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Latency or new infection? Evidence-based counseling in the era of HPV-based screening

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High-risk (HR)-HPV testing is rapidly replacing Pap smear cytology as the primary cervical cancer screening modality in both high and low-middle income countries. The use of HR-HPV testing in routine screening is strongly supported by a well-accepted natural history model of cervical cancer (Figure 1) and evidence from numerous observational studies and randomized trials. However, we operate in a context of relative uncertainty when it comes to our ability to provide evidence-based answers to patients' concerns about their HR-HPV test results. All cancer screening programs are associated with the anxiety of screening positive for cancer or precancer. However, testing for HPV, which is a sexually transmitted infection (STI), introduces an entirely new psychosocial burden in women participating in cervical cancer screening. In our zeal to validate and implement HR-HPV-based screening advances, we have perhaps neglected to generate a complete individual-level understanding of the natural history of HPV infection over a woman's lifespan.

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To illustrate these gaps, consider a woman who was 35 years old when HPV testing was introduced as part of her routine screening program, and has completed three cycles of HPV testing. Her first ever HPV test was positive, the second negative, and the third again positive. As illustrated in Figure 2, each step of the diagnostic chain precipitates new anxieties and concerns about what the testing results mean, her risk of cancer, her ability to proactively intervene, and the implications on her intimate relationships. These questions are complex and the answers elusive because of the remaining uncertainties in our understanding of the natural history of HPV infection in individuals across their lifespan[1]. The green natural history transitions in Figure 1 illustrate the two most critical areas of uncertainty in an otherwise well-established model: First, do the antibodies developed after natural infection confer protection against reinfection with the same HPV type? and second, once we test HPV negative, has the virus completely cleared or has it become latent? While extant data cannot provide unequivocal answers, a comprehensive review of HPV natural history studies does, in fact, provide strong 'circumstantial evidence' that the HPV natural history in an individual can follow a number of non-mutually exclusive pathways over the course of a lifetime.

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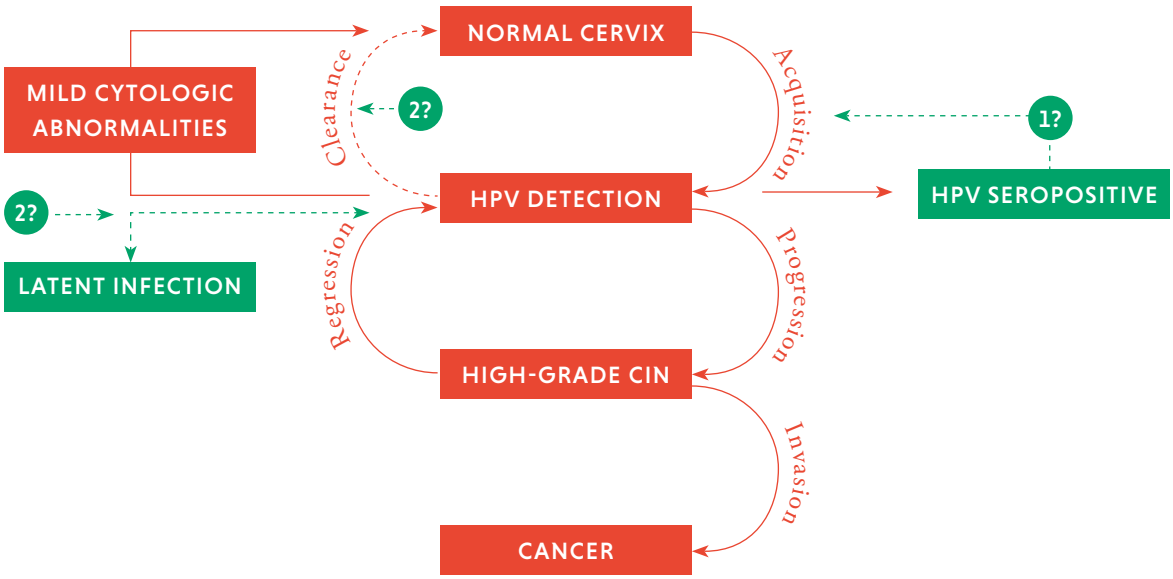
Figure 1

Schematic model of the natural history of HPV infection and cervical cancer



Natural history model of HPV infection and cervical cancer. Transition states in red represent a well-established natural history model of cervical cancer caused by HPV infection. Transition states in green represent transition states in the natural history of the HPV infection over the course of a lifetime. These transitions are supported in the literature but consensus agreement regarding the frequency of the transition and proportion of all infections following these paths has not been reached. The dashed lines reflect the uncertainty in the natural history of HPV. Namely, it is unclear whether anti-HPV antibody developed following natural HPV infection protects against reinfection (1), and whether loss of HPV detection reflects virologic clearance or establishment of viral latency (2).

While we are still trying to understand which of these pathways predominate in any population or at various ages, the evidence is strong enough to provide more specific answers to address individual patient concerns.

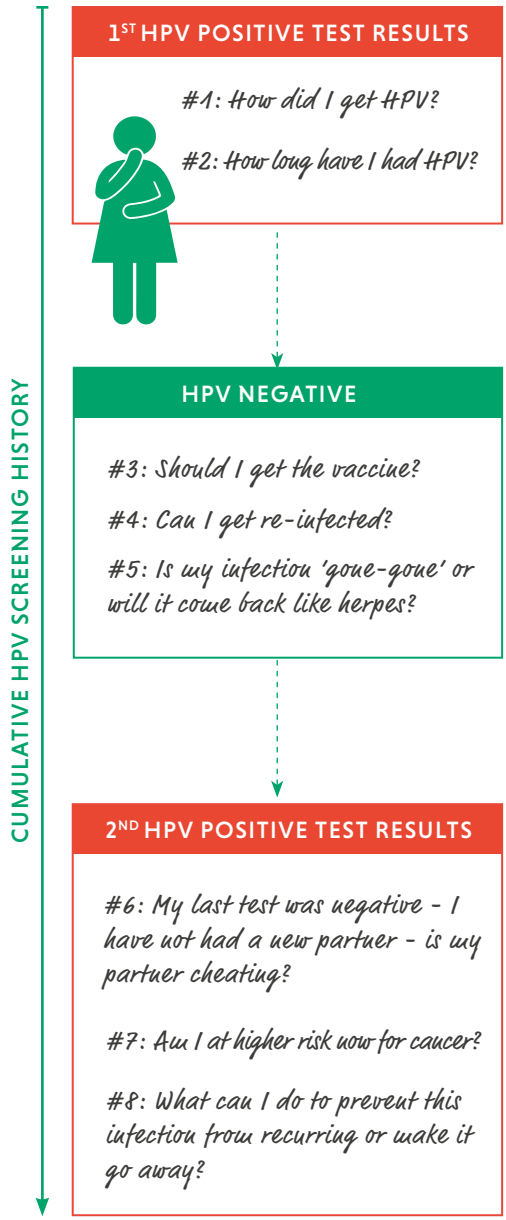
In Figure 3, we illustrate in the center an initial HPV positive screening test result. The collective literature suggests that the answer to the question "How did I get HPV?" may reasonably be one of several options as shown in the upper part of Figure 3. This may be a recently acquired infection from a new sex partner or possibly a re-infection from a long-term partner. It could also represent a false-positive result due to deposition of HPV DNA from a recent sexual encounter that is present in the genital tract but not causing an infection. These explanations are more likely if

the woman is young and sexually active. While younger women acquire new partners at a much higher rate than older women, we note that new partners increase the risk for new HPV detection at any age. However, since new partner acquisition rates decline as women age, the fraction of detectable HPV that is attributable to a new partner is estimated to be substantially lower in older, compared with younger women[2,3]. It is also possible that this first HPV test result reflects long-term persistent infection. This path is more highly correlated with lifetime sexual history than with current sexual behaviors. Finally, the positive result could reflect autoinoculation to the genital tract from the anus or another epithelial site. In general, the lack of an HPV testing history in a woman dealing with her very first HPV test result allows us to make generalized explanations for "where did this come from and how long have I had it?". The best we can do is to say "probably from sexual activity, either recently or sometime in your distant past".

The answers to the questions that follow next in this accumulated HPV testing history are less straightforward. In our example, this woman is re-tested 1 year later and her test is negative. This is a reassuring result in the context of worry about a disease diagnosis since it is widely accepted that persistent detection of HR-HPV is the primary risk factor for progression to precancer/cancer. However, it raises different concerns about what going from HPV test positive to test negative means about her future risk. Can we assure her that the virus is really gone or is just 'hiding out somewhere'? (Figure 2 uncertainty #5). Can she get re-infected now that she has 'cleared' the virus

Figure 2

Patient concerns through repeated HPV screening results



Patient concerns as HPV testing history accumulates through participation in HPV-based screening programs. ▶

and if yes, should she get the vaccine to protect against re-infection? (Figure 2 uncertainty #3)? When she is tested again in 3 years, she is again positive for HR-HPV, raising questions about partner infidelity and/or whether she is destined to have this virus and the associated cancer risk for the rest of her life.

To answer these questions, the literature provides credible evidence that a 'cleared' HPV result may represent at least two different natural history paths. It may truly indicate viral eradication; in this case the woman is no longer infected, and either develops protective immunity from re-infection or does not, in which case she is at continued risk of either re-infection with the offending type from her same partner or from a new partner. If recurrent HPV detection occurs on this natural history path, it will be due to her current sexual activity. It is believed that a susceptible woman in this scenario would benefit from prophylactic HPV vaccination.

In a second scenario, the 'cleared' HPV does not represent viral eradication at all, but simply control of the infection below the limits of detection. Convincing evidence from multiple studies of immune compromised, sexually abstinent[1], older, less sexually active populations[2,3], and adolescents with long-term intensive follow-up[4] support the existence of this path. This scenario is sometimes referred to as 'HPV latency', though it is still unclear whether HPV establishes a strictly defined latent viral state or just persists at extremely low viral loads that are not detectable by most assays. These semantic differences are irrelevant distinctions in the clinical context. The important fact is that in this path, an infected woman tests HPV negative. The evidence is clear that there is a definable and not uncommon risk that these 'controlled, undetectable' infections recur. Studies suggest that recurrent detection of the same type occurs in at least 10-20% of type-specific infections observed to clear[1]. We note in figure 3 that a return to positivity through this path is related to the ability to retain immune control[1] rather than recent sexual exposures[2], and therefore there is no need to suspect infidelity in a relationship as a requisite explanation for an HPV test result transition from negative to positive. Rather, the latency path is dependent on the cumulative sexual history (i.e., past exposures), as the likelihood of harboring a latent infection with reactivation potential increases with higher number of past sexual partners[5]. And, since women accumulate more partners with age, the fraction of HPV positive tests that are attributable to this path of latent virus reactivation (or intermittent detection of low viral loads) is higher in older than younger women[2,3].

With respect to the value of HPV immunization in this natural history scenario, it has long been assumed that prophylactic vaccines will only protect against newly acquired infection. However, data from the mid-adult female vaccine trials show very clear efficacy in the subgroups of women who have baseline antibodies against vaccine type HPV (suggesting past infection)[6]. Because current sexual activity was not included in this analysis, it is unclear whether vaccine-induced antibodies protected against re-infection (if natural antibodies from seropositive individuals were not protective), or whether vaccines reduced the risk of HPV reactivation, perhaps through reduced lateral spread and autoinoculation. The validity of proposals such as HPV-FASTER[7], which seek to implement

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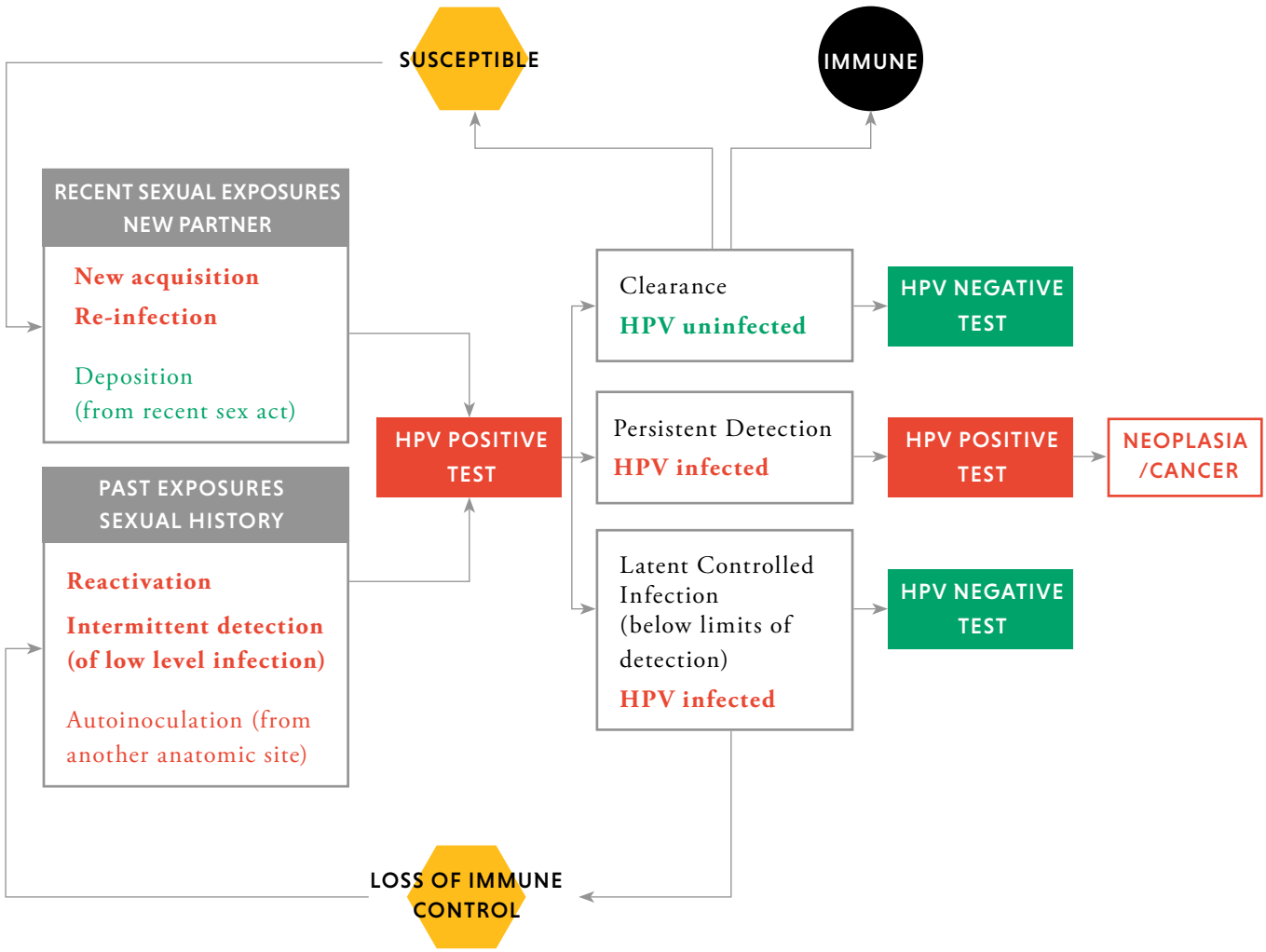
Figure 3

Individual HPV natural history paths over a lifespan



HPV infection: Natural history paths over a woman's lifetime and impact on HPV-based screening test results. Shaded rectangles represent clinical HPV screening test results; red shading indicates HPV test positive, green shading HPV test negative. Green font represents scenarios in an HPV uninfected individual, red font represents an HPV infected individual.

an integrated screening and vaccination program in women up to age 45 years, would benefit greatly from studies designed to differentiate these two possible explanations for vaccine effectiveness in women with prior infection.

Finally, a history of non-consecutive positive HPV screening results will become more and more common as women accumulate an HPV test history. While we know that persistent detection in consecutive tests poses a significantly greater risk of progression, we will need to continue to monitor whether risk of precancer/cancer is increased in women with non-consecutive positive tests relative to those who consistently test negative.

The integration of HR-HPV testing into screening has enabled the development of more sensitive, feasible, and cost-effective programs to accelerate the reduction in global cervical cancer burden. As we continue to scale-up these programs and hone optimal screening and management algorithms, development and delivery of educational messages to address women's questions and concerns about their HR-HPV testing results remains critical. In addition, continued research is needed to fill in the gaps in our understanding of individual-level HPV natural history to guide patient-provider counseling about test results. ■

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