New Approaches in the Evaluation for High-Risk Human Papillomavirus Nucleic Acid Detection Devices

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Microbiology Devices Panel Meeting
Gaithersburg, Maryland
March 8, 2019

Purpose of Meeting

- Discuss scientific topics that will inform FDA recommendations on high risk (HR) HPV device development and evaluation
- Obtain panel recommendations for approaches to clinical study design and the establishment of HR HPV device performance characteristics
- Explore potential pathways for innovation in HR HPV device regulation that are less burdensome and more streamlined

HR HPV Device Background

- HR HPV devices are used in cervical cancer screening to assess a woman's risk for harboring an early, treatable precancer, where precancer is defined as a lesion that could progress to cancer if left untreated
- HR HPV devices are designed to detect clinically relevant infections
  - Clinically relevant is defined as:
    1. Types with known carcinogenicity[1] (i.e., "high risk" types such as 16, 18, 45, 31, 33, 35, 39, 51, 52, 56, 58, 59, *66*, 68)
    2. Infections associated with CIN2+ lesions
- The clinical cutoffs of HR HPV devices are set separately by each manufacturer and validated in a clinical study using CIN2+ as an endpoint

[1]According to the International Agency for Research on Cancer (IARC)

Approval Milestones

- HR HPV devices are class III medical devices regulated by the Division of Microbiology Devices in the Office of In Vitro Diagnostics and Radiological Health at CDRH:
  - **1991:** First HPV device approved to detect high and low risk HPV
  - **2000:** Indication revised to include **ASC-US triage** for women to determine need for colposcopy referral
  - **2003:** HR HPV testing approved to be used in routine cervical cancer screening as an **Adjunct** to cytology in women aged 30 and older
  - **2014:** Indication for **Primary HPV Screening** for women aged 25 years and older

HR HPV Device Indications for Use (1)

ASC-US Triage:

In women 21 years and older with ASC-US (atypical squamous cells of undetermined significance) cervical cytology results, the [device trade name] can be used to determine the need for referral to colposcopy.

Adjunct:

In women 30 years and older, the [device trade name] can be used together with cervical cytology to adjunctively screen to detect high risk HPV types. This information, together with the physician's assessment of screening history, other factors, and professional guidelines, may be used to guide patient management.

HR HPV Device Indications for Use (2)

Primary Screening:

In women 25 years and older, the [device trade name] can be used as a first-line primary cervical cancer screening test to detect high risk HPV, including 16 and 18. Women who test negative for the high risk HPV types by the [device trade name] should be followed up in accordance with physician's assessment of screening and medical history, other risk factors, and professional guidelines. Women who test positive for HPV genotypes 16 and/or 18 by the [device trade name] should be referred to colposcopy. Women who test HR HPV positive and 16/18 negative by the [device trade name] (12 other HR HPV positive) should be evaluated by cervical cytology to determine the need for referral to colposcopy.

Reasons for Re-evaluation of Current Approaches

1. Broader knowledge of cervical carcinogenesis from published research
2. Decreased prevalence of vaccine targeted HR HPV infections due to HPV vaccination
3. Evolving screening and patient management guidelines
4. Safety and effectiveness data from previous HR HPV device approvals

Topics for Panel Discussion

1. **Clinical Study Design: Benefits and Risks**
    a. Supplementing from referral populations
    b. Using archived specimens
    c. Capping the vaccinated population

2. **Colposcopy Referral Protocol in Clinical Studies**

3. **Indications for use**
    a. Consolidating the indications for use to encompass one general screening population
    b. Removing reference to specific triage tests and clinical actions

4. **Data Analyses to Support Indications for Use**
    a. Composite molecular comparator
    b. Relative device performance

5. **Clinical Endpoint Comparator**
    a. Mixed histological/molecular comparator

1. Clinical Study Design

- HR HPV studies have enrolled between 10,000 and 40,000 women depending on the indications sought by the sponsor
- These large sample sizes are due to the low prevalence of CIN2+ and CIN3+ in the US screening population
- HR HPV vaccination will likely lower prevalence of CIN3+ further, presenting a challenge for clinical studies

Discussion Topic: How can sponsors reasonably obtain a sufficient number of HR HPV positive and CIN3+ women in a clinical study supporting HR HPV device approval?

1. Clinical Study Design

Proposals:

a. Supplement prospective population with subjects recruited from colposcopy clinics

b. Allow the use of archived specimens from biobanks, repositories, laboratories, etc.

c. Cap the proportion of vaccinated women

1. Clinical Study Design

Proposal	Benefits	Risks
Supplement with women from colposcopy clinics	– Higher prevalence of HR HPV positive women – More likely to enroll women with CIN3+	– Not representative of screening population – May have higher viral loads
Utilize archived specimens	– Can test a large number of specimens without burden of prospective enrollment – Potential access to longitudinal information	– Potentially limited resources – Colposcopy/biopsy not performed under standardized protocol
Cap vaccinated population	– Likely a higher prevalence of HPV positivity and CIN3+ (provided limited herd immunity)	– Performance may not necessarily be representative of device once vaccination rates are higher – May not be effective once herd immunity plays greater role

Clinical Study Design

Panel Question 1

Would the panel recommend one or a combination of the following three proposals to increase the number of women positive for CIN3+ and/or HR HPV in clinical studies:

1. **Supplementing from referral clinics**
2. **Utilizing archived specimens**
3. **Capping the vaccinated population**

2. Colposcopy Referral Protocol in Current HR HPV Device Clinical Studies

Populations referred to colposcopy for biopsy removal and/or ECC :

Cytology Result	HPV result (investigational)	HPV result (FDA-approved test)	Refer to colposcopy
>ASC-US	Any	Any	Yes
ASC-US	Pos	Neg	Yes
ASC-US	Neg	Pos	Yes
ASC-US	Pos	Pos	Yes
ASC-US	Neg	Neg	Yes
NILM	Neg	Neg	Random subset (e.g., 5%)
NILM	Pos	Neg	Yes
NILM	Neg	Pos	Yes
NILM	Pos	Pos	Yes

2. Colposcopy Referral Protocol

- **2012 ASCCP Consensus Guidelines**:
  - NILM/HR HPV negative should return for re-screening in 5 years
  - ASC-US/HR HPV negative should return for re-screening in 3 years
- Accordingly, a subset of NILM/HR HPV double negative woman and all ASC-US/HR HPV double negative women participating in a clinical study will undergo a procedure (colposcopy/biopsy) that they would not normally undergo as part of standard of care

Discussion Topic: Given how guidelines have evolved over the years, is it still appropriate to have these populations of women undergo colposcopy/biopsy for the evaluation of a HR HPV device?

2. Colposcopy Referral Protocol

Benefits of referring ASC-US/HR HPV double neg and NILM/HR HPV double neg populations	**Risks of referring ASC-US/HR HPV double neg and NILM/HR HPV double neg populations**
• Ensures an unbiased clinical performance evaluation • Prevents making assumptions regarding CIN2+/CIN3+ state in double negative women • Better estimate of CIN2+/CIN3+ prevalence in women missed by multiple HR HPV devices	• Identification and overtreatment of transient lesions • Potential underestimation of device sensitivity • Potential optimization of devices to cross react with low-risk types in order to have better sensitivity

Colposcopy Referral Protocol

Panel Question 2

Regarding the NILM/HR HPV double negative and ASC-US/HR HPV double negative populations in clinical studies supporting HPV device approval:

Do the benefits of colposcopy referral for the assessment of verification bias outweigh the risks associated with the procedure and potential overtreatment?

Please discuss for each of the two populations separately.

3. Indications for Use

- There are three main indications for use for which HR HPV devices have received FDA approval:
  - ASC-US triage in women aged 21+
  - Adjunct to cytology for women aged 30+
  - Primary screening for women aged 25+
- Challenges:
  - Tying device indications to specific populations and clinical actions may result in misalignment with future changes to clinical guidelines
  - Certain populations overlap between the indications, resulting in redundant analyses

Discussion Topic: How to simplify device indications for use and make them independent of potential changes in clinical practice?

3. Indications for Use

Proposal:

1. Consolidate the indications to encompass one general screening population
2. Remove references to specific triage tests
3. Remove references to specific clinical actions based on results

Example of new indication(s) for use (IFU):

[Description of technological characteristics of test and trade name] is a qualitative in vitro test for the detection of Human Papillomavirus in cervical specimens collected by a clinician using [collection device/media]. This assay should be used to test women presenting for routine cervical cancer screening to assess the risk for cervical dysplasia and cancer. Women who test positive or negative for the HR HPV types [list types detected from test] should be triaged/followed-up in accordance with professional guidelines, the physician's assessment of screening and medical history, and other risk factors.

3. Indications for Use

Benefits of New IFU	Risks of New IFU
• Enrolled population will be relevant to current screening practices • Accommodates future changes to screening populations • New triage strategies will not require a change to device IFU • Prevents misalignment with future changes to clinical guidelines	• Generalized wording will not provide specifics on the populations who are tested in the study • Device will not be analyzed as part of a screening algorithm, so data will not show a direct depiction of device performance when it is used in a specific way

Indications for Use

Panel Question 3

Regarding the indications for use (IFU), do the benefits outweigh the risks for:

A. **Consolidating the indications to encompass one general screening population**
B. **Removing references to specific triage tests and clinical actions?**

Please discuss any potential risk mitigation measures if the new IFU statement were to be used.

4. Data Analyses to Support Indications

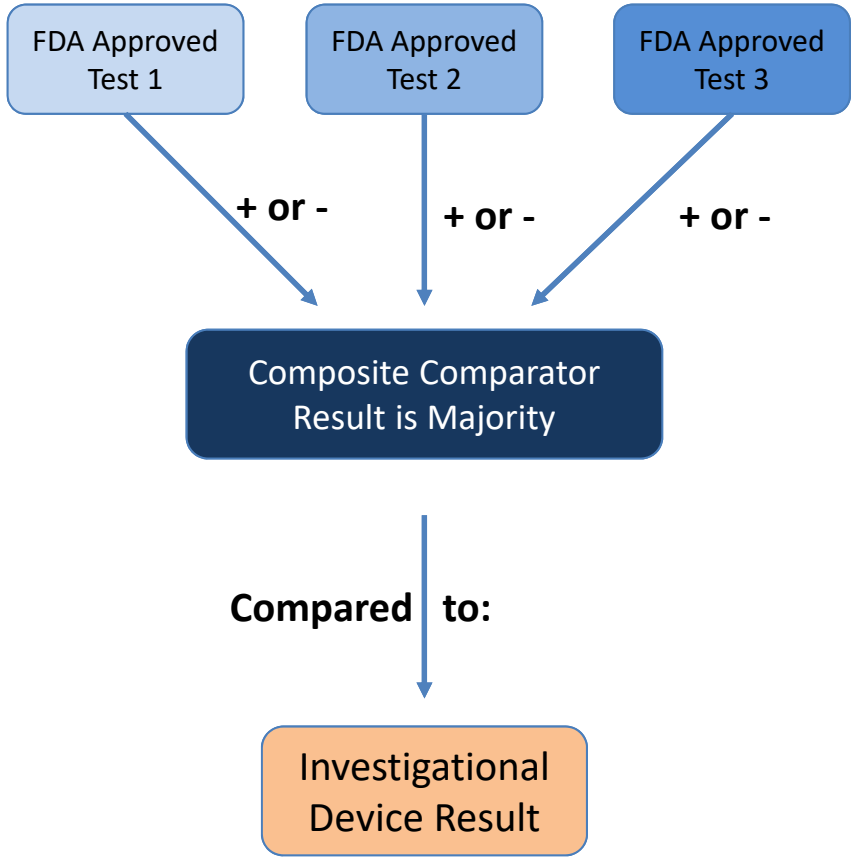
- There are five HR HPV devices that have been FDA approved
- Several of these devices have been clinically validated in the "real world" setting by real world evidence post approval
- Usage of HPV as a biomarker for cervical cancer is firmly established science

Discussion Topic: How could we begin to incorporate device to device comparisons for performance evaluation in premarket submissions?

4. Data Analyses to Support Indications

Proposal 1: Composite Comparator

- Colposcopy referral and histology adjudication would **NOT** be part of the clinical protocol.
- Investigational device performance evaluated against a composite comparator consisting of three FDA approved devices.
- All patients would be managed as per standard of care



4. Data Analyses to Support Indications

Proposal 2: Relative performance against a clinical endpoint comparator that includes histology

- The relative clinical performance between an investigational HR HPV device and an FDA-approved device against a clinical endpoint comparator that includes histology would be evaluated

4. Data Analyses to Support Indications

Proposal	Benefits	Risks
Composite Comparator	- May lead to more efficient clinical studies - Multiple devices can be assessed in a single patient - No colposcopy/biopsy referral against standard of care since histology is not part of comparator	- Evaluation of devices' common outputs only - Cannot assess clinical relevance of different device results - Will not have histology to confirm population includes women at highest risk

4. Data Analyses to Support Indications

Proposal	Benefits	Risks
Relative Performance	- Provides information about new and approved devices and clinical relevance of differences - Adds objectivity to evaluation; potential histologic variances can be normalized	- Can be performed only for common outputs between devices - May still need large study size (unless proposals during clinical study design discussion are acceptable)

Data Analyses to Support Indications

Panel Question 4

Please discuss whether the following types of data evaluations are acceptable for the assessment of safety and effectiveness for new HR HPV devices:

A. **Adoption of a molecular composite comparator method**
B. **Evaluation of relative performance against a clinical endpoint comparator**

Please discuss the benefits and risks to these approaches, as well as minimum acceptable performance criteria.

5. Clinical Endpoint Comparator

Challenges with utilizing purely histological clinical endpoint comparator:

- Lesions may have non-HR HPV etiologies, which may have less validity as a surrogate endpoint for cervical cancer
- **HPV vaccination:** A larger proportion of the remaining lesions are likely to be HR-HPV negative, affecting performance estimates of newer devices.
- **HPV vaccination:** The distribution of HPV genotypes causing lesions in the study will change depending on proportion of vaccinated/non-vaccinated women and herd immunity effects

Discussion Topic: What clinical endpoint comparator should be used to assess performance?

5. Clinical Endpoint Comparator

Proposal: Mixed histological/molecular comparator consisting of both histology and HPV typing

Benefits	Risks
- Informs the type of "false negative" results a device yields - Assess clinical performance for genotyping outputs that are unique to the investigational device - More accurately assesses a device's ability to detect lesions caused by vaccine targeted and non-targeted types	- May be difficult to determine what histology/genotype combination constitutes a "positive" comparator result since we do not know which lesions will ultimately progress to cervical cancer

5. Clinical Endpoint Comparator

Histology Diagnosis	HPV typing result using molecular comparator				
	High Risk HPV positive			Low Risk HPV positive	HPV Neg
	16, 18, 45, 31, 33, 52, 58	35, 39, 51, 56, 59, 68	66*		
NEG				NEG	NEG
CIN1				NEG	NEG
CIN2					
CIN3	POS	POS			
CIN3+	POS	POS			

**HPV 66 is considered separately; as of 2009, the International Agency for Research on Cancer (IARC) no longer classifies this type as "carcinogenic." However, most HR HPV devices still include detection for this genotype.*

Clinical Endpoint Comparator

Panel Question 5

If the panel recommends assessing HR HPV device performance against a clinical endpoint comparator:

A. **Is utilizing a mixed histological/molecular comparator acceptable?**

B. **If so, how should the combination of HPV result and histological diagnosis factor in when assigning "comparator positive" and "comparator negative" results?**

Panel Questions

Panel Question 1

Would the panel recommend one or a combination of the following three proposals to increase the number of women positive for CIN3+ and/or HR HPV in clinical studies:

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2. **Utilizing archived specimens**
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Thank you!

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