# Planning the change to HPV testing as the primary screening test within the CervicalCheck programme

## Background

Cervical cancer is preceeded by precancerous changes which do not cause symptoms and are not visible to the naked eye. These changes can be present for between ten and fifteen years before a cancer develops. Most of these changes arise in squamous epithelium (skin like defensive tissue usually on the outside of the cervix) and the condition is called cervical intraepithelial neoplasia (CIN). Less frequntly, changes can occur in glandular epithelium (mucous producing glands usually found on the inside of the cervix) known as Adenocarcinoma in situ or AIS(1). Glandular changes are more difficult to detect, harder to diagnose and more challanging to treat(2). Almost all occur as a result of infection with specific types of the human papillomavirus (HPV)(3).

Screening aims to reduce the risk of cancer through the early detection and treatment of precancerous abnormalities. Organised population based organised Cervical Screening Programmes constitute important public health measures which have proven to be effective at reducing cancer rates(4). The main components of such programmes include a defined population to be screened, the screening interval and the screening test(s) used.

## Coverage

Effective programmes aim for more than 80% coverage of the population through a system of reminders (call and recall)(5). There is a long history of organised cervical screening in the Netherlands, the UK, and New Zealand where national programmes were established in the 1980s and early 1990s. Reductions in the mortality from invasive cervical cancer of up to 70% have been observed(6,7). In 2018, CervicalCheck - the National Cervical Screening Programme in Ireland marked ten completed years of providing free testing through primary care settings to the approx. 1.1 million women aged 25-60 years(8). The coverage rate for CervicalCheck for the five years to 31 December 2017 was **79.6%** compared well with coverage rates achieved elsewhere including Australia (82.7% for the period between 2010 and 2014)(9) and the Netherlands (64% up to 2011 to 2102)(10).

Since the beginning of CervicalCheck, there has been substantial participation from younger women (84.4 per cent of women aged 25-29 years screened compared to only 69.6 per cent of women in the 55-59 year old group). It is worth noting that coverage of the older age groups continues to improve as the programme matures(11). In 2018 as part of the Cerviva research consortium, CervicalCheck commenced a project to explore the attitudes and knowledge of screening among older women. This should help to inform screening promotion for older women. In addition, coverage varies geographically across the country – in the latest annual report published in September 2017(12). it was noted that eight counties had achieved the target of 80 per cent, with one of those counties achieved higher than 90 per cent. Disappointingly, five counties still appeared with coverage levels below 75 per cent.

## Quality assurance and Cervical Screening Programmes

Defined quality assurance across each step of the screening pathway is an integral part of any programme – allowing the performance of individual components to be checked against defined quality standards. This means that women have easy access to well-trained smeartakers, timely results and seamless efficient referral to colposcopy for diagnosis and effective treatment if necessary. Quality standards have been developed for CervicalCheck, with each step of the cervical screening process being addressed by a quality assurance committee. These standards were originally published in 2009 (CervicalCheck, National Cervical Screening Programme, 2009) and updated in 2014 (CervicalCheck, National Cervical Screening Programme, 2014)(13). All stakeholders involved in the process need to work together following agreed guidance for optimum results.

## Limitations of screening tests

No cervical screening programme can prevent all cervical cancer cases. Cervical screening tests are not 100% accurate. When deciding on optimum screening schedules, there is a need to balance benefits and harms. Programmes need to take into account the risk profile of the population to be screened as well as the screening behavior patterns of individual cohorts of women in this population.

Screening tests are **not diagnostic** but aim to identify women who would benefit from further intervention. The value of any screening test is a product of it's **sensitivity** (the ability for the test to detect an underlying condition) as well as the **specificity** (the chance that a positive test has detected underlying disease). Tests with low sensitivity are more likely to result in false negative results whereas tests with low specificity are more likely to result in false positive results(14).

False negative test results can potentially lead to missed or delayed opportunities to intervene in cases of women with treatable precancerous abnormalities or early invasive cervical cancer. False positive test results lead to unnecessary colposcopy with associated anxiety for women(15). Early

colposcopy could also lead to the identification of transient abnormalities leading to increased surveillance and possible unnecessary treatment. Screening programmes need to balance these risks in a trade-off between benefits and harms related to screening.

Since 2008, CervicalCheck has used Liquid-based cytology (LBC) to detect cellular (cytological) abnormalities as the primary screening test. An average of 1,250 smear (cytology) tests are performed daily as part of the programme. These are delivered by over 4000 smear takers, mainly in primary care.

The benefit of cytology is that it is a relatively specific test: a high grade result is very likely to signal the presence of high grade CIN. Cytology has known limitations with respect to sensitivity: a negative result does not necessarily mean that a high grade CIN is not present. Screening intervals are determined to take this into account. Screening starts at age 25 and with five tests at three yearly intervals between the ages of 25-40 years. Repeated testing is more likely to detect the underlying disease which can then be treated, noting that the average age of cervical cancer is 45 years. On the other hand, ccervical cancer may develop in the time between a negative screening test and a woman's next screening (interval cancer). This is more likely to happen where women have been underscreened before the false negative test. In addition, 20% of invasive cancers are glandular cancers– adenocarcinomas. These are more difficult to prevent as the precursers are more difficult to detect with cytology screening. Screening at intervals less than three years for most women has been shown to confer no additional benefit for most women but can increase the harms of screening(16).

## The Connection with HPV

The discovery that more than 99% of cervical cancers arise from a persistent infection with certain types of the human papillomavirus (HPV) provides new opportunities for cervical cancer prevention. The most obvious example of this is the school based vaccination programme has been in place since 2009 and has the potential with screening to make cervical cancer a rare disease for future generations of Irish women(17). For the women who make up the current screening population there is the possibility to enhance the effectiveness of screening by using tests which check for HPV infection by one or more of 14 HPV types associated with cervical cancer known as the high risk HPV subtypes (hr. HPV)(18).

How these tests are applied and how to interpret the results of these tests is a challange for healthcare providers. One key issue is the knowledge that transient harmless HPV infections occur in over 80% of women usually within eighteen months of initiating sexual activity(19). When an infection is detected, even with the types of HPV known as high risk types, the most likely outcome is that this infection will resolve spontaneously without causing any harm to the woman.

Newer tests continue to be developed which aim to provide more information to better quantify the risk of precancerous changes. Genotyping tests specify which of the high risk types are present -HPV 16/18 having a higher risk for high grade CIN (grades 2/3) (12-18%) than the other HPV types (known as HPV O with a 4% risk for high grade CIN) (20). Tests for molecular markers or by-products of abnormal cell proliferation aim to discriminate between a harmless infection which is likely to resolve and transforming infections which are more likely to cause precancer and, over time, cancer. Two such markers are called P16 and KI67(21). These have been incorporated into a stain which can be used on cytology slides to improve the detection of abnormal cells on a smear test. The determination of clinical pathways to select which test to apply in which order for which women will continue to be a challange for screening programmes into the future.

## HPV testing and CervicalCheck to date

For the last seven years, CervicalCheck colposcopy services have been using a combination of cytology and HPV testing to allow a more accurate definition of the risk of high grade CIN. This has been useful both following treatment as well as the management of women who have not yet been treated. Women with results categorised as low risk are eligible for discharge from colposcopy and a return to routine screening. This avoids multiple follow up visits and unnecessary testing with more effective use of resources as well as reducing unnecessary anxiety for women(22).

In 2015, CervicalCheck introduced reflex HPV testing to triage women with low grade abnormalities, a policy designed to enhance the early diagnosis and treatment of high grade CIN. When low-grade cytological abnormalities are detected, the programme laboratories test the sample for infections with certain types of the human papillomavirus (HPV). The additional information provided by this test is used to plan the next step in the programme for these women.

Without adjunctive HPV testing, these women were managed with repeat smear tests at shorter intervals, with referral to colposcopy only if these changes persisted. The need for multiple repeat tests can be worrying and inconvenient for women and can be associated with a lack of compliance and the risk of default. There is also the possibility of a delay in the identification of women who have high grade CIN/AIS or indeed the tiny minority of women who have early cancerous changes.

The use of a test for high risk HPV infections provides real time information and reassurance for women who have a very low risk of cancer, reducing the need for repeat smear tests and the possibility of default. While a positive HPV test results in more women having to have a colposcopy, it allows earlier recognition of high grade CIN/AIS which can then be treated promptly and effectively(23). The results of this policy for the first full year of operation year (September 2015-August 2016) were published in the last CervicalCheck annual report. Of the 15,046 women with low

grade changes who had HPV triage, 8062 (53.4%) were referred to colposcopy earlier due to HPV triage while 6,984 (46.4%) were recommended routine screening. During that year, the highest number of high grade abnormalities at colposcopy was recorded since the beginning of the programme highlighting the earlier detection.

Based on the overall positive experience with HPV testing as part of CervicalCheck the question arises whether it is time to consider changing the order of the primary screening tests. Instead of most women having a cytology test and only a minority being tested for HPV infection – should this be reversed? Should screening for HPV be the primary test with only a minority of women having a reflex cytology test? To inform this decision the National Screening Service (NSS) asked HIQA to carry out a HTA (health technology assessment) on the use of tests for HPV infection as part of CervicalCheck, the national cervical screening programme.

## Outcome of the HTA

In May 2017 HIQA published the HTA which recommended changes to the primary screening test – with tests for certain types of the human papillomavirus (HPV), replacing cytology as the primary test(24). Adopting this strategy should prevent more cancers while reducing the numbers of screens a woman has in her lifetime. They have found these changes would benefit women by making the screening process more clinically effective as well as reducing unnecessary tests for most women. In addition, these tests could allow the inclusion of older women into the screening programme. In addition, testing for the HPV virus will be a more appropriate strategy for the cohort of women who have received the vaccination against HPV.

## Implementation plan

CervicalCheck commenced an implementation programme to plan and deliver this major change. This will need to incorporate elements such as IT and laboratory configuration as well as the development of dedicated communication, educational and training tools. From a clinical standpoint, major changes in the quality assurance standards need to be delivered as well as major alterations to clinical guidance for both smear takers and colposcopy services. Ensuring adequate colposcopy capacity to deliver timely diagnosis and treatment requires careful planning. Changes to the monitoring framework will be important to demonstrate any improvements in outcome resulting from the change.

## Why change the test?

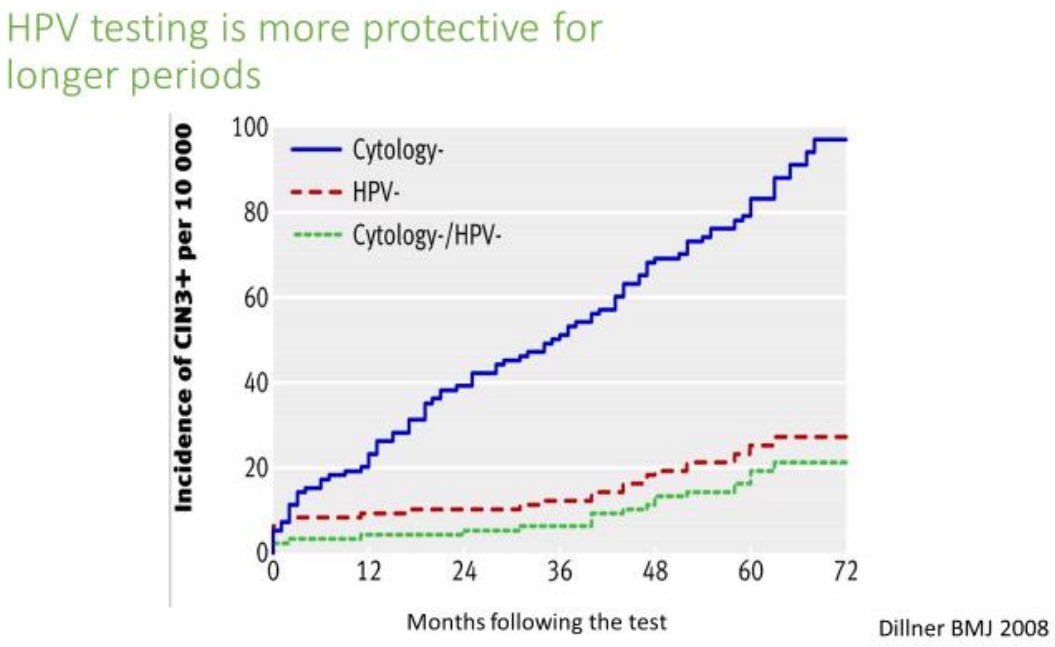
- ### HPV tests are more sensitive

  In the meta-analysis carried out by HIQA published in May 2017 the sensitivity of primary HPV screening in the detection of CIN 2+ and CIN 3+ was 95.2% and 98.2%, respectively. This was

significantly higher than the pooled sensitivity of primary cytology screening which was 75.0% and 78.0%, respectively. Thus, primary HPV screening using HC2 would result in fewer women receiving a false negative result, compared with primary cytology screening(24).

- ## HPV tests have better negative predictive value

Another marker of diagnostic accuracy of a screening test is the negative predictive value – which is a measure of the protection of the test against the development of high grade CIN over time. Evidence from long-term follow-up of women who have undergone primary cytology screening or primary HPV screening has shown that a negative HPV test at baseline has twice the protection against having high grade CIN at six years that a baseline negative cytology test has at three years (20). This has the advantage of allowing the interval between screens to be increased without sacrificing protection while simultaneously reducing unnecessary testing for women.




. ## HPV tests are less specific

Based on the HIQA meta-analysis(24) the pooled specificity of primary HPV screening in the detection of CIN 2+ and CIN 3+ was **88.2%** and **87.5%** respectively. This was lower than the pooled specificity of primary cytology screening which was **95.0%** and **95.1%**, respectively. Thus, primary HPV screening would result in more women receiving a false positive result,

compared with primary cytology screening. This has the potential to upset the balance between harms and benefits if too many women are selected for colposcopy.

## The need for a second or Triage test (test of disease)

Overall it is expected that 15% of women will test positive for Hr. HPV based on prevalence data from Irish primary screening study currently ongoing between Cerviva and CervicalCheck. Most of these women do not have precancerous changes. A second test is needed to triage women for further diagnosis and treatment. The question arises as to which triage strategy should be used. Options include traditional Cytology or Genotyping or molecular informed cytology using stains to mark cells with high levels of P16 and KI 67. The plan in 2018 was to simply to reverse the existing strategy – HPV for all with cytology for some instead of the existing strategy of cytology for all with HPV testing for some. This strategy has proven to be effective in the UK studies(25). Alternative approaches using genotyping and molecular marked cytology have been planned for other international programmes(26). In Ireland, it remains to be see what effect the events of the last year will have on the final clinical pathways when the strategy is finally introduced.

## International Context

The recommendation to switch from primary cytology screening to primary HPV screening is in keeping with developments in other high-income countries. Australia, Italy, Netherlands, New Zealand, Sweden and the UK have all recommended the implementation of primary HPV screening. In January 2017, the Netherlands was the first country with an organised cervical screening programme to fully transition from primary cytology screening to primary HPV screening at five-yearly intervals for women aged 30 to 60 years. The screening interval is extended to 10-yearly for HPV-negative women aged at least 40 years. Australia followed with five-yearly primary HPV screening for women between the ages of 25 and 69 years from December 2017. New Zealand transitioned to this strategy in 2018.

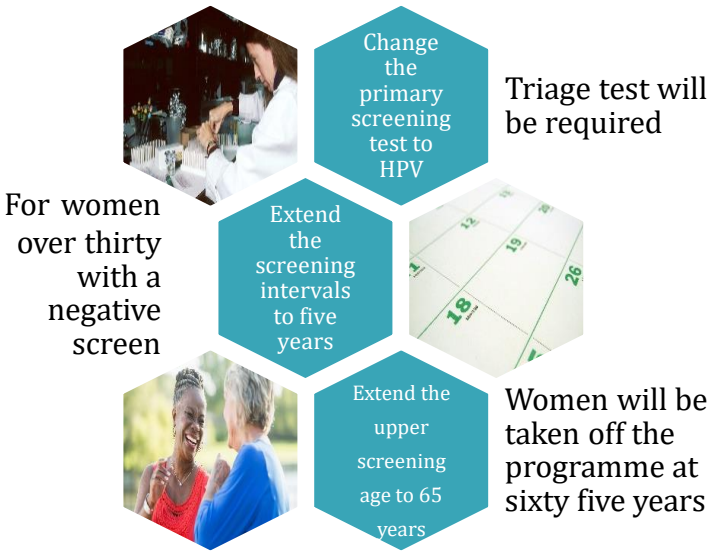
## *Question: What are the implications for referral pathways for abnormal results identified by this new process?*

### What would be the effects of the change?

- Women who attend for screening must be informed by programme literature and by the doctor or nurse they attend that the test sample **will** be tested for HPV infection. Currently, women must be informed that the sample **may** be tested for HPV infection (triage test only).
- There will be no change in how the test is carried out for the woman or for the doctor or nurse who takes the sample. There is no change in the way the sample is taken, or in the test kit used to collect the sample and despatch it to a laboratory for analysis and reporting.
- There are no proposed changes to the recommendations accompanying screening test results: routine screening, repeat in 1 year, repeat in 3 months (unsatisfactory tests) or refer to colposcopy. However, the test results that give rise to these recommendations will change.
- Every cervical screening sample will be tested for HPV infection by one or more of 14 HPV types associated with cervical cancer. Every woman that attends for a cervical screening test can know her HPV-infection status (with reference to 14 HPV types) with the test result provided to the doctor.
- Most women will be invited to attend for screening less frequently. The routine screening interval will be 5-yearly for women over 30 years of age. The routine screening interval will remain at 3-yearly for women aged up to 30 years. This is a significant change from the current screening strategy where women are screened 3- yearly and move to 5-yearly intervals only when they are over 45 years of age and have had 2 successive negative test results at a 3-yearly interval.
- Women will continue to be invited for regular screening up to 65 years of age (the current upper screening age is 60 years).
- Currently, the samples of 5.5% of women who are screened (low grade cytological abnormalities) are triaged with a second test (HPV test). This will change to a predicted 14% (the HPV prevalence rate in the population to be screened) of women screened being triaged with a second test(s) to include one or more of the following (cytology, cytology stained for P16/Ki 67, HPV genotyping).
- The number of women referred to colposcopy following screening will increase with sustained increases for a number of years before eventually reducing.

- Several factors need to be considered to develop the projections for the volume of activity in the different stages of the pathway – screening, HPV testing, cytology screening, colposcopy appointments and histology – as well as the associated costs - with the number of tests repeated after one year (HPV positive \ triage negative women) and the number of referrals to colposcopy being the key drivers.

### Planned changes to the CervicalCheck Programme




## Question: Will the CervicalCheck colposcopy service have the capacity to deal with any increased referrals?

To address this question, it is important to first look at the development of the colposcopy services during the last ten years.

### The development of colposcopy services to date

Access to timely diagnosis and treatment is important for successful cervical screening programmes. Fifteen colposcopy services across the country provide quality assured diagnosis and treatment with dedicated multidisciplinary teams. Long waiting times were a feature of colposcopy services at the start of the programme with a capacity for approximately 9000 new patients per year. Significant investments were made in providing adequate supports and facilities, including electronic linkage

between services and the programme. Service level agreements were put in place to provide resources for 16,500 new patients annually to ensure adequate quality assured capacity. It was agreed that all colposcopists should be accredited by the British Society for Colposcopy and Cervical Pathology. In 2015, the capacity for new referrals was increased to 19,500 to facilitate HPV triage. This allowed this initiative to be introduced without any significant deterioration in waiting times.

## Improvements in access to Colposcopy

Because of improved access, the number of women attending colposcopy increased significantly in the first eight years of the CervicalCheck programme with a peak of 17,909 new patients attending for the first time in the eighth year of the programme. Since 2008, the waiting times for colposcopy decreased reaching the standard of 90% less than two weeks for suspected cancer, 90% within four weeks for suspected adenocarcinoma in situ and 90% within eight weeks for low grade referrals. Increased capacity in colposcopy delivered significant improvements in waiting times. Between the fifth year of the programme and mid 2018, the waiting times surpassed national standards for all categories of smear test abnormalities(12).

## The effectiveness of CervicalCheck – detection of high grade CIN and AIS

A key objective of a cervical screening programme is the detection of high grade CIN and the yield of these abnormalities is one of the hallmarks of success. In the first ten years of CervicalCheck an estimated **65,000 cases of high grade pre-cancer** were detected. This is encouraging as is the finding that cervical cancer rates which had been rising year on year before CervicalCheck have been reducing by **seven percent per year**.

## Projected impact of the change to HPV testing on the number of women referred to colposcopy

Women are referred to colposcopy either on the basis of a positive screening test or for clinical reasons. Any change in referral pattern will impact on available capacity and require significant planning to ensure compliance with agreed waiting times.

### Referral on the basis of an abnormal screening test

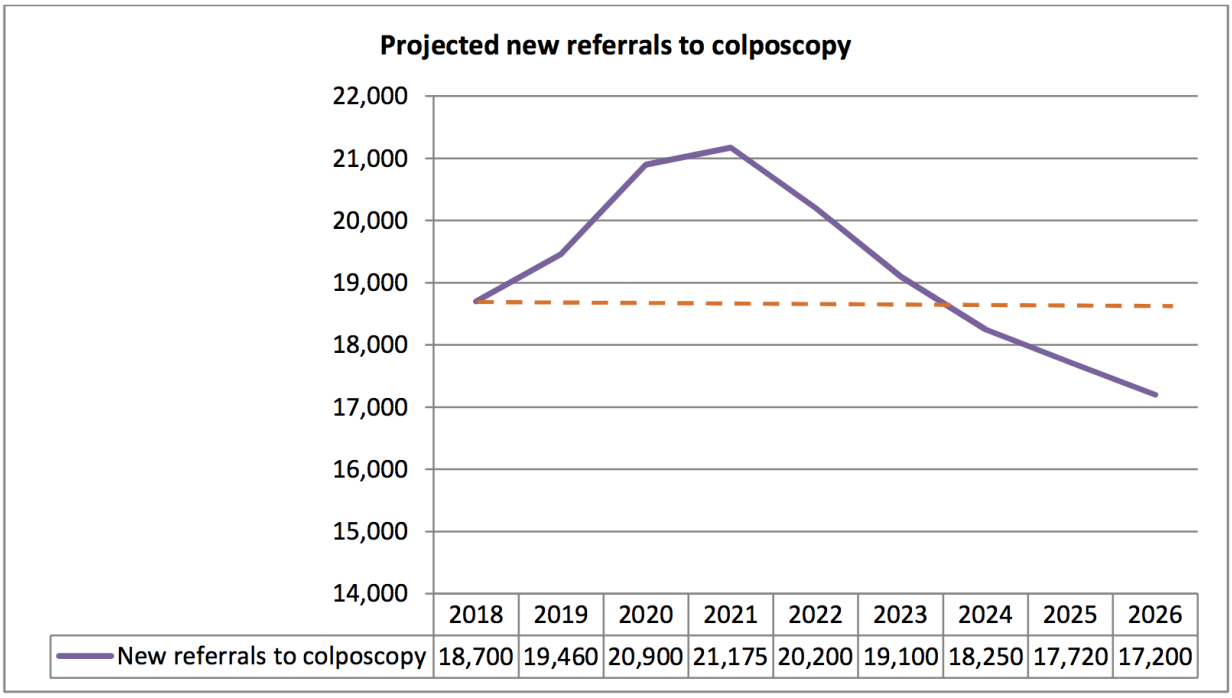
This is dependent on the number of women screened, the nature and history of those women – in particular, their age (associated with higher or lower HPV prevalence rates) and whether they have been recommended a repeat test a year earlier following a HPV positive and triage negative result,

It is anticipated that there will be an increase in the number of new referrals to colposcopy, in particular in years 2 and 3 following a change in strategy, based upon the projected number of women

to be screened and the projected abnormal reporting rates. The existing capacity within the programme colposcopy services is adequate for approximately 19,500 new referrals per annum. The number of new referrals in 2016 was approximately 18,800. Up to 2018 there existed a small amount of available capacity for new referrals but **a shortfall of between 2000 and 3000 is predicted**. This shortfall would become apparent in the second year following implementation of HPV testing. This shortfall will need to be planned and delivered in advance to ensure a quality assured service.

Estimations are that the numbers in this category will drop beyond year three of the new programme as the numbers of women tested reduce (following a recommendation of a five-year recall instead of three years).

**Projected impact on colposcopy (CervicalCheck 2018) based on projected abnormal screening test results (2018) ***




| | 2018 | 2019 | 2020 | 2021 | 2022 | 2023 | 2024 | 2025 | 2026 |
|---|---|---|---|---|---|---|---|---|---|
| New referrals to colposcopy | 18,700 | 19,460 | 20,900 | 21,175 | 20,200 | 19,100 | 18,250 | 17,720 | 17,200 |

Table 4: *Projected referrals to colposcopy, 2018 (current strategy), 2019-2026 (changed strategy)*

*These projected figures delivered to the DOH in 2017 assumed the **baseline referral rate for clinical indications of less than 20%**

### Referral to colposcopy for clinical reasons

These can include a suspicion of cervical cancer based on the appearance of the cervix or women with abnormal vaginal bleeding. Women with abnormal vaginal bleeding should ideally be seen at a gynaecology service in the first instance and only referred to colposcopy if there is a clinical suspicion of cancer or precancer. During its first ten years of operation CervicalCheck was successful in limiting the percentage of women referred for clinical reasons, reserving the capacity for women with an abnormal screening result.

In 2018, it was projected that the number of women referred to colposcopy for reasons of clinical indication would not change with the implementation of HPV testing as the numbers of these had been static for many years with overall figures of less than 20% of referrals. From the middle of 2018, these referrals have increased significantly due to the need for reassurance when smear takers became less confident of the significance of normal and benign features of the cervix. Acute gynaecology services had already been under pressure in recent years due to insufficient capacity. Increasing numbers of women with any abnormal bleeding were diverted to colposcopy instead of gynaecology to take advantage of the shorter waiting times. This has placed severe pressure on colposcopy services and poses a real risk to the viability of crucial and specialist colposcopy services. In addition, these referrals cause significant anxiety for women many of whom instead of being reassured by an additional normal test result, are still worried that they might have cervical cancer. The solution is to put in place systems to provide adequate rapid access gynaecology services to reverse this trend. This will require input from the HSE Acute Hospitals Division and is outwidth the remit of the Screening Service.

## Revision of quality standards and Clinical Guidance for colposcopy

As previously mentioned quality standards have been developed for CervicalCheck, with each step of the cervical screening process being addressed by a quality assurance committee. These standards were originally published in 2009 (CervicalCheck, National Cervical Screening Programme, 2009) and updated in 2014 (CervicalCheck, National Cervical Screening Programme, 2014). These quality standards will need to be modified to encompass the radical change from cytology to HPV based testing. Planning for these changes was well underway in the middle of 2018 with an urgent need for additional research and secretarial support identified to facilitate this process.

## Question: Did the Department of Health, Minister, or Minister's team inform, or seek an opinion from, CervicalCheck /the National Screening Service regarding offering an out-of-cycle smear test?

### When this opinion/advice was sought?

As clinical director for CervicalCheck, I attended a meeting with Dr Jerome Coffey, Dr Colm Henry and the head of screening, Mr. Charles O Hanlon, at the offices of the NSS at lunchtime on Saturday, the 28th of April 2018. Following this meeting, Mr O Hanlon called me into his office to confirm that he had been contacted by a representative from the Department of Health (DOH) to discuss a proposal to facilitate a repeat test for any woman concerned about the result of her screening test. This was the first contact to my knowledge between the DOH and the NSS on this matter.

### What opinion/advice was provided?

The immediate response emphasised by me to Mr O Hanlon that this raised the following issues

1) General Practitioners would not be able to be paid for this service as there was no mechanism for payment of out of programme tests
2) Laboratories would not have sufficient capacity
   Already laboratories had issues with recruitment and retention of cytologists given the proposed move to HPV screening. CervicalCheck had contracted for on average 250,000 tests per year. Open access for repeat testing would be difficult to plan for and difficult to deliver sufficient capacity to avoid longer waiting times for results
3) Colposcopy services will not have sufficient capacity
   Capacity for new colposcopy was based on the numbers of women screened. Again, open access for repeat testing would be difficult to plan for and difficult to deliver sufficient capacity to avoid longer waiting times for appointments
4) Most importantly, it would fundamentally undermine the screening programme.

At a follow-up discussion, within the hour, Mr O Hanlon reported that when he contacted the DOH, the

response was the decision was to proceed with this policy change in any case. No further explanation was forthcoming.

The announcement was made later that afternoon. Later that evening I stepped aside as clinical director. I have no knowledge of any subsequent discussions between the NSS, HSE and the DOH regarding this decision.

## If, in April 2018, opinion/advice was given to the Department of Health to not proceed with the free out-of-cycle smear test, has there been any correspondence with the Department since then, in relation to this?

I cannot comment on events since I stepped down from my position as clinical director on the 28th April 2018.

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