UK National Screening Committee
HPV as primary screen for cervical cancer - an evidence review

Consultation comments pro-forma

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Yes X☐ No☐

Section and / or page number	Text or issue to which comments relate	Comment *Please use a new row for each comment and add extra rows as required.*
	Introduction	The Report acknowledges that the UK programme has been effective, but includes reference to three non-UK programmes without any indication if the screening programme in these countries has been as effective, to evidence the increased sensitivity of HPV testing over conventional cytology. The three European studies are all based upon conventional cytology; as the UK has been using Liquid Based Cytology for most of the last decade these three studies should not be included as evidence to justify a change. The fourth referenced study is by the author of the report. Before

		any decision is taken to change to HPV testing for primary screening we feel there should be a further independent and objective review of the current screening programme with a like for like comparison and review of the evidence. The current evidence that is referenced does not in itself permit the justification for a change to HPV primary screening. This Institute regards the current UK cervical screening programmes as probably the most effective in the world and would caution against any decision to change the screening methodology to a system that might not be as effective.
Page 2 Summary		In the UK ARTISTIC trial there was no real difference in sensitivity between cytology and HPV primary screening in the first screening round (3 years), differences only started to appear at 6 years. This was not made totally clear in the report.
Page 2	"A 'safety check' requires routine recall at 3 years to ensure prior to moving to the anticipated extension of the screening interval to 6 years the detection of CIN3+ is sufficiently low"	This is to be applauded but it should be understood that the results will not be known until the end of year 4 at the earliest. We would question the safety of commencing rollout before this information is known and suggest a risk-based review of this proposal.
Page 3	"Initial data indicated that HPV followed by cytology had not increased baseline referrals when compared with cytology triaged by HPV"	One of the six sentinel sites has seen a gradual and large increase in the number of referrals since the start of the pilots with the percentage of women referred increasing from 4% to 6%. A rise of 50%. The true impact on overall referrals will not be known until the end of year 4 at the very earliest.
	"Early data censored in July/August indicated that 8.5% of screened women were HPV positive/cytology	We note that this figure varies across the six sites with one site showing a figure of 11.7%. This represents an extra 3% of women

	negative"	having early repeat tests. We believe 8% is a significant underestimate.
	"Detection rates of CIN grade 2 or worse and CIN3 were significantly higher amongst women who had primary HPV screening compared with primary cytology"	This statement is made in the introductory summary but in the discussion section of the pilot report it rightly states that there is insufficient data at this time to make this assumption. We would strongly advocate the avoidance of definitive statements in the absence of definitive evidence. Furthermore, data from one of the pilot sites shows that high grade detection rates have increased in both the HPV and cytology screened populations over the first two years of the pilot and there is no difference in high grade rates in the two populations. Of particular note is the fact that the high grade rate in the cytology screened population is 1.86%, in the HPV screened population it is 1.81%. This could be random variation but could also represent a small but significant decrease in sensitivity in the HPV arm. This difference should not be discounted or dismissed. Additionally the paper makes no reference at any point to the fact that in the first round of screening in ARTISTIC 15% of CIN 2+ cases tested negative in the HPV arm. More consideration should be given to the impact that this will have on the new programme when linked to extended screening intervals It is also worth noting that in the first round of screening three of 12 cancers in the ARTISTIC trail had tested negative for HPV.
8.The evidence supporting primary HPV screening	"Crucially for screening, a recently published pooled analysis of all four trials involving over 176,000 women with a median of 6.5 years follow up, showed clear evidence of a reduction in the incidence of cancer in the	We refer to our initial comment that three of the four trials quoted are from European screening programmes using conventional

	HPV arms compared with cytology alone; the hazard ratio for developing cancer was 0.6[18].”	cytology and so are inappropriate for comparative purposes. In addition with reference to the last point All 5 cancers discovered in ARTISTIC up to 8 years after baseline were in the HPV arm. None were in the cytology arm

Page 6	The cumulative rate of CIN2+ over a mean of 6 years, was 1.41% (1.19-1.65) for negative cytology at baseline compared with 0.87% (0.70-1.06) over 6 years for negative HPV. The corresponding data for CIN3+ was 0.63 (95% CI 0.48-0.80) for negative cytology compared with 0.28 (95% CI 0.18-0.40) for a negative HR HPV test[8]. For HPV negative women over 50 years, the cumulative risk over six years was only 0.16% (95% CI 0.07-0.34), suggesting the potential to extend the screening interval for women over 50 to 10 years.	We recognise the validity of this data but feel that the more accurate comparison to make would be to compare the protection offered by HPV screening at the extended intervals of 6 and 10 years with the protection offered by the **current** programme using cytology at 3 and 5 years.
Page 7	This means that co-testing would have required 20,000 additional cytology and up to 1500 colposcopies to detect 11 CIN3 lesions (PPV<1%).	We acknowledge that overall co-testing does not represent value for money but with the proposed intervals and the known false negative risk for HPV testing (in ARTISTIC 15% of CIN2+ cases were HPV negative) one test (at age 25) until the age of 31 may result in a significant number of cases of high grade CIN progressing to cancer by that age. This assumption is based on the fact that 46% of cases of severe dyskaryosis occur in women aged under 30. It is acknowledged that a single co-test at age 25 would add cost to the programme but would provide extra protection for the up to 15% of women with high grade disease who would have a false negative HPV test and would offer a potential saving in respect of the subsequent treatment costs that would be incurred.
9.4.What proportion of women with HPV	**"**around 8% of screened women aged 25-64 might be expected to be HPV positive/cytology negative."	The figure of 8%, while a fair approximation of HPV positivity/cytology negative, is an over simplification of the actual breakdown of incidence according to age. In one of the sentinel

positive results will be cytology negative? Can this be broken down by under 30s and over 30s?		sites the figure is 11.7% overall but with 21% under 30 with the 8% only applying to those women aged over 30. It is important to recognise the significantly higher percentage in the under 30 age group and the risk this could present in respect of false negative tests.
9.5.Have cut-offs for HPV testing been agreed and has the frequency of screening been agreed?	To compare the tests robustly in the primary screening setting would require very large expensive studies which cannot be justified.	There is emerging and significant evidence to suggest that performance of the five platforms being used in the pilot sites is highly variable; we therefore believe that this statement is ill advised. The screening that women will receive in the future will depend on the choice of HPV testing platform and this must therefore be either the most sensitive or most cost effective. Results from the Horizon project in Denmark and those recently published by Sheffield Teaching Hospitals point to significant variation in performance
9.6.What is the proposed diagnostic pathway for HPV positive women?	"Several sites however have started to refer women who are persistently types 16/18 positive at 12 months. This is because some tests offer a 16/18 readout, and the specificity of HPV positivity can be increased by restricting referral to the highest risk types in terms of disease. If employed immediately, too many young women would be referred, on the other hand recall at 12 months for 16/18 positive and further recall at 24 months for other high risk positives will allow the highest risk women to be colposcoped and allow further clearance to occur in those with lower risk types"	We believe that this policy has significant merit but needs further evaluation through observation of current practice in the pilot sites. We estimate that detailed information that will inform as to the safest and most cost effective option will not be available until the end of year 4 at the very earliest.

12. Cost effectiveness of HPV primary screening	In general strategies using HPV as a sole primary screening test were both cost saving and life years saving.	It is not clear that any of the costings include accurate colposcopy costs or include the increased cost of histopathology that will result from increased referrals and the resulting increase in the number of biopsies taken for histological assessment. There is the potential for the proposed changes to have a significant impact of the histopathology biopsy workload that does not appear to have been investigated. We feel that greater consideration needs to be given to the impact this may have in relation to pathology laboratory staffing and costs.
14.1. Laboratory capacity and reconfiguration	Commissioning more centralised services will present some challenges.	National commissioning will be essential and there is concern that this brief acknowledgement could represent an underestimation of the actual scale of the proposal. The paper recognises the associated changes in staffing and mentions redeployment but it does not evaluate in any way the potential cost of retraining, redundancies or TUPE movements.
	Given around 3 million screened women per year	We believe this is an underestimate. Nearly four million women are invited each year and last year 3.5 million samples were processed by laboratories. It is recognised that this will fall with new screening algorithms and intervals but the reduction will not be felt from year 1.

	concentrating cervical screening to around 15 labs in England, perhaps two each in Scotland and one each for Wales and Northern Ireland	While not within the remit of the cervical screening programme and therefore this paper, any change of this scale and nature will have a profound impact on laboratories delivering a cytopathology and histopathology service. The paper does not consider the wider impact on the currently co-existent diagnostic cytology service if a major consolidation of screening services were to occur. All hospitals and trusts providing a combined screening and diagnostic cytology service will be aware of the associated service issues that would arise as a consequence of any reorganisation/large centralisation. There is no mention or consideration of the impact this might have to patient care in these other areas. Additionally there is no discussion of how colposcopy MDT meetings might function when laboratories are serving large areas or the potential impact that this might have on patient care. This aspect of a quality screening service should be taken into consideration.

14.2. The computer system	Should HPV screening be introduced, the increasingly personalised screening intervals and varying results will require a modern IT system	We agree entirely with this and would suggest that this needs to be resolved before role out can occur.
14.3. Implications for staffing	These include the age range of the cytoscreeners which tends towards older staff, the potential to redeploy from cytology to HPV testing, and cytology staff seeking new posts when it becomes clear that redundancy threaten	While many staff are aged 40+ many still have a significant number of years before they will retire at age 65/67. Only a small number (no more that 30 nationwide) could possibly be redeployed to HPV testing. As such we believe that more work on the redundancy and associated costs to individual Trusts needs to be undertaken (see also 14.1 comment). We would be concerned that in view of the risks we have already identified as a consequence of the proposed changes to the screening programme that Trusts across the UK might not be willing to take on a future role in the provision of cervical screening services.
15. Conclusion	In conclusion, there is grade A evidence to support a switch from primary cytology to primary HPV testing in cervical screening. This should save life years and cost less, increasingly so as the vaccinated population grows older	The conclusion suggests that there is grade A evidence for a switch, despite frequent earlier references in all three consultation documents to the need for further evidence. We believe that the strength of the evidence will not be known until a full screening round has completed within the pilot sites and it is likely the full risks and benefits will not be known until two full screening rounds have completed in 2019

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COMMITTEE . FEBRUARY 2015

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Page 5	The Summary results by age group section on page five contains the following: "If the HPV results are restricted to those sites for which colposcopy outcomes are available for primary cytology, the PPV of colposcopy for CIN2 is significantly lower for HPV primary screening (40.9% vs 44.2%, p=0.048) for ages 24-29 "The peak number of cases is observed in the 25–29 year old age group (1,406 or 16.0%), followed closely by cases in women aged 30-34 (1208 or 13.8%), and aged 35-39 (1171 or 13.3%). Nationally, for the first time, the peak incidence is observed in those aged 25-29, followed by those aged 35-39."	The numbers here are so low that the conclusions must be open to question. This age group now has the highest number of cases of cervical cancer (reference 1): HPV primary screening will therefore result in larger numbers of women of this age group being referred to achieve the same outcome. The report acknowledges that further data is necessary to inform the optimum protocol
Table 1B		Table 1B shows the percentage of HPV positive tests ranging from 10.9% to 15.7% of all tests. As indicated above, the reasons for such a large range need further investigation. In the absence of more information there is the risk that laboratories might choose a

		platform that does NOT give the best clinical outcomes.
Table 10		Table 10 shows the PPV of HPV for referral to be as low as 24.1% in women age 50 to 64, this compares with the Cervical Screening Programme statistical bulletin 2013-14 setting an achievable standard for laboratory reporting range between 72.7% and 92.2%. The lowest figure recorded by any laboratory in the 2013-14 report was 60.9%. A PPV of 24.1% would trigger an investigation into the laboratory, and is also likely to undermine confidence in the programme amongst the public.
Cost-effectiveness of HPV primary screening: summary of existing evidence.	"Based on the existing literature there is evidence to suggest that HPV primary screening may be cost effective compared to current cytology based screening practice in the UK, however further analyses using data from the NHS Cervical Screening Programme primary HPV screening pilot would determine whether these outcomes are replicated when implementing primary HPV screening in the UK screening setting."	We would strongly support waiting for the study to be completed before making a final decision.

Please return to Adrian Byrtus (Evidence Review & Policy Development Manager)adrian.byrtus@nhs.net**by 30th October**