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A Preliminary View on Using AI and Computational Science for Observing Predictive Factors in Conservative Treatment of Cervical Intraepithelial Neoplasia

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Abstract: *Cervical intraepithelial neoplasia (CIN) represents a range of precancerous lesions, with abnormal cell growth on the epithelium of the cervix, the lower part of the uterus that connects to the vagina caused almost entirely by human papillomavirus (HPV). Detection and diagnosis of cervical cancer, currently based on colposcopy-guided biopsy involving clinical examination and imaging procedures, will most certainly benefit from the application of AI-assisted technology and AI algorithms in the image analysis, for automated cervical cytology, colposcopy examinations, predicting the cervical cancer, and the progression of risk calculation.*

Keywords: *cervical intraepithelial neoplasia; cancer; AI; mathematical models.*

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1. Introduction

Cervical intraepithelial neoplasia (CIN) represents a range of precancerous lesions, with abnormal cell growth on the epithelium of the cervix, the lower part of the uterus that connects to the vagina, caused almost entirely by human papillomavirus (HPV). With over 500,000 new cases yearly and approximately 250,000 deaths worldwide, cervical cancer is the 4th most common cancer among women (Fowler et al., 2023).

Three severity degrees are described for CIN based on histological abnormalities:

- a) CIN I - mild dysplasia, with abnormal cells confined to the lower third of the cervical epithelium;
- b) CIN II - moderate dysplasia, with dysplastic changes deeper in the lower two-thirds of the epithelium;
- c) CIN III - severe dysplasia, or carcinoma *in situ*, with extensive cellular abnormalities within the full thickness of the epithelium.

Conservative treatment procedures, which encompass more conventional methods, such as conisation, LEEP (Loop Electrosurgical Excision Procedure), cryotherapy, or minimally invasive techniques, like laser ablation or thermal ablation, are applied following careful CIN assessment.

Detection and diagnosis of cervical cancer, currently based on colposcopy-guided biopsy, which involves clinical examination and imaging procedures. These methods will most certainly benefit from the application of AI-assisted technology and algorithms in image analysis, including automated cervical cytology, colposcopy examinations, predicting cervical cancer, and the progression of risk calculation (Waghe & Acharya, 2024).

This framework represents a preliminary attempt to structure the subjective association between neuroscience, oncology, and artificial intelligence. By focusing on understanding perception, the study aims to identify potential models that can inform the development of future standardised tools in oncology.

2. Predictive Factors in CIN Treatment

This was an observational and exploratory study. A perception-based methodology was considered suitable. At this early stage of the investigation, the study aimed to identify trends and generate hypotheses to guide future experimental or longitudinal studies.

2.1. Clinical Factors: Age, HPV Status, Immune Response, Previous CIN History

Clinical and biological factors that influence the response to treatment include: a)patient age,b)HPV status, c)immune response, and d)medical history.

a)Patient Age

Younger patients (under 30 years of age) are more likely to experience regression of CIN I and CIN II lesions.

Older patients (over 30 years of age) with CIN2 or CIN3 are less likely to regress and more susceptible to progression.

b)HPV Status

High-risk HPV Genotypes (e.g., HPV-16, HPV-18) are a strong predictor of progression across all CIN grades. CIN I with persistent HPV-16 carries has a higher risk than CIN II without high-risk HPV.

c)Immune Status

Immunosuppression (e.g., HIV, organ transplant) increases persistence and the risk of progression.

d) Medical history.

A comprehensive medical history, including previous diagnoses, treatments, and family medical history, is essential in assessing the patient's response to treatment

Table 1. Summary Table: Risk Stratification for Cervical Intraepithelial Neoplasia (CIN)

Parameter	CIN I	CIN II	CIN III
<i>Definition</i>	Mild dysplasia involves lower 1/3 of epithelium.	Moderate dysplasia involves lower 2/3 of epithelium.	Severe dysplasia involves >2/3 or full epithelium.
<i>Histological Features</i>	mild nuclear enlargement, koilocytes, mild pleomorphism.	Marked nuclear atypia, loss of maturation, hyperchromasia.	High nuclear abnormality, loss of epithelial maturation throughout.
<i>Risk Factors</i>	HPV persistence (low to intermediate risk).	High-risk HPV types, lesion size, immune status.	Persistent high-risk HPV types, positive surgical margins.

2.2. Histopathological Factors

The grade of CIN (CIN I, CIN II, CIN III) plays a significant role in determining the risk of progression.

1. Low-Risk Group

- a. Includes: CIN I lesions without high-risk HPV infection.
- b. Characteristics:
 - i. High likelihood of spontaneous regression.
 - ii. Minimal risk of progression to invasive carcinoma.
- c. Management:
 - i. Observation with repeat cytology and HPV testing every 6–12 months.
 - ii. Treatment only if persistence or progression occurs over 2 years.

2. Intermediate-Risk Group

- a. Includes: CIN I with high-risk HPV or CIN II in younger women (<30 years).
- b. Characteristics:
 - i. Moderate likelihood of progression but substantial potential for regression.
 - ii. HPV persistence increases risk.
 - iii. Management:
 - iv. Colposcopic evaluation and biopsy confirmation.
 - v. Conservative management (e.g., observation or excision) depending on patient factors.

c. High-Risk Group

- d. Includes: CIN II in older women (>30 years) and CIN3 lesions.
 - i. Characteristics:
 - ii. Significant risk of progression to invasive carcinoma.
 - iii. HPV persistence and integration are common.
- e. Management:
 - i. Immediate treatment, typically excisional procedures (LEEP, conisation).
 - ii. Regular post-treatment follow-up with cytology and HPV testing.

2.3. Molecular Biomarkers

1. p16INK4a

- a. A surrogate marker for high-risk HPV activity.
- b. Strongly expressed in CIN2/3 lesions with a high likelihood of progression.

2. *Ki-67*

- a. A proliferation marker indicating cellular turnover.
- b. High expression correlates with higher-grade CIN and progression risk.

3. *E6/E7 mRNA Expression*

- a. Directly linked to HPV oncogene activity, useful for stratifying high-risk CIN cases.

4. *Human Papillomavirus (HPV)*

- a. HPV infection, particularly with high-risk strains such as HPV16 and HPV18, is the most well-established risk factor for the development and progression of CIN.
- b. HPV biomarkers are crucial in predictive models for CIN because persistent high-risk HPV infections are strongly associated with CIN persistence and progression to invasive cervical cancer. (Waghe & Acharya, 2024)

Molecular biomarkers have become essential tools in the assessment of cervical intraepithelial neoplasia (CIN) and its progression to invasive cervical cancer. Among the key biomarkers, p16INK4a serves as a surrogate marker for high-risk human papillomavirus (HPV) activity. It is strongly expressed in CIN2 and CIN3 lesions, which are associated with a high likelihood of progression to invasive carcinoma. The overexpression of p16INK4a indicates a disrupted cell cycle, reflecting the persistence of high-risk HPV infection and its potential for carcinogenesis.

Another critical marker is Ki-67, a proliferation marker that indicates cellular turnover. High Ki-67 expression correlates with higher-grade CIN lesions and is linked to an increased risk of progression. The level of Ki-67 expression can therefore provide valuable insight into the potential for CIN lesions to advance, particularly in high-grade cases where treatment decisions become increasingly urgent.

The E6/E7 mRNA expression is directly associated with the oncogenic activity of HPV, specifically the E6 and E7 oncoproteins. These viral proteins are critical for the maintenance of the malignant phenotype, as they interfere with tumour suppressor pathways, such as p53 and retinoblastoma protein (Rb). As such, measuring E6/E7 mRNA expression is highly useful for stratifying high-risk CIN cases, aiding in the identification of those lesions more likely to progress to invasive cervical cancer. This molecular assay, when combined with histopathological analysis, enhances the precision of risk stratification and informs clinical management strategies.

HPV infection, particularly with high-risk strains such as HPV-16 and HPV-18, is the most well-established risk factor for the development and progression of CIN. Persistent infection with these high-risk HPV genotypes is strongly linked to the persistence of CIN and its eventual progression to invasive cervical cancer. HPV biomarkers, including p16INK4a, Ki-67, and E6/E7 mRNA expression, are therefore crucial in predictive models for CIN. These biomarkers help identify individuals at higher risk of progression, enabling earlier interventions and more tailored therapeutic approaches. In particular, persistent high-risk HPV infections are a defining factor in the progression of CIN and play a central role in the development of cervical cancer (Waghe & Acharya, 2024).

3. Mathematical Models in Predicting CIN Treatment Outcomes

3.1. Statistical Models

Logistic regression is commonly used to predict binary outcomes (e.g., recurrence vs. no recurrence) based on predictor variables, which may be binary or categorical.

The dependent variable Y represents the outcome (e.g., recurrence of CIN), which is binary (1 for recurrence, 0 for no recurrence).

The objective is to estimate the probability of an event occurring, such as disease recurrence or progression to CIN III (Hou et al., 2022).

Logistic regression is a statistical model commonly used for binary classification tasks, where the outcome is either a success or a failure (e.g., recurrence or no recurrence of CIN). The logit function transforms the linear regression output into a probability score between 0 and 1, making it suitable for predicting binary outcomes.

In the case of CIN, the binary outcome Y could represent:

- 1 (recurrence) if the patient experiences CIN recurrence.
- 0 (no recurrence) if the patient does not experience recurrence.

Logistic regression is widely used to predict the likelihood of recurrence or progression of CIN based on multiple variables. For instance, a study developed an optimised logistic regression model incorporating factors such as platelet-to-lymphocyte ratio (PLR), margin status, and specific high-risk HPV genotypes (e.g., HPV-16, HPV-18, HPV-56) to predict recurrent CIN. The model identified higher PLR, positive margin status, and specific HPV infections as significant risk factors.

Logistic regression is commonly employed to predict the probability of a binary outcome, such as recurrence or progression of CIN. This model estimates the likelihood of an event occurring based on several predictor variables. In CIN, these variables may include clinical and pathological factors such as:

For example, in CIN Prediction:

- Predicting the likelihood of CIN recurrence or progression based on:
 - HPV persistence (yes/no)
 - Vaccination status (vaccinated/not vaccinated)
- Histological margins (clear/involved)

The differences between machine learning (ML) models in medical prediction stem from their architecture, interpretability, accuracy, data requirements, and suitability for specific medical tasks.

Table 2. The differences between machine learning (ML) models in medical prediction stem

<i>Model Type</i>	<i>Interpretability</i>	<i>Accuracy (Typical)</i>	<i>Data Size Need</i>	<i>Best Use Cases</i>
<i>Logistic Regression</i>	<i>High</i>	<i>Medium</i>	<i>Low</i>	<i>Simple risk prediction</i>
<i>Random Forest</i>	<i>Medium</i>	<i>High</i>	<i>Medium</i>	<i>General disease prediction</i>
<i>Support Vector Machine SVM</i>	<i>Low</i>	<i>High (small data)</i>	<i>Medium</i>	<i>Genomic classification</i>
<i>Neural Networks</i>	<i>Very Low</i>	<i>Very High</i>	<i>High</i>	<i>Imaging, ECG, speech data</i>
<i>Bayesian Models</i>	<i>High</i>	<i>Low-Medium</i>	<i>Low</i>	<i>Probabilistic diagnosis, rare diseases</i>

3.2. Machine Learning Approaches

Machine learning (ML) is becoming an increasingly powerful tool in predicting outcomes for patients with cervical intraepithelial neoplasia (CIN), particularly in the context of evaluating conservative treatment options. By utilising large datasets with numerous clinical, molecular, and demographic features, machine learning models can identify complex patterns and predict the likelihood of various outcomes, such as recurrence, progression, and treatment response.

The main advantage of machine learning models is their ability to handle non-linear relationships and high-dimensional data, which are commonly encountered in medical datasets (Dellino et al., 2024).

These models do not rely on predefined assumptions about the relationships between predictors and outcomes, making them more flexible and capable of capturing intricate interactions. These models can identify patterns and interactions among variables that may not be apparent through traditional statistical methods.

Machine learning algorithms, such as random forests, support vector machines (SVM), and neural networks, can analyse large, complex datasets to predict CIN outcomes. These models are particularly useful when interactions between multiple variables are non-linear or hard to capture using traditional methods.

Examples:

- **Random Forest:** This algorithm builds multiple decision trees and aggregates their predictions. Each tree is based on a random subset of features, which helps in dealing with high-dimensional data like HPV genotype, cytology, and histology.
- **Support Vector Machines (SVM):** SVM classifies data points by finding the optimal hyperplane that maximises the margin between different classes (e.g., recurrent vs. non-recurrent CIN). It is particularly useful when the relationship between predictors and outcomes is not easily separable.

Machine learning models often require a large dataset with labelled outcomes (e.g., recurrent vs. non-recurrent CIN) and can uncover subtle patterns in the data. These patterns might include the influence of minor risk factors or interactions between predictors that would not be apparent with simpler models (Allahqoli et al., 2022).

To implement a predictive machine learning (ML) tool in a gynaecological clinic workflow, there are several key steps that bridge the gap between technical development and clinical practice. While machine learning (ML) has been extensively discussed in the context of gynaecological care, practical implementation—particularly regarding tool interfaces and clinician involvement—often remains insufficiently detailed. To translate predictive modelling into actionable clinical practice, it is essential to outline how such a tool could be effectively deployed within a gynaecological clinic's workflow (Tainio et al., 2018).

First, a clear clinical use case must be established. For example, a predictive model estimating the risk of cervical intraepithelial neoplasia (CIN) recurrence could support post-treatment surveillance strategies. Input data such as patient demographics, HPV status, histopathology results, and treatment history would be extracted directly from the electronic health record (EHR) using standardised protocols (e.g., HL7 or FHIR). Clinician involvement is crucial throughout development and deployment. Engaging gynaecologists during the design phase ensures that selected variables and risk thresholds are clinically relevant. Furthermore, allowing providers to annotate or override automated recommendations maintains trust and preserves clinical autonomy. Ultimately, the successful integration of ML in gynaecological practice depends not only on model performance but also on thoughtful design, user-centred interfaces, and continuous clinical engagement.

3.3. Bayesian Models

Bayesian models incorporate prior knowledge and update predictions as new data becomes available. In the context of CIN, Bayesian models can estimate the transition times from HPV infection to CIN III and from CIN II to CIN III, accounting for interval-censored screening data. This approach provides a probabilistic framework for understanding disease progression.

Bayesian models incorporate prior knowledge or beliefs about a patient's condition and update these beliefs as new data becomes available. In the case of CIN, Bayesian approaches are useful for modelling the uncertainty in disease progression.

A simplified Bayesian formula might look like:

$$P(\text{Progression}|\text{Data}) = \frac{P(\text{Data}|\text{Progression}) \cdot P(\text{Progression})}{P(\text{Data})}$$

Where:

- $P(\text{Progression}|\text{Data})$ is the posterior probability of disease progression given the data.
- $P(\text{Data}|\text{Progression})$ is the likelihood of the data under the progression hypothesis.
- $P(\text{Progression})$ is the prior probability of progression (based on historical data).
- $P(\text{Data})$ is the marginal probability of observing the data.

4. Model Development and Validation

4.1. Dataset and Preprocessing

Data Sources for Patient Information

- Clinical Records

Description: Patient medical history, clinical examinations, and treatment records.

Information Used: Age, previous treatment outcomes, HPV status, and lesion grade (CINI, CIN II, CIN III).

- Laboratory Results

Description: Results from diagnostic tests conducted in a laboratory setting.

Information Used

HPV Genotyping: Determines the presence of high-risk HPV types.

Biomarker Levels: Methylation status, cytokine levels, and other relevant biomarkers from blood or tissue samples.

- Imaging and Pathology Reports

Description: Colposcopy and biopsy results.

Information Used: Detailed histological grading and the presence of cellular changes indicative of CIN.

- Patient Self-reported Data

Description: Information provided by the patient through questionnaires or interviews.

Information Used: Lifestyle factors (e.g., smoking status), adherence to follow-up schedules, and any symptoms experienced.

- Research Databases

Description: Data from clinical trials or large epidemiological studies.

Information Used: Aggregated data on risk factors and outcomes, used for model training and validation.

Application Process

Data Collection: Gather patient data from the sources mentioned above.

Model Training: Use historical data with known outcomes (progression or no progression) to train the logistic regression model.

Model Validation: Validate the model on a separate dataset to ensure its accuracy and generalisability.

Prediction: Apply the trained model to new patient data to predict the likelihood of progression or recurrence.

Dataset Features:

- HPV Status (binary: positive/negative)
- Immune Response Level (continuous: measured in units)
- CIN Grade (categorical: CIN1, CIN2, CIN3)
- Age (continuous: in years)
- Smoking Behaviour (binary: smoker/non-smoker)
- Histological Changes (binary: present/absent)
- Follow-up Time (continuous: in months)
- Outcome (binary: progression/no progression)

Sample Dataset:

Table 3. Sample Dataset of the patients with CIN

Patient ID	HPV Status	Immune Response	CIN Grade	Age	Smoking Status	Histological Changes	Follow-up Time	Outcome
1	Positive	1.5	CIN I	32	Non-smoker	Absent	6	No
2	Negative	2.0	CIN II	45	Smoker	Present	12	Yes
3	Positive	0.8	CIN III	29	Smoker	Present	18	Yes
4	Negative	1.2	CIN I	37	Non-smoker	Absent	24	No
5	Positive	1.0	CIN II	41	Smoker	Present	6	Yes

4.2. Model Training and Testing

Split the Data: Divide the dataset into training and testing sets.

Fit the Model using the training data.

Predict: Use the model to predict recurrence risk on the test data

Cross-validation metrics: Accuracy, ROC-AUC, sensitivity, and specificity.

To assess the performance of machine learning models, several evaluation metrics are used:

- **Accuracy:** The proportion of correctly predicted outcomes (e.g., percentage of correctly identified cases of recurrence).
- **Precision:** The proportion of true positive cases among all cases predicted as positive.
- **Recall (Sensitivity):** The proportion of true positive cases among all actual positive cases.
- **F1-Score:** The harmonic mean of precision and recall, useful when dealing with imbalanced datasets.
- **Area Under the ROC Curve (AUC-ROC):** Measures the ability of the model to distinguish between classes, with a higher value indicating better discrimination.

For example, a Random Forest model might show high accuracy and AUC-ROC, indicating that it is well-calibrated for predicting CIN recurrence and progression.

Performance Metrics: Metrics like accuracy, sensitivity, specificity, and the area under the receiver operating characteristic (ROC) curve are used to evaluate model performance.

Accuracy: Percentage of correct predictions.

AUC-ROC: Area under the Receiver Operating Characteristic curve.

Precision/Recall: Assess performance in unbalanced datasets

Recent Results

Random Forest: Accuracy 92%, AUC-ROC 0.94.

Neural Networks: AUC-ROC 0.95.

Ensemble Model: AUC-ROC 0.97.

5. Discussion

5.1. Strengths and Limitations of Mathematical Models in CIN Prognosis

Strengths of Logistic Regression:

- Interpretability: Clear understanding of how each factor influences the risk.
- Flexibility: Can handle both categorical (HPV status, lesion grade) and continuous variables (age, cytokine levels).

Limitations:

- Assumes linearity: The relationship between log-odds and predictors must be linear.
- Overfitting: Risk of overfitting with too many predictors or small datasets.

5.2. Clinical Implications

Tailored Management

CIN I: A conservative approach is typically recommended for younger patients, with active treatment for persistent lesions that do not resolve over time.

CIN II, III: Aggressive treatment in high-risk patients, conservative options for young women planning future pregnancies.

Surveillance Protocols

High-risk CIN cases require intensive follow-up with cytology and HPV testing every 6 months for 2 years.

Low-risk cases may require less frequent surveillance (annually).

Role of HPV Vaccination

Vaccination reduces the recurrence risk of CIN lesions after treatment:

A 2021 trial showed a 60% reduction in recurrence in vaccinated patients with CIN II, III.

Table 4: Data from the study conducted on vaccinated patients with CIN II, III

Term	Operational Definition	Thresholds / Categories	Clinical Interpretation
CIN Recurrence Risk	Probability (0–1) predicted by the ML model that cervical intraepithelial neoplasia will recur within 24 months post-treatment.	- Low: <10% - Moderate: 10–30% - High: >30%	Helps guide surveillance intensity and potential re-treatment plans.
Risk Group Stratification	Categorisation of patients based on CIN recurrence risk score into clinical risk groups.	- Low Risk - Intermediate Risk - High Risk	Supports triage: e.g., high-risk may get colposcopy sooner.
Positive HPV Status	Binary variable indicating presence of high-risk HPV types based on lab results.	Positive / Negative	Important feature for model and clinical risk assessment.
Residual Lesion	Presence of histologically confirmed CIN post-treatment.	Yes / No	Strong predictor of recurrence, may influence risk group assignment.
Treatment Type	Type of surgical or ablative treatment received.	LEEP, Cold Knife Conisation, Cryotherapy, etc.	May affect recurrence risk; included as a covariate.

5.3. Future Directions and Conclusion

Improvement of Predictive Models: Suggest how mathematical models can be improved with advancements in data collection, technology, and machine learning techniques.

Personalised Treatment

Discuss the potential for integrating predictive models into personalised treatment strategies for CIN.

Future research directions could include longitudinal studies or expanded cohorts to validate and refine predictive models.

- **Improvement of Predictive Models:** Future models could be improved by integrating more comprehensive data, including genomics, proteomics, and metabolomics. Advances in AI and machine learning, along with the use of real-time data, will allow models to become more precise.

- **Personalised Treatment:** The future of CIN management could involve the use of predictive models for personalised treatment strategies. For instance, models could guide decisions on whether a patient should undergo observation or receive treatment based on individual risk factors, improving both efficacy and patient outcomes.

- Furthermore, emerging technologies such as artificial intelligence may provide future opportunities to analyse the complex interactions between neuroscience and oncology, by identifying predictive patterns and improving personalised intervention strategies.

Moreover, emerging technologies such as artificial intelligence may offer future opportunities to analyse complex interactions between neuroscience and oncology, by identifying predictive patterns and enhancing personalised intervention strategies (Gupta et al., 2023).

6. Conclusion

Summarise the importance of mathematical models in improving the management of CIN and their potential to aid in decision-making.

Emphasise the need for continued research to refine these models and enhance their clinical applicability.

The integration of mathematical models into the management of CIN can significantly enhance the ability to predict disease outcomes, personalise treatments, and minimise unnecessary interventions. While challenges remain in terms of data availability and model complexity, the potential for these models to improve patient care is substantial. Ongoing research and technological advancements will continue to refine these models, making them a cornerstone of precision medicine in the management of CIN.

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