HPV type attribution in high grade cervical lesions in the United States

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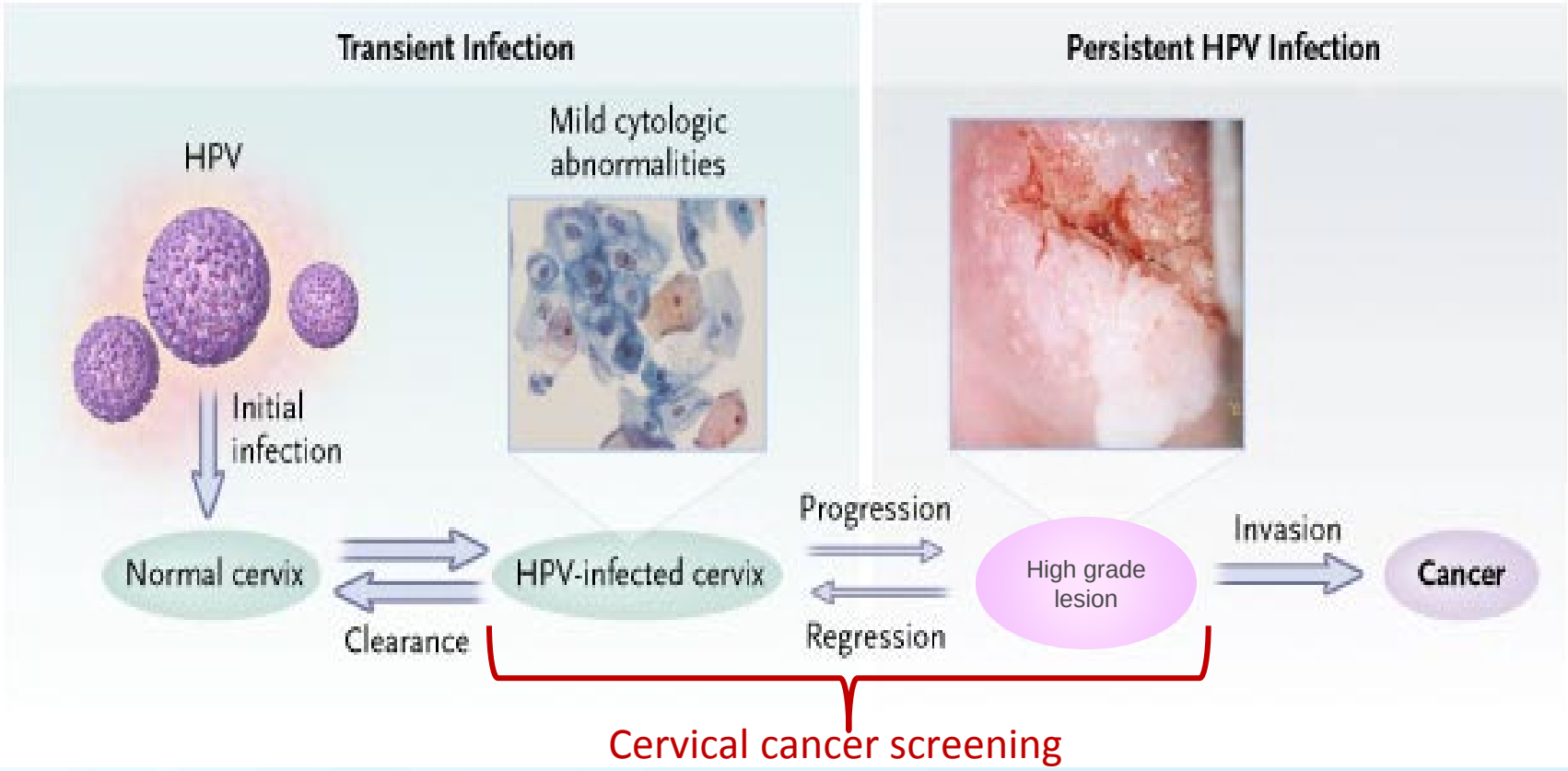
Overview

- Natural history of HPV-associated cervical disease
- Review data on HPV type distribution in high grade cervical lesions worldwide
- Methods to estimate individual HPV type attribution in high grade cervical lesions
- HPV type attribution in high grade cervical lesions in U.S. females

Natural history of cervical infection



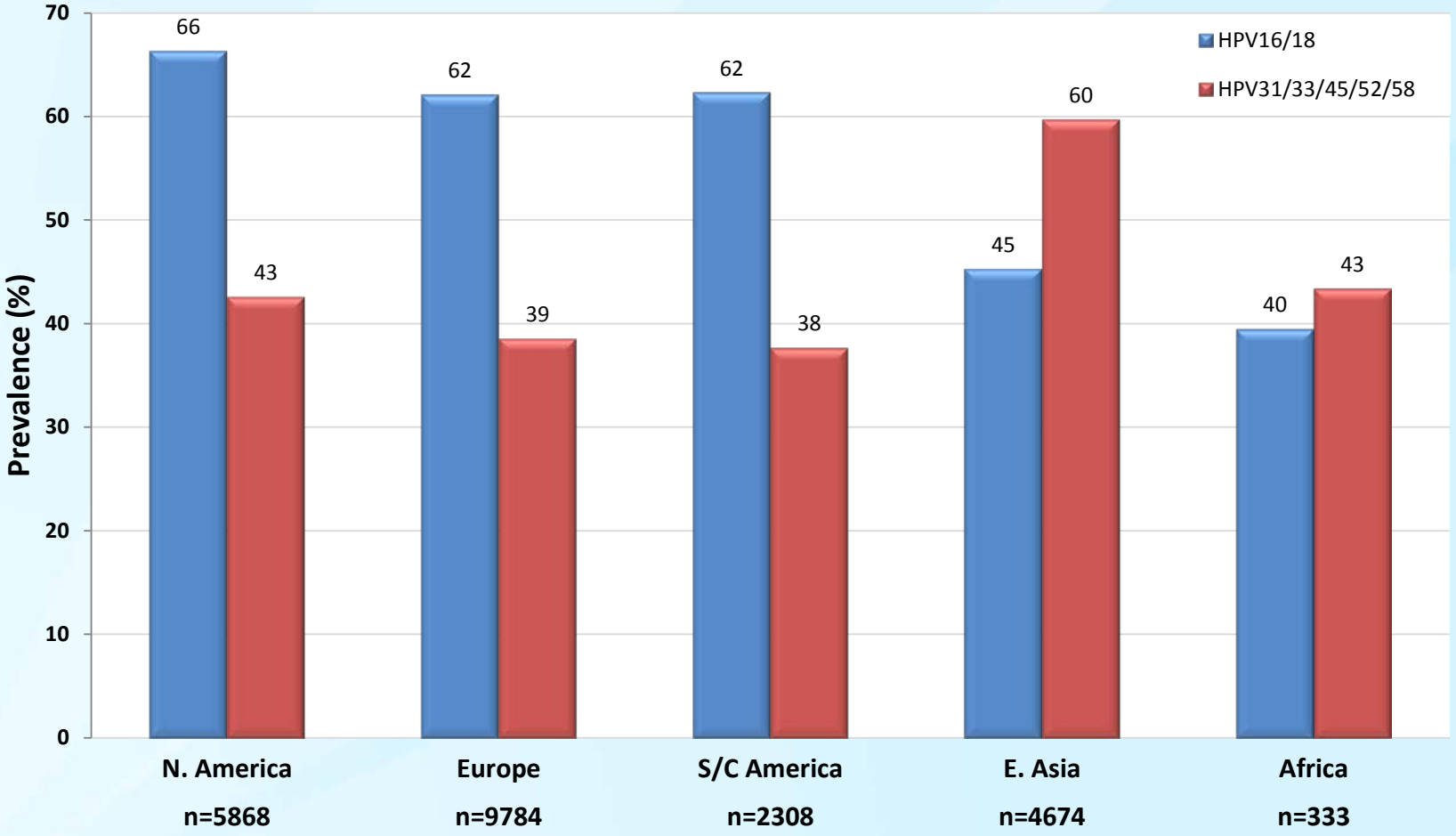
Wright and Schiffman. NEJM 2003

High grade cervical lesions

- Cervical intraepithelial neoplasia (CIN) grade 2 and 3 and adenocarcinoma in situ (AIS) (CIN2+)
- Associated with high-risk (oncogenic) HPV types
- About 30% progress to cervical cancer
- HPV 16 is most common type in CIN2/3 lesions;
  HPV 18 is most common type in AIS lesions
- Main endpoints in vaccine efficacy trials
- Used to monitor vaccine impact in some countries with established screening programs

Schiffman et al. Obs Gyn 2010; McCredie et al. Lancet Onc 2008; Massad et al. JLGTD 2013

HPV type detection in high grade cervical lesions by region



Guan et al. Int J Ca 2012

Objectives

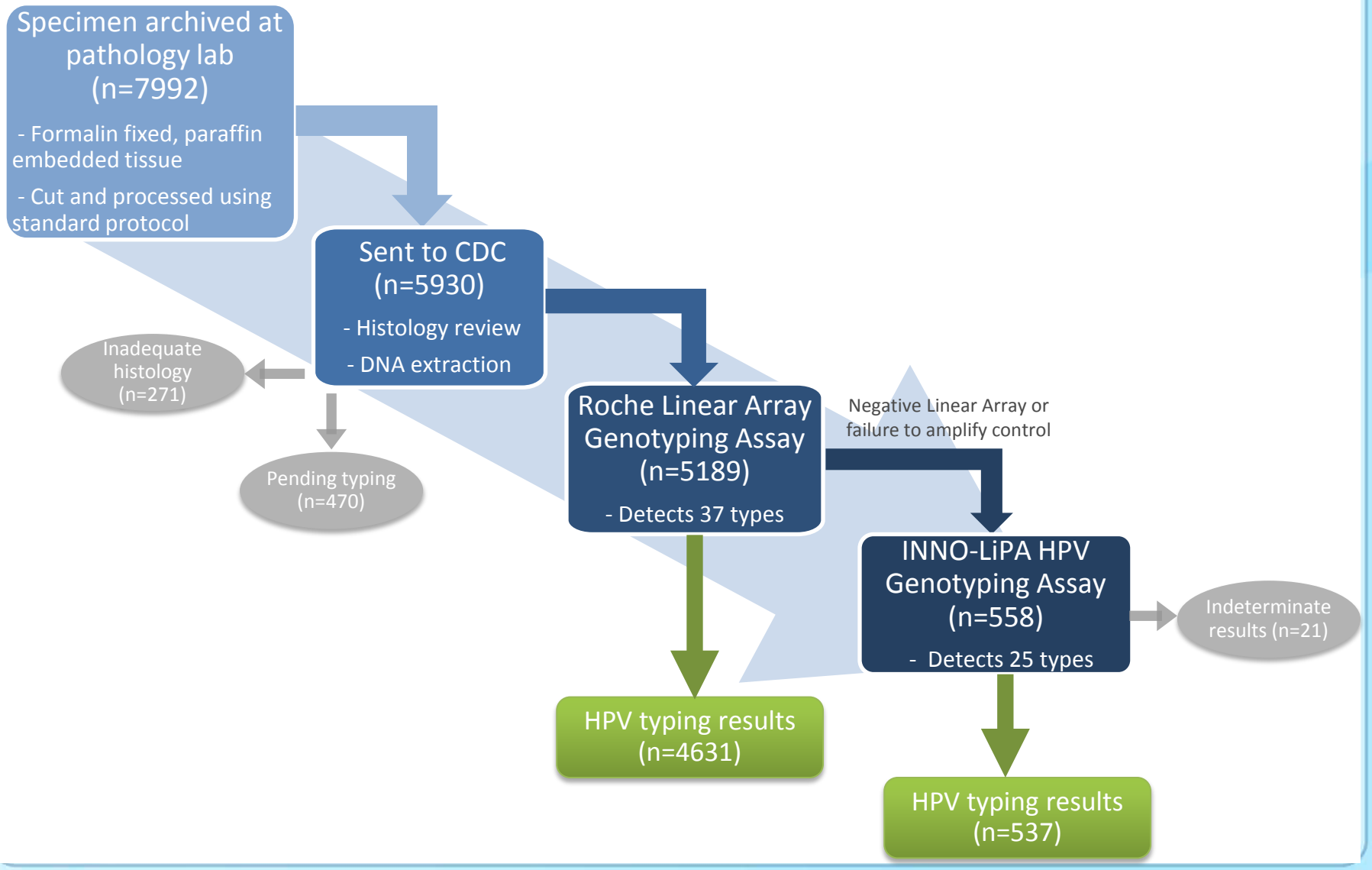
- Evaluate high-risk HPV type attribution to cervical intraepithelial neoplasia (CIN) 2 and 3 and adenocarcinoma in situ (AIS) (CIN2+)
  - U.S. women aged 21-39 years
  - Diagnosed from 2008 through 2011
- Examine HPV type attribution by age and race/ethnicity

HPV-IMPACT Project

- Population-based sentinel surveillance system established in 2008
- Monitor HPV vaccine impact on high grade cervical lesions and associated HPV types
- Five sites: California, Connecticut, New York, Oregon and Tennessee
- Histopathology laboratories serving catchment areas:
  - Report histologically confirmed CIN2+ diagnoses in adult residents of catchment (18 and older)
  - Submit archived diagnostic tissue from women under age 40 years for HPV DNA typing

Hariri et al. Ca Causes Control 2011

Laboratory methods



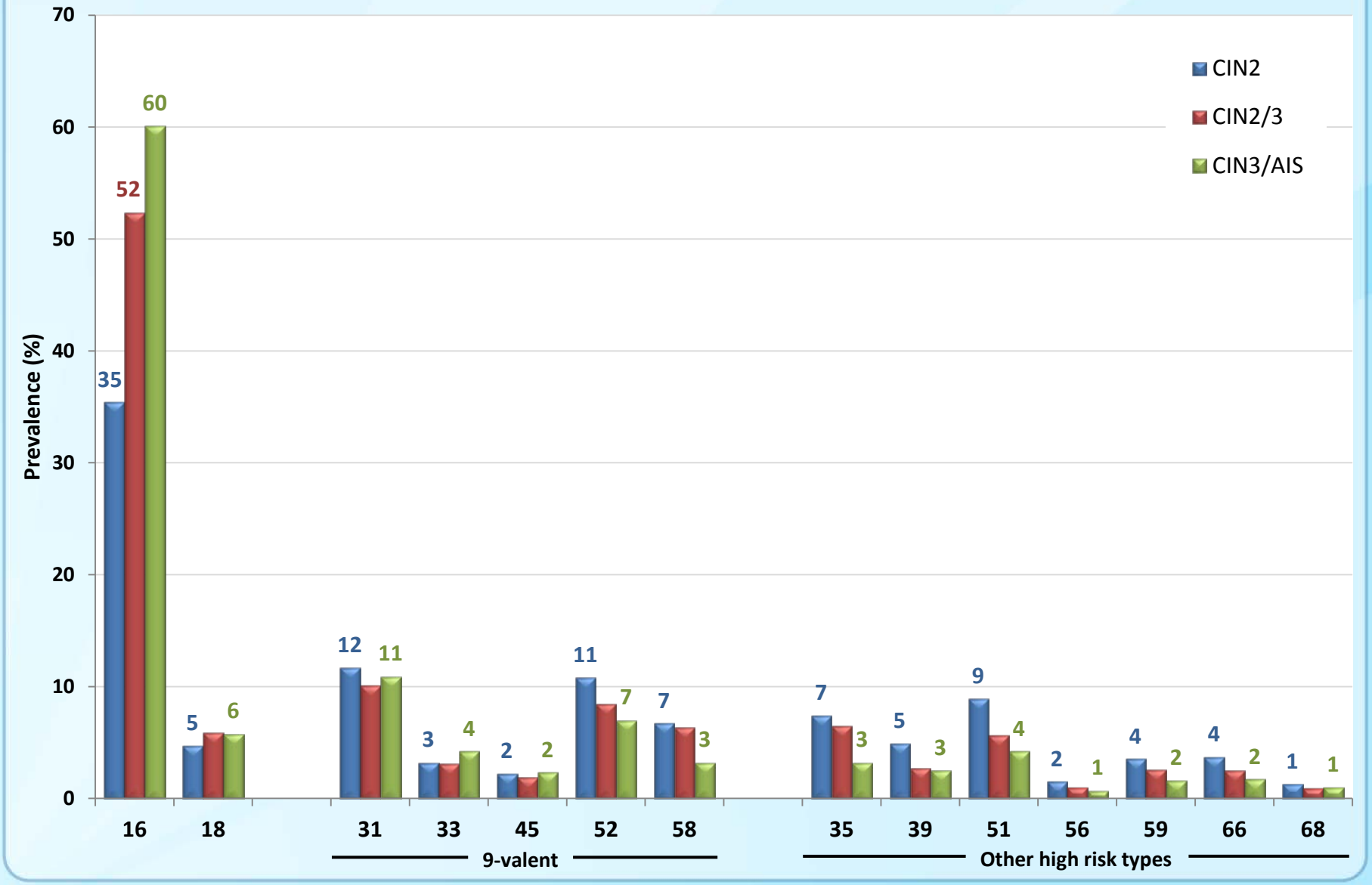
HPV typing results, 2008-2011

	CIN2+	
	N	(%)
Specimens typed	5189	
HPV positive	5028	(97.3)
Single type	3975	(79.1)
Multiple types	1053	(20.9)
16/18	2724	(52.7)
31/33/45/52/58	1616	(31.3)

HPV typing results by histologic grade, 2008-2011

	CIN2+	CIN2	CIN3/AIS
	N (%)	N (%)	N (%)
Specimens typed	5189	2402	1905
HPV positive	5028 (97.3)	2310 (96.7)	1857 (97.8)
Single type	3975 (79.1)	1766 (76.5)	1538 (82.8)
Multiple types	1053 (20.9)	544 (23.5)	319 (17.2)
16/18	2724 (52.7)	959 (40.1)	1252 (65.9)
31/33/45/52/58	1616 (31.3)	828 (34.6)	524 (27.6)

High-risk HPV type detection by histologic grade



Type attribution in cervical lesions with multiple HPV types

- Presence of single HPV type in CIN2+ lesions is considered to indicate causal association
- Multiple HPV types detected in ~20% of CIN2+ lesions
- Role of each HPV type in co-infected lesions less clear
- Different methods used to attribute individual HPV types or groups of types to cervical lesions
- Used to evaluate potential impact of HPV vaccines

HPV type attribution methods

Hierarchical

- Based on single type frequency in each disease grade (CIN2, CIN2/3, CIN3/AIS)
- Case attributed to most oncogenic type (16 or 18 regardless of other types)

Example: Hierarchical attribution of CIN3 specimen with HPV 16 and 31

HPV 16 = 1

HPV 31 = 0

Total contribution of specimen = 1

Proportional*

- Weight types proportional to the type frequency in single infections in each disease grade (proportion of A as single type ÷ (proportion of A as single type + proportion of B as single type + proportion of C …))

Example: Proportional attribution of CIN3 specimen with HPV 16 and 31

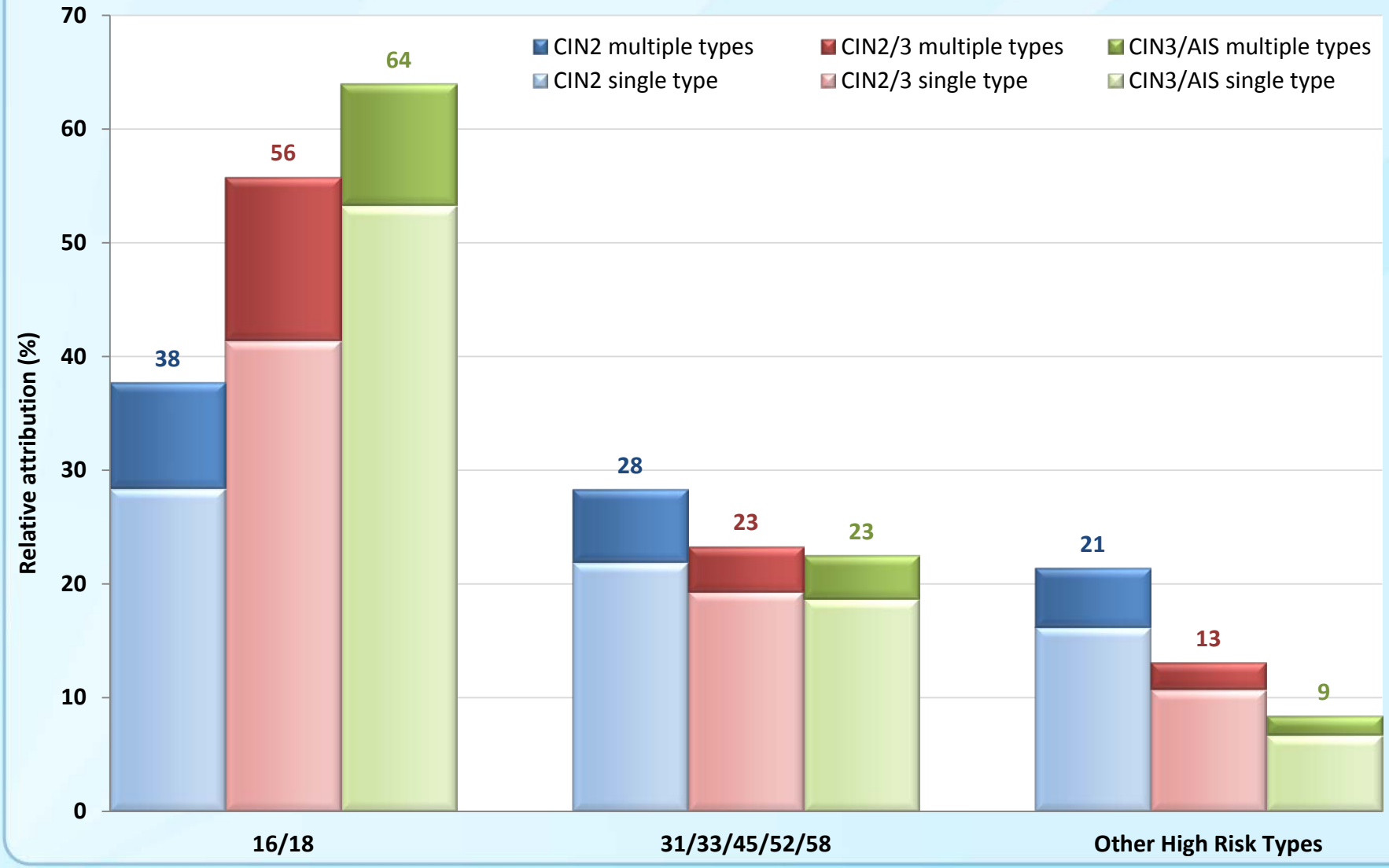
HPV 16 = 61.05 ÷ (61.05 + 9.10) = 0.87

HPV 31 = 9.10 ÷ (61.05 + 9.10) = 0.13

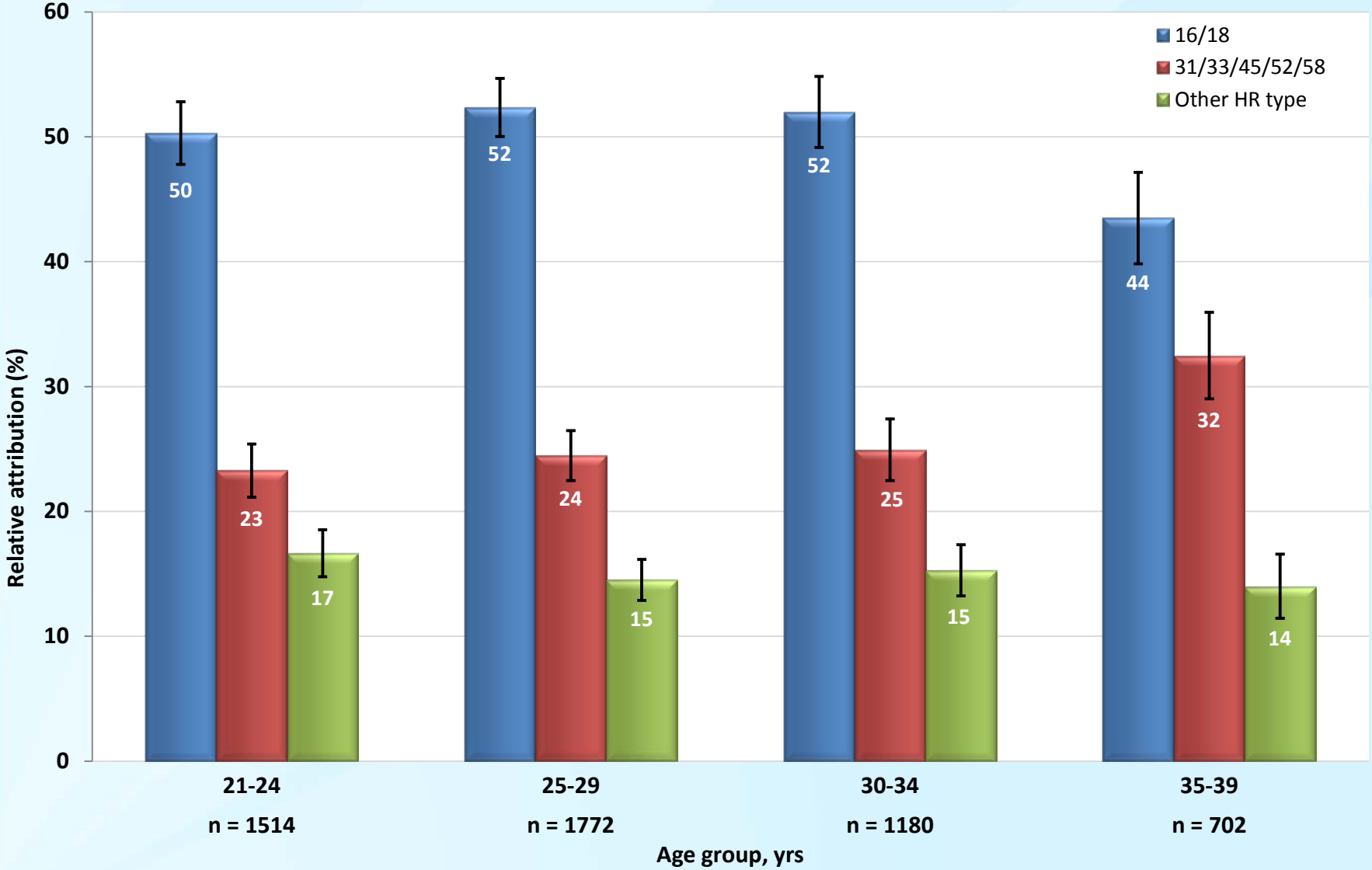
Total contribution of specimen = 0.87 + 0.13 = 1

*Used proportional attribution as there was very little difference in the 2 methods

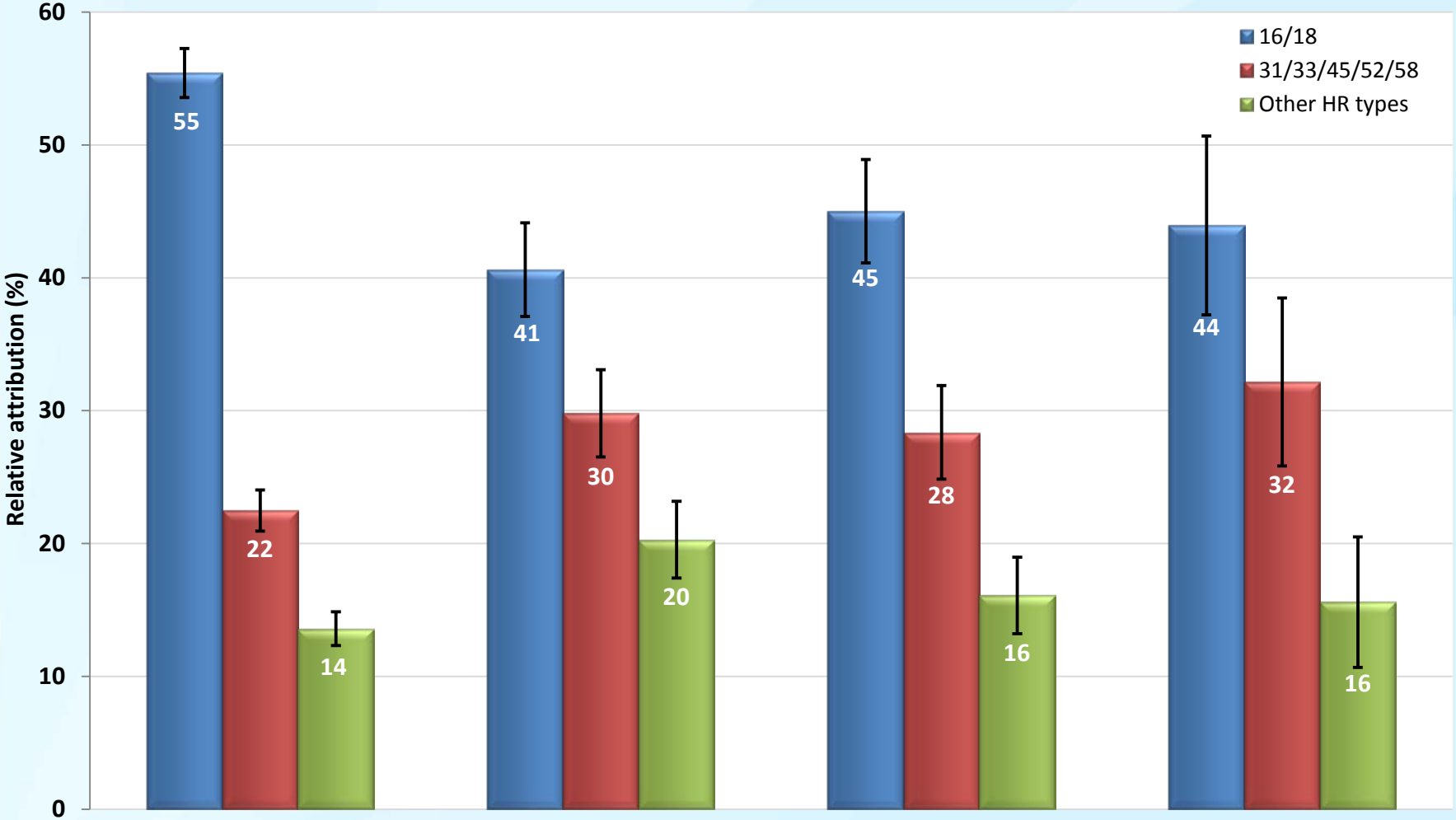
Proportional HPV type attribution by histologic grade



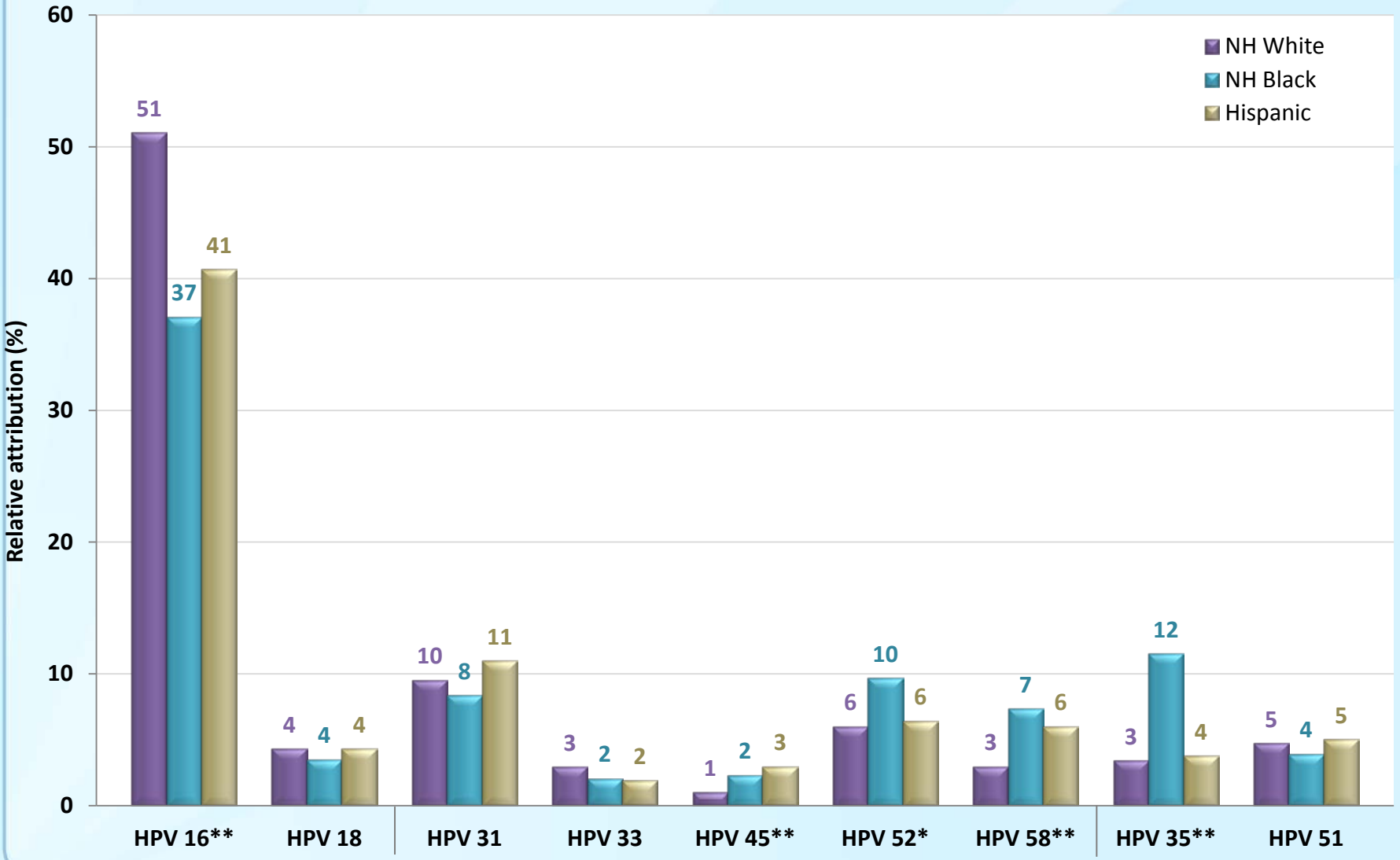
Proportional HPV type attribution in CIN2+ lesions by age group



Proportional HPV type attribution of CIN2+ lesions by race/ethnicity



High-risk HPV type attribution in CIN2+ lesions by race/ethnicity



* p<0.01
**p<0.001

Summary

- 50% CIN2+ lesions attributable to HPV16/18
  - Range 40% in CIN2 to >60% in CIN3/AIS
- Additional 25% of CIN2+ lesions attributable to HPV31/33/45/52/58 included in the candidate 9-valent vaccine
- Higher proportion of lesions due to HPV16/18 in women under 35 years
  - Stronger carcinogens
  - Faster progression to disease
- Highest proportion of CIN2+ lesions across all racial/ethnic groups attributable to HPV16/18
- Higher proportion of CIN2+ lesions attributable to HPV16/18 in non-Hispanic white women compared to other racial/ethnic groups
  - Reasons for differences are not clear but may be due to differences in underlying prevalence of HPV types or screening and treatment

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