Editorial

Improving the Pap Test with Artificial Intelligence

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Ever since Dr. George Papanicolaou invented the Pap test, the cytology community has actively been engaged in improving this already successful cervical cancer screening test. We have witnessed a positive impact from adopting The Bethesda System (TBS) for Reporting Cervical Cytology, utilizing liquid-based cytology, leveraging computer-assisted screening, and more recently employing molecular analysis (e.g. HPV testing). As we enter an era of computational pathology, we once again have the opportunity to further enhance the Pap test. Computational pathology encompasses the use of computers to analyze digitized pathology images, typically exploiting artificial intelligence (AI) methods.[1] However, as we seek to apply such innovative technology we need to additionally perform a cost-benefit analysis of implementing these tools. Furthermore, we need to resolve whether such solutions are complimentary, synergistic or redundant. In other words, going forward we need to ask ourselves if evaluating Pap tests by cytomorphology, with or without the aid of AI, should be replaced solely with molecular testing (i.e. primary screening with an HPV test alone), or proceed by combining these helpful modalities. The same dilemma will arise for other difficult areas in cytopathology (e.g. atypical urothelial cells, indeterminate thyroid aspirates, suspicious biliary brushings) where both molecular and AI-based methods are being developed to solve these challenges.

In this edition of *Cancer Cytopathology*, Tao and colleagues report on their successful development of a deep learning model to distinguish high-risk digitized SurePath slides from

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atypical squamous cells of undetermined significance (ASC-US) slides.[2] They also demonstrate that their AI-based triage system can effectively serve as a substitute for high-risk human papillomavirus (hrHPV) testing to predict cervical intraepithelial neoplasia (CIN) lesions of CIN2 and above (i.e. CIN2/3, adenocarcinoma in situ, invasive squamous cell carcinoma and adenocarcinoma). Their training dataset was comprised of 300 abnormal (150 low-grade squamous intraepithelial lesions, 120 high-grade squamous intraepithelial lesions, 30 squamous cell carcinomas) and 300 negative intraepithelial lesion or malignancy (NILM) Pap slides. They used whole slide images of these cases scanned at 40x with one Z focal layer, from which they extracted over 60,000 smaller image tiles. Abnormal cells were annotated according to criteria from the 2014 TBS. To validate the performance of their deep learning algorithm, their test dataset incorporated 1,967 ASC-US cases, of which many had hrHPV co-testing results and a subset had histological follow-up information. When triaging cases with ASC-US cytology for CIN2+, the AI-based system developed by these authors achieved equivalent sensitivity (92.9% vs. 89.3%) and higher specificity (49.7% vs 34.3%) than hrHPV testing.

To date, many published studies have reported the successful application of machine learning to Pap tests.[3-8] Several commercial solutions have also been developed that were slowly adopted into routine cytology practice to help automate screening of the Pap smear. These include the early PAPNET system introduced around 1992, followed by the ThinPrep Imaging System (Hologic) and FocalPoint GS Imaging System used with SurePath slides (Becton Dickinson).[9-10] Today, there are newer systems on the market designed to specifically analyze digitized Pap tests with improved whole slide imaging capability and better AI-based algorithms. These include the Genius Digital Diagnostics System (Hologic), CytoProcessor (DATEXIM) and CytoSiA system (OptraScan).

Several valuable lessons can be learned from applying computer-aided diagnosis (CAD) to cervical cancer screening and diagnosis.[11] Foremost, it is clear that regulatory approval for cytology AI-based solutions is foreseeable since the U.S. Food and Drug Administration already approved computer-assisted screening for this purpose almost two decades ago. Cytology

vendors also owned the entire process including pre-imaging (e.g. fixation, specimen processing, staining) and imaging steps, unlike certain companies today that offer AI-based tools independent of addressing problematic pre-imaging steps. The cytology community may remember that despite initial disruption to their clinical workflow, adoption of computer-assisted screening occurred despite initial criticisms. These solutions also addressed an actual problem (e.g. the need for Pap test automation and improved accuracy), rather than the approach some AI start-up companies have taken today which is to present pathology laboratories with a solution even though there is often no pressing problem that needs to be currently solved. Moreover, there were favorable outcomes reported after employing CAD for Pap test screening such as improved sensitivity and productivity, but this in turn required workload limits be re-adjusted. Cytologists also (reluctantly) accepted that in a minority of cases CAD failed to detect all abnormalities (e.g. atypical glandular cells). Finally, reimbursement for both technical and professional components provided the necessary driver for adoption and financial return for investing in this expensive technology.

The publication from Tao and colleagues is provocative, because these researchers eloquently demonstrate how an AI-based solution can be independently employed instead of hrHPV testing to triage women presenting with ASC-US on their Pap tests.[2] Despite the fact that HPV testing is commonly being used in many clinical settings to triage women with ASC-US cytology, we have been made aware of several shortcomings of HPV testing.[12] For example, HPV testing may miss HPV-negative cervical lesions including certain SILs and squamous cell carcinoma. Perhaps applying an AI-based solution alone or together with HPV testing is the answer to cervical cancer screening in the HPV negative population, serving as a catchment system to avoid missed lesions. Of course, Tao and colleagues only used squamous cells to train their deep learning model. To also detect infections and abnormal glandular lesions one would need to further train such a deep learning algorithm.

The cytology community should be excited about the emergence of AI-based solutions designed to augment and not replace what we do. We accordingly need to embrace these promising

technologies. However, we also need to figure out how best to adopt these tools into routine practice, easily integrate them into our workflow, safely validate them for clinical use, and monitor their long term usefulness.

Disclosure: Liron Pantanowitz is on the medical advisory board of Ibex and serves as a consultant for Hamamatsu.

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