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Risk Estimation for the next generation of cervical cancer prevention programs

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Currently, cervical cancer screening programs typically rely on cytology as the first-line screen¹. Women found to be cytologically abnormal are triaged by carcinogenic HPV DNA testing or by repeat cytology or are referred directly to colposcopic examination. At colposcopy, biopsies are taken of any apparent lesions. Treatment is decided based on the combined cytologic, colposcopic, and histologic diagnoses during the patient's history. These decision processes are formalized in complex consensus management algorithms that narrow down the clinical management options to a course of action^{2,3}.

Consensus clinical management algorithms for cervical cancer screening require updating as new technologies, such as low-cost HPV testing^{4–6} and HPV vaccination^{7,8}, prove their potential value. However, with each new technology, the number of branches in an algorithm, reflecting every combination of possible test results with possible patient histories, increases exponentially. Thus, reaching evidence-based consensus on the appropriate clinical action will become increasingly difficult, and compliance by clinicians with complicated algorithms can suffer. HPV vaccination against the major causal HPV types will be particularly challenging to incorporate into algorithms since the amount of partial protection provided by vaccination varies greatly by age at vaccination. In the future, the algorithmic approach might collapse entirely under the even greater complexity posed by the advent of HPV type-specific tests, HPV RNA tests, and new biomarkers of risk (e.g. p16 assays)⁹. In order to take the best advantage of new technologies¹⁰ as they appear, a new approach is needed.

Instead of providing clinicians with algorithms, we propose to provide clinicians with their patient's risk of developing cervical cancer¹¹, as estimated by its surrogate endpoint of precancer (best defined as histologic cervical intraepithelial neoplasia grade 3 [CIN3] or more

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severe [CIN3+], or less precisely by CIN2+, a common treatment threshold). Clinical trials and longitudinal studies on hundreds of thousands of screened women, which incorporate the latest clinical tests, are generating voluminous data on the subsequent risk of cervical precancer. The risk of cervical precancer can be calculated at the time of screening, for women sent immediately to colposcopy, or at 1-year, 2-year, or 3-year follow-up intervals, as desired. Importantly, as new tests are introduced and as more data accrue, the risk estimates are readily updated once data-based evidence of effectiveness is solid.

Risk of cervical precancer is a unifying concept to guide management, regardless of which combination of tests a woman has undergone, because risk of cervical precancer boils down a complex battery of test results over time into a single percentage that forms a basis for action. For example, if guidelines would handle all women with the same risk of cervical precancer in the subsequent 5 years the same, regardless of which tests provide this assessment, then management could be simplified greatly and applied consistently. For example, the lowest-risk women (e.g., 33-years-old, HPV and cytology negative) might be reassured, based on the risk calculation, that their 5-year risk of CIN3+ is <1%. Guidelines, to be developed by the clinical community, might judge that further screening is therefore unnecessary for at least five years. Similarly, guidelines might agree that an immediate precancer risk of >10% justifies colposcopy referral, regardless which combinations of tests were used to measure the risk. Those with risk between 1% and 10% could be considered either for additional testing to refine their risk or for an earlier return screen than routine screening. The highest-risk women (e.g., 33-years-old, persistent HPV-16, high-grade cytology, high-grade colposcopic impression) may have >80% 5-year risk, and may be advised to have excisional treatment even if biopsy confirmation is lacking.

We are building a personalized risk tool to guide the prevention of cervical cancer. This tool will use information from clinical trials and longitudinal studies to predict a woman's risk of having cervical precancer at that moment, and of developing it over subsequent years. The tool will assign a risk based on each combination of a woman's age, current clinical test results (molecular, cytologic, and colposcopic imaging), and HPV vaccination status. When available, past clinical test results (e.g., having excisional treatment last year or testing HPV and cytology negative at the previous screening visit) can place the woman into finer risk categories that provide additional precision in the risk calculation. Risk estimates can be used to decide whether to refer a woman for colposcopically-directed biopsy, and after the biopsy results are available, the risk estimates can be updated to account for the lack of complete sensitivity of the colposcopic biopsy procedure to find precancer. As an extension of predicting current risk, the risk tool also could predict future risk of developing precancer over subsequent years to help decide when a woman should be advised to return for her next screening visit.

In clinical practice, the risk percentage can be computed using an application run on a computer or personal digital assistant (PDA) after entering the patient's age, current test results, and (if available) past test results. The output will likely include the current precancer risk and future precancer risks 1-, 3-, and 5-years in the future. Clinicians or their assistants could use the tool to compute these risks prior to patient visits and keep track of risk estimates over time in medical records. The application might also provide a measure of the reliability of the risk estimate, how each input contributed to the final risk estimate, and consensus guidelines for management based on the interpretation of the risk estimates.

A trustworthy risk estimate frees clinicians and members of consensus conferences from pondering the precancer risk implied by each combination of test results. Instead, they can focus on weighing the benefits, adverse events, and costs of possible clinical action at any risk level. Risks bands that call for similar management need not be revised based on the advent of new tests or updated risk tools. Revisions are required only when improvements to treatment

and management programs change the benefits, adverse events, and costs of action within risk bands.

Shifting from algorithms to risk-based management is not as hard as it may seem. The concept of risk is already implicit in clinical management decisions. Current algorithms obscure implicit assumptions about cancer risk based on each test, interpretation, or diagnosis. In fact, while some recommendations in the algorithms are based on firm evidence, many represent expert opinion. In contrast, the data behind the risk estimates is always available, with uncertainty in risk estimates presented in a confidence interval (e.g., a risk of 15% $\pm$ 5%).

Accurate and powerful risk estimates for combination of tests are required if clinicians are to trust a risk estimate to guide clinical practice. Unlike all other cancers, cervical precancer is predictable with unprecedented accuracy and power because we can test for its necessary cause (HPV), a precancerous lesion has been defined (CIN3+), and we can readily access the cervix for screening and effective treatment over time. As a result, more is known about the natural history of cervical lesions than any other cancer, and a risk tool can exploit this knowledge. As biomarkers for the causes and precancerous states of other cancers are discovered and developed into clinical tests, other cancers will one day be ready for large-scale prevention programs based on risk management. Cervical cancer prevention via risk estimation will be the paradigm for the rational, effective, and cost-effective way to prevent cancer.

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References

1. Schiffman M, Castle PE, Jeronimo J, Rodriguez AC, Wacholder S. Human papillomavirus and cervical cancer. *Lancet* 2007;370:890–907. [PubMed: 17826171]
2. Wright TC, Massad LS, Dunton CJ, Spitzer M, Wilkinson EJ, Solomon D. 2006 American Society for Colposcopy and Cervical Pathology-sponsored Consensus Conference. 2006 consensus guidelines for the management of women with abnormal cervical cancer screening tests. *Am J Obstet Gynecol* 2007;197:346–355. [PubMed: 17904957]
3. Wright TC, Massad LS, Dunton CJ, Spitzer M, Wilkinson EJ, Solomon D. 2006 American Society for Colposcopy and Cervical Pathology-sponsored Consensus Conference. 2006 consensus guidelines for the management of women with cervical intraepithelial neoplasia or adenocarcinoma in situ. *Am J Obstet Gynecol* 2007;197:340–345. [PubMed: 17904956]
4. Bulkman NWJ, Berkhof J, Rozendaal L, van Kemenade FJ, Boeke AJP, Bulk S, Voorhorst FJ, Verheijen RHM, van Groningen K, Boon ME, Ruitinga W, van Ballegooijen M, Snijders PJF, Meijer CJLM. Human papillomavirus DNA testing for the detection of cervical intraepithelial neoplasia grade 3 and cancer: 5-year follow-up of a randomised controlled implementation trial. *Lancet* 2007;370:1764–1772. [PubMed: 17919718]
5. Qiao YL, Sellors JW, Eder PS, Bao YP, Lim JM, Zhao FH, Weigl B, Zhang WH, Peck RB, Li L, Chen F, Pan QJ, Lorincz AT. A new HPV-DNA test for cervical-cancer screening in developing regions: a cross-sectional study of clinical accuracy in rural China. *Lancet Oncol* 2008;9:929–936. [PubMed: 18805733]
6. Sankaranarayanan R, Nene BM, Shastri SS, Jayant K, Muwonge R, Budukh AM, Hingmire S, Malvi SG, Thorat R, Kothari A, Chinoy R, Kelkar R, Kane S, Desai S, Keskar VR, Rajeshwarkar R, Panse N, Dinshaw KA. HPV screening for cervical cancer in rural India. *N Engl J Med* 2009;360:1385–1394. [PubMed: 19339719]
7. FUTURE II Study Group. Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. *N Engl J Med* 2007;356:1915–27. [PubMed: 17494925]

8. Paavonen J, Naud P, Salmeron J, Wheeler CM, Chow SN, Apter D, Kitchener H, Castellsague X, Teixeira JC, Skinner SR, Hedrick J, Jaisamrarn U, Limson G, Garland S, Szarewski A, Romanowski B, Aoki FY, Schwarz TF, Poppe WAJ, Bosch FX, Jenkins D, Hardt K, Zahaf T, Descamps D, Struyf F, Lehtinen M, Dubin G, Greenacre M. HPV PATRICIA Study Group. Efficacy of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine against cervical infection and precancer caused by oncogenic HPV types (PATRICIA): final analysis of a double-blind, randomised study in young women. *Lancet* 2009;374:301–314. [PubMed: 19586656]
9. Cuschieri K, Wentzensen N. Human papillomavirus mRNA and p16 detection as biomarkers for the improved diagnosis of cervical neoplasia. *Cancer Epidemiol Biomarkers Prev* 2008;17:2536–2545. [PubMed: 18842994]
10. Gravitt PE, Coutlee F, Iftner T, Sellors JW, Quint WGV, Wheeler CM. New technologies in cervical cancer screening. *Vaccine* 2008;26(Suppl 10):K42–K52. [PubMed: 18847556]
11. Castle PE, Sideri M, Jeronimo J, Solomon D, Schiffman M. Risk assessment to guide the prevention of cervical cancer. *Am J Obstet Gynecol* 2007;197:356.e1–356.e6. [PubMed: 17904958]