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The Onclarity Human Papillomavirus Trial: Design, methods, and baseline results

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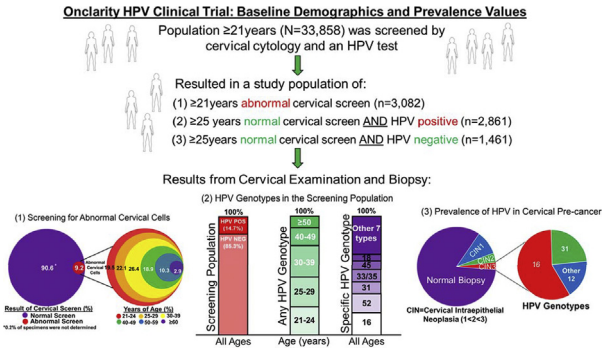
HIGHLIGHTS

- 33,858 subjects were enrolled during cervical cancer screening.
- Nine percent of the population had ≥ASC-US cytology.
- High-risk HPV was detected in about 15% of the overall population.
- Odds ratios for ≥ CIN3 to negative histology were significant for HPV 16, 18 and 31.

GRAPHICAL ABSTRACT



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ABSTRACT

Objectives. The baseline phase of the Onclarity trial was conducted to determine the screening performance of the Onclarity human papillomavirus (HPV) assay for detecting cervical cancer and precancer (≥CIN2) during triage of women ≥21 years with ASC-US cytology, as an adjunct test in women ≥30 years with normal cytology and for primary screening (HPV alone) in women ≥25 years.

Methods. 33,858 women ≥21 years were enrolled during routine clinic visits. All women with abnormal cytology, women ≥25 years that were high-risk HPV positive, and a random subset of women ≥25 years, negative by cytology and for HPV, were referred for colposcopy and cervical biopsy. Verification bias adjustment with 95% confidence intervals was applied.

Results. ASC-US prevalence was 5.8%. The overall HPV prevalence was 14.7%; for HPV 16, 18, and the 12 other HPV types it was 2.7%, 0.8%, and 11.2%, respectively. The prevalence of ASC-US and HPV was inversely proportional with age. The verification bias adjusted prevalence of ≥CIN2 and ≥CIN3 was 1.8% and 0.8%, respectively. Overall, five cases of cervical cancer were identified (all were HPV positive). The odds ratios associated with any HPV positive genotype, or with individual genotypes HPV 16, HPV 18, and HPV 31, for ≥CIN3, were statistically significant when compared to negative histology ($p < 0.0001$ for all).

Conclusions. This report provides demographic information, cytology findings, HPV genotype information, and histopathology for participants in the baseline phase of this trial and offers further evidence to support genotype-specific screening for cervical cancer and precancer.

Clinical Trial Registry URL: https://clinicaltrials.gov/ct2/show/NCT01944722.

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1. Introduction

Existing guidelines for early detection of cervical cancer or precancer in the USA include high-risk human papillomavirus (HPV) testing as part of routine screening [1]. Currently, HPV testing is recommended in three situations: (1) to determine which women ≥25 years with atypical squamous cells – undetermined significance (ASC-US) cytology need colposcopy, (2) cotesting with cytology when screening women ≥30 years, and (3) for primary screening in women ≥25 years [1,2]. Recently, the Food and Drug Administration (FDA) approved one HPV test [3] for primary screening in women ≥25 years using an algorithm incorporating both genotyping for HPV 16/18 together with cytology triage of selected HPV positive women [1,2]. Recent draft recommendations from the United States Preventative Services Task Force (USPSTF) recommend screening for women ≥30 years using either HPV primary screening or cytology alone. Cotesting is not recommend as it does not significantly increase detection of cervical intraepithelial neoplasia, grade 3 or worse (≥CIN3), compared to HPV testing alone [4]. These new recommendations suggest that HPV primary screening is likely to become widely adopted in the USA in the future. Moreover, many screening programs outside the USA have not adopted cotesting and are transforming directly from cytology-based testing to HPV primary screening [5,6].

Current HPV assays can vary in both methodology and clinical performance [7]. To be clinically valid, HPV assays should incorporate a panel of 13–15 high-risk HPV genotypes that have been defined by international consensus and cover approximately 95% of invasive cervical cancer [8]. When predicting risk for ≥CIN2, both in screening and triage populations, the threshold for a positive result associated with the current FDA-approved HPV assays are optimized for sensitivity while minimizing, as much as possible, any loss of specificity [7,9]. Currently, there are four FDA-approved HPV tests that detect 13–14 high-risk HPV genotypes [3,7,10–12], two of which, can individually detect HPV 16 and 18 [3,13], and one of which detects 16 plus pooled 18/45 [14]. A new FDA-approved assay, the Onclarity HPV assay (BD Diagnostics), can simultaneously detect 14 high-risk HPV types with individual genotyping for HPV 16, 18, 31, 45, 51, and 52; and detection of (33/58), (56/59/66), and (35/39/68) as three separate, pooled groups. A study of analytical and clinical performance indicates that this assay has a sensitivity for detection of ≥CIN2 comparable to the Hybrid Capture 2 HPV assay, with similar specificity [15].

This report provides the study design, methods, and demographics from the baseline phase of the Onclarity trial, which is a regulatory trial designed to obtain FDA-approval for use in the USA for high-risk HPV and genotyping for HPV 16, 18 and 45.

2. Materials and methods

2.1. Study design

This study was conducted in two phases: a baseline, and a three-year longitudinal phase; subject participation ends in December 2018. The baseline design and selection algorithm for women with colposcopy and biopsy, established by liquid based cytology (LBC) result, age, and HPV results are shown in Fig. 1.

Recruitment occurred consecutively during routine cervical cancer screening at 31 sites, across 17 states, between August 26, 2013 and June 12, 2015. Female subjects ≥21 years (women >65 years were included if they met USPSTF screening recommendations) were invited to join. Subjects were excluded (n = 171 total) if: not ≥21 years of age (n = 7), were enrolled into a cervical disease trial since 2007 (n = 37), were > 65 years (subject not following USPSTF

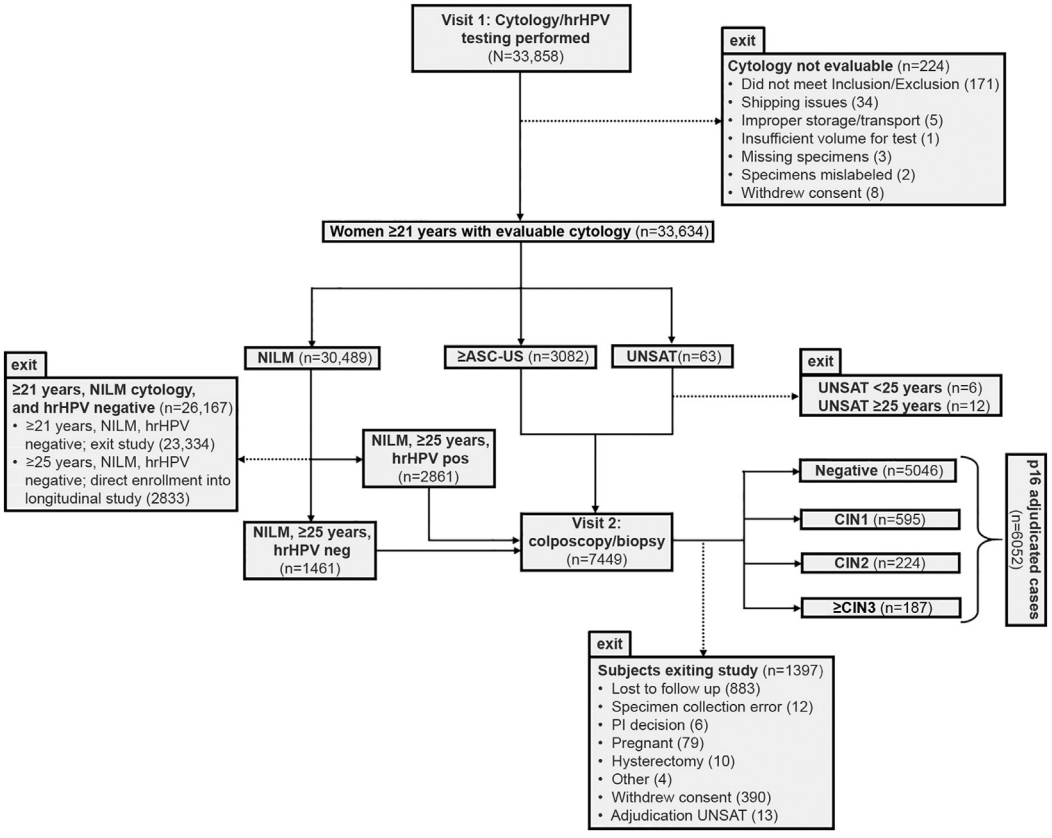

Fig. 1. Subject reconciliation during baseline enrollment and participation in this trial. Abbreviations: ≥ASC-US, atypical squamous cells of undetermined significance or greater; CIN, cervical intraepithelial neoplasia; hrHPV, high-risk human papillomavirus; NILM, negative for intraepithelial lesions or malignancies; neg, negative; p16, p16^{INK4A} protein; PI, principal investigator; pos, positive; UNSAT, unsatisfactory cytology.

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