of predictive approaches should be:

1. **A model for predicting resistance to single-agent therapy**: In the 2021 FIGO updates, chemotherapy resistance was defined as a decrease in serum β-hCG of ≤10% or an increase after ≥2 consecutive courses of chemotherapy. Through retrospective analysis of pre-treatment clinical characteristics and treatment variables, such as the severity of adverse drug reactions and the rate of hCG decline after treatment initiation, this aspect aims to predict resistance to single-agent therapy.
2. **A model for assessing resistance to multi-agent chemotherapy**: This goal focuses on identifying predictors of resistance to each different multi-agent regimen (EMA/CO, FAEV, etc.), helping to select the most appropriate treatment plan for each patient. However, for low-risk patients, establishing predictors of multi-agent resistance may lack an evidence base, as most patients do not commence

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Study 6	Inclusion criteria and cases	Primary treatment	Methodology	Risk/prognostic factors considered	Characteristics of the new model	Notes
Parker et al. 2022 [51]	4191 cases (Charing Cross Hospital,1958-2019; Sheffield Trophoblastic Disease Centre,1973-2019, UK)	Single-agent chemotherapy (MTX): low risk Multi-agent chemotherapy (EMA/CO): high risk	**Primary outcome**: Resistance to chemotherapy **Scored data (SD)**: Complete set of 8 FIGO 2000 system parameters (0\1\2\4) **Raw data (RD)**: Specific continuous variables: Age, interval from index pregnancy, pretreatment hCG level **Objectives:** To simplify the FIGO 2000 **Data analysis:** Linear, multivariate logistic regression, and nonlinear multilayer perceptron to build new models. Assessing the consistency of the model using the FIGO 2000 as a standard with a fixed false positive rate (FPR) of 11.9%	Model1: All 8 variables (SD) Model2: All 8 variables (SD+RD) Model3: Non-imaging variables (SD) Model4: Non-imaging variables (SD+RD) Model5: Imaging variables (maximum tumour size, metastatic site and metastatic numbers) (SD) Model6: Imaging variables (maximum tumour size, metastatic site and metastatic numbers) + pre-treatment hCG (RD))	Six new simplified models incorporating different risk factors were constructed. These models showed minimal improvement in performance compared to the FIGO Prognostic Scoring System	1) The FIGO 2000 is still considered the gold standard 2) Evaluating resistance to multi-agent chemotherapy is not possible within the FIGO prognostic system. Therefore, using the FIGO prognostic system as the basis for assessment may lead to confusion 3) The authors believed that there is little significance in optimizing the FIGO Prognostic Scoring System

Study 7	Inclusion criteria and cases	Primary treatment	Methodology	Risk/prognostic factors considered	Notes
Parker et al. 2024 [52]	**Training set**: 4191 cases in Parker's 2022 study **Validation set:** 144 cases (2019/05-2020)	Single-agent regimens: for low-risk patients Multi-agent regimens (EMA/CO, M-EA): for high-risk patients	**Primary outcome**: Resistance to chemotherapy **Objective**: To find one or two-factor models matched to FIGO **Data analysis:** Using multivariate logistic regression and 5FCV to find the best models	M1 (2-factor model): log pre-treatment hCG (raw data) + previous failed chemotherapy (scored data); M2 (2-factor model): log pre-treatment hCG (raw data) + site of metastases (scored data); M3 (2-factor model): log pre-treatment hCG (raw data) + number of metastases.	1. As observed in the PREDICT-GTN1 study, evaluating resistance to multi-agent chemotherapy is challenging with the FIGO system 2. The 2-factor models are highly convenient for evaluating treatment
	Comments：M2 and M3 are both 2-factor models and are favoured for ongoing validation				

Table 2: **New GTN scoring systems and the identification of prognostic indicators particularly relevant to resistance against first-line chemotherapy.**

treatment with multi-agent regimens due to ethical considerations, side effects, and costs.

3. **A model for predicting efficacy of second-line or salvage treatments in resistant cases**: This goal evaluates the effectiveness of different second-line treatments, including switching to another single-agent therapy or multi-agent therapy, for patients who have developed resistance. It also predicts which patients are likely to respond better to specific treatments. However, the prediction of outcomes from immune therapy in clinical settings is still in its infancy and hampered by the small numbers of patients receiving such treatments.
4. **A model for predicting recurrence or survival**: By integrating a range of clinical characteristics from before and after treatment, these models should predict long-term outcomes such as recurrence and mortality risks. Given that the recurrence rate in

cured GTN patients is lower than that of many other malignancies, the model should not rely on FIGO 2000. Instead, it should be redesigned through retrospective analysis to include pre- and post-treatment imaging features, hCG trends, and chemotherapy resistance history, among other factors, to evaluate the probability of recurrence. For GTN patients at higher risk of recurrence, the model could suggest increasing the frequency of post-therapy follow-ups, extending the duration of consolidation therapy, or earlier initiation of immunotherapy.

Future directions for refining FIGO 2000 for GTN: exploring genetic and molecular predictors

Attaining a "perfect" model for assessing therapy resistance in patients with GTN is hampered by current clinical characteristics and risk factors not entirely capturing the full complexity and biology of GTN resistance. Resistance in GTN is deeply ingrained at the genetic and molecular levels, and a significant breakthrough in this area would likely arise from the discovery of more effective and accessible biomarkers or deeper insights into the molecular and genetic basis of the disease. Several studies have indicated high expression of PD-L1 in placental and trophoblastic tumours,[55,56] as high as 92.3% in GTN in one study.[57] Other potential targeted treatments identified include Wee1, PARP, and MEK inhibitors.[57] In the future, a genetic and molecular-based risk stratification system may be developed for GTN, similar to that used in endometrial cancer,[58] to assist in evaluating prognosis and predicting responses to therapy alongside clinical scoring systems. These discoveries, especially when used alongside hCG assessments, could revolutionize the evaluation of GTN treatment outcomes. Such advances require further basic research into the genetic and molecular mechanisms governing GTN resistance and therapy responses.

Discussion

FIGO 2000 has been used to assess the prognosis of patients with GTN for over two decades, standardizing GTN management across different clinical settings. However, its limitations have become apparent. Primarily, in an attempt to serve multiple purposes within a single framework, FIGO 2000 is suboptimal in certain clinical scenarios. To address these challenges, we propose developing specialized scoring models tailored to specific clinical objectives, such as selecting single-agent therapy, assessing post-chemotherapy resistance, and predicting recurrence and mortality. By aligning each scoring model with a distinct clinical goal, we can improve the accuracy and effectiveness of prognostic assessments, ultimately enhancing patient outcomes.

Since the first report in 2017 demonstrating the efficacy of pembrolizumab in GTN,[59] clinical studies, including our own, have shown promise for immunotherapy in GTN, especially for persistent resistance. Indeed, a multicentre study demonstrated improved efficacy by combining anti-PD-1 therapy with chemotherapy (96.8%) compared with anti-PD-1 therapy alone (62.9%) ($p < 0.001$).[60] Nevertheless, prognostic scoring indicators to determine the optimal timing for initiating immunotherapy are lacking. Future scoring systems should incorporate predictive markers for immunotherapy response, enabling clinicians to better stratify patients who may benefit from early immunotherapy.

Advancing our understanding of the genetic/molecular dynamics of GTN is crucial for developing personalized medicine approaches. Identifying biomarkers indicative of treatment response or resistance would transform GTN care by aligning optimal therapeutic strategies to each patient. For instance, DPP4 regulates cholesterol synthesis, potentially increasing MTX resistance in GTN cells,[61] while RSK2 upregulates SOX8, contributing to enhanced chemotherapy resistance.[62] Additionally, next-generation sequencing studies of cell-free DNA from GTN patients identified mutations in genes such as *BMPR1A* and *MAP3K1*, potentially providing a biomarker for disease severity and treatment efficacy.[63] HLA-G has also been reported as a predictive biomarker of resistance to single-agent chemotherapy in gestational choriocarcinoma in transcriptomic and immunohistochemical studies.[64]

Integrating biological and genetic biomarkers into GTN prognostic models is a promising direction but requires advanced technologies, such as artificial intelligence (AI), to manage complex, high-volume data. AI could revolutionize GTN management by enabling comprehensive analysis of multi-dimensional datasets and creating sophisticated decision support systems that include diverse molecular information such as *TP53* mutations, RTK-RAS pathway changes, or PD-L1 expression, the latter crucial for immunotherapies. However, significant challenges, including the need for high-quality, diverse data and addressing ethical and regulatory issues, must be overcome to fully realize AI's potential.[65]

PSTT and ETT are rare GTN subtypes with distinct biological behaviours that pose unique challenges. Prognostic factors for PSTT/ETT differ significantly from other GTNs, including time since antecedent pregnancy,[66] disease stage, histopathological features, and the presence of recurrent/refractory disease.[67] PD-L1 expression and PI3K pathway alterations have been detected in ETT, highlighting potential therapy targets.[68] Surgery–typically total hysterectomy - remains first-line treatment, while advanced stage III and IV disease requires combined surgery-polychemotherapy.[67] However, these rare tumours are often not adequately

represented in GTN studies, leading to mixed results that fail to capture their unique characteristics. Therefore, tailored scoring systems that better predict prognosis and guide treatment decisions for PSTT and ETT patients are needed.

The rarity of GTN means that gathering sufficient patient data is challenging, mandating multicentre collaboration. Global cooperation and data sharing are essential to enhance our understanding of GTN pathobiology and improve patient care and outcome prediction. The development of new resistance assessment models informed by retrospective analyses, validated through ethical randomised controlled trials, and coupled with the implementation of recurrence prediction systems are necessary steps forward. Enhancing GTN prognostication and treatment approaches is complex, requiring scientific, clinical, and technological breakthroughs combined with adherence to ethical standards and international collaboration. By embracing these challenges and opportunities, the global health community can anticipate significant progress in GTN management, ultimately improving patient outcomes worldwide.

Outstanding questions

Developing new and clinically relevant GTN prognostic models tailored to specific clinical scenarios (e.g., predicting resistance to single-agent chemotherapy, multiagent chemotherapy, second-line treatments, immunotherapy, and the risks of recurrence or mortality) first relies on careful selection and definition of the specific clinical scenarios to target. This will require multistakeholder engagement for broad applicability. The full molecular landscapes of GTN remain unknown, mandating comprehensive efforts to characterize them using the latest multi-omics technologies, as applied to other cancers and diseases. Finally, how best to prognosticate in patients with PSTT and ETT requires specific consideration.

Contributors

LJ: Conceptualization, Methodology, Investigation and Writing-original draft.

JF: Methodology, Project administration and Writing-review.

XY: Conceptualization, Funding acquisition and Writing-review.

All authors contributed to the article and approved the submitted version. Additionally, the underlying data has been verified by Lin Jinkai and Jiang Fang.

Data sharing statement

This review is based on previously published data and literature, and no new data were generated. All data supporting the findings of this review are available in the cited references.

Declaration of interests

All the authors declare no conflicts of interest.

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References

1 Ngan HYS, Seckl MJ, Berkowitz RS, et al. Diagnosis and management of gestational trophoblastic disease: 2021 update. *Int J Gynaecol Obstet*. 2021;155 Suppl 1(Suppl 1):86–93.
2 Ngan HYS. FIGO staging for gestational trophoblastic neoplasia 2000 - FIGO oncology committee. *Int J Gynecol Obstet*. 2002; 77(3):285–287.
3 Kohorn EI, Goldstein DP, Hancock BW, et al. Workshop report: combining the staging system of the international federation of gynecology and obstetrics with the scoring system of the world heath organization for trophoblastic neoplasia. Report of the working committee of the international society for the study of trophoblastic disease and the international gynecologic cancer society. *Int J Gynecol Cancer*. 2000;10(1):84–88.
4 Kohorn EI. The new FIGO 2000 staging and risk factor scoring system for gestational trophoblastic disease: description and critical assessment. *Int J Gynecol Cancer*. 2001;11(1):73–77.
5 Ngan HY, Bender H, Benedet JL, et al. Gestational trophoblastic neoplasia, FIGO 2000 staging and classification. *Int J Gynaecol Obstet*. 2003;83(Suppl 1):175–177.
6 Ngan HY, Seckl MJ, Berkowitz RS, et al. Update on the diagnosis and management of gestational trophoblastic disease. *Int J Gynaecol Obstet*. 2015;131(Suppl 2):S123–S126.
7 Brewer JI, Gerbie AB. Early development of choriocarcinoma. In: Holland JF, Hreshchyshyn MM, eds. *Choriocarcinoma*. Berlin, Heidelberg: Springer Berlin Heidelberg; 1967:45–53.
8 Hammond CB, Borchert LG, Tyrey L, Creasman WT, Parker RT. Treatment of metastatic trophoblastic disease: good and poor prognosis. *Am J Obstet Gynecol*. 1973;115(4):451–457.
9 Bagshawe KD. Risk and prognostic factors in trophoblastic neoplasia. *Cancer*. 1976;38(3):1373–1385.
10 Organization WH. *Gestational trophoblastic diseases: report of a WHO scientific group [meeting held in Geneva from 6 to 10 December 1982]*. World Health Organization; 1983.
11 Committee FO. FIGO oncology committee report. *Int J Gynaecol Obstet*. 1992;39:149–150.
12 Kawashima Y, Maeda M, Fujii T. Registry and follow-up systems of trophoblastic disease in Japan. *Semin Surg Oncol*. 1985;1(2):84–94.
13 Eysbouts YK, Massuger L, Thomas C, et al. Dutch risk classification and FIGO 2000 for gestational trophoblastic neoplasia compared. *Int J Gynecol Cancer*. 2016;26(9):1712–1716.
14 Parker VL, Pacey AA, Palmer JE, Tidy JA, Winter MC, Hancock BW. Classification systems in Gestational trophoblastic neoplasia - sentiment or evidenced based? *Cancer Treat Rev*. 2017;56:47–57.
15 Lurain JR, Casanova LA, Miller DS, Rademaker AW. Prognostic factors in gestational trophoblastic tumors: a proposed new scoring system based on multivariate analysis. *Am J Obstet Gynecol*. 1991;164(2):611–616.
16 Ngan HY, Lopes AD, Lauder IJ, Martin BH, Wong LC, Ma HK. An evaluation of the prognostic factors in metastatic gestational trophoblastic disease. *Int J Gynecol Cancer*. 1994;4(1):36–42.
17 Soper JT, Evans AC, Conaway MR, Clarke-Pearson DL, Berchuck A, Hammond CB. Evaluation of prognostic factors and staging in gestational trophoblastic tumor. *Obstet Gynecol*. 1994;84(6):969–973.
18 Kim SJ, Bae SN, Kim JH, Kim CJ, Jung JK. Risk factors for the prediction of treatment failure in gestational trophoblastic tumors treated with EMA/CO regimen. *Gynecol Oncol*. 1998;71(2):247–253.
19 Hancock BW, Welch EM, Gillespie AM, Newlands ES. A retrospective comparison of current and proposed staging and scoring systems for persistent gestational trophoblastic disease. *Int J Gynecol Cancer*. 2000;10(4):318–322.
20 Eysbouts YK, Ottevanger PB, Massuger L, et al. Can the FIGO 2000 scoring system for gestational trophoblastic neoplasia be simplified? A new retrospective analysis from a nationwide dataset. *Ann Oncol*. 2017;28(8):1856–1861.
21 Jiang F, Wan XR, Xu T, et al. Evaluation and suggestions for improving the FIGO 2000 staging criteria for gestational trophoblastic neoplasia: a ten-year review of 1420 patients. *Gynecol Oncol*. 2018;149(3):539–544.
22 Diver E, Richardson M, Liao CI, et al. Age and racial differences in the presentation of gestational trophoblastic neoplasia. *Int J Gynecol Cancer*. 2021;31(2):194–202.
23 Ngan HY. The practicability of FIGO 2000 staging for gestational trophoblastic neoplasia. *Int J Gynecol Cancer*. 2004;14(2):202–205.

24 Vree M, van Trommel N, Kenter G, et al. The influence of lung metastases on the clinical course of gestational trophoblastic neoplasia: a historical cohort study. *BJOG*. 2016;123(11):1839–1845.
25 Frijstein MM, Lok C, van Trommel NE, et al. Lung metastases in low-risk gestational trophoblastic neoplasia: a retrospective cohort study. *BJOG*. 2020;127(3):389–395.
26 Yu H, Li J, Zhu T, Xue X, Lu X. Evaluation and influence of lung metastasis on patient outcome in gestational trophoblastic neoplasia: a 10-year study at a single institution. *Eur J Obstet Gynecol Reprod Biol*. 2020;251:162–166.
27 Jiang F, Lin JK, Xiang Y, et al. The impact of pulmonary metastases on therapeutic response and prognosis in malignant gestational trophoblastic neoplasia patients: a retrospective cohort study. *Eur J Cancer*. 2022;161:119–127.
28 Epstein E, Joneborg U. Sonographic characteristics of post-molar gestational trophoblastic neoplasia at diagnosis and during follow-up, and relationship with methotrexate resistance. *Ultrasound Obstet Gynecol*. 2020;56(5):759–765.
29 Collins GS, Reitsma JB, Altman DG, Moons KG. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): the TRIPOD statement. *BMC Med*. 2015;13(1):1.
30 Cheng H, Yang J, Ren T, et al. Gestational trophoblastic neoplasia with urinary system metastasis: a single center experience. *Front Oncol*. 2020;10:1208.
31 Xiao C, Yang J, Zhao J, et al. Management and prognosis of patients with brain metastasis from gestational trophoblastic neoplasia: a 24-year experience in Peking union medical college hospital. *BMC Cancer*. 2015;15:318.
32 Yang J, Xiang Y, Wan X, Feng F, Ren T. Primary treatment of stage IV gestational trophoblastic neoplasia with floxuridine, dactinomycin, etoposide and vincristine (FAEV): a report based on our 10-year clinical experiences. *Gynecol Oncol*. 2016;143(1):68–72.
33 Savage P, Kelpanides I, Tuthill M, Short D, Seckl MJ. Brain metastases in gestational trophoblast neoplasia: an update on incidence, management and outcome. *Gynecol Oncol*. 2015;137(1):73–76.
34 Borella F, Cosma S, Ferraioli D, et al. From uterus to brain: an update on epidemiology, clinical features, and treatment of brain metastases from gestational trophoblastic neoplasia. *Front Oncol*. 2022;12:859071.
35 Garner EIO, Garrett A, Goldstein DP, Berkowitz RS. Significance of chest computed tomography findings in the evaluation and treatment of persistent gestational trophoblastic neoplasia. *J Reprod Med*. 2004;49(6):411–414.
36 Darby S, Jolley I, Pennington S, Hancock BW. Does chest CT matter in the staging of GTN? *Gynecol Oncol*. 2009;112(1):155–160.
37 Hao J, Zhou W, Zhang M, et al. Direct comparisons of efficacy and safety between actinomycin-D and methotrexate in women with low-risk gestational trophoblastic neoplasia: a meta-analysis of randomized and high-quality non-randomized studies. *BMC Cancer*. 2021;21(1):1122.
38 Sita-Lumsden A, Short D, Lindsay I, et al. Treatment outcomes for 618 women with gestational trophoblastic tumours following a molar pregnancy at the charing cross hospital, 2000-2009. *Br J Cancer*. 2012;107(11):1810–1814.
39 Hasanzadeh M, Tabari A, Homae F, Shakeri M, Bakhshandeh T, MadaniSani F. Evaluation of weekly intramuscular methotrexate in the treatment of low risk gestational trophoblastic neoplasia. *J Cancer Res Therapeut*. 2014;10(3):646–650.
40 Braga A, Paiva G, Ghorani E, et al. Predictors for single-agent resistance in FIGO score 5 or 6 gestational trophoblastic neoplasia: a multicentre, retrospective, cohort study. *Lancet Oncol*. 2021;22(8):1188–1198.
41 Kemin L, Mengpei Z, Rutie Y. Monotherapy for low-risk gestational trophoblastic neoplasia with score 5-6. *Front Oncol*. 2022;12:1035170.
42 Li L, Wan X, Feng F, et al. Pulse actinomycin D as first-line treatment of low-risk post-molar non-choriocarcinoma gestational trophoblastic neoplasia. *BMC Cancer*. 2018;18(1):585.
43 Ngan HYS, Seckl MJ, Berkowitz RS, et al. Update on the diagnosis and management of gestational trophoblastic disease. *Int J Gynaecol Obstet*. 2018;143(Suppl 2):79–85.
44 Lok C, van Trommel N, Massuger L, Golfier F, Seckl M. Clinical working party of the E. practical clinical guidelines of the EOTTD for treatment and referral of gestational trophoblastic disease. *Eur J Cancer*. 2020;130:228–240.
45 Bolze P-A, Riedl C, Massardier J, et al. Mortality rate of gestational trophoblastic neoplasia with a FIGO score of≥ 13. *Am J Obstet Gynecol*. 2016;214(3):390.e1–390.e8.
46 Kong Y, Yang J, Jiang F, et al. Clinical characteristics and prognosis of ultra high-risk gestational trophoblastic neoplasia patients: a retrospective cohort study. *Gynecol Oncol*. 2017;146(1):81–86.
47 Powles T, Young A, Sanitt A, et al. The significance of the time interval between antecedent pregnancy and diagnosis of high-risk gestational trophoblastic tumours. *Br J Cancer*. 2006;95(9):1145–1147.
48 Kong Y, Zong L, Cheng H, et al. Management and risk factors of recurrent gestational trophoblastic neoplasia: an update from 2004 to 2017. *Cancer Med*. 2020;9(7):2590–2599.
49 Qin J, Zhang S, Poon L, et al. Doppler-based predictive model for methotrexate resistance in low-risk gestational trophoblastic neoplasia with myometrial invasion: prospective study of 147 patients. *Ultrasound Obstet Gynecol*. 2021;57(5):829–839.
50 Weng Y, Liu Y, Benjoed C, et al. Evaluation and simplification of risk factors in FIGO 2000 scoring system for gestational trophoblastic neoplasia: a 19-year retrospective analysis. *J Zhejiang Univ Sci B*. 2022;23(3):218–229.
51 Parker VL, Winter MC, Tidy JA, et al. PREDICT-GTN 1: can we improve the FIGO scoring system in gestational trophoblastic neoplasia? *Int J Cancer*. 2023;152(5):986–997.
52 Parker VL, Winter MC, Tidy JA, et al. PREDICT-GTN 2: two-factor streamlined models match FIGO performance in gestational trophoblastic neoplasia. *Gynecol Oncol*. 2024;180:152–159.
53 Aletaha D, Neogi T, Silman AJ, et al. 2010 Rheumatoid arthritis classification criteria: an American college of rheumatology/European league against rheumatism collaborative initiative. *Arthritis Rheum*. 2010;62(9):2569–2581.
54 England BR, Tiong BK, Bergman MJ, et al. 2019 update of the American college of rheumatology recommended rheumatoid arthritis disease activity measures. *Arthritis Care Res*. 2019;71(12):1540–1555.
55 Veras E, Kurman RJ, Wang TL, Shih IM. PD-L1 expression in human placentas and gestational trophoblastic diseases. *Int J Gynecol Pathol*. 2017;36(2):146–153.
56 Bolze PA, Patrier S, Massardier J, et al. PD-L1 expression in premalignant and malignant trophoblasts from gestational trophoblastic diseases is ubiquitous and independent of clinical outcomes. *Int J Gynecol Cancer*. 2017;27(3):554–561.
57 McNally L, Wu S, Hodges K, et al. Molecular profiling of gestational trophoblastic neoplasia: identifying therapeutic targets. *Gynecol Oncol*. 2024;184:111–116.
58 Oaknin A, Bosse TJ, Creutzberg CL, et al. Endometrial cancer: ESMO clinical practice guideline for diagnosis, treatment and follow-up. *Ann Oncol*. 2022;33(9):860–877.
59 Ghorani E, Kaur B, Fisher RA, et al. Pembrolizumab is effective for drug-resistant gestational trophoblastic neoplasia. *Lancet*. 2017;390(10110):2343–2345.
60 Wang X, Cang W, Liu X, et al. Anti-PD-1 therapy plus chemotherapy versus anti-PD-1 therapy alone in patients with high-risk chemorefractory or relapsed gestational trophoblastic neoplasia: a multicenter, retrospective study. *eClinicalMedicine*. 2023;59:101974.
61 Yuan W, Yong W, Zhu J, Shi D. DPP4 regulates DHCR24-mediated cholesterol biosynthesis to promote methotrexate resistance in gestational trophoblastic neoplastic cells. *Front Oncol*. 2021;11:704024.
62 Wu S, Shao M, Zhang Y, Shi D. Activation of RSK2 upregulates SOX8 to promote methotrexate resistance in gestational trophoblastic neoplasia. *Lab Invest*. 2021;101(11):1494–1504.
63 Luo L, Lin L, Zhang X, et al. Next-generation sequencing panel analysis of clinically relevant mutations in circulating cell-free DNA from patients with gestational trophoblastic neoplasia: a pilot study. *Biomed Res Int*. 2020;2020:1314967.
64 Bolze PA, Lopez J, Allias F, et al. Transcriptomic and immunohistochemical approaches identify HLA-G as a predictive biomarker of gestational choriocarcinoma resistance to monochemotherapy. *Gynecol Oncol*. 2020;158(3):785–793.
65 Molnar MJ, Molnar V. AI-based tools for the diagnosis and treatment of rare neurological disorders. *Nat Rev Neurol*. 2023;19(8):455–456.
66 Schmid P, Nagai Y, Agarwal R, et al. Prognostic markers and long-term outcome of placental-site trophoblastic tumours: a retrospective observational study. *Lancet*. 2009;374(9683):48–55.
67 Horowitz NS, Goldstein DP, Berkowitz RS. Placental site trophoblastic tumors and epithelioid trophoblastic tumors: biology, natural history, and treatment modalities. *Gynecol Oncol*. 2017;144(1):208–214.
68 Cho HW, Ouh YT, Min KJ, et al. The impact of previous cesarean section (C/S) on the risk for post-molar gestational trophoblastic neoplasia (GTN). *Gynecol Oncol*. 2020;156(3):606–610.