Swedish experience with extended genotyping

Miriam Elfström, PhD

Center for Cervical Cancer Elimination, Karolinska University Hospital & Karolinska Institutet

Regional Cancer Center of Stockholm-Gotland

Center for Cervical Cancer Elimination

Karolinska Institutet

KAROLINSKA UNIVERSITY HOSPITAL

I have no conflicts of interest to declare

My perspective:

- Chair of the Swedish National Working Group for Cervical Cancer Prevention
- Head of Unit, Center for Cervical Cancer Elimination, Karolinska University Hospital

Increasingly rapid programmatic developments
Example of changes in an established screening context

1967
- Program initiated, for 50 years the program was based on set intervals and cytological analysis

2015
- HPV-based screening for women over 30 (cytology ages 23-29)
  - Evidence from the European trials (Ronco et al., Lancet 2014)

2018
- Partial-genotyping recommended with shorter follow-up for HPV 16/18 positives among women over 30
  - Evidence from analyses of interval cancers, protective effect of cytology decreased (later published in Edvardsson et al., Acta Cyt 2021; Wang et al., IJC 2024)

2022
- HPV-based screening with extended genotyping for all women in the program, ages 23-70
  - Evidence from analyses of screening age <30 where PPV of cytology decreased in vaccinated populations (Lei et al., BJC 2020)

Implementation context

- Population-based organized cervical screening
  - Individual invitations with annual reminders for non-attenders, results in high coverage over a screening interval
- Women ages 23-70 targeted for screening
  - 5-year intervals for HPV negative women ages 23-49
  - 7-year intervals for HPV negative women ages 50-70
- HPV-based screening with extended genotyping for all ages as of 2022, primary self-sampling can be used as an alternative to clinician-based sampling
  - No change in recommendations for vaccinated cohorts, yet
- National recommendations and clinical guidelines with regional implementation

Distribution of types in cancer cases, by age and screening attendance (before vaccination)

Table 1. Age-specific HPV type distribution of invasive cervical cancer cases by screening status in last 10 years.

	Age <30 years		Age 30–39 years		Age 40–49 years		Age 50–64 years		Age > = 65 years	
	N	%[d]	N	%[d]	N	%[d]	N	%[d]	N	%[d]
Cases that were **screened** in the last 10 years										
HPV 16	81	63.3	305	59.2	208	48.3	197	47.0	70	42.7
HPV 18	34	26.6	121	23.5	98	22.7	73	17.4	17	10.4
HPV 45	4	3.1	36	7.0	39	9.0	40	9.5	4	2.4
Intermediate oncogenic types[a]	8	6.3	30	5.8	29	6.7	29	7.0	24	14.6
Lower oncogenic types[b]	1	0.8	9	1.8	21	4.9	13	3.0	5	3.0
Oncogenic HPV negative[c]	0	0.0	14	2.7	36	8.4	67	16.0	44	26.8
Total	128	100	515	100	431	100	419	100	164	100
Cases that were **unscreened** in the last 10 years										
HPV 16	29	74.4	69	69.0	80	58.0	135	54.7	297	44.4
HPV 18	6	15.4	15	15.0	26	18.8	29	11.7	51	7.6
HPV 45	3	7.7	6	6.0	10	7.2	24	9.7	31	4.6
Intermediate oncogenic types[a]	1	2.6	6	6.0	9	6.5	26	10.4	105	15.6
Lower oncogenic types[b]	0	0.0	2	2.0	3	2.1	14	5.6	51	7.4
Oncogenic HPV Negative[c]	0	0.0	2	2.0	10	7.2	19	7.7	134	20.0
Total	39	100	100	100	138	100	247	100	669	100

Wang et al., PLoS Med, 2023

Impact numbers – number needed to screen and number needed to follow-up, by age

- What types should we screen for and at what age?

- Where do resources make the most difference in follow-up?

Table 4. Impact numbers—number needed to screen and follow-up to prevent or detect one cervical cancer case by HPV type and age group at screening (CIs are presented in Fig 6 and S1B Table).

	To prevent one case[a]				To detect one case[b]			
Age at screening	**Age 23–30 years**	**Age 31–40 years**	**Age 41–50 years**	**Age 51–60 years**	**Age 23–30 years**	**Age 31–40 years**	**Age 41–50 years**	**Age 51–60 years**
Numbers needed to **screen**								
HPV 16	4,747	4,808	4,959	5,114	24,518	11,409	20,674	25,527
HPV 18	50,908	14,811	23,522	22,367	49,036	29,589	45,342	71,477
HPV 45	62,546	36,764	25,137	43,635	261,524	95,775	107,841	127,637
Intermediate oncogenic types[c]	52,212	53,493	30,049	15,460	261,524	125,498	128,714	170,182
Lower oncogenic types[d]	221,345	64,862	52,585	47,338	1,176,857	330,859	221,674	297,819
Numbers needing **follow-up**								
HPV 16	289	142	68	58	1,491	336	285	292
HPV 18	1,204	137	123	87	1,160	274	237	278
HPV 45	2,007	570	236	360	8,393	1,486	1,011	1,054
Intermediate oncogenic types[c]	4,586	2,297	780	353	22,972	5,388	3,343	3,887
Lower oncogenic types[d]	16,825	2,533	1,242	982	89,457	12,920	5,237	6,178

[a]Preventable cases in each age group are defined as the difference between estimated number of cases in the next age group in the pseudo-scenario that all women were unscreened and estimated number of cases in the next age group in the pseudo-scenario that all women were screened. For age group 51–60, the preventable cases are defined as all estimated of cases at ages 61–80, regardless of further screening history.

[b]Detected cases in each age group are defined as estimated number of cases in this age group in the pseudo-scenario that all women were screened.

[c]Intermediate oncogenic types include HPV 31, 33, 52, 58 (etiological fraction >2% according to IARC's data [4]).

[d]Lower oncogenic types include HPV 35, 39, 51, 56, 59, 66, 68 (etiological fraction <2% according to IARC's data [4]).

CI, confidence interval; HPV, human papillomavirus; IARC, International Agency for Research on Cancer.

Wang et al., PLoS Med, 2023

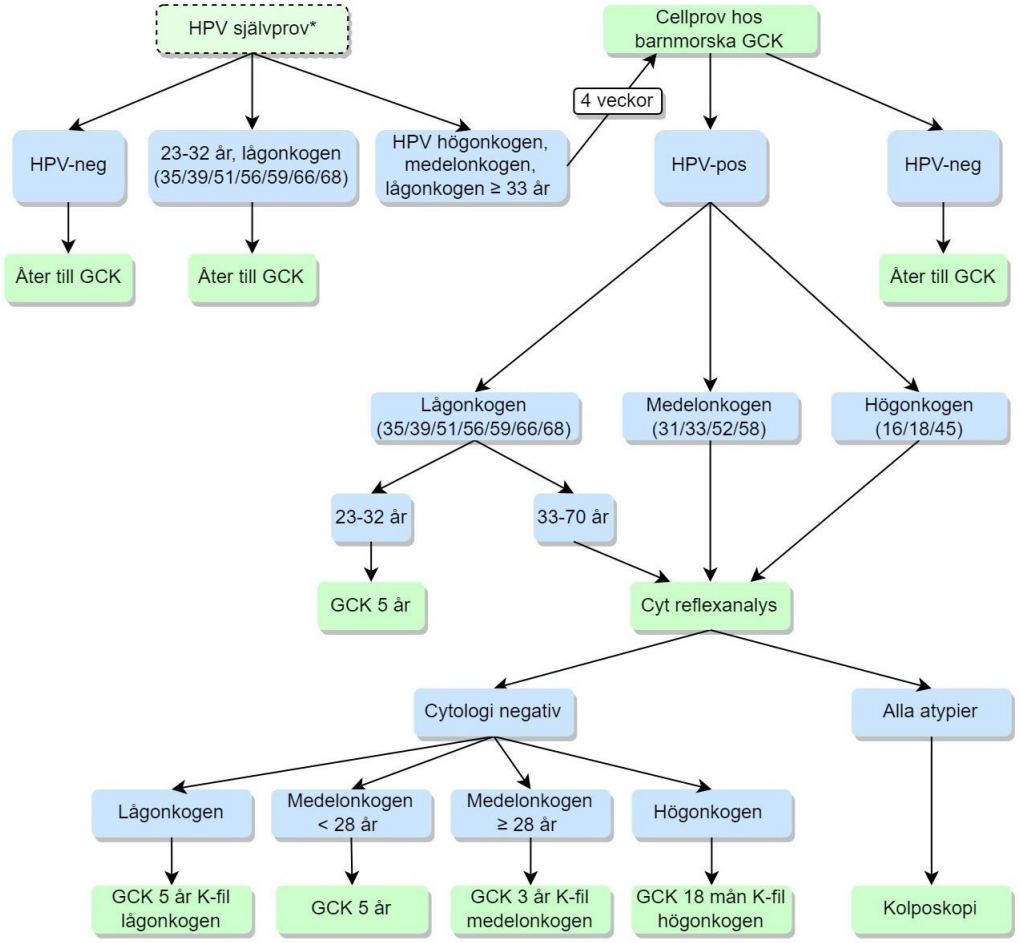
Risk-stratified screening according to age and HPV type

Follow-up of HPV positivity is determined by **age and type-group**

- HPV 16, 18, 45 (high oncogenicity, vaccine types) - reflex testing with cytology from age 23
  - Cytology positive to colposcopy
  - Cytology negative to repeat testing after 18 months
- HPV 31, 33, 52, 58 (medium oncogenicity, vaccine types) – reflex testing with cytology from age 23
  - Cytology positive to colposcopy
  - Cytology negative
    - Age <28 – new sample after 5 years
    - Age >28 – new sample after 3 years
- HPV 35, 39, 51, 56, 59, 66, 68 (low oncogenicity, non-vaccine types) – reflex testing with cytology from age 33
  - Cytology positive to colposcopy
  - Cytology negative to repeat testing after 5 years

Flow for triage of HPV positive screening samples

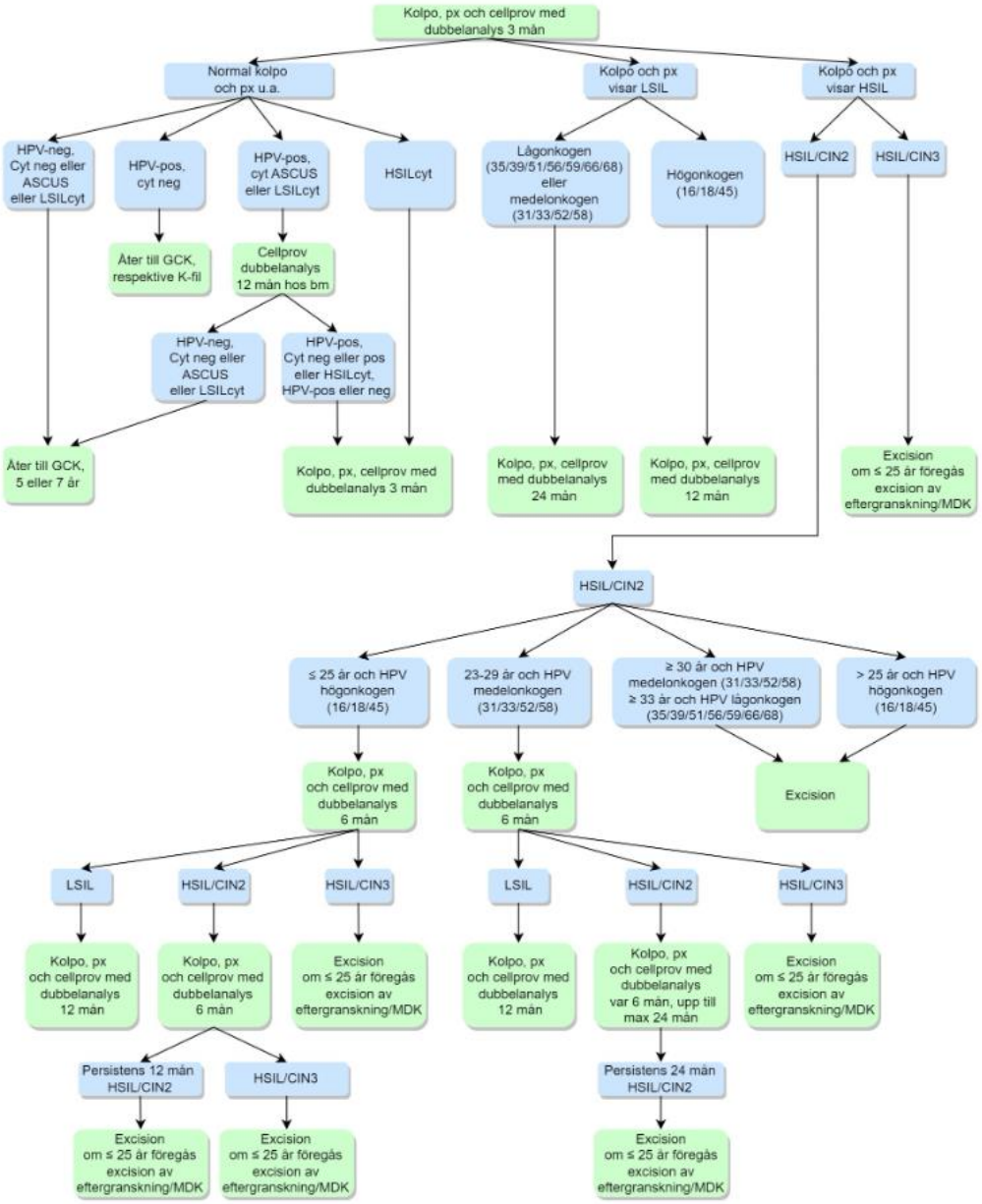
- This flow-chart applies for routine screening
- Long-term non-attenders that participate with self-sampling are referred directly to colposcopy
  - To avoid loss to follow-up by requiring multiple visits
  - And because the risk for underlying disease in this group is higher
    - In the direct-send arm of the Stockholm self-sampling trial, the PPV for CIN2+ among women with HPV infection was 47.2%



*När kvinnan har valt självprovtagning.

Use of genotyping in clinical work-up and treatment

- Referral to colposcopy and biopsy with persistence - age- and type-group defined (high, medium, low-oncogenicity)
  - Biopsy confirmed LSIL
    - High oncogenic – repeat after 12 months
    - Low/medium – repeat after 24 months, investigating if this can be a repeat test instead of colposcopy
  - Follow-up after biopsy confirmed HSIL in women under 33 is stratified by HPV type-group
    - Ages <25 and high oncogenicity and 23-29 and medium oncogenicity – repeat after 6 months and if still persistent then excisional treatment
    - Ages >25 years and high oncogenicity HPV then excisional treatment
    - Low oncogenic types not triaged until age 33
  - More ambitious follow-up for AGC detected in screening and confirmed in follow-up biopsy
- Prioritization based on age, severity of the lesion, and HPV type important for the impact of the program and resource use
  - Avoid overtreatment among youngest women (Wiik et al., BMC Med., 2022)
  - Consider differences in regression/progression based on HPV type (Kylebäck et al., AJOG 2022)
  - Insure more rapid follow-up by reserving colposcopy resources for those with highest risk



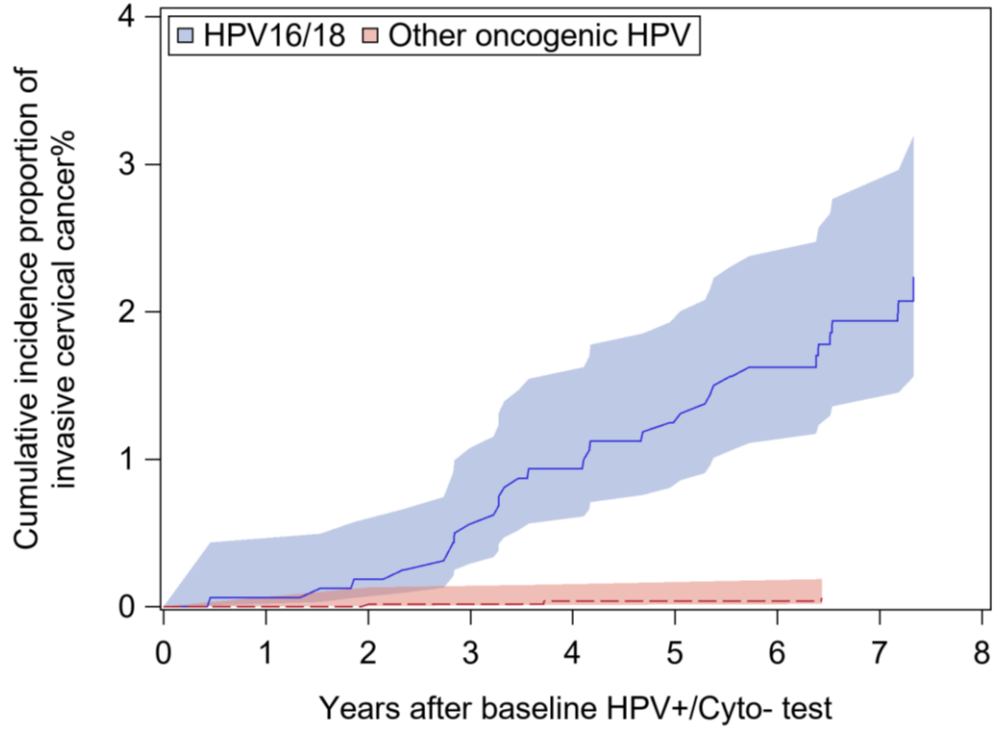
https://kunskapsbanken.cancercentrum.se/diagnoser/livmoderhalscancerprevention/vardprogram/kolposkopi-och-utredning-av-avvikande-cellprov/

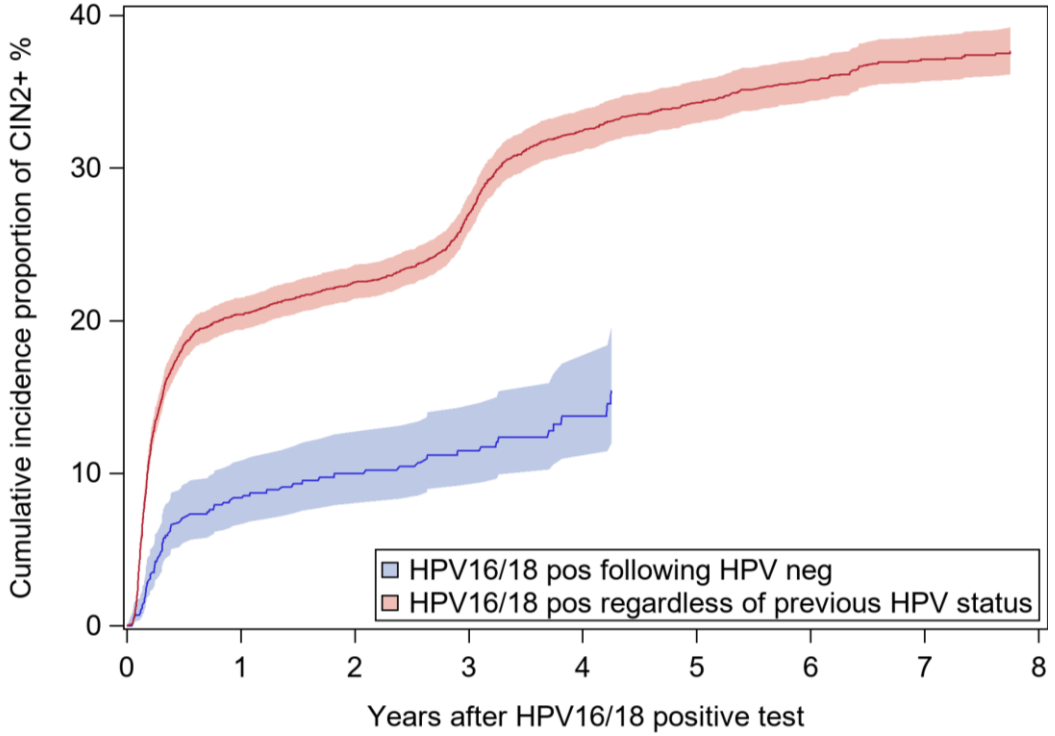
Flow for follow-up of HPV positive ASCUS/LSIL

- Increasingly complex follow-up schemes appealing from a risk-management perspective
- Balance with feasibility of translation into practice and updating as new evidence emerges

Where are we headed?
Further optimization of the guidelines for HPV 16/18 is proposed

Follow-up of randomized health services trial of HPV-based screening implementation in women ages 30+ in Stockholm





Wang et al., under preparation; Elfström et al., PLoS Med 2021

Where are we headed?

- Further optimization of screening needed when the risk in population decreases (impact of vaccination)
- 98% decline in HPV16 prevalence and a 99% decline in HPV18 prevalence among the 2000-born compared to the 1984-born

	Birth Cohort	HPV16	HPV18	HPV31	HPV45	HPV51	HPV52	HPV33/58	HPV35/39/68	HPV56/59/66
No Vaccination	1970	1.82	0.64	2.37	1.18	1.27	1.64	0.91	3.00	3.64
	1971	2.27	0.59	1.01	0.67	1.09	1.01	1.68	3.02	3.86
	1972	2.10	0.55	1.45	0.95	0.50	1.30	1.45	3.66	3.06
	1973	1.99	0.48	1.43	0.91	0.65	1.43	0.95	2.12	2.52
	1974	2.13	0.64	1.00	1.29	1.29	1.57	1.00	1.65	2.89
	1975	2.17	0.58	1.62	1.08	0.67	0.96	0.75	2.54	2.25
	1976	2.07	0.97	1.35	0.89	0.68	1.27	1.06	2.79	1.95
	1977	2.07	0.75	1.85	1.50	0.62	1.41	1.02	2.78	2.34
	1978	2.48	0.41	1.69	0.83	0.87	1.36	1.16	2.69	2.27
	1979	2.50	0.70	1.56	1.25	0.86	0.78	0.98	2.19	2.62
	1980	2.39	0.60	1.94	1.08	0.75	1.27	1.08	2.83	2.87
	1981	2.56	0.67	1.50	0.94	0.63	1.50	1.02	2.13	2.32
	1982	2.35	0.74	1.92	0.74	1.02	1.25	0.82	2.35	2.62
	1983	1.82	0.75	1.22	0.89	0.72	1.29	1.25	3.04	3.04
	1984	2.61	0.84	2.32	1.09	0.47	1.20	1.42	2.98	2.40
	1985	2.29	0.69	1.80	1.11	1.01	1.42	1.28	2.71	2.81
	1986	3.07	0.56	2.05	1.13	0.92	1.59	1.41	2.44	2.65
	1987	3.33	0.75	1.92	1.14	1.14	1.30	1.27	3.20	2.94
	1988	3.12	0.96	2.10	1.02	0.74	1.91	1.20	2.90	2.84
	1989	2.74	0.74	2.14	1.77	1.09	2.17	1.66	2.97	3.71
	1990	2.90	0.78	2.07	1.56	1.36	2.12	1.95	4.38	3.50
	1991	2.92	0.79	3.04	2.10	1.67	2.49	2.33	4.06	4.11
	1992	2.67	0.48	2.47	2.29	1.71	3.22	2.64	5.41	5.36
Catch-up vaccination	1993	2.41	0.72	2.15	2.36	2.17	3.69	2.92	4.70	4.58
	1994	2.63	0.48	2.50	1.46	1.43	2.73	2.69	4.25	4.63
	1995	1.90	0.71	2.07	1.80	2.17	3.70	2.95	5.33	5.26
	1996	1.85	0.69	1.88	2.48	2.32	4.42	3.61	5.52	5.64
	1997	2.58	0.36	3.02	2.94	2.25	5.19	4.43	6.76	6.92
	1998	2.11	0.31	2.04	1.84	2.38	4.84	4.34	5.49	7.57
School-based vaccination	1999	0.73	0.20	1.62	2.07	3.02	5.09	4.46	6.23	7.83
	2000	0.54	0.09	1.28	2.02	3.19	5.55	4.93	6.89	8.15

Gray et al., available as pre-print https://ssrn.com/abstract=4962462

Where are we headed?

Among school-based HPV vaccination birth cohorts (ages 23-25 currently) compared to pre-vaccination cohorts

- NNS increased to 229,377 for HPV16
- NNS increased to 773,085 for HPV18

Gray et al., pre-print

Table 4. Impact numbers—number needed to screen and follow-up to prevent or detect one cervical cancer case by HPV type and age group at screening (CIs are presented in Fig 6 and S1B Table).

	To prevent one case[a]				To detect one case[b]			
Age at screening	**Age 23–30 years**	**Age 31–40 years**	**Age 41–50 years**	**Age 51–60 years**	**Age 23–30 years**	**Age 31–40 years**	**Age 41–50 years**	**Age 51–60 years**
Numbers needed to **screen**								
HPV 16	4,747	4,808	4,959	5,114	24,518	11,409	20,674	25,527
HPV 18	50,908	14,811	23,522	22,367	49,036	29,589	45,342	71,477
HPV 45	62,546	36,764	25,137	43,635	261,524	95,775	107,841	127,637
Intermediate oncogenic types[c]	52,212	53,493	30,049	15,460	261,524	125,498	128,714	170,182
Lower oncogenic types[d]	221,345	64,862	52,585	47,338	1,176,857	330,859	221,674	297,819
Numbers needing **follow-up**								
HPV 16	289	142	68	58	1,491	336	285	292
HPV 18	1,204	137	123	87	1,160	274	237	278
HPV 45	2,007	570	236	360	8,393	1,486	1,011	1,054
Intermediate oncogenic types[c]	4,586	2,297	780	353	22,972	5,388	3,343	3,887
Lower oncogenic types[d]	16,825	2,533	1,242	982	89,457	12,920	5,237	6,178

[a]Preventable cases in each age group are defined as the difference between estimated number of cases in the next age group in the pseudo-scenario that all women were unscreened and estimated number of cases in the next age group in the pseudo-scenario that all women were screened. For age group 51–60, the preventable cases are defined as all estimated of cases at ages 61–80, regardless of further screening history.

[b]Detected cases in each age group are defined as estimated number of cases in this age group in the pseudo-scenario that all women were screened.

[c]Intermediate oncogenic types include HPV 31, 33, 52, 58 (etiological fraction >2% according to IARC's data [4]).

[d]Lower oncogenic types include HPV 35, 39, 51, 56, 59, 66, 68 (etiological fraction <2% according to IARC's data [4]).

CI, confidence interval; HPV, human papillomavirus; IARC, International Agency for Research on Cancer.

Wang et al., PLoS Med, 2023

Concluding thoughts

- Significant differences in type-specific risk for cervical cancer has been mapped and known

- Applying this information in real-life screening is still an area of significant, needed development
  - Changing risk in population
  - More strategic use of resources, limit harms
  - Translate detailed information on risks into clear stratifications and rational logistics
  - Support programs and associated clinicians in risk communication

- Work does not stop here - monitoring and evaluation to examine risks over time, the impact of vaccination, and protection through multiple rounds of HPV-based screening
  - Program will not be static, one-size-fits-all anymore
  - Risk-based and continuously updated

Thank you for your attention

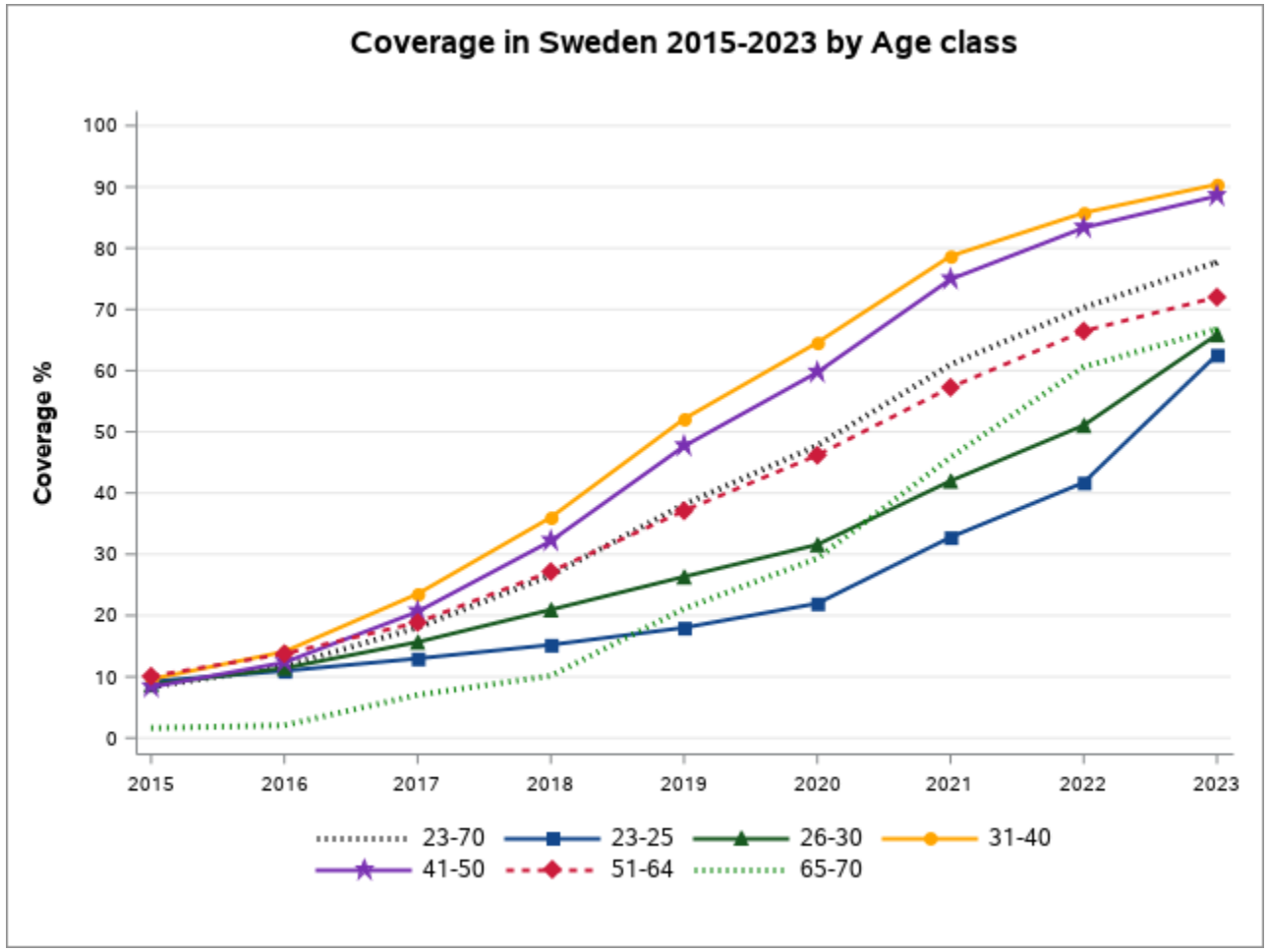
miriam.elfstrom@regionstockholm.se | miriam.elfstrom@ki.se

https://nkcx.se/index_e.htm

https://kunskapsbanken.cancercentrum.se/diagnoser/livmoderhalscancerprevention/vardprogram/

https://www.socialstyrelsen.se/kunskapsstod-och-regler/regler-och-riktlinjer/nationella-screeningprogram/slutliga-rekommendationer/livmoderhalscancer/

NKCx – monitoring of test coverage by age (HPV only)



NKCx – monitoring of test coverage by region (HPV only)