

[Review]

The potential utility of HPV Genotyping in screening and clinical management

Introduction

Although successful, cytology-based programs have several limitations, including poor sensitivity for precancerous lesions and poor reproducibility. In addition, the cytology-based program is costly due to frequently applied, inefficient screening. Much interest has been shown in improving the efficiency of cervical cancer screening programs while maintaining the overall effectiveness.

Natural History of Human papillomavirus and carcinogenic human papillomavirus testing.

Based on knowledge of the central role of persistent carcinogenic HPV in cervical carcinogenesis, testing has been introduced to improve the efficiency and maximize the sensitivity of cervical cancer screening and the carcinogenic HPV DNA testing (Hybrid capture 2) with cytology is approved for primary screening of women aged 30 years and older. The international agency for research on Cancer has endorsed the use of carcinogenic HPV testing alone as an option in primary cervical cancer screening.

Rationale for Genotyping

Despite its promise, carcinogenic HPV testing has an important limitation: poor positive predictive value (PPV). HPV genotyping may be useful for differentiating lower or higher risk in women who test carcinogenic HPV positive, because risk for cervical precancer and cancer (\geq CIN III) varies among carcinogenic HPV genotypes and genotype-specific persistence is strongly linked to presence or development of \geq CIN III. Given that HPV-16 and -18 infections account for 70% of all cervical cancer and only 30% are attributable to the other approximately 13 carcinogenic HPV genotypes, HPV-16, -18 should warrant special consideration.

A potentially more powerful use of HPV genotyping assays could be the monitoring of genotype specific HPV infections. No accepted definition of clinically important persistence exists, but follow-up strategies targeting abnormalities lasting more than approximately 1 year begin to distinguish infections and associated lesions that pose great risk from those posing lower risk. Persistence of a given carcinogenic HPV genotype poses a greater risk for cervical precancerous lesions than testing positive for different carcinogenic HPV genotypes on repeat visits.

Risk assessment

The concept of risk stratification (distinguishing the few women at risk from the many who are not at risk) is the principle underlying any screening test. In this point, HPV genotyping may provide more powerful risk stratification than previously achievable with cytology and carcinogenic HPV testing alone. Those who test positive for HPV 16, 18 have an elevated risk and might warrant colposcopy. Women who test positive for carcinogenic HPV for whom HPV16, 18 infections have been ruled out, might warrant watchful waiting until they show evidence of elevated risk. The absolute risk for \geq CIN III in women who test positive for HPV 16 (and perhaps those with evidence of long term viral persistence) in any population is very high, and in some circumstances could warrant treatment in the absence of a confirmatory biopsy diagnosis, given the less than perfect sensitivity of colposcopy to detect precancer.

Applications

The most useful application of HPV genotyping is in primary screening. If HPV test is accepted for primary screening, a validated and reliable HPV genotyping test could be used to identify the population at risk who test positive for HPV 16, 18 or are persistently infected with any carcinogenic HPV genotypes. Carcinogenic HPV testing is restricted to being an adjunct to cytology for general screening of women aged 30 years and older. In case of HPV genotyping, it could be applied to slightly younger women (around 25) since it could potentially better discriminate between more and less risky HPV through actually measuring HPV persistence. HPV 16, 18 vaccinated populations will show a reduced burden of related infections and cervical cancer and a positive screening test will be more ambiguous. Monitoring persistence of the weaker carcinogens could potentially improve the PPV of screening in populations vaccinated with HPV 16 and 18 through better identifying those at risk.

Misuse of HPV genotyping

Conducting more tests without changing clinical practice only increases the costs of screening without providing greater programmatic efficiency or patient benefit. Experts have suggested that when HPV genotyping with a validated clinical test becomes available, women who test positive for HPV 16 or 18 might benefit from immediate colposcopy whereas those who test negative only must undergo screening in 12 months. However, if the outcome of introducing HPV16, 18 is colposcopy for those who test positive and 6 month follow up for those who test negative, the benefits of risk stratifying this population would be nullified and a concomitant increase in screening costs would occur. In addition, there is another potential exploitation of HPV genotyping to screen young women for suitability for HPV vaccination. However, testing negative for these HPV genotypes does not rule out past exposure to, and therefore successful clearance of, those infectious, nor is there evidence to show that prescreening women for the vaccine-targeted types is cost-effective.

Practical considerations

Several practical categories of considerations for conducting HPV genotyping assays to detect women at elevated risk for cervical precancer and cancer warrant discussion: 1) clinical performance 2) reliability 3) cost 4) provider and patient acceptability 5) practical clinical algorithms, 6) women lost to follow-up, and 7) user friendliness.

Future research

How the risk for \geq CIN III is modulated by increasing duration of infection is unknown. As a corollary, how long persistent carcinogenic HPV infections can be monitored safely before the associated risk is high enough to warrant treatment is also unknown. Advancements in colposcopy are necessary to fully appreciate the benefit of HPV genotyping in identifying women at greatest risk for precancer while less aggressively managing those at lower risk.

Conclusion

HPV genotyping has the clinical potential to improve cervical cancer screening through identifying women at very high risk for cervical precancer and cancer among those at risk. However, several practical concerns must be addressed before HPV genotyping can improve the accuracy of screening and focus clinical management on those at greatest risk. Of equal concern is whether these assays will be used judiciously to improve patient management and care.

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