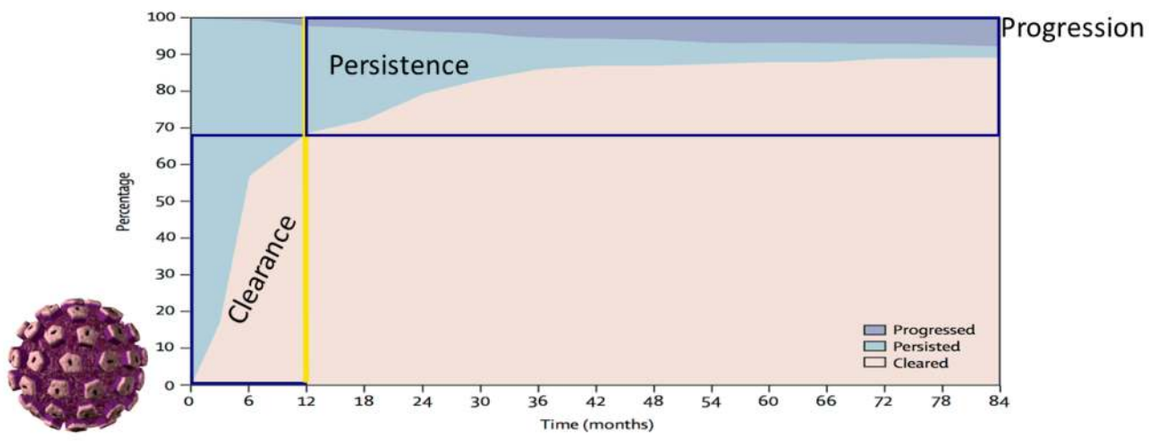
Evidence for clinical utility of extended HPV genotyping in persistence tracking and follow-up after abnormal results and colposcopy and test-of-cure

Jeff Andrews, MD, FRCSC

Declaration of Conflict of Interest: Worldwide Medical Director, Women's Health & Cancer, BD Life Sciences.

Natural history of HPV infections
Average clearance, persistence, & progression



Schiffman M, Castle PE, Jeronimo J, Rodriguez AC, Wacholder S. Human papillomavirus and cervical cancer. *Lancet*. 2007;370(9590):890–907.

Follow-up guidelines and standards of care for surveillance

- HPV-positive, non-16/18, NILM cytology
  - Cotest in 12 months
- Colposcopy for lesser abnormalities, impression negative or low-grade, biopsy ≤CIN1
  - Cotest in 6-12 months
- Excisional treatment of high-grade CIN
  - Cotest in 6-12 months

Follow-up cotest results

- HPV-negative and cytology NILM
- HPV-negative and cytology ASC-US/LSIL
- cytology HSIL/ASC-H/AGC and any HPV result
- HPV-positive and cytology NILM
  - Clearance of prior genotype and new infection OR same-genotype persistence?
- HPV-positive and cytology ASC-US/LSIL
  - Clearance of prior genotype and new infection OR same-genotype persistence?

Systematic Review Results

- Follow-up after abnormal screening result
  - among those with repeated HPV-positive results, same genotype persistence was associated with substantially elevated risk for high-grade lesions compared to the pooled risk of positive for any type
  - HPV 16 had the greatest tendency to persist and the highest probability for progression when persistent
  - HPV 18, 31, 33 were the high-risk HPV types other than HPV 16 associated with high absolute risks for progression
  - Women with low-grade cytology and positive HPV, those testing negative for the highest-risk types of HPV (16/18/31/33/45/52/58) may not need immediate colposcopy and biopsy, if clinical decisions are risk-based

Systematic Review Results

- Post-colposcopy follow-up
  - among those with repeated HPV-positive results, same genotype persistence was associated with substantially elevated risk for high-grade lesions compared to the pooled risk of positive for any type
  - An invited editorial accompanying one of the articles stated, "*The future of screening and management will rely on the identification of patients who have the highest risk for developing CIN 2+ and, when appropriate, aggressively treating those at highest risk. There are many known risk factors for the development of CIN such as HPV status, persistence of HPV, known history of CIN, smoking, and HPV vaccine status, and it has become evident that HPV persistence is perhaps the most important risk factor.*" and "*Although present treatment guidelines do not specifically stratify treatment and follow-up based on the presence of certain genotypes, it is perhaps time to seriously consider this: it is time to graduate to greater utilization of type-specific testing.*"[Huh 2017 AJOG]

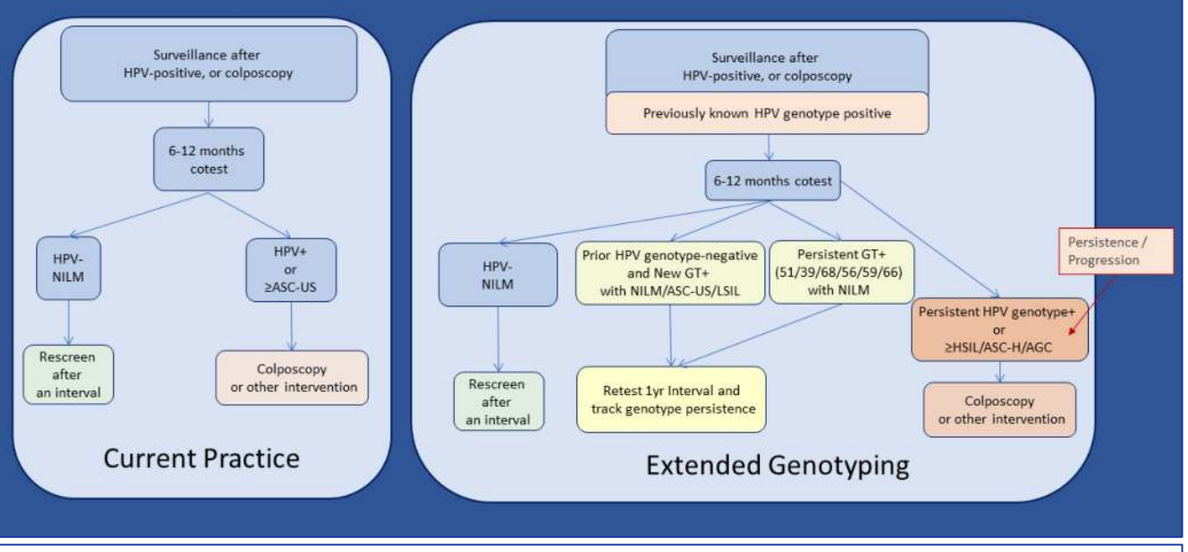
Systematic Review Results

- Test-of-cure
  - same genotype persistence was associated with substantially elevated risk for high-grade lesions compared to the pooled risk of positive for any type
    - genotyping had significantly higher sensitivity and specificity to predict residual/recurrent high-grade CIN
    - almost all disease found at ToC visit was associated with type-persistent hrHPV – 100% in most studies
    - specificity (same genotype clearance) was 100% in most studies
  - proportion of HPV-positive women at ToC with same-genotype persistence (versus new HPV) varied by population from 30% to 80%
  - HPV 16 persistence conferred highest risk

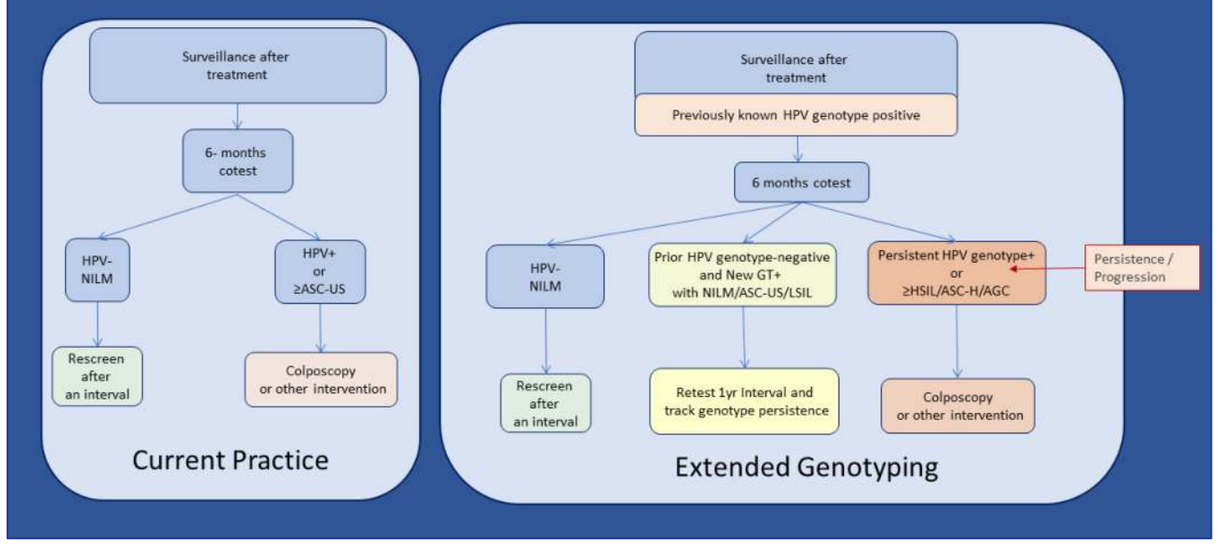
Systematic Review Conclusions

- Women with follow-up cotesting may have type-specific persistence, or clearance, or a new HPV infection
  - the risk posed by a new genotype infection is significantly lower than the risk posed by a type-specific persistent infection
  - Risk-based management should differ between these
- Genotype results could be grouped into 3-4 risk tiers (stratification) for NILM results with same genotype persistence
  - genotypes will be grouped into tiers according to similar risk values, based on local thresholds for management actions
- need more studies, meta-analysis
- need clinically validated assays to be tested

Persistence tracking after screening/colposcopy, with extended genotyping (*apply equal management for equal risk*)



Persistence tracking after treatment of CIN, with extended genotyping (*apply equal management for equal risk*) (Test of Cure)



Citations Follow-Up Abnormal and Colposcopy

- Schlecht NF, Kulaga S, Robitaille J, Ferreira S, Santos M, Miyamura RA, Duarte-Franco E, Rohan TE, Ferenczy A, Villa LL, Franco EL. Persistent human papillomavirus infection as a predictor of cervical intraepithelial neoplasia. JAMA. 2001;286:3106–14
- Kjær SK, Frederiksen K, Munk C, Iftner T. Long-term absolute risk of cervical intraepithelial neoplasia grade 3 or worse following human papillomavirus infection: role of persistence. J Natl Cancer Inst. 2010 Oct 6;102(19):1478-88.
- Note: Dr. Kjaer has a new publication pending submission to JNCI, to be published in 2018; first author = Sand
- Kitchener HC, Canfell K, Gilham C, Sargent A, Roberts C, Desai M, Peto J, on behalf of the ARTISTIC trial study group. The clinical effectiveness and cost-effectiveness of primary human papillomavirus cervical screening in England: extended follow-up of the ARTISTIC randomised trial cohort through three screening rounds. Health Technol Assess. 2014;18(23):1-196.
- Nakamura Y, Matsumoto K, Satoh T, Nishide K, Nozue A, Shimabukuro K, Endo S, Nagai K, Oki A, Ochi H, Morishita Y, Noguchi M, Yoshikawa H. HPV genotyping for triage of women with abnormal cervical cancer screening results: a multicenter prospective study. Int J Clin Oncol. 2015 Oct;20(5):974-81.
- Castle PE, Rodríguez AC, Burk RD, Herrero R, Wacholder S, Alfaro M, Morales J, Guillen D, Sherman ME, Solomon D, Schiffman M; Proyecto Epidemiológico Guanacaste (PEG) Group. Short term persistence of human papillomavirus and risk of cervical precancer and cancer: population based cohort study. BMJ. 2009 Jul 28;339:b2569.
- Gage JC, Schiffman M, Solomon D, Wheeler CM, Castle PE. Comparison of measurements of human papillomavirus persistence for postcolposcopic surveillance for cervical precancerous lesions. Cancer Epidemiol Biomarkers Prev 2010;19(7):1668-74
- Elfgren K, Elfström KM, Naucler P, Arnheim-Dahlström L, Dillner J. Management of women with human papillomavirus persistence: long-term follow-up of a randomized clinical trial. Am J Obstet Gynecol 2017;216:264.e1-7.
- Matsumoto K1, Oki A, Furuta R, Maeda H, Yasugi T, Takatsuka N, Mitsuhashi A, Fujii T, Hirai Y, Iwasaka T, Yaegashi N, Watanabe Y, Nagai Y, Kitagawa T, Yoshikawa H; Japan HPV And Cervical Cancer Study Group. Predicting the progression of cervical precursor lesions by human papillomavirus genotyping: a prospective cohort study. Int J Cancer. 2011 Jun 15;128(12):2898-910.

Citations Test-of-Cure

- Brismar S, Johansson B, Borjesson M, Arbyn M, Andersson S. Follow-up after treatment of cervical intraepithelial neoplasia by human papillomavirus genotyping. Am J Obstet Gynecol. 2009;20:17.
- Elfgren K, Jacobs M, Walboomers JM, Meijer CJ, Dillner J. Rate of human papillomavirus clearance after treatment of cervical intraepithelial neoplasia. Obstet Gynecol. 2002;100:965–71.
- Gosvig CF, Huusom LD, Andersen KK, Iftner A, Cederkvist L, Svare E, Iftner T, Kjaer SK. Persistence and reappearance of high-risk human papillomavirus after conization. Gynecol Oncol 2013;131:661-6
- Jones J, Saleem A, Rai N, Shylasree T.S, Ashman S, Gregory K, Powell N, Tristram A, Fiander A, Hibbitts S. Human Papillomavirus genotype testing combined with cytology as a 'test of cure' post treatment: The importance of a persistent viral infection. Journal of Clinical Virology. 2011;52:88–92.
- Venturoli S, Ambretti S, Cr icca M, Leo E, Costa S, Musiani M, Zerbini M. Correlation of high-risk human papillomavirus genotypes persistence and risk of residual or recurrent cervical disease after surgical treatment. J Med Virol. 2008 Aug;80(8):1434-40
- Söderlund-Strand A, Kjellberg L, Dillner J. Human Papillomavirus Type-Specific Persistence and Recurrence After Treatment for Cervical Dysplasia. Journal of Medical Virology. 2014;86:634–641.
- Nobbenhuis MA, Meijer CJ, van den Brule AJ, Rozendaal L, Voorhorst FJ, Risse EK, Verheijen RH, Helmerhorst TJ. Addition of high-risk HPV testing improves the current guidelines on follow up after treatment for cervical intraepithelial neoplasia. BJC. 2001;84:796–801.
- Kang WD, Oh MJ, Kim SM, Nam JH, Park CS, Choi HS. Significance of human papillomavirus genotyping with high-grade cervical intraepithelial neoplasia treated by a loop electrosurgical excision procedure. Am J Obstet Gynecol. 2010;203:72.
- Vintemyr OK, Iversen O, Thorensen S. et al. Recurrent high-grade cervical lesion after primary conization is associated with persistent human papillomavirus infection in Norway. Gyencol Oncol. 2014;133:159–166.
- Heymans J, Benoy IH, Poppe W, Depuydt CE. Type-specific HPV genotyping improves detection of recurrent high-grade cervical neoplasia after conisation. Int J Cancer. 2011;129:903–9.