New/Alternative Approaches to Clinical Study Design & Evaluation of HPV nucleic-acid tests

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Introductory Remarks

- Celebration of International Women's Day – March 8th
- Appreciation and Acknowledgement
- Disclosure Statement

International Women's Day

HPV Assays detect infection and disease risk

Simple detection of HPV infection is not enough to protect patient safety and perform effectively

- HPV assays must:
  - accurately detect infection AND establish performance relevant to a patient's risk for precancer
  - be applicable to the screening population
  - cannot be biased towards detection of infection at the expense of identifying precancer disease risk
- HPV assays are becoming increasingly important:
  - Adoption of HPV primary screening due to high assay sensitivity
  - Lengthened patient screening intervals with improved NPV
  - Increase in vaccination rates and shifts in genotype prevalence

Question:

Based on the existing abundance of scientific data, robust publications, device approvals and changes in clinical patient management, how do we:

- *reduce the existing validation burden for new HPV assays or indications?*
- *maintain appropriate patient safety protection?*

It is about the study population and the intended screening population

- How should the mix of non-disease and disease samples (i.e., CIN2+/CIN3+) be derived?
- How is safety ensured for future screening populations with a new device?
  - HPV assays need to perform well in the general screening population (not just in a subset population)
  - Study populations need to be representative of the screening population and evaluable by:
    - age, cytology, target loads near the clinical cut off, screening history, and other factors
  - The screening population is changing

It is about the study population and the intended screening population

- NPV is the critical primary screening metric for evaluating assay performance
  - Mandates requirements for:
    - Significant number of screen negative subjects undergoing colposcopy at baseline for study endpoints
    - 3 year longitudinal data
    - Well-characterized biobank of residual samples
- Use of biobanks and well-characterized archived samples are reasonable options, provided they adequately represent a screening population
- Limiting the proportion of vaccinated subjects (to increase the prevalence of disease) creates a conundrum
  - Capping must be accomplished in a manner that allows sufficient statistical power to understand performance in future highly vaccinated screening populations
- Samples cannot solely be derived from a referred population
  - Viral loads associated with high-grade CIN are different than those in a screening population

It is about the study population and the intended screening population

- ***Viral loads are generally higher in HSIL and lower in NILM … the clinical performance of any HPV assay depends on the study population***

	No. of women		No. of clinic visits, mean		HPV-16 E7 DNA load, mean ± SD[a]		Adjusted OR[b] (95% CI)
Finding	CIN-3	No CIN-3	CIN-3	No CIN-3	CIN-3	No CIN-3	
Overall	286	535	4.23	4.76	3.18 ± 1.05	2.57 ± 1.42	1.46 (1.29–1.64)
Normal	30	126	4.28	4.73	2.40 ± 1.05	1.61 ± 1.29	1.66 (1.16–2.37)
ASCUS	86	154	4.05	4.77	3.08 ± 1.03	2.53 ± 1.30	1.51 (1.17–1.94)
LSIL	76	195	4.39	4.83	3.38 ± 0.99	2.94 ± 1.35	1.34 (1.07–1.69)
HSIL	94	60	4.03	4.69	3.35 ± 1.00	3.45 ± 1.07	0.86 (0.61–1.20)

NOTE. ASCUS, atypical squamous cells of undetermined significance; HSIL, high-grade squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion.

[a] Data are $\log_{10}$ copies per nanogram of cellular DNA.

[b] The odds ratio (OR) denotes the 2-year cumulative risk of CIN-3 per 1 $\log_{10}$ increase in viral load, after adjustment for age at enrollment, current use of hormonal contraceptives, lifetime number of male sex partners, and study arm.

Xi, L. F., Kiviat, N. B., Galloway, D. A., Zhou, X. H., Ho, J., & Koutsky, L. A. (2008). Effect of cervical cytologic status on the association between human papillomavirus type 16 DNA load and the risk of cervical intraepithelial neoplasia grade 3. *The Journal of infectious diseases*

Question

What considerations are crucial when contemplating a least burdensome clinical study design?

A simple molecular comparator is problematic

Use of a 2 out of 3 molecular comparator has challenges:

- Not all comparator assay designs and outputs are the same (consensus primers, genotype specific primers/probes, etc.)
- Potential for establishing performance (as compared solely against comparators) that is “acceptable” (indicating detection of infection), but non-clinically relevant (lacking relation to pre-cancer)
  - No apparent way to establish NPV performance metrics to inform how the assay will perform in a primary screening environment
  - No apparent way to inform clinicians about other key performance metrics: specificity, colposcopy rates, longitudinal performance

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An augmented molecular comparator is an improvement

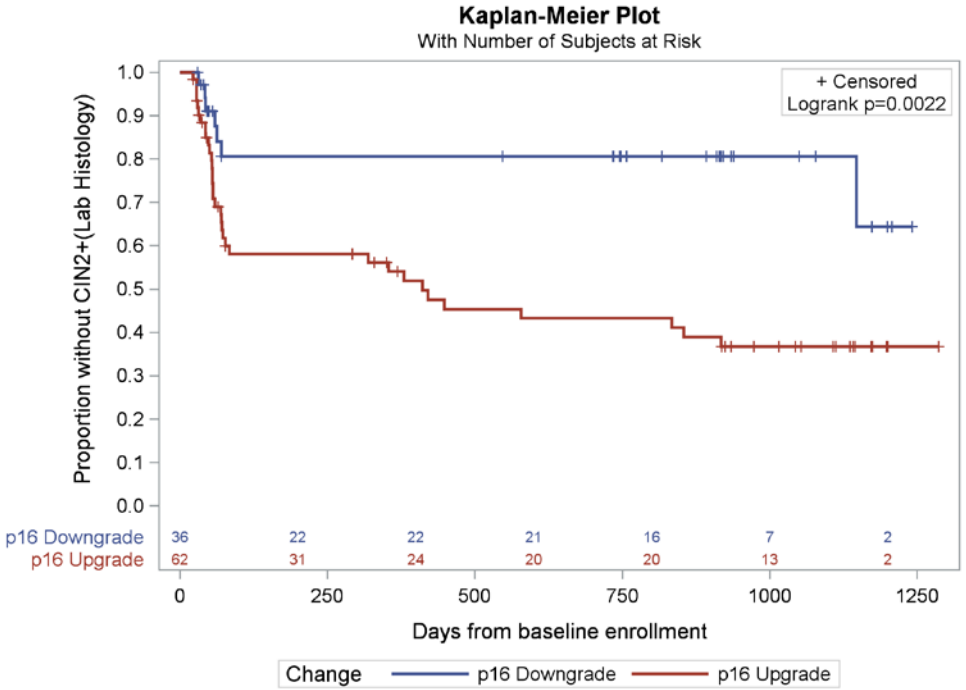
Use of histopathologic information in conjunction with a molecular comparator improves assessment of performance risk.

- Inclusion of histologically defined disease precursors (i.e., CIN2+/CIN3+) as a component of a molecular comparator improves the ability to assess clinical performance risk
- Histopathologic reference standards have evolved and are critical to consider when assigning “comparator positive” vs “comparator negative” results
    - Biomarkers (p16), Microdissection with PCR on actual lesion
- As histopathology science continues to evolve, HPV assays should be validated against the best clinical endpoints used by the medical community at the time of the study

Performance experience with p16 biomarker

Use of CIN2+ as a disease surrogate can be improved:

Addition of p16 according to LAST* guidelines improved the predictive value of CIN2+ as representative of true pre-cancer



*Darragh, T. M., et al (2012). The lower anogenital squamous terminology standardization project for HPV-associated lesions: background and consensus recommendations from the College of American Pathologists and the American Society for Colposcopy and Cervical Pathology. *Archives of pathology & laboratory medicine*

Forward Looking Comments

Additional Considerations

Future of risk-based screening and patient management strategies

- Multiple opportunistic screening paradigms and management approaches coexist
  - Liquid-based cytology with optional triage to HPV
    - to discriminate risk between high (colposcopy) and low (return to screen)
  - Primary HPV and triage of positives to improve the PPV
    - cytology and/or partial genotyping (16, 18)
  - Cotesting with sorting by cytology and partial genotyping
- Future strategies
  - Extended HPV genotyping beyond types 16 and 18 to discriminate risk
  - Immunohistochemical dual-staining cytology to discriminate risk
  - Molecular biomarkers and epigenetic marker panels
  - Possible screen-triage-triage strategies

Future of risk-based screening and patient management strategies

- Risk-based guidelines are necessary
- Critical patient management information is:
  - Genotype(s)
  - Persistence
- Different options exist now for triage of HPV-positive results and more are on the horizon
- HPV assays that report results for specific genotypes beyond 16, 18 and 45 align well with triage screening strategies that leverage the differential oncogenic risk of HPV genotypes.
  - The ability to utilize an extended genotyping assay design in a diagnostic environment is dependent on several factors
    - Clinical practice guideline developments
    - New approaches to HPV IVD diagnostic development guidelines

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Summary and Conclusions

Safety and effectiveness should remain the priority

- Test samples should be representative of the intended use population and appropriately challenge the assay to ensure clinical validity
- Assay outputs must be validated as being clinically relevant to disease precursors
- The effectiveness (PPV) of the HPV test result is improved by triage, but the screen-triage or screen-triage-triage may be uncoupled for regulatory purposes

Vaccination is progressing and vaccinated cohorts are entering the screening population

- lowering the prevalence of vaccine genotypes,
- reducing the HPV 16/18 disease burden,
- altering the proportion of ASC-US, CIN2, and challenging colposcopy

Summary and Conclusions

Diagnostic use of HPV assays that report extended genotype results will

- allow the clinical community to utilize real-world assay outputs to evolve screening guidelines
- improve the ability to triage patients and discriminate risk categorically

Thank you!