AUSTRALIA: THE RESEARCH AND POLICY RESPONSE

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Australian Centre for the Prevention of Cervical Cancer

VCS Pathology

Population Health

Digital Health

Australian HPV Reference Laboratory

C4 NHMRC Centre of Research Excellence in Cervical Cancer Control

ROSE FOUNDATION · EMPOWERS WOMEN · ELIMINATES CERVICAL CANCER

DISCLOSURES

Compass is a partnership between the Daffodil Centre (Cancer Council NSW & University of Sydney) and the Australian Centre for Prevention of Cervical Cancer (ACPCC), which is a government-funded not-for-profit charity. Compass is supported by the Australian government. The ACPCC has received equipment and a funding contribution from Roche Molecular Diagnostics.

compass
Future directions in cervical screening

A JOINT INITIATIVE OF ACPCC AND CANCER COUNCIL NSW

Australian Centre for the Prevention of Cervical Cancer

The Daffodil Centre
A partnership between Cancer Council and The University of Sydney

COMPASS TRIAL INTRODUCTION

A number of randomised controlled trials (RCTs) of primary HPV screening vs. cytology screening have been conducted in unvaccinated populations.

However, it is now 15 years since HPV vaccines were first introduced, and young vaccinated cohorts will increasingly be entering screening programs worldwide.

No prior RCT has directly assessed the relative performance of cervical screening approaches in a population with substantial uptake of HPV vaccine.

Dual-stained cytology (DS) for p16/Ki67 is potentially a more effective triage than liquid-based cytology (LBC) after primary HPV screening, but data from HPV-vaccinated populations is limited.

WHY IS COMPASS IMPORTANT?

What we know:

- HPV testing is more effective at detecting CIN2/3 in an initial round of screening than cervical cytology[1]
- Because these detected lesions are then treated, this has been shown to lead to long term protection against development of CIN3+ disease in subsequent rounds of screening.
- HPV screening provides greater protection against invasive cervical cancer compared to cytology.[2]

Sources:
1. Arbyn M et al. Vaccine 2012
2. Ronco et al., Lancet 2014

WHY IS COMPASS IMPORTANT?

What we **don't** know:

- Will this improved performance for HPV vs. cytology screening be sustained (or even improved) in a vaccinated population?

- How should HPV positive women be triaged, and will triage test performance be the same in a vaccinated population compared to an unvaccinated population?

- What will be the impact of primary HPV if starting at a younger age (25 years) on downstream health services (particularly colposcopy referrals), in a vaccinated population?

SCREENING IN A VACCINATED POPULATION

Compass trial

Individually-randomised open-label RCT of 5-yearly HPV screening versus 2.5-yearly liquid-based cytology (LBC) screening in Australia[1,2]

Conducted in vaccinated and unvaccinated women

Two phases

The Pilot (Phase 1):
~5,000 women, recruited 2013-2014

The Main Trial (Phase 2):
~ 76,000 women, recruited 2015-2019

Primary comparison of HPV vs. LBC screening

Secondary comparison of LBC vs. Dual-Stain cytology triage in HPV positive women

Sentinel experience for the renewed National Cervical Screening Program in Australia

Sources:
1. Canfell, K, Saville, M, Caruana, M, Gebski, V, Darlington-Brown, J, Brotherton, J, Heley, S, Castle, P.E. Protocol for Compass: a randomised controlled trial of primary HPV testing versus cytology screening for cervical cancer in HPV-unvaccinated and vaccinated women aged 25–69 years living in Australia BMJ Open 2018 8(1)e016700. doi: 10.1136/bmjopen-2017-016700. Trial registration: NCT02328872
2. Canfell K, Caruana M, Gebski V, ..Castle PE, Saville M. Cervical screening with primary HPV testing or cytology in a population of women in which those aged 33 years or younger had previously been offered HPV vaccination: Results of the Compass pilot randomised trial. PLoS Med. 2017

TRIAL DESIGN

METHODS: PILOT PHASE

In the Pilot Phase ~5,000 women aged 25-64 were recruited from 2013-2014

Pilot randomised 1:2:2 to:

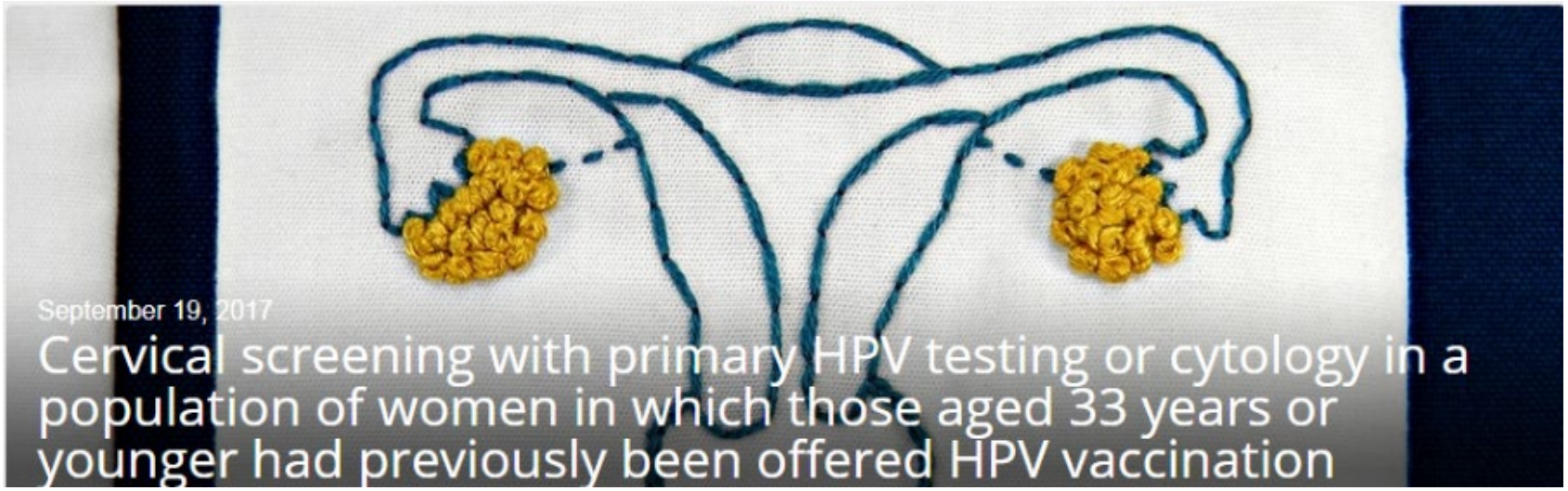
- Image-read LBC screening with HPV triage of low-grade cytology ('LBC screening')
- HPV screening with those in whom HPV (16/18) detected referred to colposcopy and with LBC triage for other those in whom HPV (not 16/18) detected ('HPV+LBC triage'), or
- HPV screening with those in whom HPV (16/18) detected referred to colposcopy and with dual-stained cytology triage for those in whom HPV (not 16/18) detected ('HPV+DS triage').

UPDATE ON PROGRESS

Supporting the National Cervical Screening Program

RESULTS (PILOT):

Primary randomisation, CIN2+/CIN3+ detection in HPV vs. LBC screen-negative women

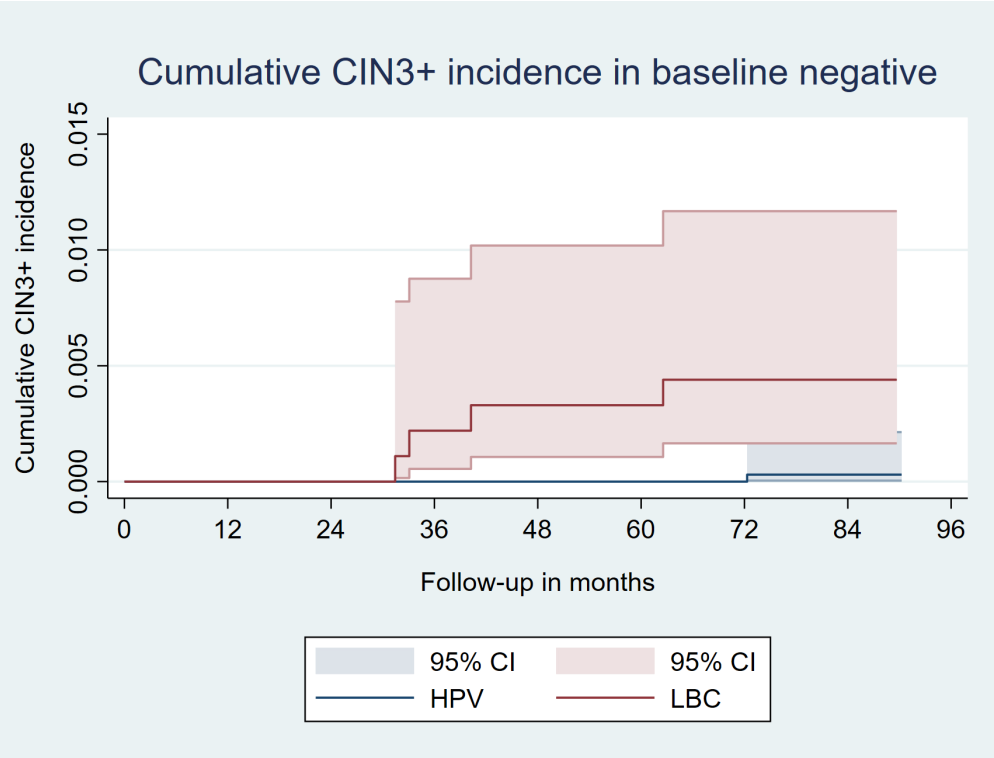


In the initial screening round, primary HPV screening was associated with significantly increased detection of CIN2+ compared to cytology (0.1% vs. 1.1%; p_{diff}=0.003).

Source:
Canfell K, Caruana M, Gebski V, ..Castle PE, Saville M. Cervical screening with primary HPV testing or cytology in a population of women in which those aged 33 years or younger had previously been offered HPV vaccination: Results of the Compass pilot randomised trial. PLoS Med. 2017

RESULTS (PILOT):

5-7 year CIN3+ outcomes in HPV vs. LBC screen-negative women



	HPV		LBC			
	Cases/N	Incidence rate (95% CI)	Cases/N	Incidence rate (95% CI)	IRR (HPV vs LBC) (95% CI)	P-value
All ages	1/3331	0.03% (0.00% - 0.17%)	4/911	0.44% (0.12% - 1.12%)	0.07 (0.01 – 0.61)	0.0014

Preliminary data - do not copy or distribute

Deaths and CIN2 cases are censored.

RESULTS (PILOT):

5-7 year CIN2+/CIN3+ outcomes in HPV vs. LBC screen-negative women

Rate per 1000 in baseline screen-negative women

		HPV	LBC	IRR
HPV FOCAL	CIN2+	3.6	10.0	0.36 (0.24-0.54)
Compass	CIN2+	1.8	5.5	0.33 (0.1-1.07)
HPV FOCAL	CIN3+	1.4	5.4	0.25 (0.13-0.48)
Compass	CIN3+	0.3	4.4	0.07 (0.01-0.61)

The Compass findings are comparable to those from an unvaccinated population in HPV-FOCAL (Canada)*

Preliminary data - do not copy or distribute

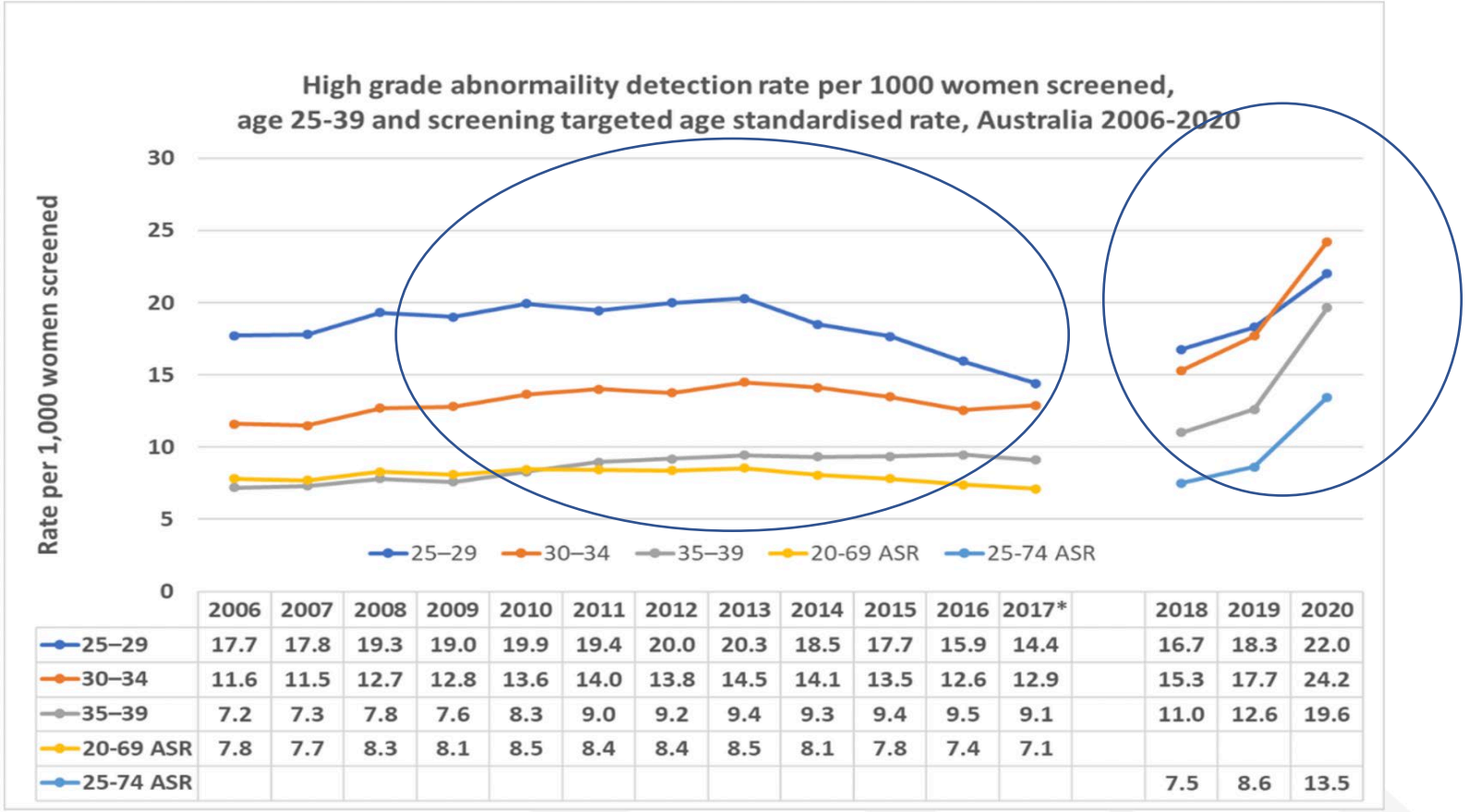
*Ogilvie G et al. Effect of Screening With Primary Cervical HPV Testing vs Cytology Testing on High-grade Cervical Intraepithelial Neoplasia at 48 Months: The HPV FOCAL Randomized Clinical Trial. JAMA 2018.

RENEWAL EXPERIENCE

Act as a sentinel experience for the renewed National Cervical Screening Program

Impact of vaccination & screening change in Australia on CIN2+

Source:
AIHW 2021 National Cervical Screening Program monitoring report



	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017*		2018	2019	2020
25–29	17.7	17.8	19.3	19.0	19.9	19.4	20.0	20.3	18.5	17.7	15.9	14.4		16.7	18.3	22.0
30–34	11.6	11.5	12.7	12.8	13.6	14.0	13.8	14.5	14.1	13.5	12.6	12.9		15.3	17.7	24.2
35–39	7.2	7.3	7.8	7.6	8.3	9.0	9.2	9.4	9.3	9.4	9.5	9.1		11.0	12.6	19.6
20-69 ASR	7.8	7.7	8.3	8.1	8.5	8.4	8.4	8.5	8.1	7.8	7.4	7.1				
25-74 ASR														7.5	8.6	13.5

Figure 11: Cervical precancer rate per 1,000 women screened, 2006-2020, Australia

PILOT: SAFETY MONITORING

Outcomes of pre-specified 2.5-year safety monitoring reported to the IDSMC

Aimed to determine cumulative CIN2+ risk following LBC screening of 10% of baseline HPV screen negative women

- 390 women in the safety monitoring cohort
- 167 eligible women according to the pre-specified criteria included in main analysis (follow-up with LBC @2.25-2.75 years)
  - **No CIN2+ detected** in this group at time of IDSMC report

- Subsequently, end-trial (non-pre-specified) analysis found that 358 (91%) of women allocated to safety monitoring had at least one more episode.
  - **One CIN3+ (0.3%) detected** in this group via a second HPV test.

METHODS: COMPASS MAIN TRIAL

In the Main Trial, 75,875 women aged 25-74 were recruited from 2015-2019

Recruitment was stratified by age cohort to reflect those offered vaccination vs. not (born after 1 July 1980; at recruitment vaccinated group approx. <40 years; currently <43 years of age) :

Younger cohort offered vaccination (16,18,6,11): 39,708 women*

Vaccination with quadrivalent vaccine, complete-course coverage across birth cohorts within this group ranged from ~0%–80%

Older cohort not offered vaccination: 36,167 women.*

*Not accounting for subsequent withdrawals or deaths of trial participants

METHODS: COMPASS MAIN TRIAL

Primary randomisation at 2:1 to HPV vs. LBC screening

Main outcomes for primary screening to be reported in 2026 - these are CIN3+ at 5+ years in: all randomised women (primary endpoint) and screen-negative women (main secondary endpoint).

A total of 50,732 were randomized to HPV screening, of these 43,693 were routine screeners.

Of the 43,693 routinely HPV-screened women:

- 576 had HPV (16/18) detected, 1.8% in younger cohort and 0.8% in older cohort.
- 3,396 had HPV (not 16/18) detected, 12.4% in younger cohort and 3.0% in older cohort.

METHODS: COMPASS MAIN TRIAL

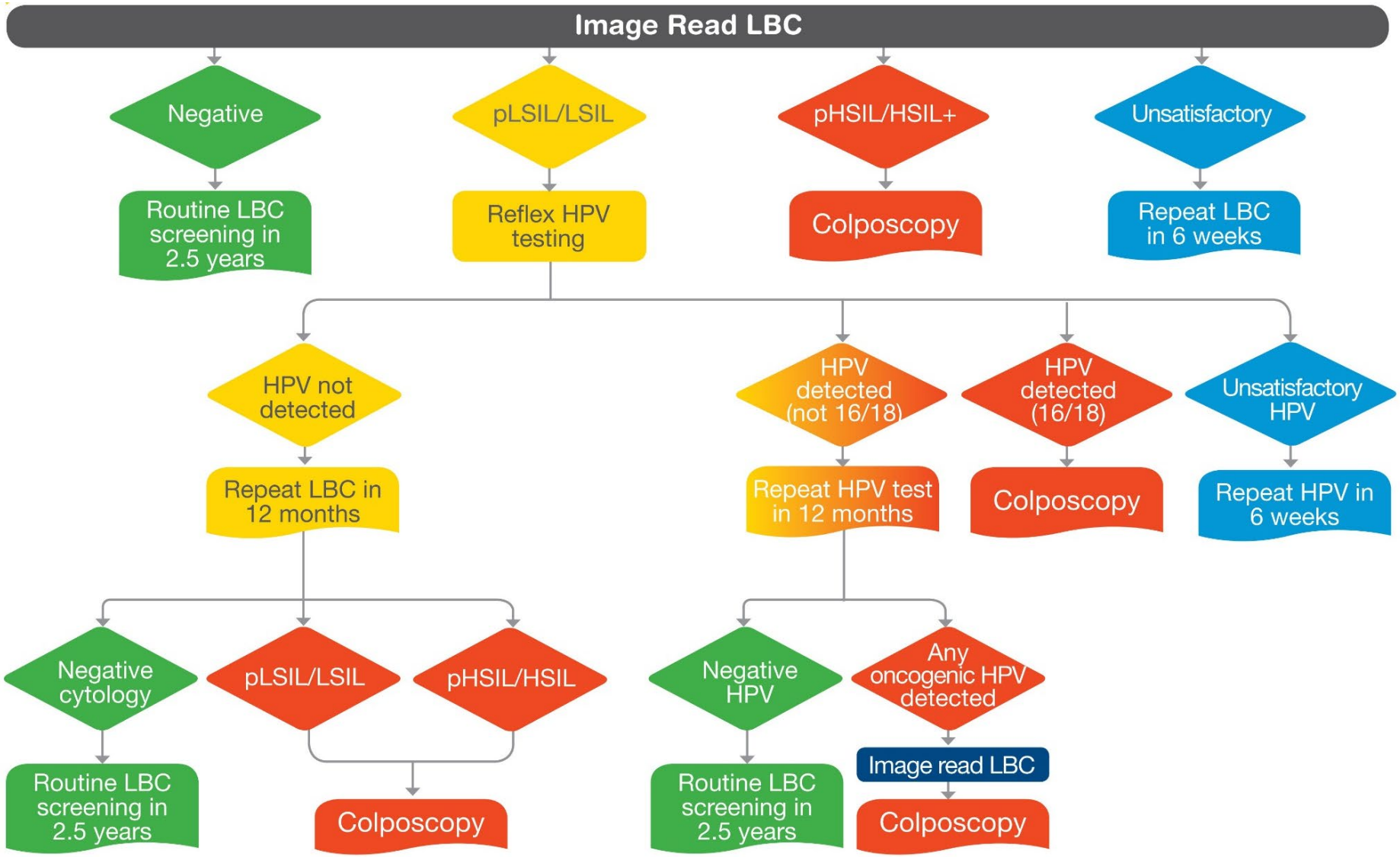
Secondary randomisation at 1:1 for LBC vs. DS triage

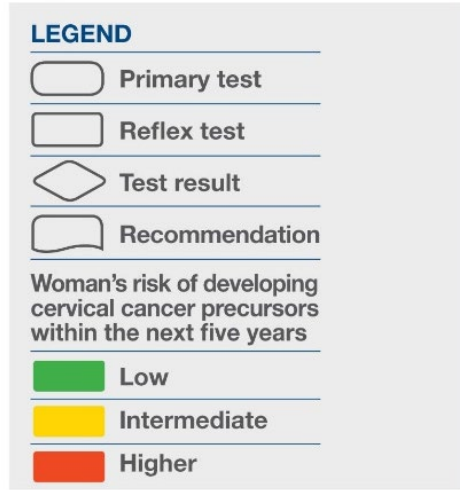
Women in whom HPV (not 16/18) detected were prospectively secondarily-randomized at 1:1 to DS vs. LBC triage, and women with HPV (16/18) detected were referred directly to colposcopy

12-month follow-up testing with HPV and a further 6 months follow-up for histological outcomes.

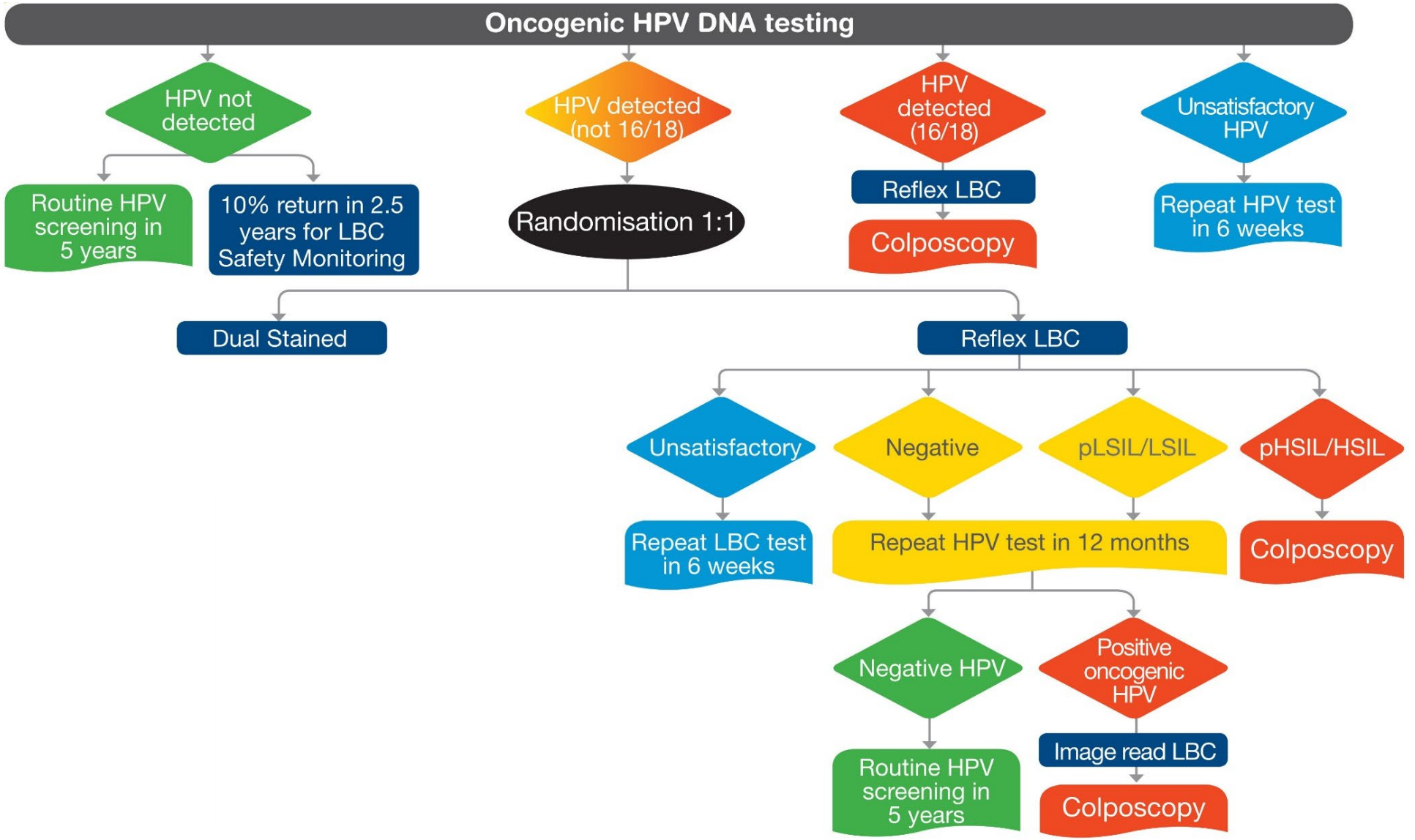
Trial IDSMC has approved interim analysis of relative performance as a secondary endpoint within HPV-screened arm.

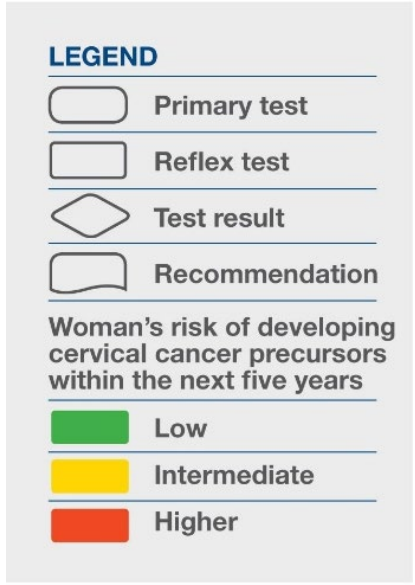
LBC PRIMARY SCREENING ARM



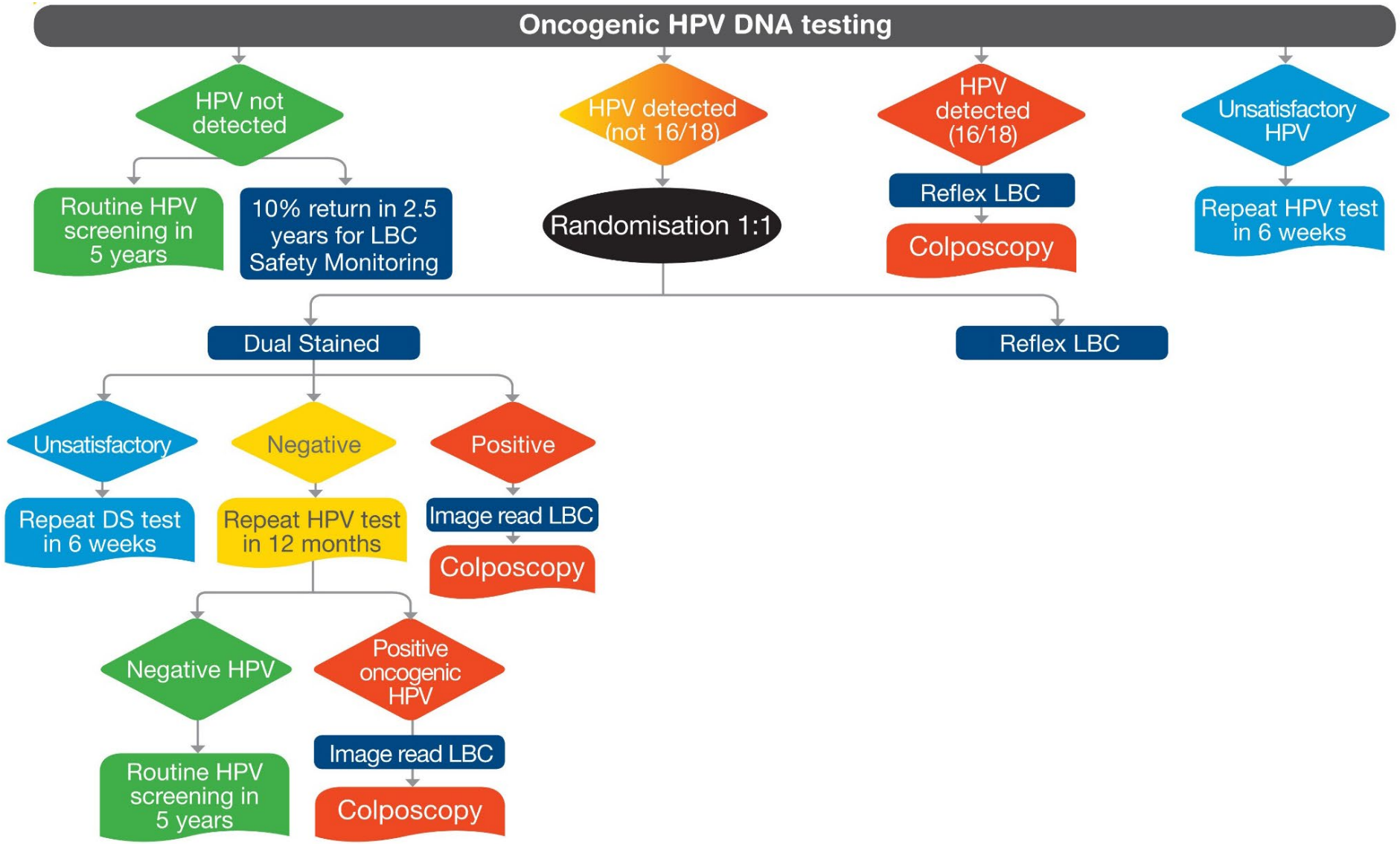


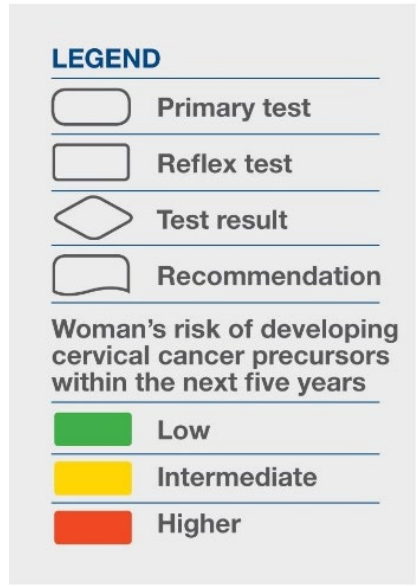
HPV PRIMARY SCREENING ARM





HPV PRIMARY SCREENING ARM





PROGRESS ON MAIN TRIAL

Trial participants complete their participation in the trial at the time of the 5-year exit test, an HPV test in all arms, after allowing for any required follow-up when HPV is detected.

Those in whom HPV (not 16/18) is detected require at least 12 months follow-up, and a further six months, if HPV is again detected to allow time for colposcopy and biopsy.

This means that the last participant should complete follow-up by June 30th 2026.

Over 50,000 participants have completed follow-up, including all in the older, non-vaccinated cohort.

MAIN TRIAL: SAFETY MONITORING

Outcomes of pre-specified 2.5-year safety monitoring reported to the IDSMC

Aimed to determine cumulative CIN2+ risk following LBC screening of 10% of baseline HPV screen negative women

- 2,140 women in the safety monitoring cohort
- 1,414 eligible women according to the pre-specified criteria examined for a CIN2+ result

- **2 cases CIN2+ detected (0.14%)** in this group at time of most recent IDSMC report

EMERGING EVIDENCE

Accuracy of dual-stained cytology vs liquid-based cytology for triage of HPV women in an HPV population: results from the Compass Trial in Australia

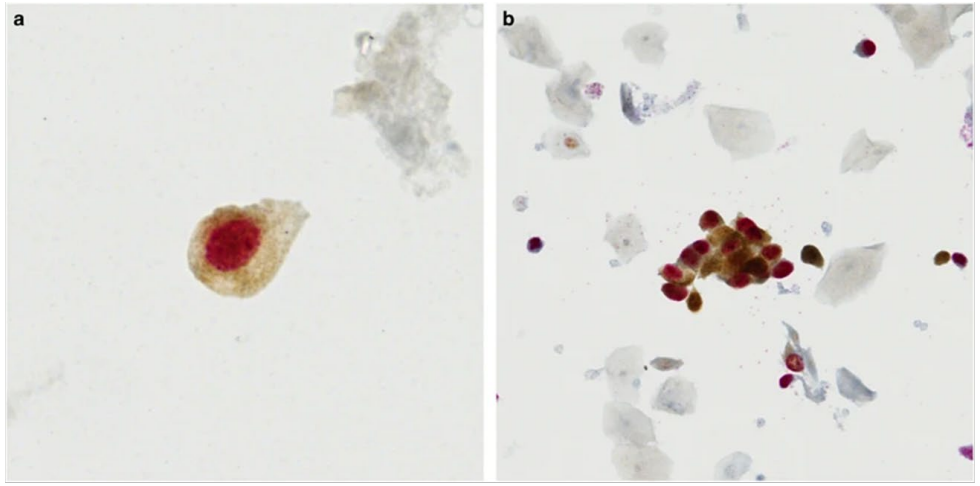
IPVC 2023
Public Health Oral

Canfell K,* Saville M,* Caruana M, Gebski V, de Sanjose S, Brotherton J, Franco E, Wentzensen N, Castle P, Arbyn M on behalf of the Compass trial group†

* Joint first authors
† Investigator and Scientific Advisory Group also includes: Franco E, Whelan B, Taylor S, Armstrong B , Carter J, Skinner R, Garland S, Grulich A, Anderson L, Wrede D, Tan J, Lord S, Collins J, Anderson S, Bourke S, Hawkes D, Tan G, Pakes W, Butler A, Asher R , Bateson D, Velentzis L, Jennett C, Smith M.
Independent Data and Safety Monitoring Group includes: Quinn M, Blomfield P, Wright G, Sharples K.
Other Study Team Members include: Egger S, Pagotto A, McLachlan C, Kumar V, Holt S, Sweeney D.

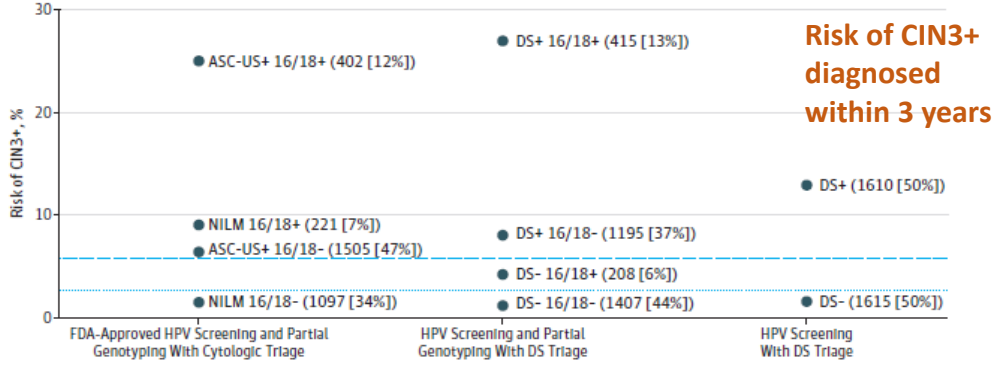
INTRODUCTION: DS CYTOLOGY

- In the appropriate setting, dual-stained cytology (DS) for p16/Ki67 is potentially a more effective triage than liquid-based cytology (LBC) after primary HPV screening
- Data from cohort studies demonstrates that DS, alone or in combination with HPV 16/18 partial genotyping, can improve risk stratification for future CIN3+
- However, randomised trial data & data from HPV-vaccinated populations are limited.
- The aim of this study was to use data from the large-scale Compass RCT to examine the comparative performance of DS vs. LBC in unvaccinated and vaccinated cohorts of women



(**a**) A p16/Ki-67 dual-stain positive single cell. (**b**) A p16/Ki-67 dual-stained cluster of cells.

Figure 2. Risk of Cervical Intraepithelial Neoplasia Grade 3 or Worse (CIN3+) in Strata of Cytologic Testing, Dual Stain (DS), and Human Papillomavirus (HPV)16/18



Sources:
1. Ebisch RMF, Horst JVD, Hermsen M, Rijstenberg LL, Vedder JEM, Bulten J et al., Modern Pathology 2017.
2. Wentzensen N, Clarke M, Bremer R, et al., JAMA Internal Med 2019

TEST POSITIVITY RATES

	Younger Cohort	Older Cohort
	Positivity	Positivity
DS	34.7% (32.2% - 37.3%) (468/1348)	30.9% (25.9% - 36.3%) (98/317)
LBC (ASC-H threshold)*	7.6% (6.3% - 9.2%) (103/1353)	7.0% (4.5% - 10.4%) (23/327)

DETECTED DISEASE IN EACH ARM

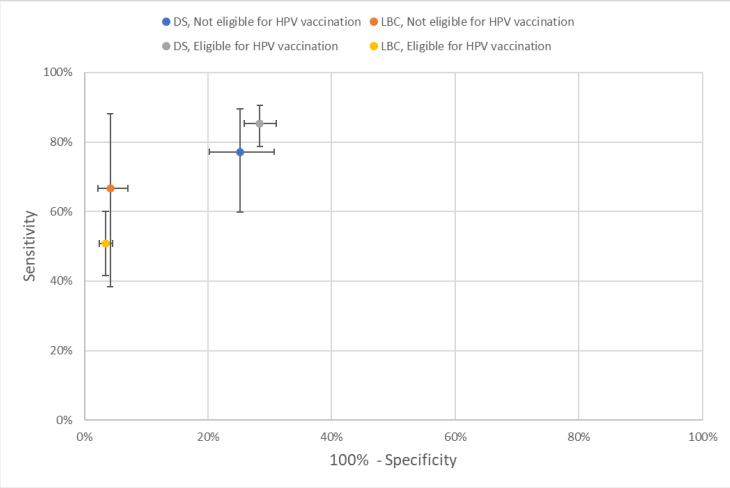
Underlying CIN2+ and CIN3+ rates in those in HPV (not 16/18)

	DS	LBC (ASC-H threshold)	DS – LBC	p-value
CIN2+				
Younger Cohort	11.1% (9.5% - 12.9%) (150/1348)	8.9% (7.4% - 10.5%) (120/1353)	2.3% (-0.0% - 4.5%)	0.0504
Older Cohort	11.0% (7.8% - 15.0%) (35/317)	4.6% (2.6% - 7.5%) (15/327)	6.5% (2.3% - 10.6%)	0.0022
CIN3+				
Younger Cohort	5.7% (4.5% - 7.1%) (77/1348)	4.7% (3.7% - 6.0%) (64/1353)	1.0% (-0.7% - 2.7%)	0.2513
Older Cohort	6.0% (3.6% - 9.2%) (19/317)	3.1% (1.5% - 5.6%) (10/327)	2.9% (-0.3% - 6.1%)	0.0725

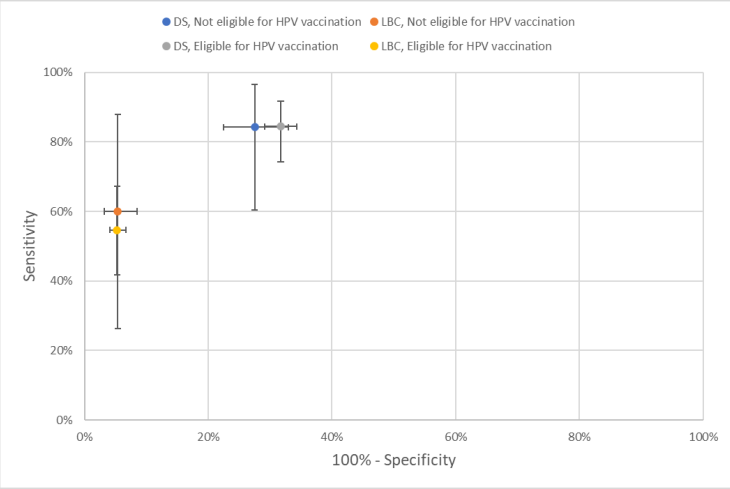
- In the older cohort, a significant difference was observed in detected disease in each arm, suggesting ascertainment bias potentially due to LTFU in this pragmatic trial.
- If present this issue more heavily impacts LBC arm, which referred lower proportion to colposcopy.

SENSITIVITY & SPECIFICITY

CIN2+ **Both cohorts**



CIN3+



DS vs. LBC (ASC-H threshold)	Younger cohort		Older cohort	
	Relative sensitivity	**Relative specificity**	**Relative sensitivity**	**Relative specificity**
CIN2+	1.68 (1.39 - 2.03) p<0.001	0.74 (0.71 - 0.77) p<0.001	1.16 (0.78 - 1.73) p=0.439	0.78 (0.73 - 0.84) p<0.001
CIN3+	1.54 (1.21 - 1.97) p=0.001	0.72 (0.69 - 0.75) p<0.001	1.40 (0.82 - 2.41) p=0.1476	0.77 (0.71 - 0.83) p<0.001

*Significant difference in sensitivity or specificity between DS and LBC.

† Test for difference in findings between two cohorts: P=0.0982 for CIN2+ relative sensitivity; P= 0.7536 for CIN3+.

RISK OVER 18-MONTH FOLLOW-UP

Risk over 18 months	Younger cohort		Older cohort	
	PPV	1-NPV	PPV	1-NPV
CIN2+				
DS	27.4% (23.4% - 31.6%) (128/468)	2.5% (1.6% - 3.8%) (22/880)	27.6% (19.0% - 37.5%) (27/98)	3.7% (1.6% - 7.1%) (8/219)
LBC (ASC-H threshold)	59.2% (49.1% - 68.8%) (61/103)	4.7% (3.6% - 6.0%) (59/1250)	43.5% (23.2% - 65.5%) (10/23)	1.6% (0.5% - 3.8%) (5/304)
CIN3+				
DS	13.9% (10.9% - 17.4%) (65/468)	1.4% (0.7% - 2.4%) (12/880)	16.3% (9.6% - 25.2%) (16/98)	1.4% (0.3% - 4.0%) (3/219)
LBC (ASC-H threshold)	34.0% (24.9% - 44.0%) (35/103)	2.3% (1.6% - 3.3%) (29/1250)	26.1% (10.2% - 48.4%) (6/23)	1.3% (0.4% - 3.3%) (4/304)

If disease under-ascertainment is occurring in LBC arm, this may be an underestimate

COMPARISON WITH THE IMPACT FINDINGS

Noting differing thresholds for cytology (Compass threshold ASC-H+, IMPACT threshold ASCUS+)

	Sensitivity			Specificity			PPV			1 - NPV		
	Compass Younger cohort	Compass Older cohort	Impact	Compass Younger cohort	Compass Older cohort	Impact	Compass Younger cohort	Compass Older cohort	Impact	Compass Younger cohort	Compass Older cohort	Impact
CIN2+												
DS	85.3% (78.6% - 90.6%) (128/150)	77.1% (59.9% - 89.6%) (27/35)	81.4% (77.1% - 85.1%) (298/366)	71.6% (69.0% - 74.2%) (858/1198)	74.8% (69.3% - 79.8%) (211/282)	57.5% (55.6% - 59.5%) (1376/2391)	27.4% (23.4% - 31.6%) (128/468)	27.6% (19.0% - 37.5%) (27/98)	22.7% (21.5% - 23.9%) (298/1313)	2.5% (1.6% - 3.8%) (22/880)	3.7% (1.6% - 7.1%) (8/219)	4.7% (3.8% - 5.8%) (68/1444)
LBC	50.8% (41.6% - 60.1%) (61/120)	66.7% (38.4% - 88.2%) (10/15)	57.7% (52.5% - 62.6%) (211/366)	96.6% (95.4% - 97.5%) (1191/1233)	95.8% (93.0% - 97.8%) (299/312)	66.0% (64.0% - 67.8%) (1577/2391)	59.2% (49.1% - 68.8%) (61/103)	43.5% (23.2% - 65.5%) (10/23)	20.6% (18.9% - 22.3%) (211/1025)	4.7% (3.6% - 6.0%) (59/1250)	1.6% (0.5% - 3.8%) (5/304)	8.9% (8.0% - 10.0%) (155/1732)
CIN3+												
DS	84.4% (74.4% - 91.7%) (65/77)	84.2% (60.4% - 96.6%) (16/19)	86.6% (79.1% - 91.7%) (97/112)	68.3% (65.7% - 70.8%) (868/1271)	72.5% (67.0% - 77.5%) (216/298)	54.0% (52.1% - 55.9%) (1429/2645)	13.9% (10.9% - 17.4%) (65/468)	16.3% (9.6% - 25.2%) (16/98)	7.4% (6.7% - 7.9%) (97/1313)	1.4% (0.7% - 2.4%) (12/880)	1.4% (0.3% - 4.0%) (3/219)	1.0% (0.6% - 1.6%) (15/1444)
LBC	54.7% (41.7% - 67.2%) (35/64)	60.0% (26.2% - 87.8%) (6/10)	65.2% (56.0% - 73.4%) (73/112)	94.7% (93.4% - 95.9%) (1221/1289)	94.6% (91.6% - 96.8%) (300/317)	64.0% (62.2% - 65.8%) (1693/2645)	34.0% (24.9% - 44.0%) (35/103)	26.1% (10.2% - 48.4%) (6/23)	7.1% (6.1% - 8.0%) (73/1025)	2.3% (1.6% - 3.3%) (29/1250)	1.3% (0.4% - 3.3%) (4/304)	2.3% (1.7% - 2.8%) (39/1732)

Source:
Wright TC et al, Clinical Validation of p16/Ki-67 dual-stained cytology triage of HPV-positive women: Results from the IMPACT trial. Int J Cancer 2022

STRENGTHS

Large, prospectively randomized cohort for DS vs. LBC performance in triage of HPV (not 16/18) in a unique population and in context of vaccination.

Provides new information on relative performance in the context of LBC at ASC-H threshold as comparator

LIMITATIONS

Potential for ascertainment bias due to loss to follow-up playing out differentially in the two arms because DS had higher positivity rate at initial test - subsequent analyses will address this issue.

- Currently conducting per-protocol analysis for those HPV (not 16/18) detected and triage negative who returned for repeat HPV testing at one year.
- When the follow-up data become available, we will analyse outcomes to three years
- If present, this will drive up the reported risk in LBC triage-negative women, noting that in the current study this group includes ASCUS/LSIL.

Linkage to individual vaccination data still in progress

- Subsequent analysis will test for any differences in individual vaccination status
- Noting that in this first-gen vaccinated population, the composition of HPV (not 16/18) is expected to be largely unimpacted by vaccination (albeit with potential impact of cross-protection).

CONCLUSIONS

In this randomised ‘trial-within-a-trial’ of DS vs. LBC triage of the 3,363 women in whom HPV (not 16/18) was detected

- DS brought forward detection of CIN2+ and CIN3+ disease, with one-third of DS+ vs. ~7% for LBC at ASC-H threshold.
- DS had increased sensitivity for detection of CIN3+ when compared to LBC at an ASC-H threshold, although this was significant only for the younger cohort (~50% increase)
- Specificity tradeoff - DS had decreased specificity for the detection of CIN3+ when compared to LBC at an ASC-H threshold (relative ~20-30% decrease)
- No substantive differences were seen in the absolute or relative performance of DS in the younger cohort offered vaccination compared to the older cohort not age-eligible for vaccination.
- Findings for absolute DS performance comparable with other studies.

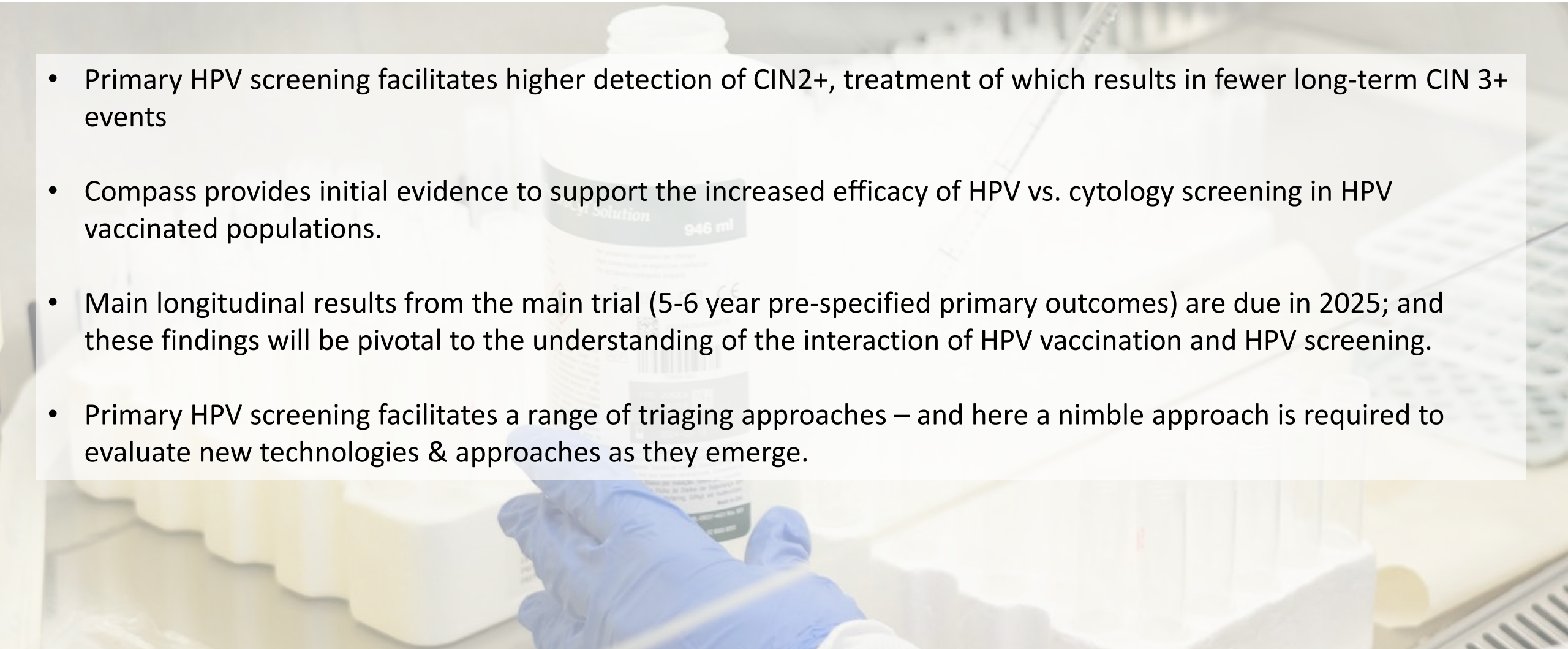
CONCLUSIONS

This has significant programmatic implications:

- DS likely has useful role in programs with partial genotyping where DS+ HPV (not 16/18) can potentially be immediately referred alongside those in whom HPV (16/18) is detected.
- Very low rates of CIN3+ disease in HPV (not 16/18) DS- women: marker of safety and indicating potential utility for longer follow-up in DS negative women, or even referral back to 5-yearly routine screening.
- DS also has potential for automation, which should facilitate implementation at scale in high-income countries.
- In countries entering the second round of HPV screening (such as Australia), use of DS triage could be considered as a sensitive mechanism to increase immediate detection of incident disease.

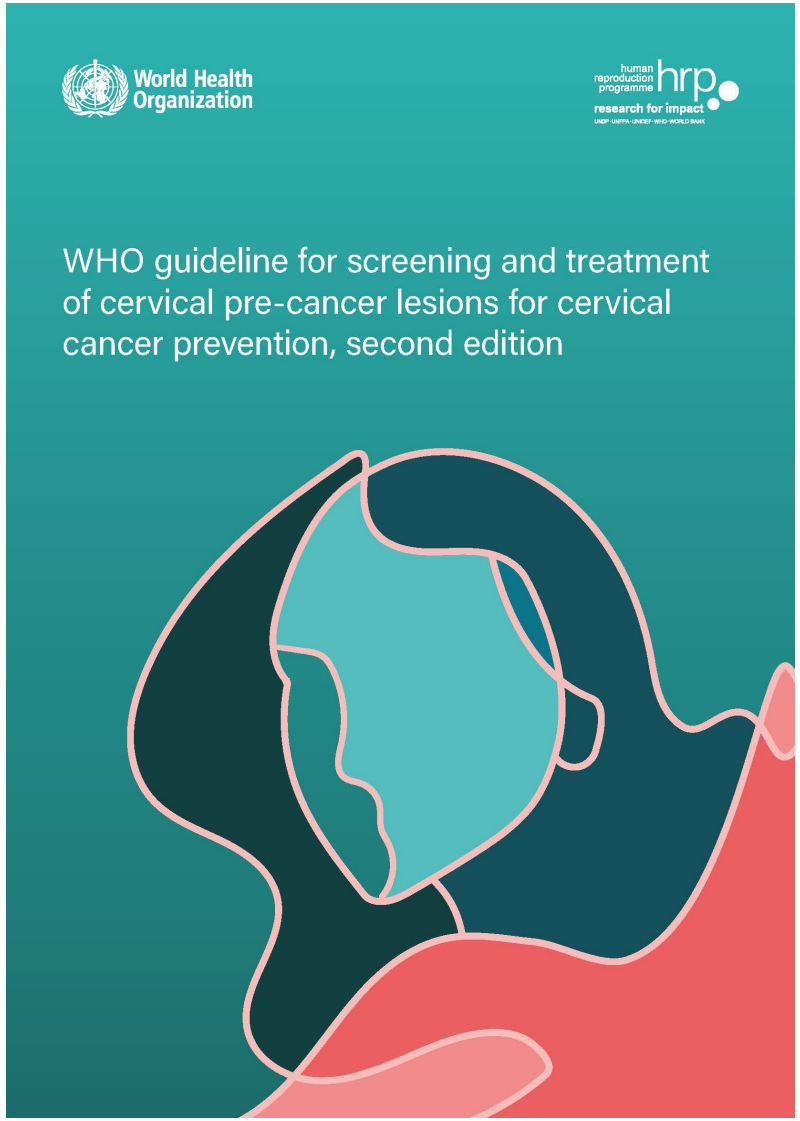
CONCLUSIONS

Primary HPV screening



- Primary HPV screening facilitates higher detection of CIN2+, treatment of which results in fewer long-term CIN 3+ events
- Compass provides initial evidence to support the increased efficacy of HPV vs. cytology screening in HPV vaccinated populations.
- Main longitudinal results from the main trial (5-6 year pre-specified primary outcomes) are due in 2025; and these findings will be pivotal to the understanding of the interaction of HPV vaccination and HPV screening.
- Primary HPV screening facilitates a range of triaging approaches – and here a nimble approach is required to evaluate new technologies & approaches as they emerge.

SIGNIFICANCE



These findings have already helped inform WHO guidelines and will be increasingly relevant to other countries as vaccination & HPV screening roll out under the banner of elimination

WHO guideline for screening and treatment of cervical pre-cancer lesions for cervical cancer prevention, 2nd edition: https://www.who.int/publications/i/item/9789240030824

World Health Organization

human reproduction programme hrp
research for impact
UNDP-UNFPA-UNICEF-WHO-WORLD BANK

PLANNED FUTURE ANALYSES

PLANNED ANALYSES

Planned manuscript submissions in the next 6-9 months

Longitudinal outcomes from the first phase of the Compass trial in Australia (pilot).

Accuracy of DS cytology vs. LBC for triage of HPV-positive women an in HPV-vaccinated population (IPVC 2023 presentation extended to 3-years of follow-up).

PLANNED ANALYSES

The ITT and per-protocol analyses of the main outcome and secondary outcomes are planned for 2027:

Main outcome

Cumulative, histologically confirmed CIN3+ at 5 years following a 5-year HPV exit testing round in both arms, in women randomised to the LBC arm vs women randomised to the HPV arm.

Secondary outcomes

- Cumulative incidence of CIN3+ in women presenting for routine screening randomised to the HPV arm who were HPV-negative at baseline, vs. CIN3+ in those randomised to the LBC arm and who were LBC-negative at baseline.
- Cumulative incidence of CIN2+ in women randomised to the HPV arm who were HPV-negative at baseline, vs. CIN2+ in women who were randomised to the LBC arm and were LBC-negative at baseline.
- Cross-sectional CIN2+ and CIN3+ detection rates in each arm at baseline.
- Cumulative incidence of CIN2+ and CIN3+ in women who have an abnormal test result at baseline.
- Cumulative CIN2+ and CIN3+ in women who were in follow-up management for a previous abnormality at baseline.

COMPASS BIOBANK

- All residual samples with any positive test, whether HPV or cytology, are bio-banked, unless the participant opted out of this request
- A randomly selected, aged matched control, is also bio-banked
- These samples will enable nested case-controlled studies of promising novel triage tests, with the added advantage that randomised 5+ year CIN2+ outcomes will be available
- 20,143 samples as of December 31st 2022

LOOKING BEYOND HPV GENOTYPE 16 AND 18

Defining HPV genotype distribution in cervical cancers in Australia prior to vaccination

Methods

- Cervical cancer specimens from 2005 to 2015 were collected from seven tertiary centres across VIC, NSW and QLD
- All cases reviewed by specialist gynaecological anatomical pathologists on the research team
- Sample size calculations based on published genotype prevalence data for cervical cancer in an Australian meta-analysis and the IARC 2006-2010 world estimate for HPV genotypes
- Sample size was sufficient to determine whether Australian genotype prevalence was significantly different from global prevalence

Source: Brotherton, J. et al. Looking beyond human papillomavirus (HPV) genotype 16 and 18: Defining HPV genotype distribution in cervical cancers in Australia prior to vaccination. IJC 2017; 141, 1576–1584.

LOOKING BEYOND HPV GENOTYPE 16 AND 18

Defining HPV genotype distribution in cervical cancers in Australia prior to vaccination

Methods (cont'd)

- Descriptive analysis primarily took place
- HPV genotypes were grouped into 16/18, 31/33/45/52/58 and "Other" for analysis
- Proportions were compared with world estimates using Pearson's X^2 test
- Association between age and HPV was also investigated using a binary regression model
- Samples were sandwich sectioned for analysis
- Cases which did not contain cervical cancer after being sectioned, were removed from analysis

Source: Brotherton, J. et al. Looking beyond human papillomavirus (HPV) genotype 16 and 18: Defining HPV genotype distribution in cervical cancers in Australia prior to vaccination. IJC 2017; 141, 1576–1584.

LOOKING BEYOND HPV GENOTYPE 16 AND 18

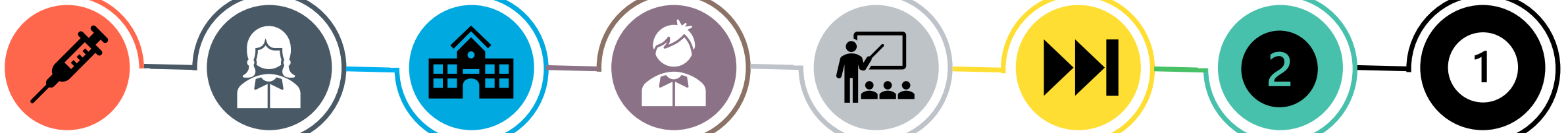
Defining HPV genotype distribution in cervical cancers in Australia prior to vaccination

Distribution of genotypes placed in 4vHPV/2vHPV and 9vHPV targeted groups, 847 Australian cervical cancers, compared with results from Serrano et al

HPV type group	Number	% of total cases $n = 847$ (95% CI)	% of HPV positive $n = 787$ (95% CI)	% of HPV positive $n = 8,977$; Serrano *et al.* global data (95% CI)
16,18	607	71.8% (68.5–74.7%)	77.1% (74.0–80.0%)	70.8% (69.8–71.7%)
31,33,45,52,58	125	14.8% (12.4–17.3%)	15.9% (13.4–18.6%)	18.5% (17.7–19.3%)
Any 9vHPV	732	86.4% (83.9–88.7%)	93.0% (91.0–94.7%)	89.4% (88.8–90.1)
Other HPV	55	6.5% (4.9–8.4)	7.0% (5.3–9.0%)	10.6% (9.9–11.2%)
Negative	60	7.1 (5.4–9.0%)	NA	NA

Source: Brotherton, J. et al. Looking beyond human papillomavirus (HPV) genotype 16 and 18: Defining HPV genotype distribution in cervical cancers in Australia prior to vaccination. IJC 2017; 141, 1576–1584.

NATIONAL HPV VACCINATION PROGRAM



2006

4vHPV vaccine

- 3 dose course
- HPV types 16/18/6/11
- Prevents infection and disease (CIN, cervical, anogenital cancers and genital warts)

2007 - 2009

Catch up

- Catch up females aged 12-26

2009

Schools

- Routine school-based vaccination for girls
- 1st yr high school
- Usual age 12-13

2013 - 2014

Catch up

- Catch up program for males at school
- Age 12-15
- (+ some GP delivery)

2015

Schools

- Routine school-based vaccination for boys and girls
- 1st yr high school
- Usual age 12-13

2017

Catch up extended

- Routine catch up extended to age 19

2018

Two dose

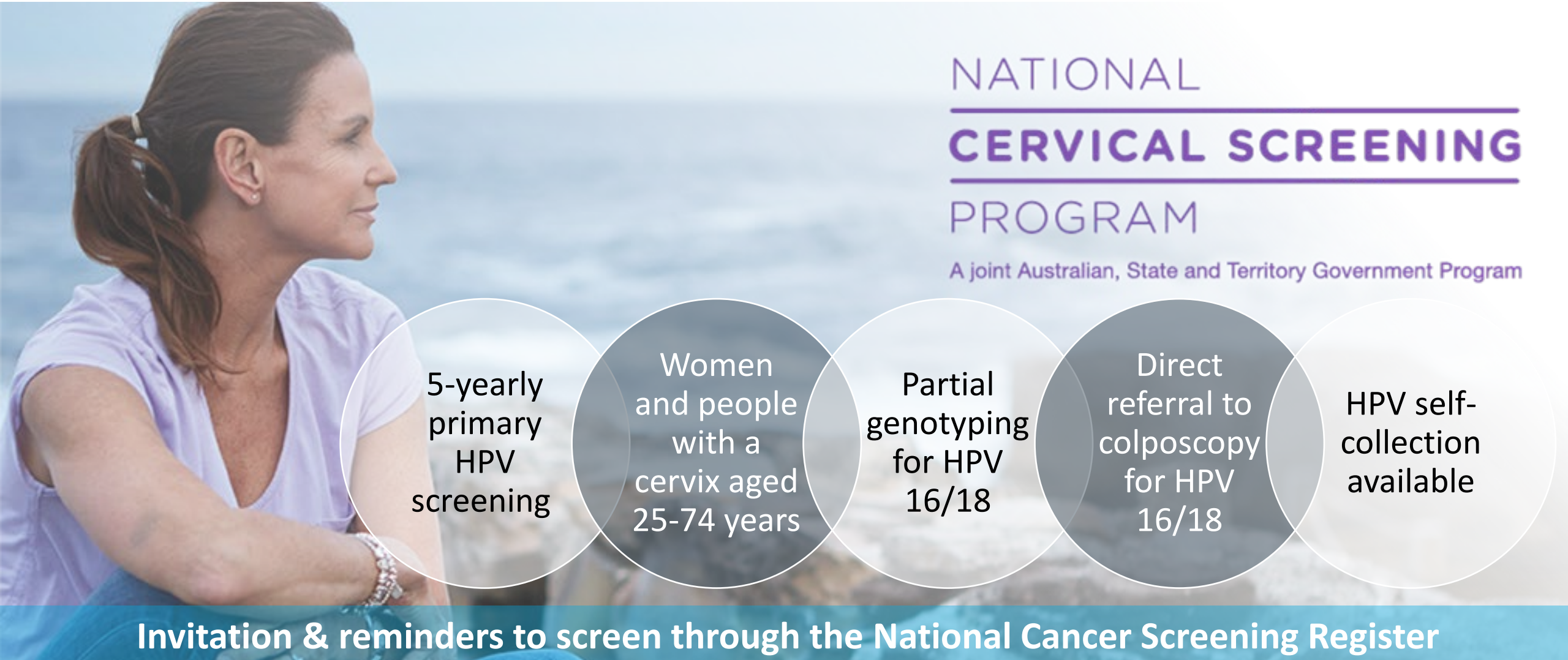
- Two dose course of 9vHPV vaccine

2023

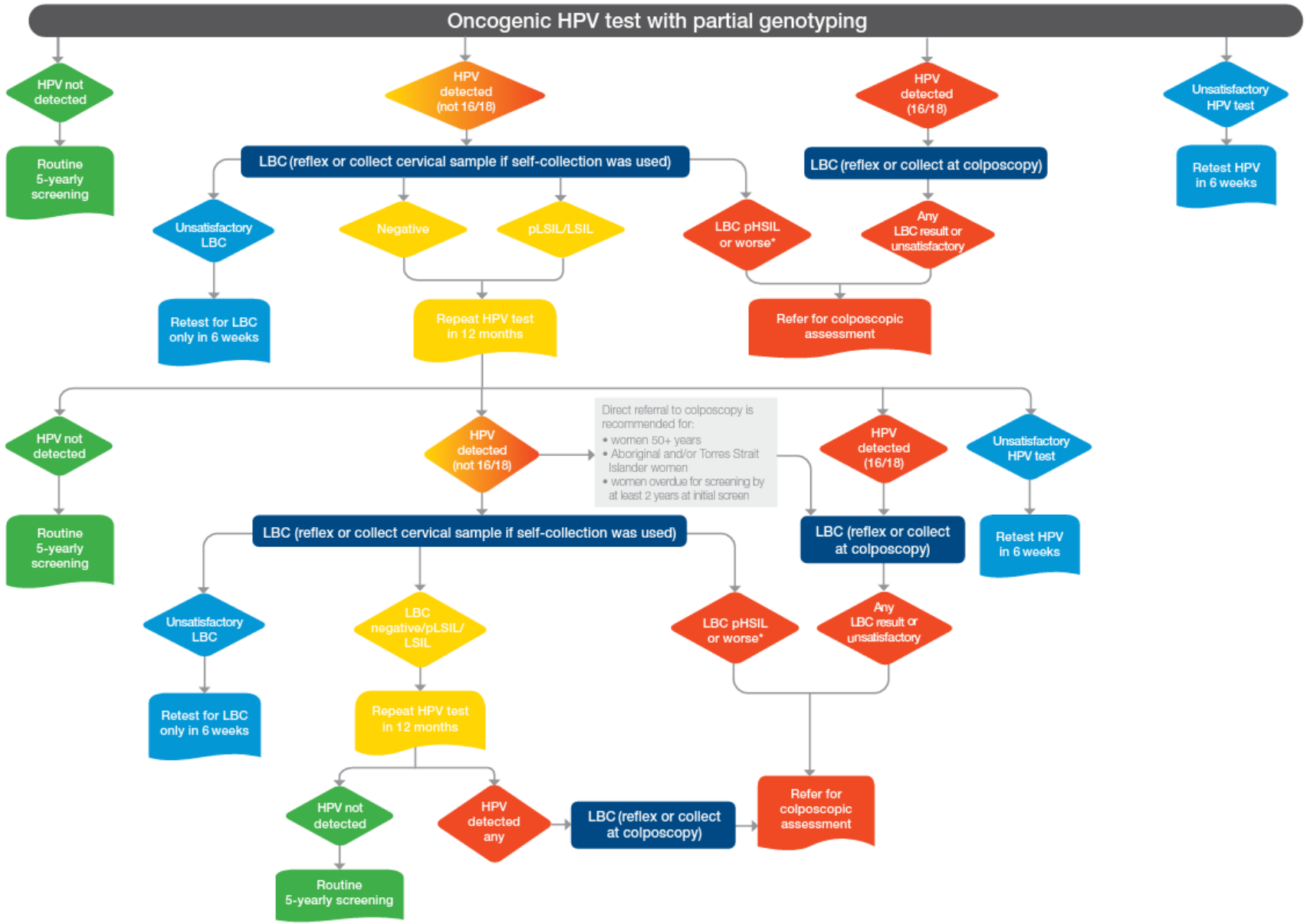
One-dose

- One dose course of 9vHPV vaccine
- Routine catch up extended to age 25

AUSTRALIA'S NATIONAL CERVICAL SCREENING PROGRAM



CERVICAL SCREENING PATHWAY (CLINICIAN COLLECTED OR SELF-COLLECTED)



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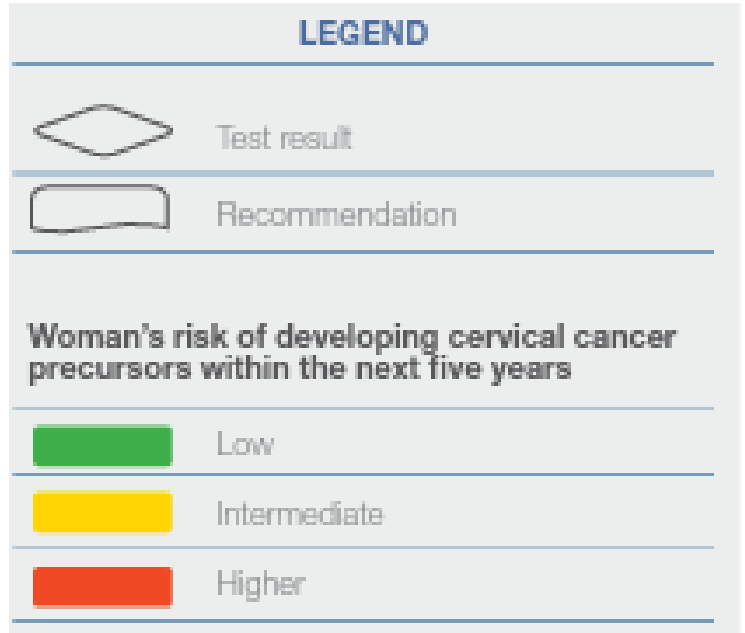
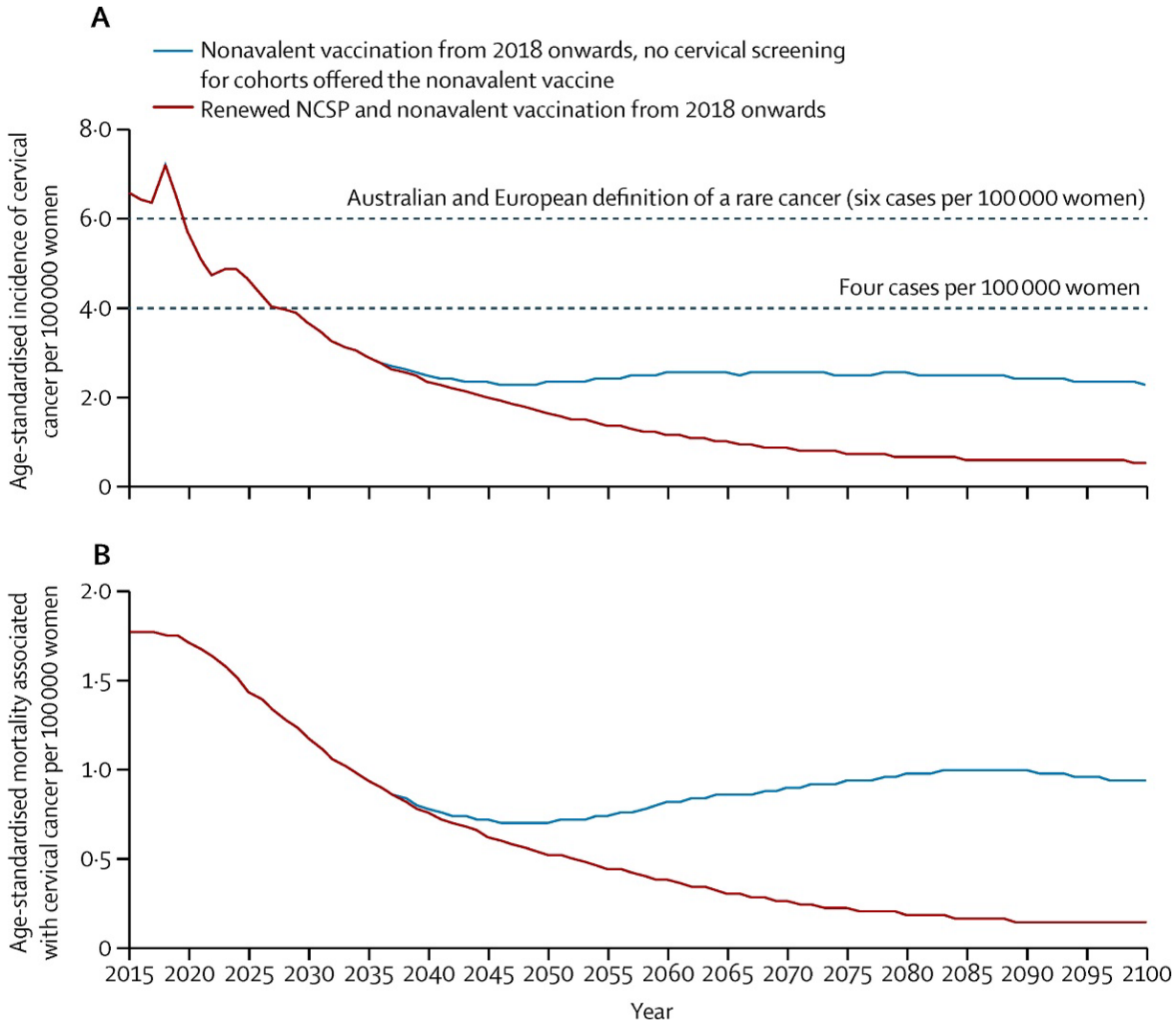


ELIMINATING CERVICAL CANCER IN AUSTRALIA



Elimination = <4 cases / 100,000

Modelling suggests that with HPV vaccination and HPV-based cervical screening, Australia can achieve the WHO's Global Strategy goal to eliminate cervical cancer as a public health problem by 2035

Source: Hall MT et al (2019) https://www.thelancet.com/journals/lanpub/article/PIIS2468-2667(18)30183-X/fulltext

EVOLUTION OF HPV TESTING

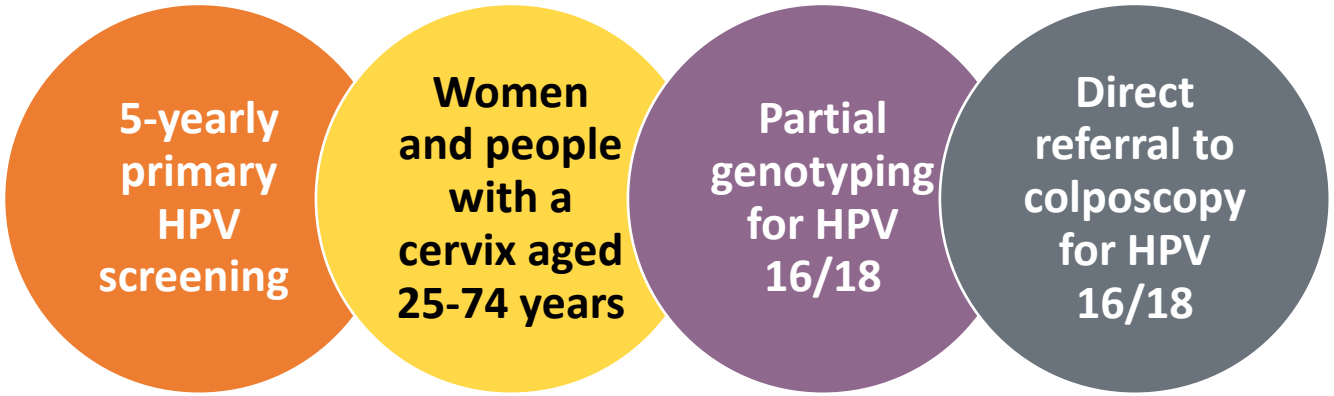
Australia

NCSP begins 1991

Switch from cytology to HPV December 2017

Self-collection a universal option July 2022

Elimination Strategy National to be launched Nov 17th



Modelling predicted relative improvements in cervical cancer incidence and mortality compared to current screening program **of at least 20%.**

Challenges:

- "Success" of the Pap program
- Push back from stakeholders, especially in relation to the longer interval and increased age of starting screening
- Management of highly complex change

Opportunities:

- The strong framework of previous program as foundation for new program
- The support at all levels of government based on strength of evidence

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Associate Investigators: Mr. David Wrede, Dr. Jeffery Tan, Dr. Jane Collins, Ms. Sandy Anderson, Dr. Siobhan Bourke, Dr. David Hawkes, Ms. Grace Tan, Dr. Wendy Pakes, Dr. Alexis Butler, Ms. Rebecca Asher, Dr Louiza Velentzis, A/Prof Megan Smith, Ms. Chloe Jennett (CCNSW)

Scientific Advisory Committee: Prof. Eduardo Franco, Prof. Bruce Armstrong, Prof. Jonathan Carter, Prof. Rachel Skinner, Prof. Suzanne Garland, Prof. Andrew Grulich, A/Prof. Lyndal Anderson, Ms Bridget Whelan (sadly deceased), Ms Susan Taylor

Independent Data and Safety Monitoring Committee: Prof. Michael Quinn, Clinical A/Prof. Penny Blomfield, Prof. Gordon Wright, A/Prof. Katrina Sharples

Other Study team members: Ms. Caitlin McLachlan, Ms. Vanessa Kumar, Ms. Amy Pagotto, Mr Daniel Sweeney, Ms. Sheree Holt.

THANK YOU!

compass
Future directions in cervical screening

A JOINT INITIATIVE OF ACPCC AND CANCER COUNCIL NSW

Australian Centre for the Prevention of Cervical Cancer

The Daffodil Centre
A partnership between Cancer Council and The University of Sydney