Cervical Screening: History, Current Algorithms, and Future Directions

3

John H.F. Smith

Abstract

This chapter describes the principles and evaluation of cancer screening programs, the evolution and history of cytology-based cervical cancer screening programs in the UK, past and contemporary terminology and algorithms for the management of abnormal cytology results, and the future application of HPV and other molecular technology in cervical cancer screening.

Principles of Screening

The criteria for appraising the validity of a screening program were first described by Wilson and Jungner for the World Health Organization (WHO) in 1968 and relate to the disease in question, the test applied, the treatment available, and the cost of intervention as shown below [1]:

1. The condition being screened for should be an important health problem.
2. The natural history of the condition should be well understood.
3. There should be a detectable early stage.
4. Treatment at an early stage should be of more benefit than at a later stage.
5. A suitable test should be devised for the early stage.
6. The test should be acceptable.
7. Intervals for repeating the test should be determined.
8. Adequate health service provision should be made for the extra clinical workload resulting from screening.
9. The risks, both physical and psychological, should be less than the benefits.
10. The costs should be balanced against the benefits.

Subsequently these criteria were expanded and embellished by the UK National Screening Committee to encompass not only the validity but also the effectiveness and appropriateness of any screening program as follows [2]:

J.H.F. Smith
Department of Histopathology and Cytology,
Royal Hallamshire Hospital,
Sheffield, UK
e-mail: john.h.smith@sth.nhs.uk

C.S. Herrington (ed.), *Pathology of the Cervix*, Essentials of Diagnostic Gynecological Pathology 3,
DOI 10.1007/978-3-319-51257-0_3

The Condition

1. The condition should be an important health problem.
2. The epidemiology and natural history of the condition, including development from latent to declared disease, should be adequately understood, and there should be a detectable risk factor, disease marker, latent period, or early symptomatic stage.
3. All the cost-effective primary prevention interventions should have been implemented as far as practicable.
4. If the carriers of a mutation are identified as a result of screening, the natural history of people with this status should be understood, including the psychological implications.

The Test

1. There should be a simple, safe, precise, and validated screening test.
2. The distribution of test values in the target population should be known and a suitable cut-off level defined and agreed.
3. The test should be acceptable to the population.
4. There should be an agreed policy on the further diagnostic investigation of individuals with a positive test result and on the choices available to those individuals.
5. If the test is for mutations, the criteria used to select the subset of mutations to be covered by screening, if all possible mutations are not being tested for, should be clearly set out.

The Treatment

1. There should be an effective treatment or intervention for patients identified through early detection, with evidence of early treatment leading to better outcomes than late treatment.
2. There should be agreed evidence-based policies covering which individuals should be offered treatment and the appropriate treatment to be offered.
3. Clinical management of the condition and patient outcomes should be optimized in all healthcare providers prior to participation in a screening program.

The Screening Program

1. There should be evidence from high-quality randomized controlled trials that the screening program is effective in reducing mortality or morbidity. Where screening is aimed solely at providing information to allow the person being screened to make an "informed choice" (e.g., Down's syndrome and cystic fibrosis carrier screening), there must be evidence from high-quality trials that the test accurately measures risk. The information that is provided about the test and its outcome must be of value and readily understood by the individual being screened.
2. There should be evidence that the complete screening program (test, diagnostic procedures, treatment/intervention) is clinically, socially, and ethically acceptable to health professionals and the public.
3. The benefit from the screening program should outweigh the physical and psychological harm (caused by the test, diagnostic procedures, and treatment).
4. The opportunity cost of the screening program (including testing, diagnosis and treatment, administration, training, and quality assurance) should be economically balanced in relation to expenditure on medical care as a whole (i.e., value for money).
5. There should be a plan for managing and monitoring the screening program and an agreed set of quality assurance standards.
6. Adequate staffing and facilities for testing, diagnosis, treatment, and program management should be available prior to the commencement of the screening program.
7. All other options for managing the condition should have been considered (e.g., improving treatment and providing other services), to ensure that no more cost-effective intervention could be introduced or current

interventions increased within the resources available.
8. Evidence-based information, explaining the consequences of testing, investigation, and treatment, should be made available to potential participants to assist them in making an informed choice.
9. Public pressure for widening the eligibility criteria for reducing the screening interval, and for increasing the sensitivity of the testing process, should be anticipated. Decisions about these parameters should be scientifically justifiable to the public.
10. If screening is for a mutation, the program should be acceptable to people identified as carriers and to other family members.
11. As described in Chap. 2, the etiology and pathogenesis of cervical neoplasia is well established and the natural history understood. While cytology-based screening for cervical precancer meets many of the Wilson and Jungner criteria, it remains open to the criticism that it has never been subjected to high-quality randomized clinical trials, in contrast, for example, to breast cancer screening [3, 4].

Epidemiology of Cervical Cancer

Globally, cervical cancer remains a major public health problem. Worldwide, cervical cancer is the fourth most common cancer in women, and the seventh most common overall, with an estimated 528,000 new cases in 2012. More than 85% of the global burden occurs in developing countries where it accounts for almost 12% of all female cancers. High-risk regions, with estimated age-standardized rates over 30 per 100,000, include Eastern Africa (42.7), Melanesia (33.3), Southern Africa (31.5), and Middle Africa (30.6) while rates are lowest in Western Europe (7.3), Northern America (6.6), Australia and New Zealand (5.5), and Western Asia (4.4) reflecting in part the success of cytology-based population screening programs in the latter. Cervical cancer remains the most common cancer in women in Eastern and Middle Africa.

There were an estimated 266,000 deaths from cervical cancer worldwide in 2012, accounting for 7.5% of all female cancer deaths, and 87% of cervical cancer deaths occur in less developed regions. The average risk of dying from cervical cancer before age 75 is three times higher in less than in more developed regions. Mortality varies 18-fold between the different regions of the world, ranging from less than 2 per 100,000 in Western Asia, Western Europe, and Australia and New Zealand to above 20 per 100,000 in Melanesia (20.6), Middle Africa (22.2), and Eastern Africa (27.6) [5].

Papanicolaou and the Development of Cytology-Based Population Screening

Donne (1844) and Pouchet (1847) first described the cytology of vaginal secretion in the mid-nineteenth century but neither description related to the diagnosis of cervical cancer [6, 7]. In 1869 Dickenson examined discharges from women with cervical cancer, but failed to find diagnostic cells [8]. It was not until 1871 that Richardson in the USA recommended cytological examination in cases of suspected cervical carcinoma and wrote: "In suspected cancer of the womb ... a small portion of the secretion from the os uteri, or from the ulcerated surface of the growth itself, should such exist, must therefore be removed by means of a probe or pair of forceps introduced through a speculum, and on examination with a power of 200 diameters will probably disclose at least a few cells on each slide, which will indicate with more or less certainty the character of the morbid formation." In 1886 Friedlaender also used this method but warned against diagnosing carcinoma from the cytology alone [6].

Papanicolaou first systematically used the vaginal smear, and ever since the technique has been associated with his name as the "Pap test" or "Pap smear." George N. Papanicolaou qualified in medicine in Athens in 1904 and as a junior postgraduate specialized in the experimental study of reproduction. In 1913 he emigrated to New York, where he studied the estrous cycle in

animals and the human menstrual cycle by examination of vaginal smears [9]. During his studies on patients in the Women's Hospital, New York, Papanicolaou identified malignant cells in vaginal smears, and in 1928 he gave his first paper on this subject at a conference, entitling it "New cancer diagnosis" [10].

Simultaneously, and independently, cancer cells were recognized in cervical smears by the Romanian pathologist Aurel Babes in Bucharest. Babes and Daniel first presented their new method for the diagnosis of carcinoma of the cervix, using a platinum loop to transfer material from the affected area to glass slides which were then air-dried and stained by the Giemsa technique, to the Bucharest Gynaecological Society in 1927 and the results were published the following year [11–13]. Simultaneously, the Italian gynecologist Odorico Viana, influenced by Babes, reported on the successful diagnosis of cervical cancer by the smear technique [14, 15].

Although the lesion we now recognize as cervical intraepithelial neoplasia (CIN)/squamous intraepithelial lesion (SIL) (see Chap. 6), the precursor of invasive squamous cell carcinoma of the cervix, had been recognized by the third decade of the twentieth century, Papanicolaou's report and the others referred to above received little attention, and Papanicolaou returned to a study of reproductive endocrinology in the 1930s. In 1939 Joseph Hinsey was appointed to the department of anatomy at Cornell and encouraged Papanicolaou to return to his work on cancer detection using the vaginal smear. Hinsey also arranged collaboration with Herbert Traut, a gynecologist trained in pathology, and Andrew Marchetti, chairman of the department of obstetrics and gynecology at Cornell, such that every woman admitted to the gynecology service at Cornell was required to have a vaginal smear, and these samples were made available for Papanicolaou to examine. In 1940 Papanicolaou obtained funding from the Commonwealth Fund, which enabled him to develop a new staining technique which included wet fixation in an ether-alcohol solution [16]. He subsequently demonstrated that the vaginal smear permitted an earlier diagnosis of cervical cancer and that this was made possible because vaginal smears had been taken repeatedly. Papanicolaou described the technique as exfoliative cytology from the Greek *ex*, away, and Latin *folium*, leaf, the analogy of vaginal smears being to that of leaves falling from a tree [17]. In 1941, Papanicolaou and Traut published their seminal paper entitled "The diagnostic value of vaginal smears in carcinoma of the uterus," and this was followed 2 years later by the monograph *Diagnosis of Uterine Cancer by the Vaginal Smear*, funded by the Commonwealth Fund and beautifully illustrated with camera lucida watercolor drawings by Murayama [18]. It should be noted that the Papanicolaou classification provided a measure of the likelihood of the presence of invasive cervical cancer, whereas contemporary cervical cytology classifications provides an evaluation of the likelihood of the presence of preinvasive disease (see below).

These publications altered the opinion of the medical profession, and many gynecologists became enthusiastic about the possibility of identifying cancer of the cervix at an early and curable stage. Cervical cancer detection by cytology was strongly supported by the American Cancer Society and the National Cancer Institute, and subsequent studies confirmed the value of cytology, to detect not only cancer but also precancerous changes [18–23]. In 1947 Papanicolaou began offering cytology training courses at Cornell, the First National Cytology Conference was held in Boston in 1948, the forerunner of the American Society of Cytopathology was founded in 1951, the first International Cancer Cytology Congress was held in Chicago in 1956, and the International Academy of Cytology was founded in 1957. The emergence of a body of trained exfoliative cytologists made possible the rapid development of population screening, first by the vaginal smear and soon after by cervical scraping using a wooden spatula introduced by Ayre [24]. Ruth M. Graham published the first modern comprehensive cytology text, *The Cytologic Diagnosis of Cancer*, in 1950 and Papanicolaou published his *Atlas of Exfoliative Cytology* in 1954 [25].

By the mid-1950s screening for cervical cancer by exfoliative cytology had been widely

introduced in North America and elsewhere, and the evidence of its benefits in terms of reduction in mortality progressively accumulated: the reduction in mortality was clearly directly related to the intensity of screening [26–35].

Cervical Cancer Screening in the UK (1950–1985)

After the Second World War, a small number of British gynecologists and pathologists, aware of the introduction of exfoliative cytology for cervical cancer screening in North America, began to explore the possibility of introducing a similar screening program in the recently established National Health Service. In 1951 an initial discussion was held by the section of obstetrics and gynecology of the Royal Society of Medicine after which a number of cytologists went to North America to visit Papanicolaou, Ruth Graham, Ayre, and others. Following a further conference at the Royal College of Obstetricians and Gynaecologists in 1955, Sir William Gilliatt and Dame Hilda Lloyd, both past presidents of the College, established a committee to look into the matter and further developed links with Papanicolaou and Ruth Graham and also with Professor Alex Agnew, H. Fidler, and D. A. Boyes in Vancouver.

Prior to the establishment of a comprehensive national population-based cervical cancer screening program, a number of well-known gynecologists were instrumental in the establishment of exfoliative cytology of the female genital tract at various centers: Chassar Moir in Oxford; McLaren in Birmingham; Way in Newcastle; Anderson in Edinburgh; Nixon at University College Hospital, London; Miss G. Hill at the Royal Free Hospital, London; McClure Browne at the Hammersmith Hospital; and Sir Dugald Baird in Aberdeen. In 1960 Sir Dugald Baird initiated the first population screening program to cover all women at risk of developing cervical cancer in North East Scotland, and Dr. J. Elizabeth Macgregor was appointed to manage the program and the laboratory [31, 33–36]. Dr. Erica Wachtel, who worked with Prof. McClure Browne at the Hammersmith Hospital, practiced exclusively in cytopathology and was the first practitioner to be appointed professor of cytopathology in the UK [37]. The first NHS consultant cytopathologist, O. A. N. Husain, was appointed to St. Stephen's Hospital, London, in 1961 [38].

Following the reports of J. M. G. Wilson of the DHSS [39, 40], a comprehensive National Cervical Cytology Screening Service was established in 1967. In 1964, in preparation for this service, five training schools were set up to teach the skills of cytodiagnosis – at the Hammersmith and Royal Free Hospitals, London; Birmingham; Manchester; and Newcastle. A national request/report form (HMR101) was introduced in 1967, which in modified form persists until today, and in the first year of the service half a million smear tests were performed. Expansion was rapid and by 1970 nearly 2.5 million tests per year were being recorded, increasing to 3.9 million in 1986. Most of the increase in the number of smears had been from general practitioners, rising from 27% of all smears in 1973 to 43% in 1980.

Women aged 35–60 years were screened at five yearly intervals with some opportunistic screening of women in antenatal and sexual health clinics. A manual record card-based screening registry for England was established at Southport to recall women for repeat tests.

UK Terminology of Cervical Cytology and Histology

The Papanicolaou classification system for cytological diagnosis introduced in 1954 was intended to apply to all types of cytology specimen to indicate the degree of certainty that cancer was present or absent: there was no correlation with cytology in the context of a program intended to identify precancerous lesions [25] (Table 3.1).

The entity of carcinoma in situ, the immediate precursor lesion of invasive squamous cell carcinoma of the cervix, in which the constituent cells morphologically looked like the cells found in invasive squamous cell carcinoma, had been recognized from the late nineteenth century [41–44]. However by the early 1950s, surface lesions of the

Table 3.1 Papanicolaou classification of cytology reports

Class I	Negative	Absence of atypical or abnormal cells
Class II	Negative	Atypical cells present but without abnormal features
Class III	Suspicious	Cells with abnormal features suggestive but not conclusive for malignancy
Class IV	Positive	Cells and cell clusters fairly conclusive for malignancy
Class V	Positive	Cells and cell clusters conclusive for malignancy

cervix with abnormal but less marked histological features had been identified, for which a number of terms were suggested including anaplasia, basal cell hyperplasia, atypical metaplasia, and atypical hyperplasia. In 1953 Regan proposed the term dysplasia, from the Greek *dys*, bad, and *plasia*, molding, which he divided into three grades, mild, moderate, and severe. This proposal was endorsed by the First International Congress of Exfoliative Cytology and the World Health Organization: in the latter the abnormal cells were described in terms of their histological correlation [45, 46]. Dysplasia appeared to have a lower risk of progression to cancer than carcinoma in situ, and consequently, at that time, women found to have carcinoma in situ were recommended to have a hysterectomy, while those with dysplasia were not immediately treated [47, 48].

During the establishment of the cervical screening program in the UK, it became apparent that a variety of terminology was being used to describe the morphological appearances of neoplastic cells derived from in situ and invasive cervical squamous lesions. In particular the practice in many laboratories of calling cells thought to be derived from carcinoma in situ "malignant cells" and using "dyskaryosis" to imply that nothing more than dysplasia was present began to be questioned in the light of the conclusive evidence from Richart that dysplasia and carcinoma in situ of the cervix were a "lesional continuum" [49]. A working party of the British Society for Clinical Cytology (BSCC) recommended that the terminology in the WHO publication *Cytology of the Female Genital Tract* be adopted for normal cellular components of a cervical smear (e.g., superficial, intermediate, and parabasal squamous cells; endocervical cells; endometrial cells) and the term "dyskaryosis" adopted for neoplastic squamous and glandular cells, irrespective of whether the cytologist thought that they were derived from an in situ or invasive lesion [50] (Table 3.2).

Table 3.2 Definition of dyskaryosis

Disproportionate nuclear enlargement
Irregularity in nuclear form and outline
Hyperchromasia
Multinucleation
Irregular chromatin distribution, which may be stippled, clumped, or stranded with condensation beneath the nuclear membrane
Abnormalities of the number, size, and form of nucleoli

Eight years later, a second BSCC working party endorsed the recommendation of dyskaryosis as the preferred terminology and recommended a three-grade system of mild, moderate, and severe dyskaryosis, based on the nuclear-cytoplasmic area of the dyskaryotic cells, which correlated with cells from the surface of CIN 1, CIN 2, and CIN 3, respectively. They also provided guidance on cytological features which were suggestive of the presence of invasive squamous carcinoma. This recommendation was universally adopted in the UK cervical cancer screening programs [51] (Table 3.3).

The 1986 working party also recognized that "There are smears in which the evidence is such that it is impossible to decide if the cells are the product of inflammation or if they have neoplastic potential" and suggested that such samples be described as showing borderline abnormalities. In 1994, a joint working party of the National Health Service Cervical Screening Programme (NHSCSP), the BSCC, and Royal College of Pathologists provided guidance on the diagnosis and management of borderline nuclear changes in squamous and glandular cells and their distinction from reactive or inflammatory change and neoplastic change [52].

In 2002, conscious of the widespread adoption of the two-tiered Bethesda system for reporting

Table 3.3 BSCC terminology in gynecological cytopathology (1986)

Grade	Morphological features	Histological correlate
Mild dyskaryosis	The abnormal nucleus occupies less than half the area of the cell, which has plentiful thin translucent cytoplasm with angular borders resembling a superficial or intermediate squamous cell	CIN 1
Moderate dyskaryosis	The abnormal nucleus occupies one half to two-thirds of the area of the cell. There is more disproportionate nuclear enlargement than in mild dyskaryosis, and nuclear morphology tends to be more abnormal than in mild dyskaryosis. The cytoplasm resembles that of intermediate, parabasal, or superficial cells.	CIN 2
Severe dyskaryosis	The abnormal nucleus practically fills the cell or at least two-thirds of its area and is surrounded by a narrow rim of thick dense cytoplasm. Affected cells may be round, oval, elongate, or polygonal	CIN 3

cervical cytology, originally developed in 1988 and subsequently modified in 2001, which reflected clinical practice and management in terms of low- and high-grade abnormality, the BSCC held a conference at which it was agreed that a two-tier system should also be introduced in the NHSCSP [53–58]. The revised BSCC terminology for cervical cytology was published in 2008 [59] and implemented in the NHSCSP in 2013. This terminology aligns closely with the Bethesda system, reflects contemporary understanding of the biology of human papillomavirus (HPV) infection, and permits international comparison of data (Table 3.4). The principal change introduced by this terminology is that while dyskaryosis is retained as the descriptor of neoplastic cell nuclear morphology, it is graded by evaluation of nuclear: cytoplasmic diameter rather than area, as previous studies had shown that the former was a more reliable discriminator of mild from moderate or severe dyskaryosis, i.e. low-grade from high-grade dyskaryosis, in both conventional and liquid-based cervical cytology preparations [60].

The NHS Cervical Screening Program (1986–2004)

Despite the establishment of the cervical screening program as described above, it was clear by the mid-1980s that it had had little impact on the incidence or mortality from cervical cancer. In 1985 a leading article in *The Lancet* drew attention to this fact and specifically commented that the most successful cancer screening programs are organized as public health cancer control programs, specifically directed toward a reduction of mortality; call the age group at greatest and most immediate risk (30 years +) based on population registers and keep on trying to call persistent non-attenders; concentrate first upon women who have never had a smear; and put "someone in charge" (a manager) of the process who can be held to account [61]. In 1988 health circular HC (88)1 directed District Health Authorities to give priority to screening for prevention of cervical cancer and in particular implementation of a call and recall system from lists of women held on Family Practitioner Committee (primary care) computers starting not later than 31 March 1988. All women aged 20–64 were to be invited for screening at least every 5 years (some health authorities elected to invite women every 3 years) and adequate facilities made available for prompt investigation treatment and follow-up of women with abnormal smear results [62]. General practitioners were also offered a financial incentive based on the proportion of their practice female population eligible for cervical screening that were tested. Initially the NHS cervical screening program was managed by a multidisciplinary National Coordinating Network but subsequently a director, Professor Julietta Patnick, and support

Table 3.4 BSCC terminology (2008): comparison with other terminologies (from Denton et al. [59])

BSCC 1986 and NHSCSP	BSCC proposed new terminology	The Bethesda system 2001	ECTP terminology	AMBS 2004
Negative	Negative	Negative for intraepithelial lesion or malignancy	Within normal limits	Negative
Inadequate	Inadequate	Unsatisfactory for evaluation	Unsatisfactory due to	Unsatisfactory
Borderline nuclear change	Borderline change, squamous, but not otherwise specified	Atypical squamous cells of undetermined significance (ASC-US)	Koilocytes (without changes suggestive of intraepithelial neoplasia) Squamous cell changes (not definitely neoplastic but merit early repeat)	Possible low-grade squamous intraepithelial lesion
	Borderline change, high-grade dyskaryosis not excluded	ASC-H (cannot exclude HSIL)		Possible high-grade squamous intraepithelial lesion
	Borderline change in endocervical cells	Atypical endocervical, endometrial, or glandular (NOS or specify in comments) Atypical endocervical or glandular cells, favor neoplastic	Atypical glandular cells (qualify)	Atypical endocervical cells of undetermined significance Atypical glandular cells of undetermined significance
Mild dyskaryosis	Low-grade dyskaryosis (includes all cases of koilocytosis provided that no high-grade dyskaryosis is present)	Low-grade squamous intra-epithelial lesion (LSIL)	Mild dysplasia (CIN1)	Low-grade squamous intraepithelial lesion
Moderate dyskaryosis	High-grade dyskaryosis	High-grade squamous intra-epithelial lesion (HSIL)	Moderate dysplasia (CIN2)	High-grade squamous intraepithelial lesion
Severe dyskaryosis		HSIL	1. Severe dysplasia (CIN3) 2. Carcinoma in situ (CIN3)	
Severe dyskaryosis? invasive	High-grade dyskaryosis? invasive	Squamous cell carcinoma	1. Severe dysplasia? invasive 2. Invasive squamous cell carcinoma	Squamous cell carcinoma
? Glandular neoplasia	? Glandular neoplasia, endocervical, non-cervical	1. Endocervical carcinoma in situ 2. Adenocarcinoma – endocervical, endometrial, extrauterine, not otherwise specified	Adenocarcinoma AIS, endocervical, endometrial, extrauterine NOS	Endocervical adenocarcinoma *in situ* Adenocarcinoma

BSCC British Society for Clinical Cytology, *ECTP* European Commission Training Programme, *AMBS* Australian Modified Bethesda System

staff were appointed in 1994 [63, 64]. Over the succeeding two decades, in collaboration with the relevant professional bodies, the NHSCSP produced a comprehensive series of guidance documents related to all aspects of the cervical cancer screening process from invitation to attend screening to treatment of identified abnormality. In particular, the first NHSCSP commissioned guidance entitled *Achievable standards, benchmarks for reporting and criteria for evaluation* and, thereby henceforth known as ABC 1, gave guidance on specimen adequacy, management of smear abnormality, evaluation of the program, internal quality control (IQC), and external quality assurance (EQA) [65] (Table 3.5). In relation to IQC and EQA, ABC 1 introduced achievable standard ranges for cytology reporting by laboratories and individuals, and in subsequent years these ranges were amended based on the mandatory returns (KC61) submitted by laboratories in the preceding year (Table 3.6). In the first of two subsequent editions of ABC, published in 2000, guidance on reporting of cervical smears was reinforced and where necessary revised, new performance indicators were introduced, and pitfalls in cytological diagnosis leading to false-positive and false-negative results described [66, 67]. In the second subsequent edition of ABC, published in 2013, adoption of the revised BSCC terminology for cervical cytology was mandated, management of cytological abnormality updated following the implementation of HPV triage and test of cure, and performance indicators for evaluating cervical cytopathology expanded to encompass not only individual and laboratory cytology performance but also the performance of related colposcopy and histopathology services [68–70].

The success of the reorganized English cervical screening program as NHSCSP was evidenced by the progressive fall in incidence of cervical cancer in the succeeding two decades: this has now largely stabilized

Table 3.5 ABC 1: recommendations for management

Management	Cytology result
Routine recall	Negative
Repeat smear at shorter interval than recommended routine recall	Inadequate sample and the first occurrence of mild dyskaryosis or borderline change A second repeat sample may be requested for inadequate samples or borderline change, but after three such smears colposcopy must be recommended. The repeat interval may vary between 3 and 12 months but is usually 6 months Annual repeat smears are recommended for 5 years after treatment of CIN 2 and CIN 3 At least two negative smears at least 6 months apart, after mild dyskaryosis, borderline change or treatment of CIN 1 before a woman returns to routine screening or screening is ceased at age 65
Referral for gynecological opinion	Moderate, severe, and ungraded dyskaryosis; invasive squamous and glandular neoplasia should all be referred on the first occurrence. Colposcopy should be recommended on the second occurrence of mild dyskaryosis

Herbert et al. [142]

Table 3.6 ABC 1: criteria for evaluating cervical cytology and monitoring the accuracy of screening

Measurement	Achievable range
Sensitivity of primary screening with respect to the final report after rapid review of all negative and inadequate smears	>90% all abnormalities >95% high-grade abnormality
Laboratory report profile: Inadequate Mild dyskaryosis and borderline change Moderate and severe dyskaryosis	 7.0 ± 2.0% 1.6 ± 0.4% 5.5 ± 1.5%
Positive predictive value (PPV) of moderate or severe dyskaryosis for the histological diagnosis of CIN 2 or worse	65–85%

Herbert et al. [142]

Fig. 3.1 Age-standardized incidence rates of invasive cervical cancer in the UK (1979–2013) (Source: Cancer Research UK. http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/cervical-cancer. Accessed August 2016)

(Fig. 3.1). The increased incidence around 2009 was the result of the increased uptake of screening due to the widely publicized diagnosis and death of a television personality [71, 72].

NHSCSP 2004 to the Present

Liquid-Based Cytology (LBC)

From the late 1980s, a number of manufacturers began to investigate the potential to produce monolayer or near-monolayer preparations of cervical cytology samples, with the intention that this would provide an optimized platform on which to employ computer-assisted image analysis microscopy. Production of near-monolayer preparations required samples to be collected in a liquid preservative – hence liquid-based cytology – and then most of the debris, blood, and exudate removed either by filtration or density gradient sedimentation, prior to preparation of the monolayer or near-monolayer sample. By the late 1990s, two systems were widely available: ThinPrep® (Hologic) and SurePath® (BD Diagnostics). In 2000 an initial evaluation by the National Institute for Clinical Excellence (NICE) suggested that LBC might be valuable technology to implement in the NHSCSP [73]. In 2003, following a further evaluation by NICE and an evaluation study in three English laboratories, the Department of Health (DoH) announced that LBC was to be used as the primary means of processing samples in the cervical screening program in England and Wales and full implementation of the new technology was to be achieved by 2008 [74, 75]. Implementation was conducted by a cascade process of laboratory conversion and training, and by late 2008 all cervical screening laboratories in England and Wales had converted to LBC. Scotland had already adopted LBC and Northern Ireland followed some time later [76].

Importantly, at the same time the DoH also announced changes in screening age range and frequency to be implemented by April 2004: women would in future be invited for their first screening test at age 25, not age 20, and screened thereafter every 3 years until age 49 and every 5 years from age 50 to 64 [77]. This policy change, based on an audit of the screening histories of women with invasive cervical cancer [78], was intended to unify and consolidate considerable variation in practice across England: as noted above the national recommendation was to screen every 5 years but some districts had elected to screen every 3 years. While concerns were raised about the effect of not screening women less than 25 years of age, it has been kept under review through the national audit of screening histories of women who develop cervical cancer: most cervical cancers in women under

age 30 years are screen detected as superficially invasive carcinomas (FIGO stage IA) [79–83].

As predicted, progressive implementation of LBC, combined with the change in screening age range and frequency, resulted in a reduction in the number of inadequate samples reported and thereby a decrease in the total number of tests examined: over 246,000 fewer tests were reported as inadequate in 2007–2008 compared with 2003–2004, the last year before LBC implementation. This also occurred against a background of an increased number of women aged 25–64 being screened, reflecting a more efficient screening program with fewer unnecessary tests outside the recommended screening age range [84]. Furthermore, the progressive loss of tests in women aged less than 25 years reduced the number of abnormal tests reported, particularly low-grade abnormalities which are most prevalent in this age group: nearly 19,000 fewer tests were reported as low grade and over 4000 as high grade in 2007–2008 compared with 2003–2004. As a result there was reconfiguration of consultant programmed activities in some laboratories to ensure maintenance of quality standards for the minimum number of abnormal tests examined annually.

Therefore, following a change in the screening age range and frequency and full implementation of LBC, a total of 269,000 fewer cervical cytology samples were examined in England in 2007–2008 compared with 2003–2004. Implementation of LBC also resulted in increased laboratory productivity and efficiency, with no adverse effect on quality. A large laboratory in Manchester reported that nearly 1 min per slide was saved during primary microscopy, and microscopy by cytopathologists, using LBC compared with conventional smear preparations. The uninterrupted hourly rate of slide examination rose from 8.6 slides for conventional smear preparations to 11.7 for LBC preparations, comparable to the data from the Scottish LBC feasibility study [76, 85]. A separate study from Scotland reported a 40% reduction in full primary screening time [86]. In the Sheffield laboratory, individual screener productivity increased by 20% in the first year following full LBC implementation [87], and productivity increases of up to 50% coupled with decreased numbers of unsatisfactory samples and an increased sensitivity for the detection of cytological abnormalities validated by subsequent histological investigation have been reported [88].

Increased productivity was also reflected in national data showing a progressive increase in the proportion of laboratories reporting results within 2 weeks of specimen receipt, an important achievement in view of the Cancer Reform Strategy objective that all women should receive the results of their test within 2 weeks by 2010 [89, 90].

As a result of LBC implementation, there was a growing mismatch between workload and capacity in some laboratories. However, a NHSCSP workforce survey revealed that over one-third of screening staff were over 50 years of age, and LBC implementation buffered laboratories against this marked demographic change [91]. In fact, some laboratories found no need to replace primary screening staff on retirement, resulting in cash-releasing cost savings.

National implementation of LBC not only resulted in improved laboratory efficiency and productivity but was also the platform for consideration of the implementation of molecular testing and automation in the NHS cervical screening programs.

HPV Testing

The recognition of the strong causal relationship between persistent infection of the genital tract with high-risk human papillomavirus (HPV) types and the occurrence of cervical cancer has resulted in the development of a number of HPV DNA and RNA detection systems in an attempt to refine existing cytology-based cervical cancer screening programs [92–95] (see Chap. 2). LBC provides an ideal platform for application of this and other molecular technologies. Detection of high-risk HPV DNA is considered to be potentially useful in four clinical applications [96]:

1. As a triage test to select which women who have low-grade cytological abnormalities in routine screening require immediate referral for colposcopy rather than cytological surveillance.

2. Follow-up of women with abnormal screening results who are negative at colposcopy and biopsy.
3. Follow-up for women treated for high-grade CIN with local ablative or excisional treatment to more rapidly and accurately identify those who have or have not been cured.
4. As a primary screening test, either alone or in combination with cervical cytology to detect cervical cancer precursors.

Triage of Low-Grade Abnormality

A meta-analysis of studies published between 1992 and 2010 comparing HPV testing with Hybrid Capture 2 (HC2) with repeat cytology in the management of low-grade cytological abnormality (borderline nuclear change/atypical squamous cells (ASCUS); mild dyskaryosis/low-grade squamous intraepithelial lesion (LSIL)) showed that HPV triage with HC2 of women with borderline nuclear change had significantly higher sensitivity than, and similar specificity to, repeat cytology. In triage of women with mild dyskaryosis, an HC2 test yielded a significantly higher sensitivity, but a significantly lower specificity, compared to repeat cytology [97]. A pilot study conducted within the initial English evaluation of liquid-based cytology demonstrated that, while HPV triage of low-grade abnormality resulted in a reduction in the rate of repeat smears but an increase in rates of referral to colposcopy, it was likely to be cost effective [98, 99]. A further evaluation of HPV triage implementation in six laboratories in the English cervical screening program (the sentinel site study) demonstrated that triaging women with low-grade cytological abnormalities by HPV testing would allow approximately a third of these women to be returned immediately to routine recall, and immediate referral for colposcopy would avoid the need for repeat cytology in the remainder. The HPV-positive rates at the six sites ranged from 34.8% to 73.3% for women with borderline cytology and from 73.4% to 91.6% for women with mild dyskaryosis, and these differences remained after the rates were standardized for age. Overall the HPV-positive rate was higher in sites using ThinPrep® than in those using SurePath® LBC [68.7% and 61.7% respectively ($p < 0.001$)], and the difference remained after adjustment for age group and initial cytology result. LBC technology was, however, confounded by site, and it was therefore not possible to determine whether this difference was due to variation in the reporting of cytology between sites. In the only site which used both technologies, there was no significant difference in positive rates between the two technologies [100]. Based on this data HPV triage of low-grade cytological abnormality was implemented in the English cervical screening program in 2011 using the algorithm developed for the sentinel site study (Fig. 3.2).

Test of Cure

Prior to 2011 NHSCSP guidance was that women treated for low-grade disease (CIN 1) required follow-up cytology at 6, 12, and 24 months and if all results were negative could return to routine screening. Women treated for high-grade disease (CIN 2 or 3 or cervical glandular intraepithelial neoplasia (CGIN)) required 6- and 12-month follow-up cytology and annual cytology for the subsequent 9 years at least before returning to screening at the routine interval. It has been estimated that in England every year more than 300,000 cytology tests were performed annually for follow-up after treatment, approximately 10% of the annual workload [101]. A number of studies prior to 2007 demonstrated that testing for high-risk HPV infection with Hybrid Capture 2 was more sensitive, though less specific, than repeat cytology in the detection of residual disease following excisional treatment of high-grade CIN, and a large prospective study from the UK showed that a negative result from a high-risk HPV test after treatment was indicative of very low risk of recurrent disease even in the presence of low-grade cytological abnormality: women who were cytology and HPV negative at 6 months could safely be returned to routine three-yearly recall [102, 103]. Evaluation of HPV as test of cure after treatment of CIN in the sentinel study

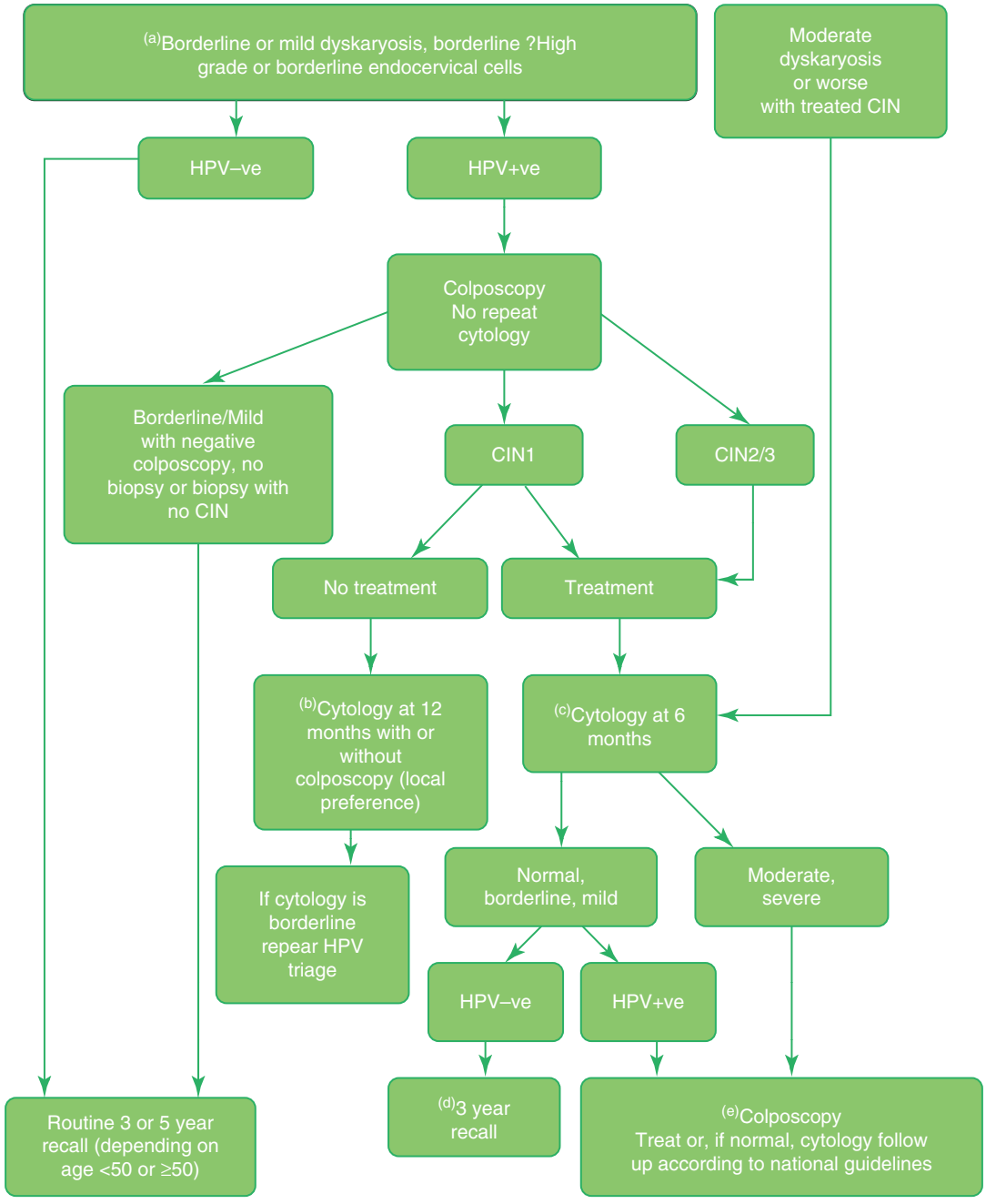

Fig. 3.2 Flow chart: triage and test of cure in the NHSCSP (© Crown Copyright 2016). This information was originally developed by Public Health England Screening(https://www.gov.uk/topic/population-screening-programmes) and is used under the Open Government Licence v3.0

demonstrated that about 85% of treated women were HPV negative at 6 months after treatment [100]. HPV test of cure was implemented with HPV triage of low-grade cytological abnormality in the English cervical screening program in 2011 (Fig. 3.2).

Automation in Cervical Screening

As noted above, LBC provides the platform for computer-assisted evaluation of cervical smears and thereby partial automation of the screening process in the laboratory, a goal which had been sought for over 50 years [104]. Early attempts at automation of the screening process using conventional cervical smears were hampered by difficulties in visualization of the cells if they were obscured by blood, inflammatory cells, or mucus; detection of the boundaries of cells and their nuclei, especially in overlapping cells or three-dimensional cell groups; a recognition that there were more similarities than differences between normal and neoplastic cells; and limited computing capacity which was unable to process the enormous volume of data generated from a single Papanicolaou smear which might contain up to 300,000 cells. LBC presents a monolayer or near monolayer of cells with clearly defined boundaries, largely devoid of obscuring blood, inflammatory cells, or mucus, and this, coupled with developments in computerized image analysis, has made semi-automated slide-scanning devices available for clinical use.

Two systems currently dominate the market and have been approved for primary cervical screening by the US Food and Drug Administration (FDA). Both consist of a highly automated microscope and an image analyzer that presents a restricted number of fields of view (FOVs) containing abnormal cells for interpretation by laboratory staff.

The BD FocalPoint™ Slide Profiler uses multiple algorithms to assign a score (0.0–1.0) to each slide (either conventional or SurePath) based on the probability of abnormality. Threshold scores are derived by separation of meaningful objects, i.e. irregular-shaped nuclei, from the background and describing each object with a set of measurement values. Slides with scores below the primary threshold, typically about 25% of a population of routine cervical screening samples, can be archived with no need for human microscopic review (no further review – NFR) resulting in a significant reduction in the workload of laboratory screening staff.

This system has been further developed as the BD FocalPoint™ GS Workstation in which the automated primary screening system is combined with an automated microscope which provides the electronic capability of locating diagnostically relevant locations in the samples above the threshold score. After reading a slide barcode, the microscope automatically positions the slide at the first relevant location, and a user-activated footswitch or mouse click moves the microscope to the next position until all locations are screened for suspicious cells or features.

The ThinPrep™ Imaging System rapidly scans and locates 22 areas of interest, known as fields of view (FOVs), in batches of ThinPrep® LBC slides and stores the coordinates which mark the position of the FOVs along with the slide identification information. Once all of the slides in a batch have been imaged, the slides are taken to a review microscope where they are reviewed by a cytology screener. The review scope automatically takes the cytology screener to each FOV in geographic order and, if any abnormalities are identified in the FOVs, the entire slide is reviewed by the cytology screener. If no abnormalities are identified in the FOVs, the slide may be signed out as negative. By directing the cytology screener to the FOVs on a slide, the amount of time required to screen a slide is dramatically reduced.

Both systems were granted FDA approval on the basis of being able to detect an equivalent or higher proportion of high-grade cytological abnormalities compared with manual reading [105, 106]. However an earlier systematic review of the literature published on the clinical and cost effectiveness of automated and semi-automated cervical screening devices including AutoPap, a predecessor of the BD FocalPoint™ Slide Profiler, by the New Zealand Health Technology Assessment program reported that the evidence base was not sufficiently strong for reliable conclusions to be drawn and recommended further trials with robust reference standards [107].

Similarly a systematic review by the UK Health Technology Assessment also concluded that previous studies had not been of sufficiently good quality to allow reliable recommendations [108].

In England, the MAVARIC trial was therefore designed to achieve a rigorous, prospective, unbiased comparison of manual and automation-assisted reading which had been powered to demonstrate non-inferiority in terms of sensitivity to detect CIN 2 or worse (CIN2+). Other objectives of the study were to compare the specificity of automation-assisted screening relative to manual, to incorporate both automated systems, and to evaluate the reliability of NFR in excluding CIN2+.

The principal finding was that automation-assisted reading was 8% less sensitive than manual reading (relative sensitivity 0.92; 95%CI 0.89–0.95) equivalent to an absolute reduction in sensitivity of approximately 6.3%, assuming the sensitivity of manual reading to be 79%. There was an increase of 0.6% in specificity relative to manual reading (relative specificity 1.006; 95%CI 1.005–1.007).

The inferior sensitivity of automation-assisted reading in the detection of CIN2 or worse combined with an inconsequential increase in specificity suggested that automation-assisted reading could not be recommended for primary cervical screening [109].

Furthermore, a large randomized trial in Finland comparing automation-assisted screening with conventional cytological screening reported no difference in the risk of cervical cancer between the automation-assisted and conventional screening methods [110].

However, in the MAVARIC study, the No Further Review facility on the BD FocalPoint™ Slide Profiler system proved to be reliable in terms of negative predictive value, missing only 1% of CIN2+ lesions associated with routine screening samples. It was considered that it could be a valuable adjunct in primary screening as this module does not require the expensive workstations required for reading the Fields of View and could reduce by up to 25% the number of slides requiring human reading; it has been subsequently utilized in this mode in a few English laboratories [111].

NHSCSP Beyond 2016: Cervical Screening in the Era of HPV Vaccination

HPV Vaccination

HPV vaccination using the bivalent vaccine (Cervarix®) against the two commonest types of HPV implicated in cervical carcinogenesis (HPV types 16 and 18) was introduced into the UK in September 2008 for girls aged 12–13 years, followed in autumn 2009 by a 2-year "catch-up" campaign to vaccinate all girls up to 18 years of age. The vaccine was originally administered as a three-dose schedule over 6 months. In 2012 Cervarix® was replaced by Gardasil®, a quadrivalent vaccine that also protects against HPV types 6 and 11, which cause about 90% of genital warts, and in September 2014 the three-dose schedule was replaced by a two-dose schedule with the doses 1 year apart.

Uptake of this school-based HPV vaccination program has been very good with more than 80% of 12–13-year-olds consistently receiving at least two of the three scheduled vaccinations, and in the last year for which data is currently available, 2014–2015, the national coverage for the completed priming (first) dose was 89.4% [112]. As a result there will be a progressive increase in the proportion of women in the screening program who have been vaccinated, with an expected decrease in prevalence of cervical neoplasia, but these women will need to continue to participate in screening since the vaccine only offers protection against about 70% of cervical cancer. A nonovalent vaccine, Gardasil 9®, which offers protection against 90% of cervical cancer, has recently been licensed for use in Europe but not yet implemented in the UK [113, 114].

A modeling study from the UK predicted that HPV 16/18 vaccination of a cohort of 12-year-old girls would result over the lifetime of each

cohort in a 23% reduction in the number of abnormal cytology tests, a 32% reduction in biopsies, and a 42% reduction in CIN treatments, assuming 100% vaccine coverage. Interestingly these estimates assumed that introduction of vaccination did not also allow a reduction in screening frequency [115]. Studies from Australia and Scotland, where HPV vaccination was introduced before England and Wales, have reported a reduction in prevalence of cytological abnormality [116, 117].

Primary HPV Testing

A progressive reduction in prevalence of cytological abnormality will result in a decrease in positive predictive value (PPV) and an increase in negative predictive value (NPV) of cytology-based programs and is the driver for adoption of high-risk HPV testing as the primary screening test with secondary triage to cytology: HPV testing is a highly standardized assay that maintains its performance characteristics under low prevalence conditions [118]. While there is good evidence that primary screening with HPV is more sensitive for detection of high-grade CIN and cancer, it is less specific, particularly in women less than 30 years of age [119, 120]. Several approaches are under evaluation to deal with the lower specificity of HPV DNA testing as associated with transient infection including HPV typing for HPV-16 and HPV-18/45; surrogate markers of viral integration such as p16; dual staining of cytology preparations with p16 and Ki67, a proliferation marker; mRNA coding for the viral E6 and/or E7 proteins; and DNA methylation with a potential clinical use recommending more aggressive management in those who are positive [121–133]. In countries such as the UK where cytology is of good quality, the most attractive option is to use HPV DNA testing as the sole primary screening modality with cytology triage of HPV-positive women [96]. However, HPV genotyping assays, particularly for HPV 16 and 18, would also permit post-vaccination surveillance to determine overall vaccine effectiveness and prevalence of non-vaccine HPV types in the vaccinated population [95]. Primary HPV screening, possibly combined with secondary molecular marker analysis, might also be a platform for self-sampling as a means of addressing the falling coverage in young women in the UK and elsewhere [128, 132–137].

Four European randomized trials comparing cytology combined with HPV testing with cytology alone over extended follow-up demonstrated a significant reduction in the incidence of cervical cancer among women screened with HPV, compared with cytology [138]. While the rates were similar until 2.5 years of follow-up, thereafter HPV-based screening provided 60–70% greater protection against cervical cancer compared with cytology alone. In addition, the ARTISTIC trial has provided additional information:

- Cytology and HPV combined would not add significantly to HPV as a stand-alone screen with cytology triage for HPV positives.
- A negative HPV test provides a similar degree of protection against subsequent CIN 2 or worse over the next 6 years as does liquid-based cytology over 3 years, indicating that screening intervals could be extended [139, 140].

A recent analysis of the ARTISTIC study and other UK data showed that HPV primary screening and LBC triage would be cost effective compared with LBC provided there was adherence to the follow-up of HPV-positive cytology-negative women [141].

A pilot study to determine the feasibility of HPV primary screening was established in the sentinel site study laboratories in 2013. In late 2015, having evaluated the available data, the UK National Screening Committee recommended that HPV primary screening should be adopted in the UK cervical screening programs. This recommendation was accepted by health ministers, and in July 2016 a public announcement was made that the UK would adopt primary HPV screening, with full implementation planned to be completed by 2019. The proposed algorithm is shown in Fig. 3.3.

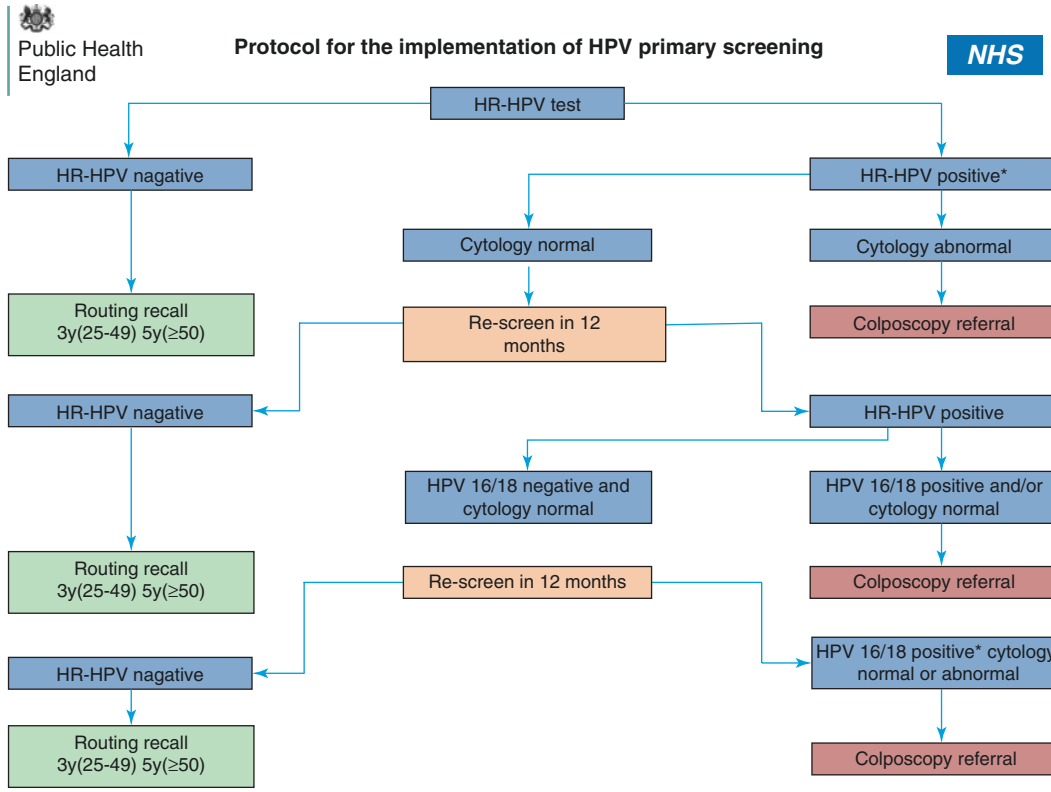

Fig. 3.3 Algorithm for HPV primary screening in the NHSCSP (© Crown Copyright 2016). This information was originally developed by Public Health England Screening (https://www.gov.uk/topic/population-screening-programmes) and is used under the Open Government Licence v3.0. Notes: (1) Applies to all women in the cervical screening program aged 25–64 years on routine call/recall and early recall. (2) Inadequate tests at any screening episode in the pathway will be repeated in 3 months. Three inadequate tests in a row will lead to a colposcopy referral. (3) Women in follow-up for cervical cancer (who still have a cervix) and CGIN/SMILE (without complete excision margins) will be screened annually with HPV testing for 10 years. * HPV16/HPV18 testing not required but may be provided automatically by the HPV test platform

References

1. Wilson JM, Jungner G. Principles and practice of screening for disease. Public Health Papers 34, 1. Geneva: World Health Organisation; 1968.
2. Public Health England. Criteria for appraising the viability, effectiveness and appropriateness of a screening programme. Public Health England. 23-10-2016. 18-7-2016.
3. Frisell J, Glas U, Hellstrom L, Somell A. Randomized mammographic screening for breast cancer in Stockholm. Design, first round results and comparisons. Breast Cancer Res Treat. 1986; 8(1):45–54.
4. Anderson TJ, Lamb J, Alexander F, et al. Comparative pathology of prevalent and incident cancers detected by breast screening. Edinburgh Breast Screening Project. Lancet. 1986;1(8480):519–23.
5. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer. 2015;136(5):E359–86.
6. Spriggs AI. History of cytodiagnosis. J Clin Pathol. 1977;30(12):1091–102.
7. Koprowska I. Concurrent discoveries of the value of vaginal smears for diagnosis of uterine cancer. Diagn Cytopathol. 1985;1(3):245–8.
8. Hajdu SI. Cytology from antiquity to Papanicolaou. Acta Cytol. 1977;21(5):668–76.
9. Stockard CR, Papanicolaou GN. The existence of a typical oestrous cycle in the guinea pig; with a study of its histological and physiological changes. Am J Anat. 1917;22:225–83.
10. Papanicolaou GN. New cancer diagnosis. Proceedings of the 3rd Race Betterment Conference, p. 528–34. 1928. Battle Creek, Michigan, Race Betterment Foundation; 1928.

11. Daniel C, Babes A. Posibilitatea diagnosticului cancerului uterin cu ajutorul frotiului. Proceedings of the Bucharest Gynaecological Society. 23-1-1927.
12. Babes A. Diagnostic du cancer du col uterin par les frottis. Presse Medicale. 1928;36:451–4.
13. Naylor B, Tasca L, Bartziota E, Schneider V. In Romania it's the Methode Babes-Papanicolaou. Acta Cytol. 2002;46(1):1–12.
14. Viana O. La diagnosi precoce del cancro uterino mediante lo striscio [The early diagnosis of uterine cancer by smears]. La Clinica Ostetrica. 1928;30: 781–93.
15. Viana O. The early diagnosis of uterine cancer by smears. Acta Cytol. 1970;14(8):544–9.
16. Papanicolaou GN. A new procedure for staining vaginal smears. Science. 1942;95(2469):438–9.
17. Koprowska I, George N. Papanicolaou – as we knew him. Acta Cytol. 1977;21(5):630–8.
18. Papanicolaou GN, Traut HF. Diagnosis of uterine cancer by the vaginal smear. New York: The Commonwealth Fund; 1943.
19. Ayre JE. A simple office test for uterine cancer diagnosis. Can Med Assoc J. 1944;51(1):17–22.
20. Ayre JE. Cervical cytology in diagnosis of early cancer. JAMA. 1948;136(8):513–7.
21. Foote FW, LI K. Smear diagnosis of in situ carcinoma of the cervix. Am J Obstet Gynecol. 1948;56(2):335–9.
22. Pund ER, Nieburgs HE. Preinvasive carcinoma of the cervix uteri; seven cases in which it was detected by examination of routine endocervical smears. Arch Pathol (Chic). 1947;44(6):571–7.
23. Pund ER, Nettles JB. Preinvasive and invasive carcinoma of cervix uteri; pathogenesis, detection, differential diagnosis, and the pathologic basis for management. Am J Obstet Gynecol. 1948;55(5):831–7.
24. Ayre JE. Selective cytology smear for diagnosis of cancer. Am J Obstet Gynecol. 1947;53(4):609–17.
25. Papanicolaou GN. Atlas of exfoliative cytology. Cambridge: The Commonwealth Fund by Harvard University Press; 1954.
26. Christopherson WM, Lundin Jr FE, Mendez WM, Parker JE. Cervical cancer control: a study of morbidity and mortality trends over a twenty-one-year period. Cancer. 1976;38(3):1357–66.
27. Christopherson WM, Scott MA. Trends in mortality from uterine cancer in relation to mass screening. Acta Cytol. 1977;21(1):5–9.
28. Anderson GH, Boyes DA, Benedet JL, et al. Organisation and results of the cervical cytology screening programme in British Columbia, 1955–85. Br Med J (Clin Res Ed). 1988;296(6627):975–8.
29. Hakama M, Louhivuori K. A screening programme for cervical cancer that worked. Cancer Surv. 1988;7(3):403–16.
30. Macgregor JE, Fraser ME, Mann EM. Improved prognosis for cervical cancers due to comprehensive screening. Acta Cytol. 1972;16(1):14–5.
31. Macgregor JE. Evaluation of mass screening programmes for cervical cancer in N.E. Scotland. Tumori. 1976;62(3):287–95.
32. Macgregor JE, Teper S. Mortality from carcinoma of cervix uteri in Britain. Lancet. 1978;2(8093):774–6.
33. Macgregor JE, Moss SM, Parkin DM, Day NE. A case-control study of cervical cancer screening in north east Scotland. Br Med J (Clin Res Ed). 1985;290(6481):1543–6.
34. Macgregor JE, Moss S, Parkin DM, Day NE. Cervical cancer screening in north-east Scotland. IARC Sci Publ. 1986;76:25–36.
35. Macgregor JE, Campbell MK, Mann EM, Swanson KY. Screening for cervical intraepithelial neoplasia in north east Scotland shows fall in incidence and mortality from invasive cancer with concomitant rise in preinvasive disease. BMJ. 1994;308(6941): 1407–11.
36. Macgregor JE, Fraser ME, Mann EM. Improved prognosis of cervical cancer due to comprehensive screening. Lancet. 1971;1(7689):74–6.
37. Wachtel E. Screening for cervical cancer. Practitioner. 1973;211(262):137–42.
38. Kocjan G, Herbert A. Nasseem Husain: homage to a pioneer of cytology automation. Cytopathology. 2015;26(4):211–6.
39. Wilson JM. Screening for cervical cancer. Mon Bull Minist Health Public Health Lab Serv. 1961;20: 214–22.
40. Wilson JM. Some aspects of the epidemiology of cervical cancer. Mon Bull Minist Health Public Health Lab Serv. 1965;24:72–81.
41. Williams J. On cancer of the uterus: being the Harveian Lectures for 1886. London: H K Lewis; 1886.
42. Cullen TS. Cancer of the uterus: its pathology, symptomatology, diagnosis, and treatment. New York: Appleton; 1900.
43. Rubin IC. The pathological diagnosis of incipient carcinoma of the cervix. Am J Obstet Gynecol. 1910;62:668–76.
44. Broders AC. Carcinoma in situ contrasted with benign penetrating epithelium. JAMA. 1932;99:1670–4.
45. Wied GL. Editorial. First International Conference of Exfoliative Cytology. Proceedings of the First International Congress of Exfoliative Cytology. Philadelphia: Appleton-Century Crofts.; 1962, p. 297.
46. Ritton G, Christopherson WM. Cytology of the Female Genital Tract. [No 8]. Geneva, World Health Organisation. International Classification of Tumours; 1973.
47. Reagan JW, Hicks DJ. A study of in situ and squamous-cell cancer of the uterine cervix. Cancer. 1953;6(6):1200–14.
48. Reagan JW, Seidemann IL, Saracusa Y. The cellular morphology of carcinoma in situ and dysplasia or atypical hyperplasia of the uterine cervix. Cancer. 1953;6(2):224–34.
49. Richart RM. Cervical intraepithelial neoplasia. Pathol Annu. 1973;8:301–28.
50. Spriggs AI, Butler EB, Evans DMD, et al. Problems of cell nomenclature in cervical cytology smears. J Clin Pathol. 1978;31:1226–7.

51. Evans DM, Hudson EA, Brown CL, et al. Terminology in gynaecological cytopathology: report of the Working Party of the British Society for Clinical Cytology. J Clin Pathol. 1986;39(9):933–44.
52. Borderline nuclear changes in cervical smears: guidelines on their recognition and management. National Coordinating Network (National Cervical Screening Programme), British Society for clinical Cytology, and Royal College of Pathologists' Working Party. J Clin Pathol. 1994;47(6):481–92.
53. The 1988 Bethesda System for reporting cervical/vaginal cytologic diagnoses. Developed and approved at a National Cancer Institute Workshop, Bethesda, Maryland, U.S.A., December 12–13, 1988. Anal Quant Cytol Histol. 1989;11(5):291–7.
54. Solomon D. The 1988 Bethesda System for reporting cervical/vaginal cytologic diagnoses: developed and approved at the National Cancer Institute Workshop in Bethesda, Maryland, December 12–13, 1988. Hum Pathol. 1990;21(7):704–8.
55. The revised Bethesda System for reporting cervical/vaginal cytologic diagnoses: report of the 1991 Bethesda workshop. J Reprod Med. 1992;37(5):383–6.
56. Solomon D, Davey D, Kurman R, et al. The 2001 Bethesda System: terminology for reporting results of cervical cytology. JAMA. 2002;287(16):2114–9.
57. Smith JH. Bethesda 2001. Cytopathology. 2002;13(1):4–10.
58. Herbert A, Gray W, Cross P. Terminology of the BSCC, European Community and the Bethesda system: the boundary between low-grade and high-grade cytology. Cytopathology. 2009;20(1):3–4.
59. Denton KJ, Herbert A, Turnbull LS, et al. The revised BSCC terminology for abnormal cervical cytology. Cytopathology. 2008;19(3):137–57.
60. Slater DN, Rice S, Stewart R, et al. Proposed Sheffield quantitative criteria in cervical cytology to assist the grading of squamous cell dyskaryosis, as the British Society for Clinical Cytology definitions require amendment. Cytopathology. 2005;16(4):179–92.
61. Cancer of the cervix: death by incompetence. Lancet 1986;326:363–4.
62. Department of Health and Social Security. HC(88)1. Health Services Management Cervical Cancer Screening. 12-1-1988. London: DHSS.
63. Farmery E, Gray M. Report of the first five years of the NHS cervical screening programme. Oxford: National Co-ordinating Network, Anglia and Oxford Regional Health Authority; 1994.
64. NHS Cancer Screening Programmes. Celebrating 15 years of achievement. NHS Cervical Screening Programme Annual Review 2003. Sheffield: NHS Cancer Screening Programmes; 2003.
65. Herbert A, Johnson J. Achievable standards, benchmarks for reporting and criteria for evaluating cervical cytopathology. 1st ed. Sheffield: NHS Cervical Screening Programme; 1995.
66. Johnson J, Patnick J. Achievable standards, benchmarks for reporting, and criteria for evaluating cervical cytopathology. Second edition including revised performance indicators. Cytopathology. 2000;11(4):212–41.
67. Johnson J, Patnick J, editors. Achievable standards, benchmarks for reporting, and criteria for evaluating cervical cytopathology. Sheffield: NHS Cancer Screening Programmes; 2000.
68. Smith J, Patnick J, editors. Achievable standards, benchmarks for reporting, criteria for evaluating cervical cytopathology. 3rd ed. Sheffield: NHS Cancer Screening Programmes; 2013.
69. Smith JH. ABC3 Part I: a review of the guidelines for terminology, classification and management of cervical cytology in England. Cytopathology. 2012;23(6):353–9.
70. Blanks RG. ABC3 Part II: a review of the new criteria for evaluating cervical cytology in England. Cytopathology. 2012;23(6):360–70.
71. Marlow LA, Sangha A, Patnick J, Waller J. The Jade Goody Effect: whose cervical screening decisions were influenced by her story? J Med Screen. 2012;19(4):184–8.
72. Lancucki L, Sasieni P, Patnick J, Day TJ, Vessey MP. The impact of Jade Goody's diagnosis and death on the NHS Cervical Screening Programme. J Med Screen. 2012;19(2):89–93.
73. National Institute for Clinical Excellence. Guidance on the use of liquid-based cytology for cervical screening. 2000. NICE Technology Appraisal Guidance No5.
74. National Institute for Clinical Excellence. Guidance on the use of liquid based cytology for cervical screening. 2003. Technology Appraisal 69.
75. NHSCSP. Modernising the NHSCSP. NICE appraisal on liquid based cytology published 22 October 2003. Advice to the service. Sheffield: NHSCSP; 2003.
76. National Advisory Group. Steering Group Report on the feasibility of introducing liquid based cytology. Scottish Cervical Screening Programmme; 2002.
77. Luesley D, Leeson S. Colposcopy and programme management. NHSCSP Publication 20. Sheffield: NHSCSP; 2004.
78. Sasieni P, Adams J, Cuzick J. Benefit of cervical screening at different ages: evidence from the UK audit of screening histories. Br J Cancer. 2003;89(1):88–93.
79. Rieck GC, Tristram A, Hauke A, Fielder H, Fiander AN. Cervical screening in 20-24-year olds. J Med Screen. 2006;13(2):64–71.
80. Herbert A, Smith JH. Women under 25 should be offered screening. BMJ. 2007;334(7588):273.
81. Herbert A, Holdsworth G, Kubba AA. Cervical screening: why young women should be encouraged to be screened. J Fam Plann Reprod Health Care. 2008;34(1):21–5.
82. Fiander AN. Cervical screening in young women aged 20–24 years. J Fam Plann Reprod Health Care. 2008;34(1):19.
83. Castanon A, Leung VM, Landy R, Lim AW, Sasieni P. Characteristics and screening history of women

diagnosed with cervical cancer aged 20–29 years. Br J Cancer. 2013;109(1):35–41.
84. Patnick J, editor. NHSCSP annual review 2006. Sheffield: NHSCSP; 2007.
85. Dowie R, Stoykova B, Crawford D, et al. Liquid-based cytology can improve efficiency of cervical smear readers: evidence from timing surveys in two NHS cytology laboratories. Cytopathology. 2006;17(2):65–72.
86. Williams AR. Liquid-based cytology and conventional smears compared over two 12-month periods. Cytopathology. 2006;17(2):82–5.
87. Gregory L, Dudding N, Smith JH. The impact of introducing liquid based cytology into a routine screening laboratory. Cytopathology. 2006;17(supplement 1):24.
88. Beerman H, van Dorst EB, Kuenen-Boumeester V, Hogendoorn PC. Superior performance of liquid-based versus conventional cytology in a population-based cervical cancer screening program. Gynecol Oncol. 2009;112(3):572–6.
89. Department of Health. Cancer Reform Strategy. 2007.
90. Patnick J, editor. NHSCSP annual review 2007. Sheffield: NHS Cancer Screening Programmes; 2008.
91. NHSCSP Workforce Survey Working Group. A survey of non-medical staff within the cervical screening programme 2002–2005. Sheffield: NHSCSP; 2006.
92. Walboomers JM, Jacobs MV, Manos MM, et al. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. J Pathol. 1999; 189(1):12–9.
93. Bosch FX, Lorincz A, Munoz N, Meijer CJ, Shah KV. The causal relation between human papillomavirus and cervical cancer. J Clin Pathol. 2002; 55(4):244–65.
94. Bosch FX, Burchell AN, Schiffman M, et al. Epidemiology and natural history of human papillomavirus infections and type-specific implications in cervical neoplasia. Vaccine. 2008;26(Suppl 10): K1–16.
95. Gravitt PE, Coutlee F, Iftner T, et al. New technologies in cervical cancer screening. Vaccine. 2008; 26(Suppl 10):K42–52.
96. Cuzick J, Arbyn M, Sankaranarayanan R, et al. Overview of human papillomavirus-based and other novel options for cervical cancer screening in developed and developing countries. Vaccine. 2008;26(Suppl 10):K29–41.
97. Arbyn M, Roelens J, Simoens C, et al. Human papillomavirus testing versus repeat cytology for triage of minor cytological cervical lesions. Cochrane Database Syst Rev. 2013;3:CD008054.
98. Moss S, Gray A, Legood R, et al. Effect of testing for human papillomavirus as a triage during screening for cervical cancer: observational before and after study. BMJ. 2006;332(7533):83–5.
99. Legood R, Gray A, Wolstenholme J, Moss S. Lifetime effects, costs, and cost effectiveness of testing for human papillomavirus to manage low grade cytological abnormalities: results of the NHS pilot studies. BMJ. 2006;332(7533):79–85.
100. Kelly RS, Patnick J, Kitchener HC, Moss SM. HPV testing as a triage for borderline or mild dyskaryosis on cervical cytology: results from the sentinel sites study. Br J Cancer. 2011;105(7):983–8.
101. Smith JH. The future of cervical screening in the UK. Diagn Histopathol. 2009;15(7):330–4.
102. Chan BK, Melnikow J, Slee CA, Arellanes R, Sawaya GF. Posttreatment human papillomavirus testing for recurrent cervical intraepithelial neoplasia: a systematic review. Am J Obstet Gynecol. 2009;200(4):422–9.
103. Kitchener HC, Walker PG, Nelson L, et al. HPV testing as an adjunct to cytology in the follow up of women treated for cervical intraepithelial neoplasia. BJOG. 2008;115(8):1001–7.
104. Husain OA. The history of automated cell scanners. In: Grohs HK, Husain OA, editors. Automated cervical cancer screening. New York: Igaku-Shoin; 1994. p. 3–14.
105. Biscotti CV, Dawson AE, Dziura B, et al. Assisted primary screening using the automated ThinPrep Imaging System. Am J Clin Pathol. 2005;123(2): 281–7.
106. Wilbur DC, Black-Schaffer WS, Luff RD, et al. The Becton Dickinson FocalPoint GS Imaging System: clinical trials demonstrate significantly improved sensitivity for the detection of important cervical lesions. Am J Clin Pathol. 2009;132(5):767–75.
107. Broadstock M. Effectiveness and cost effectiveness of automated and semi-automated cervical screening devices: a systematic review of the literature. N Z Med J. 2001;114(1135):311–3.
108. Willis PH, Barton P, Pearmain P, Bryan S, Hyde C. Cervical screening programmes: can automation help? Evidence from systematic reviews, an economic analysis and a simulation modelling exercise applied to the UK. Health Technol Assess. 2005;9:1–207.
109. Kitchener HC, Blanks R, Dunn G, et al. Automation-assisted versus manual reading of cervical cytology (MAVARIC): a randomised controlled trial. Lancet Oncol. 2011;12(1):56–64.
110. Anttila A, Pokhrel A, Kotaniemi-Talonen L, et al. Cervical cancer patterns with automation-assisted and conventional cytological screening: a randomized study. Int J Cancer. 2011;128(5):1204–12.
111. Kitchener HC, Blanks R, Cubie H, et al. MAVARIC – a comparison of automation-assisted and manual cervical screening: a randomised controlled trial. Health Technol Assess. 2011;15(3):iii–xi, 1.
112. Public Health England. Human Papillomavirus (HPV) vaccination coverage in adolescent females in England: 2014/15. 1-12-2015. PHE. 8-8-2016.
113. Joura EA, Giuliano AR, Iversen OE, et al. A 9-valent HPV vaccine against infection and intraepithelial neoplasia in women. N Engl J Med. 2015;372(8):711–23.
114. Gardasil 9: new HPV vaccine approved in the European Union. 2015. 8-8-2016.
115. Franco EL, Cuzick J, Hildesheim A, de Sanjose S. Chapter 20: issues in planning cervical cancer

screening in the era of HPV vaccination. Vaccine. 2006;24(Suppl 3):S171–7.
116. Brotherton JM, Fridman M, May CL, et al. Early effect of the HPV vaccination programme on cervical abnormalities in Victoria, Australia: an ecological study. Lancet. 2011;377(9783):2085–92.
117. Pollock KG, Kavanagh K, Potts A, et al. Reduction of low- and high-grade cervical abnormalities associated with high uptake of the HPV bivalent vaccine in Scotland. Br J Cancer. 2014;111(9):1824–30.
118. Palmer TJ, McFadden M, Pollock KG, et al. HPV immunisation and cervical screening–confirmation of changed performance of cytology as a screening test in immunised women: a retrospective population-based cohort study. Br J Cancer. 2016;114(5):582–9.
119. Arbyn M, Anttila A, Jordan J, et al. European guidelines for quality assurance in cervical cancer screening. Second edition – summary document. Ann. Oncologia. 2010;21(3):448–58.
120. Wright Jr TC, Massad LS, Dunton CJ, et al. 2006 consensus guidelines for the management of women with abnormal cervical screening tests. J Low Genit Tract Dis. 2007;11(4):201–22.
121. Naucler P, Ryd W, Tornberg S, et al. Efficacy of HPV DNA testing with cytology triage and/or repeat HPV DNA testing in primary cervical cancer screening. J Natl Cancer Inst. 2009;101(2):88–99.
122. Cox JT, Castle PE, Behrens CM, et al. Comparison of cervical cancer screening strategies incorporating different combinations of cytology, HPV testing, and genotyping for HPV 16/18: results from the ATHENA HPV study. Am J Obstet Gynecol. 2013;208(3):184.
123. Denton KJ, Bergeron C, Klement P, et al. The sensitivity and specificity of p16(INK4a) cytology vs HPV testing for detecting high-grade cervical disease in the triage of ASC-US and LSIL pap cytology results. Am J Clin Pathol. 2010;134(1):12–21.
124. Tambouret RH. Use of immunohistochemical staining for p16 in gynecological cytology. Cancer Cytopathol. 2016;124(9):611–2.
125. Petry KU, Schmidt D, Scherbring S, et al. Triaging Pap cytology negative, HPV positive cervical cancer screening results with p16/Ki-67 Dual-stained cytology. Gynecol Oncol. 2011;121(3):505–9.
126. Ikenberg H, Bergeron C, Schmidt D, et al. Screening for cervical cancer precursors with p16/Ki-67 dual-stained cytology: results of the PALMS study. J Natl Cancer Inst. 2013;105(20):1550–7.
127. Wentzensen N, Fetterman B, Castle PE, et al. p16/Ki-67 dual stain cytology for detection of cervical precancer in HPV-positive women. J Natl Cancer Inst. 2015;107(12):djv257.
128. Hesselink AT, Heideman DA, Steenbergen RD, et al. Combined promoter methylation analysis of CADM1 and MAL: an objective triage tool for high-risk human papillomavirus DNA-positive women. Clin Cancer Res. 2011;17(8):2459–65.
129. De Strooper LM, van Zummeren M, Steenbergen RD, et al. CADM1, MAL and miR124-2 methylation analysis in cervical scrapes to detect cervical and endometrial cancer. J Clin Pathol. 2014;67(12):1067–71.
130. De Strooper LM, Meijer CJ, Berkhof J, et al. Methylation analysis of the FAM19A4 gene in cervical scrapes is highly efficient in detecting cervical carcinomas and advanced CIN2/3 lesions. Cancer Prev Res (Phila). 2014;7(12):1251–7.
131. Verhoef VM, van Kemenade FJ, Rozendaal L, et al. Follow-up of high-risk HPV positive women by combined cytology and bi-marker CADM1/MAL methylation analysis on cervical scrapes. Gynecol Oncol. 2015;137(1):55–9.
132. Verhoef VM, Heideman DA, van Kemenade FJ, et al. Methylation marker analysis and HPV16/18 genotyping in high-risk HPV positive self-sampled specimens to identify women with high grade CIN or cervical cancer. Gynecol Oncol. 2014;135(1):58–63.
133. De Strooper LM, Verhoef VM, Berkhof J, et al. Validation of the FAM19A4/mir124-2 DNA methylation test for both lavage- and brush-based self-samples to detect cervical (pre)cancer in HPV-positive women. Gynecol Oncol. 2016;141(2):341–7.
134. Gravitt PE, Belinson JL, Salmeron J, Shah KV. Looking ahead: a case for human papillomavirus testing of self-sampled vaginal specimens as a cervical cancer screening strategy. Int J Cancer. 2011;129(3):517–27.
135. Gravitt PE, Rositch AF. HPV self-testing and cervical cancer screening coverage. Lancet Oncol. 2014;15(2):128–9.
136. Gok M, van Kemenade FJ, Heideman DA, et al. Experience with high-risk human papillomavirus testing on vaginal brush-based self-samples of non-attendees of the cervical screening program. Int J Cancer. 2012;130(5):1128–35.
137. Cervical Screening Programme: England, Statistics for 2014–15. http://www.hscic.gov.uk/pubs/cervical1415 . 2016. 8-8-2016.
138. Ronco G, Dillner J, Elfstrom KM, et al. Efficacy of HPV-based screening for prevention of invasive cervical cancer: follow-up of four European randomised controlled trials. Lancet. 2014;383(9916):524–32.
139. Kitchener HC, Almonte M, Gilham C, et al. ARTISTIC: a randomised trial of human papillomavirus (HPV) testing in primary cervical screening. Health Technol Assess. 2009;13(51):1–iv.
140. Kitchener HC, Gilham C, Sargent A, et al. A comparison of HPV DNA testing and liquid based cytology over three rounds of primary cervical screening: extended follow up in the ARTISTIC trial. Eur J Cancer. 2011;47(6):864–71.
141. Kitchener HC, Canfell K, Gilham C. The clinical effectiveness and cost-effectiveness of primary human papillomavirus cervical screening in England: extended follow-up of the ARTISTIC randomised trial cohort through three screening rounds. Health Technol Assess. 2014;18(23):1–196.
142. Herbert A, Johnson J, Patnick J. Achievable standards, benchmarks for reporting and criteria for evaluating cervical cytopathology. Cytopathology. 1995;6:301–3.