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Personalised management of women with cervical abnormalities using a clinical decision support scoring system

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HIGHLIGHTS

- The Clinical Decision Support Scoring System can estimate with high accuracy the histological status of women attending for cytology-based screening.
- Artificial neural networks improve the prediction of CIN2 or worse when compared with cytology and/or HPV DNA test.
- The Clinical Decision Support Scoring System can optimise the personalised management of women with abnormalities at cervical screening.

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ABSTRACT

Objectives. To develop a clinical decision support scoring system (DSSS) based on artificial neural networks (ANN) for personalised management of women with cervical abnormalities.

Methods. We recruited women with cervical abnormalities and healthy controls that attended for opportunistic screening between 2006 and 2014 in 3 University Hospitals. We prospectively collected detailed patient characteristics, the colposcopic impression and performed a series of biomarkers using a liquid-based cytology sample. These included HPV DNA typing, E6&E7 mRNA by NASBA or flow cytometry and p16INK4a immunostaining.
We used ANNs to combine the cytology and biomarker results and develop a clinical DSSS with the aim to improve the diagnostic accuracy of tests and quantify the individual's risk for different histological diagnoses. We used histology as the gold standard.

Results. We analysed data from 2267 women that had complete or partial dataset of clinical and molecular data during their initial or followup visits (N = 3565). Accuracy parameters (sensitivity, specificity, positive and negative predictive values) were assessed for the cytological result and/or HPV status and for the DSSS. The ANN predicted with higher accuracy the chances of high-grade (CIN2+), low grade (HPV/CIN1) and normal histology than cytology with or without HPV test. The sensitivity for prediction of CIN2 or worse was 93.0%, specificity 99.2% with high positive (93.3%) and negative (99.2%) predictive values.

Conclusions. The DSSS based on an ANN of multilayer perceptron (MLP) type, can predict with the highest accuracy the histological diagnosis in women with abnormalities at cytology when compared with the use of tests alone. A user-friendly software based on this technology could be used to guide clinician decision making towards a more personalised care.

1. Introduction

The introduction of a systematic call and recall screening programme in the UK over the past 20 years has resulted in a profound

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decrease in the incidence and mortality from invasive cervical cancer as pre-invasive lesions (cervical intraepithelial neoplasia; CIN) can be detected by the screening programme and treated appropriately [1]. One in ten women screened has an abnormal result [2].

The traditional simple algorithms and management strategies for women with low- or high-grade abnormalities at cytology have been effective at reducing the incidence of cervical cancer, albeit based on clinical tests with limited sensitivity and specificity. Establishing that HPV is causally associated with cervical cancer has led to major advances in cervical cancer primary and secondary prevention but has also set new challenges for the future [3]. Previously established recommendations and management algorithms are likely to be less applicable in future screening settings, while new tests exploring the viral genome may allow a more efficient and personalised management of women with positive screening results.

Advances in technology and scientific techniques created new horizons for improved understanding of the diseases' processes at a molecular level. In the field of cervical pre-invasive and invasive diseases, this allowed an in-depth exploration of the neoplastic mechanisms at a molecular level and led to the development of new test and biomarkers, many of which have become commercially available. With the explosion of new biomarkers targeting the viral DNA detection, the expression of oncoproteins and other cellular processes that promote carcinogenesis in the host, questions on how to best use these in different clinical settings are becoming increasingly difficult to answer. With a continuously evolving evidence base, the development of a clinical decision support scoring system is a current unmet need. This can assist clinicians to use these new technologies to promote preventiont and improve targeted management.

This prospective study aims to develop a clinical decision support scoring system (DSSS) exploiting artificial neural network (ANN) systems and novel molecular markers for the personalised management of women with abnormalities at cytology-based screening.

2. Material and methods

2.1. Study population — inclusion and exclusion criteria

This was a multicentric prospective study that recruited patients from three University Hospitals. Ethical approval was obtained from the local research regulatory bodies. All women gave informed consent.

We included women that presented for opportunistic cytology-based screening between 2006 and 2014 and agreed to participate. We only included women that had cytology taken (even if this was inadequate). We included women with cytological abnormalities as well as normal controls. All women underwent a colposcopic evaluation with or without biopsy for histological diagnosis. We included all women irrespective of their age, ethnicity and menopausal status. Women who were HIV or hepatitis B/C positive or women with autoimmune disorders were excluded.

2.2. Sample collection and tests

We prospectively collected detailed patient characteristics and recorded the colposcopic findings. We obtained a liquid-based cytology sample (LBC)(ThinPrep®) at the first visit before proceeding to the colposcopic assessment. The cytology was assessed by two experienced cytopathologists. The results were reported according to the revised Bethesda classification system (TBS2001 system) [4,5].

The remaining material was used to test a series of test and HPV-related biomarkers. These included: a) HPV DNA typing using the CLART® Human Papillomavirus 2 (GENOMICA) kit for the simultaneous detection of 35 different HPV genotypes by PCR amplification of a fragment within the highly conserved L1 region of the virus [6]; b) nucleic acids sequence based amplification (NASBA) assays [7] (NucliSENSEasyQ® HPV v1.0) that was used for the identification of E6/E7 mRNA of the HPV types: 16, 18, 31, 33 and 45; c) the PermiFlow® (Invirion Diagnostics, LLC, Oak Brook, IL) kit for the identification of E6/E7 mRNA expression of high-risk HPV (subtypes: 16, 18, 26, 31, 33, 35, 39, 40, 42, 43, 44, 45, 51, 52, 53, 54, 56, 58, 59, 61, 62, 66 and 68) using FLOW cytometry [8] and d) the immunocytochemical expression of p16INK4a using the CINtec® cytology double staining (p16/Ki67) kit [9]. Some of the included women had only results for some of these markers but not all. This was the case if some of the laboratory tests yielded invalid results or in cases where the material was insufficient for the processing of the whole set of biomarkers.

We used histology as the gold standard for the assessment of the accuracy parameters of the tests. The histology was taken by colposcopically-directed punch biopsies or by conisation (usually large loop excision of the transformation zone — LLETZ) for women requiring treatment. If histology was available from both punch biopsies and treatment cones, the most severe lesion was documented. If histology was not available as not clinically indicated (i.e. normal cytology and colposcopy), these women were considered as 'clinically normal' (CN) cases. The histological samples were prepared and fixed according to standard histopathology protocols. The three-tiered cervical intraepithelial neoplasia (CIN) grading system was used for reporting histological diagnosis.

2.3. Analysis

We aimed to classify each subject into one of three groups: a) normal or clinically normal, b) CIN1 and c) CIN2 or worse. The latter included cases with CIN2, CIN3, squamous cell carcinoma (SCC), adenocarcinoma (Adeno-Ca) or other histological types of cancer (Ca).

2.3.1. Decision support scoring system

The application of artificial intelligence in medicine is not new [10–20]. The concept of the ANNs was first introduced by McCullogh and Pitts in 1943 [21] and described complex computational models inspired by the human brain nervous system. ANNs employ advanced processes of machine learning and pattern recognition [22,23]. They have the ability to learn from data and can subsequently provide predictions on unknown data. This makes ANNs suitable for classification and prediction tasks in clinical and practical situations. The non-linear design of the ANNs allows them to process complex data patterns, in contrast to many traditional methods based on linear techniques.

ANNs are constructed with similarities to a biological neural network, using artificial neurons interconnected with each other. This architecture is supported by mathematical algorithms governing the neuron interactions. In practice, they are typically described as 'black boxes' due to their inherent complexity that does not produce human understandable rules. Despite this, the process for the creation of a useful ANN system involves several typical steps: A) data collection; B) preprocessing that may include data normalisation, conversion to numeric values and scaling in a predefined range; C) ANN model selection, for example back propagation, learning vector quanisers, self-organizing maps, and radial basis function networks [22,24]; D) selection and configuration of ANN Parameters; E) ANN training by feeding the system with data and the correct output and by adjusting the neuron weights that allows the identification of the required ANN parameters; and F) performance evaluation of the system on a set of known and unknown data. If the performance is deemed satisfactory, this is ready for use in clinical practice.

In this study, the DSSS was based on an ANN implemented by a multilayer perceptron (MLP) [24]. To assess the DSSS performance, various statistical measures were extracted: specificity, sensitivity, positive and negative predictive values (PPV and NPV), false positive and false negative rates (FPR and NPR) and overall accuracy (OA). These were subsequently compared with accuracy parameters for cytology (at the clinical thresholds of ASCUS+, LSIL+, HSIL+) and/or HPV DNA test.