SCUOLA DI DOTTORATO
UNIVERSITÀ DEGLI STUDI DI MILANO-BICOCCA

Department of Medicine and Surgery

PhD program: **Public Health** Cycle **XXXVII**

Curriculum in **Research and Evaluation in Health Services and Technologies**

BUDGET IMPACT ANALYSIS OF THE IMPLEMENTATION OF AN ORGANIZED CERVICAL CANCER SCREENING PROGRAM BASED ON PRIMARY HPV AND CYTOLOGY STRATIFIED BY VACCINATION STATUS IN THE METROPOLITAN AREA OF MILAN.

Surname **De Nard** Name **Francesca**

Registration number **896609**

Tutor: **Prof. Lorenzo Giovanni Mantovani**

Co-tutor: **Diego Iemmi**

Supervisor: **Paolo Angelo Cortesi**

Coordinator: **Prof. Luigi Badano**

ACADEMIC YEAR 2024/2025

CONTENTS

ABSTRACT

Background. Cervical cancer is largely preventable through vaccination and screening; however, disparities in access and inefficient resource use persist. Prior to 2022, cervical cancer screening in the Metropolitan Area of Milan was conducted solely in the opportunistic setting, likely resulting in high rates of inappropriate testing and unequal participation. In 2022, an organized screening program based on primary HPV testing with cytology triage, stratified by vaccination status, was launched. This study aimed to assess the year-to-year impact of the program's implementation on the screening budget, both organized and opportunistic, from 2024 to 2033.

Methods. A Budget Impact Model (BIM) was developed to simulate annual volumes of screening tests, colposcopies, and associated expenditures over the period 2024-2033, according to a predefined implementation plan. Model inputs were derived from screening registries and administrative health databases covering 2018-2019 (pre-implementation) and 2022-2023 (post-implementation). Parameters included age, round, vaccination status and test-specific participation rates, HPV positivity rates, colposcopy referral rates, and average follow-up colposcopies. One-way sensitivity analyses were conducted to identify parameters most affecting total costs and service demand. The AdViSHE checklist was provided to describe the validation efforts for the conceptual and the computing framework, and calibration was performed using real-world data from 2024 cervical cancer screening program in the Metropolitan Area of Milan.

Results. The implementation of organized screening substantially increased publicly funded screening coverage (from 12.5% to 40%), shifting the test mix from cytology to primary HPV DNA testing. The program is projected to generate a temporary surge in colposcopy demand (2025-2027), reflecting the detection of prevalent lesions in previously unscreened women. Annual screening costs are expected to rise initially – peaking in 2025 (€2.65 million) and 2030 (€2.61 million) – before stabilizing at sustainable levels. Five alternative scenarios were simulated to explore more sustainable policy options. Among them, the co-test scenario - in which the program performs co-tests prior to follow up colposcopies – proved to be the less costly option, while allowing for potential future increases in participation. Sensitivity analyses identified HPV participation rate, HPV positivity with normal cytology, and HPV referral rates as the main drivers of both organized screening costs and colposcopy volumes.

Conclusions. The transition from opportunistic to organized HPV-based screening in Milan produced significant benefits in terms of coverage, efficiency and equity, despite short-term

increases in diagnostic workload and moderate long-term cost growth. Policymakers should carefully plan transitional phases, ensuring adequate colposcopy and laboratory capacity. Continued investments in organized screening, integration with vaccination and follow-up programs, and regulation of opportunistic testing are essential to maximize the long-term public health benefits and economic sustainability of HPV-based cervical cancer screening.

1 INTRODUCTION

1.1 Cervical cancer elimination strategies

Globally, cervical cancer ranks as the fourth most common cancer and the third cause of cancer-related death in women, with an estimated 660,000 new cases and 350,000 deaths in 2022(Bray *et al.*, 2024). Most cases arise from persistent infection with oncogenic strains of human Papillomavirus (HPV)(Crosbie *et al.*, 2013), a sexually transmitted virus for which highly effective and cost-effective screening strategies(Ronco *et al.*, 2014; Mezei *et al.*, 2017; Harasani *et al.*, 2025) and vaccines(Jit *et al.*, 2014; Drolet *et al.*, 2019) are available. The highest cervical cancer-related mortality rates are observed in low- and middle-income countries (Fig. 1), reflecting inequitable access to screening, vaccination and treatment services(Li *et al.*, 2025). Owing to its infectious etiology, cervical cancer became the first non-communicable disease to be targeted for elimination(The Lancet Infectious Diseases, 2024): in 2020, the World Health Organisation (WHO) launched the Cervical Cancer Elimination Initiative (CCEI), setting the '90-70-90' targets to be achieved in all countries by 2030: full HPV vaccination of 90% 15-year-old girls, screening coverage of 70% with at least two high-performance HPV tests for women aged 35 and 45 years, and treatment provision for 90% of women diagnosed with cervical precancers or invasive cancers(World Health Organisation, 2020).

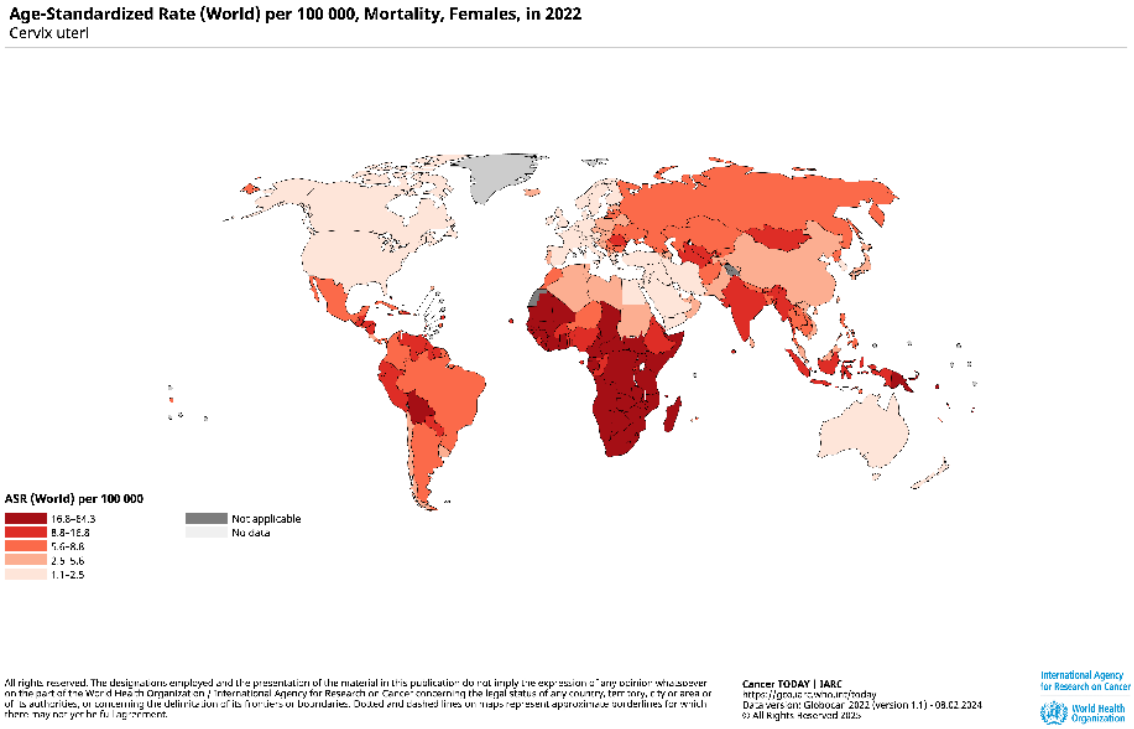


Figure 1. Global cervical cancer mortality heathmap (GLOBOCAN 2022).

In Italy, cervical cancer accounts for approximately 3,152 annual new cases and 1,011 deaths annually(HPV Information Centre, 2023), ranking as the fifth most common cancer among women under 50 years of age(Italian Association of Medical Oncology, 2020). The Italian Ministry of Health adopted the CCEI prevention targets through the most recent National Prevention Plan(Italian Ministry of Health, 2020) and National Immunization Plan(Italian Ministry of Health, 2023).

For primary prevention, HPV vaccination is recommended in Italy for all 12-year-old girls and boys(Italian Ministry of Health, 2023). However, vaccination coverage remains suboptimal, with 70% of girls and 58% of boys fully vaccinated by age 15(Italian Ministry of Health, 2025).

For secondary prevention, the transition from cytology-based to primary HPV-based cervical cancer screening, along with the implementation of tailored screening strategies for fully vaccinated women, has been recommended at the national level(Italian Ministry of Health, 2020).

Randomised controlled trials have demonstrated that primary HPV screening starting at age 30 provides 60-70% greater protection against invasive cervical carcinomas, offers longer-term protection, and is more cost-effective compared with conventional cytology-based screening (Ronco *et al.*, 2014)(Berkhof *et al.*, 2010). By 2021, most Italian regions had initiated the implementation of population-based cervical cancer screening programs using primary HPV testing, gradually extending coverage from age 30 onward, replacing the previously recommended cytology-based approach (Italian Ministry of Health, 2020; Bechini *et al.*, 2024) (Figure 2).

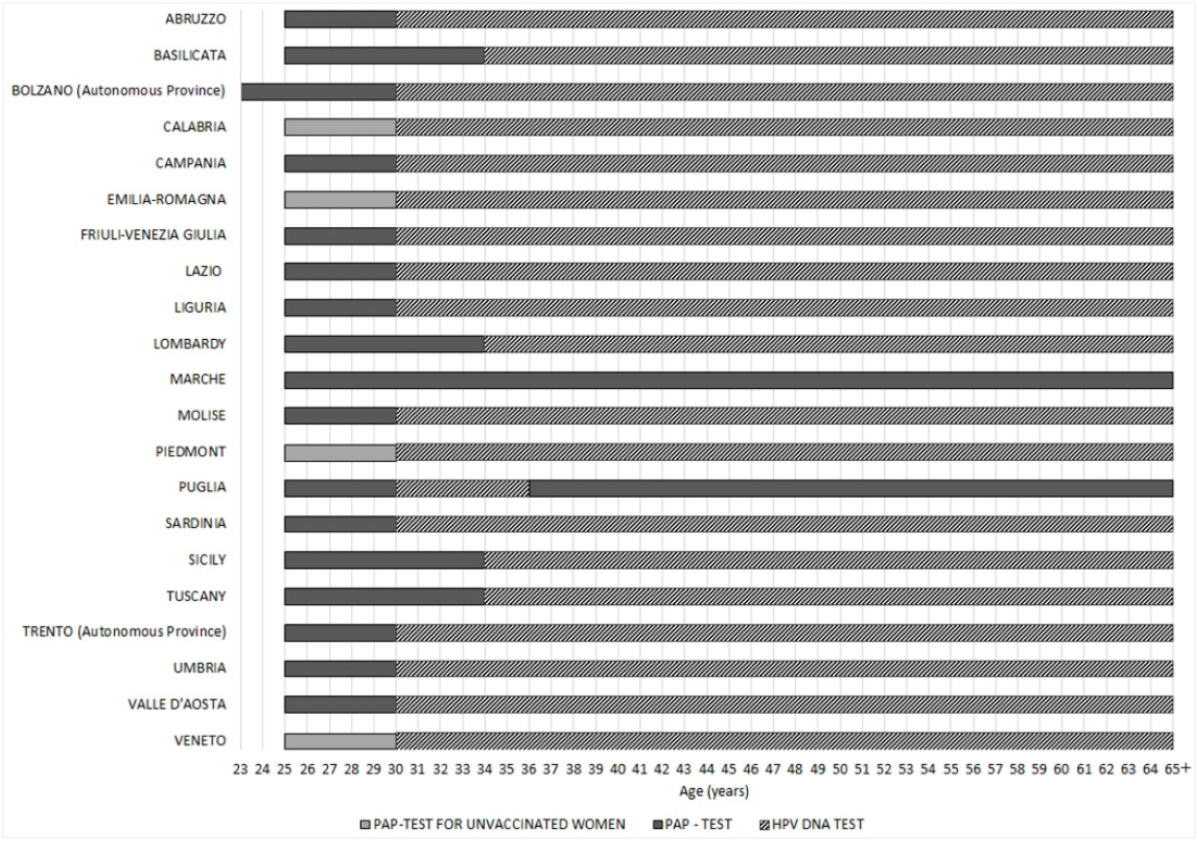


Figure 2. Cervical cancer secondary prevention strategy by age across Italian Regions(Bechini *et al.*, 2024).

The tailored screening strategy stratified by vaccination status implies that fully vaccinated women postpone the starting age of screening to 30 years, while primary cytology continues to be offered every 3 years to unvaccinated women aged 25-29(Giorgi Rossi *et al.*, 2017). Full vaccination is defined as completion of a two-dose HPV vaccine series administered before age 15. Tailored screening strategies stratified by vaccination status have been shown to be cost-effective in modelling studies(Goldhaber-Fiebert *et al.*, 2008; Naber *et al.*, 2016; Pedersen *et al.*, 2018). In 2021, Veneto became the first region to implement this change, which requires record linkage between the regional vaccination and screening databases(Martello *et al.*, 2023).

1.2 Organized and opportunistic cervical cancer screening

Organized, population-based screening programs differ from spontaneous (opportunistic) screening by ensuring the following key elements(European Commission, 2015):

- A defined, evidence-based screening policy that ensures effective and appropriate detection, diagnosis and treatment (including target population, tests, intervals, referral pathways, diagnostic work-up, treatment, and follow-up strategies);
- An accountable and autonomous governance system;

- An effective call-recall system to manage invitations, including repeated invitations and second-level assessments;
- Quality assurance in all phases of the screening process;
- Centralized screening databases, including record linkage to other health registries and databases, to ensure regular monitoring and quality reporting.

The organized approach is recommended because it provides effective quality assurance, promotes equity and accessibility through the personal invitation of each eligible individual, and contributes to cost reduction while mitigating the risk of overdiagnosis(European Commission, 2015).

In Italy, organized cervical, colorectal and breast cancer screening programs are included in the Ministry of Health's list of essentials health services (Essential Assistance Levels, LEA), which are nationally funded and must be provided free of charge, or with limited copayment, to all citizens (Italian Ministry of Health, 2017). The organization and delivery of LEA are the responsibility of the regional governments and their respective Regional Health Services. To ensure access to eligible individuals not reached by organized screening programs, spontaneous (opportunistic) screening tests can be financially covered by Regional Health Services when performed within the screening intervals approved by the LEA(Italian Republic, 2000).

For cervical cancer screening, women aged 25-29 years are offered a cytology (Pap test) every three years; while women aged 30-64 years are offered either a cytology test every three years or an HPV DNA test every 5 years.

Despite the proven effectiveness and cost-effectiveness of population-based cervical cancer screening, only 39% of Italian women in the target age group are invited to participate in an organized program, and among those invited, 37% actually participate(Italian National Screening Observatory, 2022). Nationwide screening coverage reaches 78% when both organized and opportunistic cervical cancer screening are considered, with opportunistic screening remaining the most common practice(Network PASSI, 2021).

1.3 The roll-out of organized cervical cancer screening in the Metropolitan Area of Milan

In the Lombardy Region, the burden of cervical cancer accounts for 550 annual new cases and 99 deaths(Italian Association of Medical Oncology, 2019).

In 2018, only 25% of women in the target age group were invited to participate in an organized cervical cancer screening program, and of those invited, 50% attended (Deandrea and

Schivardi, 2020). During the COVID-19 pandemic (2020-2021), invitation coverage and attendance further dropped to 16% and 46%, respectively(Deandrea and Odelli, 2023).

The Agency for Health Protection (AHP) of the Metropolitan Area of Milan, covering the provinces of Milan and Lodi(Regional Council of Lombardy, 2015), provided an organized cytology-based screening program only in the province of Lodi until 2022, achieving 84% invitation coverage and 41% attendance in 2018(Deandrea, 2020). The eligible population in the province of Milan, comprising 888,108 women aged 25-64 years(Italian Institute of Statistics, 2022), had not previously been reached by an organized cervical cancer screening program. Although regional screening coverage was very low before 2022 (12% in 2018), opportunistic screening uptake was estimated to be higher than 60%(Deandrea, 2020). However, total screening coverage remains unknown since Lombardy does not participate in the PASSI national surveillance system(Network PASSI, 2021).

The transition to HPV-based cervical cancer screening was formally introduced in Lombardy in 2017(Regional Council of Lombardy, 2017). Under that policy, primary cytology was offered every 3 years to women aged 25-33, while primary HPV DNA testing was offered every 5 years to women aged 34-64. However, by 2022, HPV-based screening had been implemented only in few Provinces of the Region(Deandrea, 2020). In line with recommendations from the National Screening Observatory, in 2022 the transition age for primary HPV testing was lowered to 30 years, and a tailored screening strategy was introduced for vaccinated women, moving the starting age for screening to 30 years(Regional Council of Lombardy, 2023a).

The AHP of the Metropolitan Area of Milan began scaling up primary HPV testing in early 2022 in the province of Lodi. In September 2022, the roll-out of the HPV-based screening program was started in the province of Milan, with stratification by vaccination status implemented in both territories.

1.3.1 Budget Impact Analysis

A Budget Impact Analysis (BIA) evaluates the expected changes in expenditure for a specific budget holder following the adoption of a new intervention(Sullivan *et al.*, 2014). A BIA can be conducted as a stand-alone analysis or as a complement to other health economic evaluations, such as Cost-Effectiveness Analysis (CEA), to provide a more comprehensive economic assessment of a healthcare intervention(Sullivan *et al.*, 2014). A CEA is a pharmacoeconomic method that informs decisions about whether an intervention represents good value for money compared with an alternative scenario, using comparative assessment of health outcomes and costs. In contrast, a BIA supports decision making by informing health

service planners and commissioners about whether an intervention is financially affordable relative to a comparator, by quantifying its impact on the health care budget(Yagudina *et al.*, 2017). Unlike CEA, BIA is usually performed over a short-term time horizon, and its perspective is typically that of the budget holder (e.g., national health system, regional health authority, insurance company, or hospital)(Mauskopf *et al.*, 2007). A Budget Impact Model (BIM) is the computational framework used to project the year-over-year resource use and budgetary implications associated with adopting a new health technology for a defined budget holder, accounting for the size of the target population, uptake rates, and unit costs over a specific time horizon, (Mauskopf *et al.*, 2007; Willis *et al.*, 2024).

BIA is a relatively recent method in Health Technology Assessment (HTA)(Mauskopf, 1998; Trueman, Drummond and Hutton, 2001) and has gained worldwide acceptance among decision makers. Several countries have published guidelines and guidance documents to support its implementation (Chugh, De Francesco and Prinja, 2021). The main outcomes of a BIA are total costs and cost differentials; however, secondary outcomes such as the year-to-year intervention uptake can inform resource allocation and planning at each time point.

The Wilson and Jungner criteria for evaluating cancer screening strategies, adopted by the WHO, state: "The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole"(Andermann *et al.*, 2008). Therefore, evaluations of screening programs should include both cost-effectiveness and budget impact analyses.

1.3.2 BIA in cancer screening

Economic evaluations of cancer screening programs present some specificities. First, different payers may be involved depending on the healthcare financing system, since screening, treatment and follow-up encompass both inpatient and outpatient care. Second, the design of a program may vary according to the screening and follow-up tests employed, screening intervals, and access restrictions(Sullivan *et al.*, 2014). Finally, for slow-developing cancers such as cervical cancer, the positive financial impact of prevention (e.g. through detection and treatment of precancerous lesions before they progress to invasive cancers) or early treatment may be only become evident in the long term, often decades later(Jahn *et al.*, 2019).

A literature review of BIA research published between 2000 and 2008 found that most studies investigated new drugs or treatments, with only one out of 34 analysing the financial impact of a public health intervention(Orlewska and Gulácsi, 2009). Since then, the number of BIA

studies has increased rapidly, and systematic reviews have been published focusing on specific conditions or interventions(Jahn *et al.*, 2019). A systematic review of BIA studies published between 2010 and 2018(Jahn *et al.*, 2019) identified 19 studies evaluating cancer screening programs, including three on cervical cancer screening(Shi *et al.*, 2012; Wright *et al.*, 2016; Petry *et al.*, 2017). The review showed a sharp increase in BIA publications over time, with 12 studies published between 2016 and 2017 compared to seven studies during 2011-2015(Jahn *et al.*, 2019). Most publications originated from high-income countries, with only one study conducted in China(Jahn *et al.*, 2019). More than half of the studies exhibited major deviations from guidelines regarding time horizons, comparator selection, model validation, uncertainty analysis, and information about assumed participation rates(Jahn *et al.*, 2019).

Through an extended MEDLINE literature review and manual reference screening -including peer-reviewed studies and grey literature- we identified 13 additional BIA studies on cervical cancer screening programs published in English, Italian, Spanish or Portuguese(Ronco *et al.*, 2012; Diaz *et al.*, 2018; Parra *et al.*, 2018; Shen *et al.*, 2018; Dreyer, Maske and Stander, 2019; Pista *et al.*, 2019; Garay *et al.*, 2021; Amézquita *et al.*, 2022; Kositamongkol *et al.*, 2023; Hafidz *et al.*, 2024), beyond the three studies included in the above-mentioned systematic review. Key characteristics of all 13 studies are summarized in Table 1. All were published between 2012 and 2023. Of note, the proportion of studies conducted in middle-income countries increased in the second half of the publication period (14% *vs* 67%), compared with those conducted in high-income countries.

The screening scenarios evaluated differed substantially between middle- and high-income countries. In middle-income countries, studies assessed interventions such as visual inspection with acetic acid (VIA)(Shi *et al.*, 2012; Hafidz *et al.*, 2024) or Lugol's iodine (VILI)(Shi *et al.*, 2012) for primary screening or triage after HPV detection, and self-sampling for HPV testing(Shen *et al.*, 2018; Kositamongkol *et al.*, 2023), in addition to co-testing(Parra *et al.*, 2018) and HPV testing with 16/18 genotyping(Parra *et al.*, 2018; Dreyer, Maske and Stander, 2019; Garay *et al.*, 2021; Amézquita *et al.*, 2022; Kositamongkol *et al.*, 2023) compared with traditional(Parra *et al.*, 2018; Garay *et al.*, 2021; Amézquita *et al.*, 2022; Kositamongkol *et al.*, 2023) or liquid-based cytology(Dreyer, Maske and Stander, 2019). By contrast, studies conducted in high-income countries mainly evaluated liquid-based cytology(Ronco *et al.*, 2012), primary co-testing(Lew *et al.*, 2016; Wright *et al.*, 2016; Petry *et al.*, 2017; Parra *et al.*, 2018) or HPV-based strategies with different screening intervals (3/5 years), with or without triage approaches such as reflex cytology, 16/18 genotyping(Lew *et al.*, 2016; Wright *et al.*, 2016; Pista *et al.*, 2019), 16/18 genotyping plus reflex cytology or reflex 16/18 genotyping +

reflex cytology(Skroumpelos *et al.*, 2015), or reflex pi-16/Ki-67 dual staining(Petry *et al.*, 2017; Tjalma, Kim and Vandeweyer, 2017) compared with traditional cytology.

In most studies, HPV testing every 5 years was found to be less costly than cytology(Ronco *et al.*, 2012; Lew *et al.*, 2016; Wright *et al.*, 2016; Petry *et al.*, 2017; Tjalma, Kim and Vandeweyer, 2017; Diaz *et al.*, 2018; Pista *et al.*, 2019) and co-testing(Lew *et al.*, 2016; Petry *et al.*, 2017). Regarding cost-effectiveness, HPV-based screening was identified as the dominant strategy in studies that performed both BIA and CEA(Ronco *et al.*, 2012; Lew *et al.*, 2016), consistent with findings from a recent systematic review on cervical cancer screening HTA(Sefuthi and Nkonki, 2022). Among triage strategies for HPV positive result, the less costly and most cost-effective options varied depending on the setting and interventions under evaluation. Petry et al(Petry *et al.*, 2017) reported the lowest annual cost for HPV testing at 5-year intervals with reflex cytology and dual staining as triage for ASC-US and L-SIL results. Pista et al(Pista *et al.*, 2019) found HPV testing with cytology triage less costly but less clinically effective(Pista *et al.*, 2019) or cost-effective(Lew *et al.*, 2016) compared with HPV testing with 16/18 genotyping and cytology triage.

One BIA study conducted in Italy(Ronco *et al.*, 2012) found that HPV testing every five years, with cytology triage starting at age 34, was the less costly and more cost-effective strategy. This evidence later informed the adoption of national policy for cervical cancer screening(Italian Ministry of Health, 2020).

References	Research question	Screening strategies	Population and model type	Findings
Shi et al (Shi *et al.*, 2012) (China, 2012)	What are the aggregated costs associated with cervical cancer screening, diagnosis and treatment in rural China?	VIA only, combined VIA/VILI, HPV screening (HPVcare) with self- or clinician-sampling, compared with no screening	47,750 eligible women aged 30-59 years. Micro-costing model	Aggregated direct medical costs of screening found to be $2.24, $2.64, $7.49, and $7.95 for VIA only, combined VIA/VILI, careHPV (self-sampling) and careHPV (clinician-sampling) respectively. Aggregated direct non-medical costs of screening found to be $2.16, $2.20, $0.68, and $2.15 for VIA only, combined VIA/VILI, careHPV (self-sampling) and careHPV (clinician-sampling) respectively.
Ronco et al (Ronco *et al.*, 2012) (Italy, 2012)	What are the aggregated costs associated with HPV-based organized cervical cancer screening and LBC compared with cytology-based cervical cancer screening?	HPV primary screening with cytology triage every 5 years (1st study) and LBC every 3 years (2nd study), compared with conventional cytology every 3 years	Costs calculated per 100.000 (1st study) and 10.000 (2nd study) screened women (hypothetical population). Micro-costing cohort model	Aggregated costs of screening per screened woman of a lifetime basis (34-64 years) found to be higher for cytology (€365.61) compared with HPV screening (€284.37). Costs per round per screened woman were higher for LBC than for conventional cytology (€44.5 vs €35.43). Updated estimates with more recents costs estimates: €236,72 (HPV screening) vs €365,61 (cytology screening).
Wright et al (Wright *et al.*, 2016) (USA, 2016)	What are the clinical and budgetary impacts of HPV primary screening with HPV 16/18 genotyping, compared with current screening strategies (cytology and co-testing)?	HPV primary screening with HPV 16/18 genotyping every 3 or 5 years compared with cytology every 3 years and co-testing every 3 or 5 years	50,497,448 (calculated based on data) women aged 30-65 years. Decision tree and Markov model	Co-testing with genotyping every 3 years (incidence=5.5 per 100,000 women, annual cost per screened patient=$61) or 5 years (7.4 per 100,000 women, $37) slightly more effective, but more costly than HPV primary screening every 3 years (6.2 per 100.000 women, $48) or every 5 years (8.1 per 100,000 women, $30).
Skroumpelos (Skroumpelos *et al.*, 2015) (Greece, 2015)	What is the economic impact of alternative cervical cancer screenings strategies for women aged 25-65 using different algorithms for primary screening methods including cytology alone or hrHPV testing and genotyping?	The compared strategies were: (1) triennial hrHPV testing with 16/18 genotyping and reflex cytology, (2) triennial hrHPV testing with reflex genotyping and reflex cytology, (3) annual cytology alone	Population not reported. Decision tree and Markov model	The annual cost of strategy 1 was estimated at €14,568,412 compared to the costs of strategy 2 and 3 which were estimated at €38,109,522 and €18,209,511 respectively.
Petry et al (Petry *et al.*, 2017) (Germany, 2017)	What are the clinical and budgetary impacts of Pap cytology compared with HPV primary screening scenarios?	Four HPV primary screening scenarios (co-testing, HPV testing with three different triage methods – cytology +p16/Ki-67 dual staining, p16/Ki-67 dual staining alone, HPV genotyping+p16/Ki-67 dual staining) every 3/5 years compared with annual Pap cytology (+reflex HPV test)	16 million eligible women. Markov cohort model	All HPV scenarios associated with lower total annual costs (€117-136 millions vs €177 millions) and fewer deaths compared with Pap screening (1.5-3 per 100.000 women in 10 years vs 4.1 per 100.000). Greatest clinical impact reached with the genotyping scenario. The lower annual cost (€117 millions) was reached with HPV tests at 5-year intervals with cytology triage and dual staining for L-SIL and ASC-US results. Superior incidence and mortality outcomes but higher costs for the 3-years interval HPV test scenario.

References	Research question	Screening strategies	Population and model type	Findings
Tjalma et al (Tjalma, Kim and Vandeweyer, 2017) (Belgium, 2017)	What is the budget impact of cervical cancer screening programs based on primary HPV screening with dual-stain cytology triage compared with cytology screening?	Primary HPV screening with p16/Ki67 dual-stain cytology triage every 5 years, compared with primary cytology every 3 years	4,663,532 eligible women aged 25-65 years. Markov model	HPV scenario associated with a 21% budget reduction representing an annual cost saving of 5.3 million euros (€3.5 per screened patient). For women aged 30-65, HPV scenario associated with a 22% budget reduction representing an annual cost saving of 5 million euros (€4 per screened patient).
Lew et al (Lew *et al.*, 2016) (New Zealand 2016)	What are the clinical and budgetary impacts of different cervical cancer screening strategies?	16 primary HPV screening strategies were compared with current practice (cytology every 3 years, based on a 4x4 combination of: -screening and triage approach: (1) primary HPV, cytology triage for all HPV+, (2) primary HPV with partial genotyping, (3) co-testing, (4) co-testing with partial genotyping -exclusive HPV approach or switch from primary cytology at different age ranges Two vaccination scenarios were modelled (without and with vaccination, with current uptake).	2.3 million women aged <85 years. Dynamic model of HPV transmission and vaccination coupled with a deterministic Markov model	Screening according to current practice predicted to cost $31.7 million (unvaccinated) and $25.9 million in 2017. Primary HPV with cytology triage (1) and (2) were associated with a 3-12% decrease in costs, whereas co-testing strategies (3) and (4) were associated with a 12-26% increase in costs. Primary HPV screening with partial genotyping and direct referral for 16/18+ and LBC triage (2a) for 25-69 women for others proved to be the most cost-effective strategy. Cytology triage for all HPV+ (2b) irrespective of genotype proved to be the most effective strategy, although higher than New Zealand's WTP.
Diaz et al (Diaz *et al.*, 2018) (Catalunya 2018)	What are the comparative costs of cervical cancer screening based on opportunistic cytology screening versus an organized program based on primary HPV screening?	Opportunistic cytology screening at 3-year intervals for women aged 25-64 years compared with organized program based on primary HPV screening with cytology triage at 5-year intervals for women aged 35-65 years + cytology for women aged 25-34 years	979,177 eligible women aged 35-64 years. Calibrated Markov model	Total annual discounted costs estimated to be higher with cytology (€13,331,540 = €8,017,296 direct medical costs + €1,894,100 direct non-medical costs + €3,420,144 indirect costs) compared with the HPV organized scenario (€10,270,938 = €5,443,275 direct medical costs + €1,035,478 direct non-medical costs + €3,404,079 indirect costs + €388,106 programmatic costs).
Shen et al (Shen *et al.*, 2018) (Kenya, 2018)	What are the costs of cervical cancer screening with a CHC strategy compared with an opportunistic strategy?	CHC screening *vs* HPV screening in government clinics (both strategies to be conducted with self-sampling for HPVcare analysis)	2,899 women screened in the CHC arm, vs 2,042 women screened in the government clinic arm. Micro-costing model	Costs found to be higher for the government screening strategy ($29,56 per screening) than for the CHC strategy ($25 per screening).
Parra et al (Parra *et al.*, 2018) (Peru, 2018)	What are the clinical and budget impacts of HPV testing with genotyping or co-testing compared with conventional cytology for cervical cancer screening?	Annual conventional cytology compared with co-testing every 5 years and HPV with 16/18 genotyping every 5 years (immediate referral for 16/18+, cytology triage for OHR+)	4,000 eligible women (hypothetical population). Markov cohort model	The incremental total annual cost per screened woman was found to be $0.62 for HPV with 16/18 genotyping and $1.37 for co-testing, compared to annual conventional cytology. Both HPV screening strategies showed higher CIN2+ detection.

References	Research question	Screening strategies	Population and model type	Findings
Pista et al (Pista *et al.*, 2019) (Portugal, 2019)	What are the comparative costs of two HPV screening strategies (HPV pooled test with cytology triage, HPV test with 16/18 genotyping and cytology triage) vs cytology with ASC-US HPV triage in organized cancer screening?	Two HPV screening strategies with 5-year intervals (comparator 1: HPV pooled test with cytology triage, comparator 2: HPV test with 16/18 genotyping and cytology triage) vs cytology with ASC-US HPV triage with three-year intervals	2,078,039 eligible women aged 25-64 years. Decision tree and Markov model	Average annual costs found to be €34.43 million for cytology screening, vs €29.07 million and €29.26 million for comparator one and comparator 2 respectively. Comparator 1 shows higher screening costs (€24.41 million) but lower diagnosis costs (€1.2 million) compared to comparator 2 (€24.3 million and €1.53 million respectively). Average cost per screening higher for comparator 2 than comparator 1 (€14.08 *vs* €13.99). Better clinical outcomes with comparator 2.
Dreyer et al (Dreyer, Maske and Stander, 2019) (South Africa, 2019)	What are the clinical and budget impacts of replacing primary LBC with primary HPV-based screening strategies?	Two cycles of hrHPV test with 16/18 genotyping every 5 years compared with 2 cycles of LBC screening with a 10-year interval	1,712,605 hypothetically compliant 30-65 yo women. Decision tree and Markov model	The total predicted costs were found to be R2,088,178,790 for LBC and R4,843,342,084 for hrHPV. The annual costs per screened patient were R61 and R283 respectively. hrHPV proved to have a higher detection rate.
Garay et al (Garay *et al.*, 2021) (Argentina, 2021)	What are the cost-effectiveness and budgetary impact of a screening strategy based on HPV with genotyping compared with cytology?	Annual cytology *vs* 5-yearly hrHPV with 16/18 genotyping and reflex cytology	9,141,793 eligible women aged 30-65 years. Decision tree and Markov model	HPV strategy proved to be more costly than cytology in the first 5 years (cumulative cost $102,341 million *vs* $88,282 million) but saves money in the 20 years ($385,005 million vs $380,052 million) time horizon. HPV strategy showed a better clinical performance.
Amézquita et al (Amézquita *et al.*, 2022) (Colombia, 2022)	What is the budgetary impact of HPV DNA genotyping with reflex cytology compared with conventional cytology?	Two screening cycles of HPV DNA genotyping with reflex cytology every 18 months compared with annual conventional cytology	10,219 screened women aged 30-65 years Decision tree and Markov model	The average cost per screening cycle with the HPV test was estimated at COP $129,201,363 and with cytology at COP $ 186,309,952, i.e. a saving of COP $57,108,589 (31%).
Kositamongkol et al (Kositamongkol *et al.*, 2023) (Thailand, 2023)	What are the cost-utility and budget impacts of implementing cervical cancer screening using HPV self-sampling?	Four screening policies were compared: (1) additional self-collected samples for HPV testing every 5 years, (2) clinician-collected samples for HPV test only every 5 years, (3) biennial clinical-collected samples for cytology (current practice) and (4) no screening	20 million eligible women aged 25-65 years. Decision tree and calibrated Markov model	Strategy (1) found to be less costly than (2) and (3) (lifetime costs: THB33,052, THB38,850, and THB40,124 respectively). Regarding the cost-utility analysis, additional HPV self-sampling proved to be dominant at different screening uptake rates.
Hafidz et al (Hafidz *et al.*, 2024) (Indonesia, 2024)	What are the cost-effectiveness and budget implications of HPV testing and VIA compared with cytology?	HPV testing or VIA every 3-5 years compared with cytology every 3-5 years.	2.11 million 30 yo women. Markov model	Compared to screening every 3 years, VIA is the less costly strategy (lifetime costs $96.09 per screened patient), followed by cytology ($120.65) and HPV ($262.93). Total costs in the first 10 years are 2.3 times higher with HPV, VIA and cytology combined than in the scenario with VIA and Pap smear only. Cytology is the most cost-effective modality, while HPV has the potential to be cost-effective by reducing unit cost.

Table 1. General information on cervical cancer screening Budget Impact Analysis (BIA) studies, target populations and findings. VIA: visual inspection with acetic acid; VILI: visual inspection with Lugol's iodine; CHC: community health campaign; hrHPV: high risk HPV; LBC: liquid-based cytology; WTP: willingness to pay, OHR: other hrHPV, non-16 non-18. CIN: cervical intraepithelial neoplasia. COP: Colombian pesos; THB: Thai Baht. Adapted from Jahn et al(Jahn *et al.*, 2019)

2 PURPOSE OF THE ANALYSIS

To support public health decision-making as well as budget and resource planning during and after the roll-out of the cervical cancer screening program, it is necessary to move from an initial pilot phase toward a scaled-up model of program implementation. Specifically, it is essential to generate evidence on the total and annual number of tests, procedures, and related costs, and to evaluate how these may affect the cervical cancer screening budget and organizational structure of the AHP.

This Budget Impact Analysis (BIA) assessed the expected change in the annual volumes and costs of organized and opportunistic cervical cancer screening tests and procedures over the first decade following the implementation, compared with previous interventions (opportunistic screening only, primarily cytology-based). The analysis was conducted through the development and validation of a Budget Impact Model (BIM), from the perspective of the budget holder in the province of Milan: the AHP of the Metropolitan Area of Milan.

In addition, the BIA projected the expected expenditure under different organizational scenarios, with the aim of maximizing the affordability of screening given the potential budgetary constraints. Finally, the analysis provided an estimate of the initial impact of program implementation on the coverage of regionally funded cervical cancer screening.

3 MATERIALS AND METHODS

The BIA framework was developed in accordance with the ISPOR principles of good practice(Sullivan *et al.*, 2014), with a methodological focus on BIA in cancer screening(Jahn *et al.*, 2019).

3.1 Health intervention under assessment and its comparator

3.1.1 The local cervical cancer screening network

In the Lombardy region, organized cervical cancer screening programs rely on networks of clinical centers (CCs), which deliver screening services under the governance of the local AHP in terms of organization and quality assurance. CCs are administered by public or accredited private health institutions that sign an annual contract with the local AHP. These contracts define the minimum expected number of tests and the corresponding quality indicators(Regional Council of Lombardy, 2021).

As of January 2024, in the province of Milan, 48 CCs provided first-level tests (cytology and HPV DNA testing), while 16 referral CCs performed colposcopies. Overall, 8 public health institutions and 3 private health institutions administered the CCs (Fig.3).

Figure 3. The cervical cancer screening program network in the Provinces of Milan and Lodi. Different health institutions are depicted with different colors. ASST Lodi (yellow) covers the entire province of Lodi. Hearts indicate first-level CCs, while 'H' indicate referral CCs for colposcopy. Image generated with Google MyMaps, last accessed January 21, 2024.

Midwives and gynecologists use an online screening software (OSS) provided by the AHP (Fig. 4). The OSS records patients' screening history, diagnostic results, and -based on the conclusions of each screening round- schedules subsequent rounds according to local guidelines(Regional Council of Lombardy, 2023a). Each first-level CC is assigned one or more postcodes, and the OSS generates monthly invitations for eligible female residents through real-time integration with the regional registry.

Cervical sample collection kits are supplied by the accredited reference laboratory (HUB-SOCCU), administered by the public health institution ASST Santi Paolo e Carlo. After sample collection, clinical data are registered in the OSS, which generates a unique barcode applied to each sample to ensure 1:1 matching with the participant's screening ID. These barcodes safeguard personal data during transport. Samples are packaged, transported, and delivered to HUB-SOCCU. Following analyses, the OSS -integrated with the HUB-SOCCU's software- retrieves the results.

For women not requiring clinical referral, the OSS manages results via postal communication(Regional Council of Lombardy, 2023a), ensuring the proper content and timing. Results requiring referral for colposcopy are communicated through telephone counseling, with direct scheduling of appointments by the Screening Unit's healthcare staff. Colposcopies are performed by gynecologists, who, if necessary, performs biopsies or additional second-level tests (including surgery when indicated), and determine follow-up timing.

First-level conclusions and follow-up pathways are automated within the OSS based on workflows adapted from regional guidelines, making them highly predictable. In contrast, second-level and the relative follow-up pathways are determined by clinical decision-making and are strongly influenced by local clinical practice and individual physician judgment.

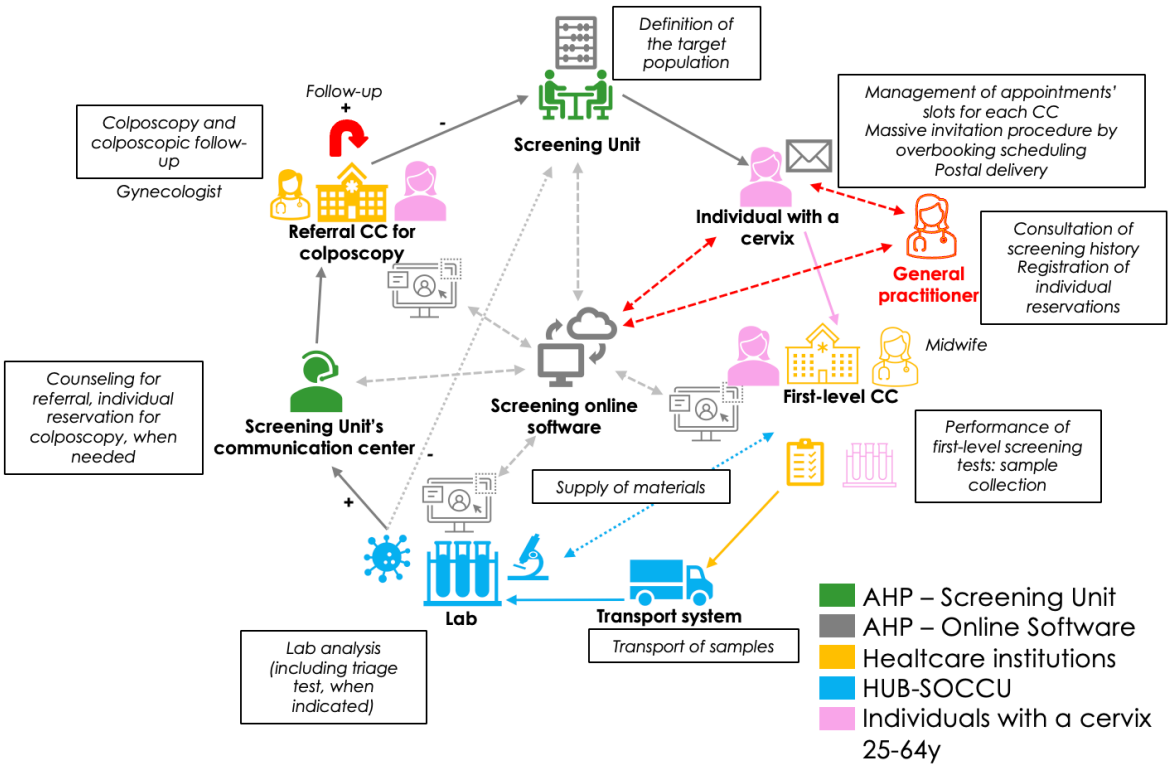


Figure 4. Cervical cancer screening program's organizational workflow. The online screening software (OSS) manages complex functions, from massive invitations to automated management of following rounds according to test results and local guidelines. The red color indicates functions that were still under construction as of January 2024.

For women who have already received at least one invitation, the program may apply restrictions(Regional Council of Lombardy, 2023a), most often when a valid opportunistic screening test has already been performed during the previous screening interval. Restrictions may be applied automatedly, by extracting test records from the AHP Data Ware House (DWH), or manually, when women submit their clinical report to the Screening Unit. The DWH collects data on all outpatient tests and procedures performed by prescription by accredited institutions within the Regional Health System, enabling reimbursement procedures.

Finally, the tailored screening strategy for fully vaccinated women is managed automatedly as a temporary restriction until the age of 30, based on record linkage with the Regional Vaccine Registry.

3.1.2 AHP's phased rollout plan

The introduction of the primary HPV DNA test within the cytology-based program of the province of Lodi in early 2022 served as a pilot. The rollout of the new test was phased, to minimize the impact of shifting test distribution over time, moving from a 3-year interval to a predominantly 5-year interval(Lynge *et al.*, 2012). The primary HPV test was initially offered to older women as an "exit test" (if negative) and was then progressively extended to younger

age groups. Age cut-offs were determined by modelling the 10-year distribution of invitations against the resident population using Excel® and demographic data from the Italian National Institute of Statistics (Istat, 2021). In 2022, only women aged 50-64 were eligible for the primary HPV DNA test; in 2023, eligibility was extended to women aged 47-64; and beginning in 2024, all women aged 30-64 became eligible (Fig. 5).

The roll-out of the program in the Milan Province, where no organized screening program had previously been implemented, required a different approach. However, the plan had to align with the age cut-offs already established for Lodi, since the OSS system did not allow province-specific cut-offs. To evenly distribute the number of required colposcopies -given that colposcopy referral rates are higher among younger age groups and for the primary HPV DNA test- we initially targeted the extremes of the eligible age range, then progressively extended invitations to intermediate age groups, reaching full coverage in approximately eight years (Fig. 5).

To determine the optimal age cut-offs for balancing the number of first- and second-level tests, we modeled, in Excel®, the annual number of invitations required under each age-cut-off scenario, taking the resident population (Istat 2021) and test- and age-specific colposcopy referral rates(Pesola *et al.*, 2021) into account. Participation rates were assumed to be constant across age groups, and adherence to colposcopy was assumed to be 100%. The scenario showing the most homogeneous distribution of first- and second-level tests was selected to guide the implementation plan (Fig. 6).

The organized screening program follows an opt-out policy: the entire eligible population is actively invited, while each invitee may decide whether to participate or not. The program also allows opt-in participation: eligible women who are not actively invited may still access screening through “on demand” invitations. During the first two years of implementation, the test offered was determined by the cut-offs established for the Province of Lodi(Fig. 5).

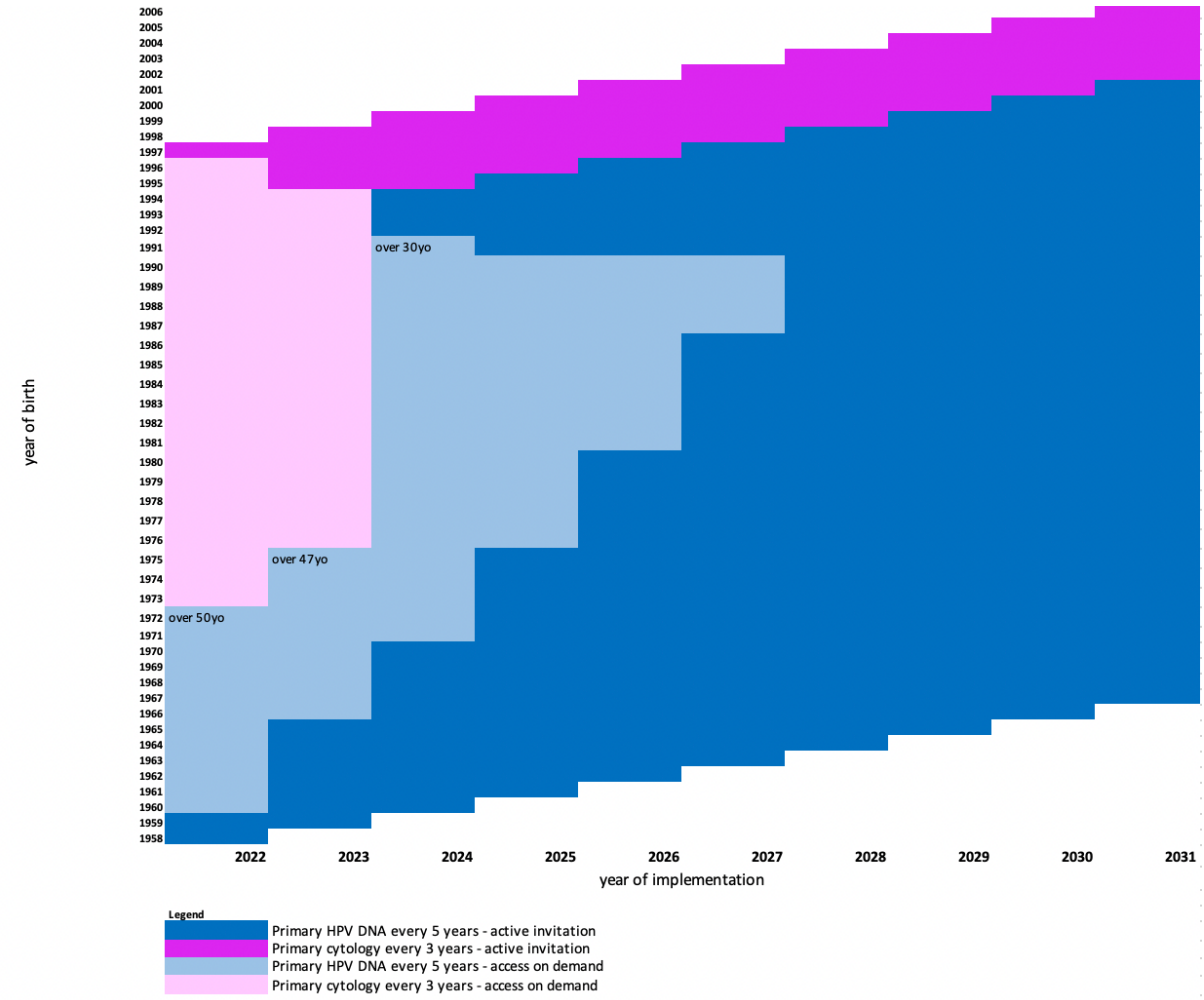


Figure 5. AHP 10-year phased rollout plan for the province of Milan. Age cut-offs for the extension of active invitations are shown in darker colors; while opt-in cut-offs are shown in lighter colors.

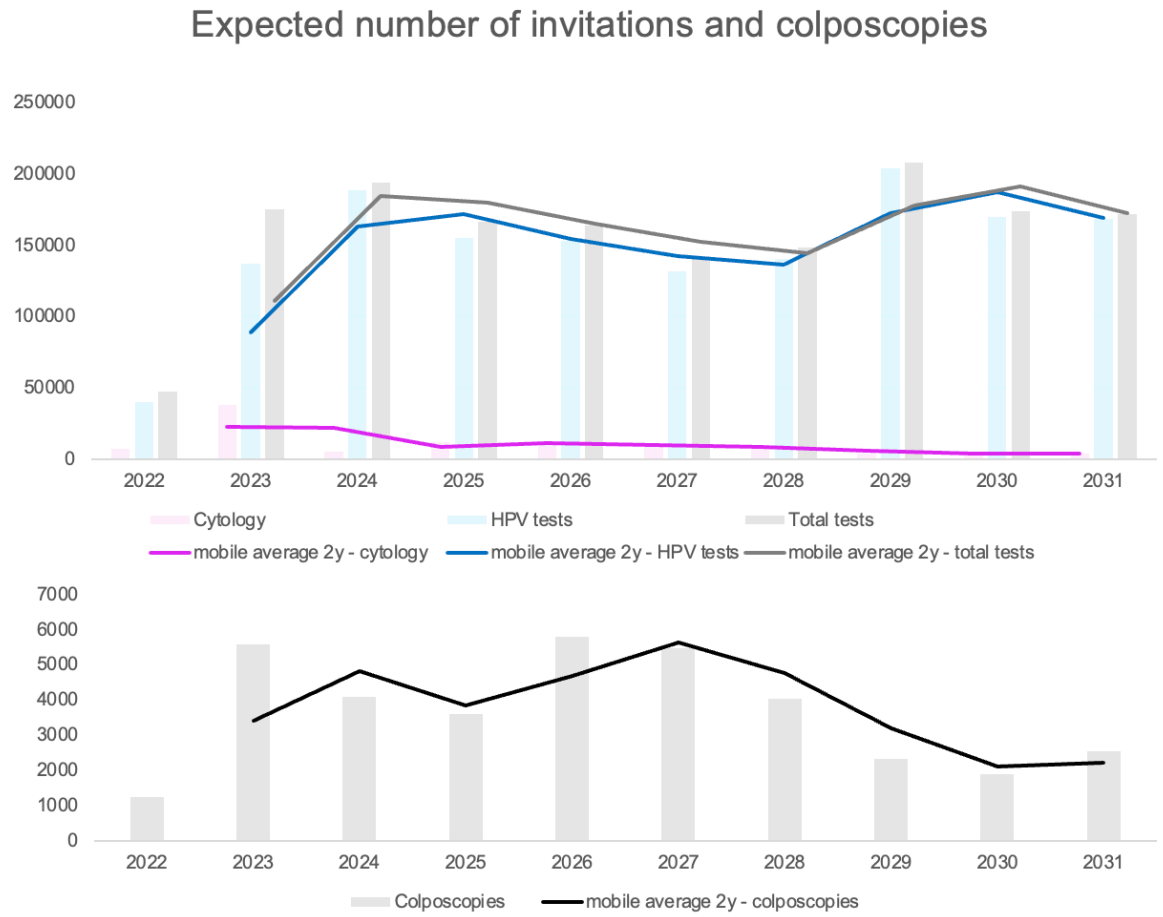


Figure 6. Ten-year projection of annual invitations and colposcopies, assuming a 100% participation rate.

3.2 Perspective

We adopted the perspective of the budget holder for screening tests and procedures, namely the AHP of the Metropolitan Area of Milan.

Only direct medical costs related to first- and second-level screening procedures were considered in the BIA.

The present analysis focused on the annual budget impact over the first 10 years of roll-out of the newly introduced organized HPV-based program, with the aim of informing the budget holder's decisions on resource allocation for tests and procedures under its direct governance. In Lombardy, the governance of organized screening ends once patients require higher levels of care, such as hospitalization or follow-up for metastatic cancer. These patients are entitled to free care in a clinical setting, outside the organized screening program(Regional Council of Lombardy, 2023a).

Non-medical costs (e.g. patient transportation), including programmatic costs (e.g. mailing of invitations and results letters, management of recalls, software purchasing and update, and

additional staff) were not assessed, as these have already been shown to be lower in HPV-based organized programs compared with opportunistic screening(Diaz *et al.*, 2018).

Similarly, all procedures, admissions, and indirect or intangible costs occurring after a cervical cancer diagnosis were excluded. In fact, primary HPV-based cervical cancer screening has already been demonstrated to be cost-effective in reducing both the incidence of cervical cancer and the associated costs, when compared with cytology-based organized programs and with the no-screening scenario(Accetta *et al.*, 2010). Finally, as cervical cancer is a slow-developing condition, the positive financial impact of prevention is expected to emerge only after several decades.

3.3 Time horizon

Total annual costs and annual costs per screened woman aged 25-64 were projected for the first 10 years of rollout starting from 2024 (2024-2033).

3.4 Budget Impact Model

The *intervention (usual) scenario* was simulated using a decision tree cohort Budget Impact Model developed in Excel® (Fig. 7). The BIM tracks each birth cohort across subsequent invitation rounds, estimates the expected annual number of first-level tests and colposcopies for both organized and opportunistic screening, and incorporates a cost-calculator.

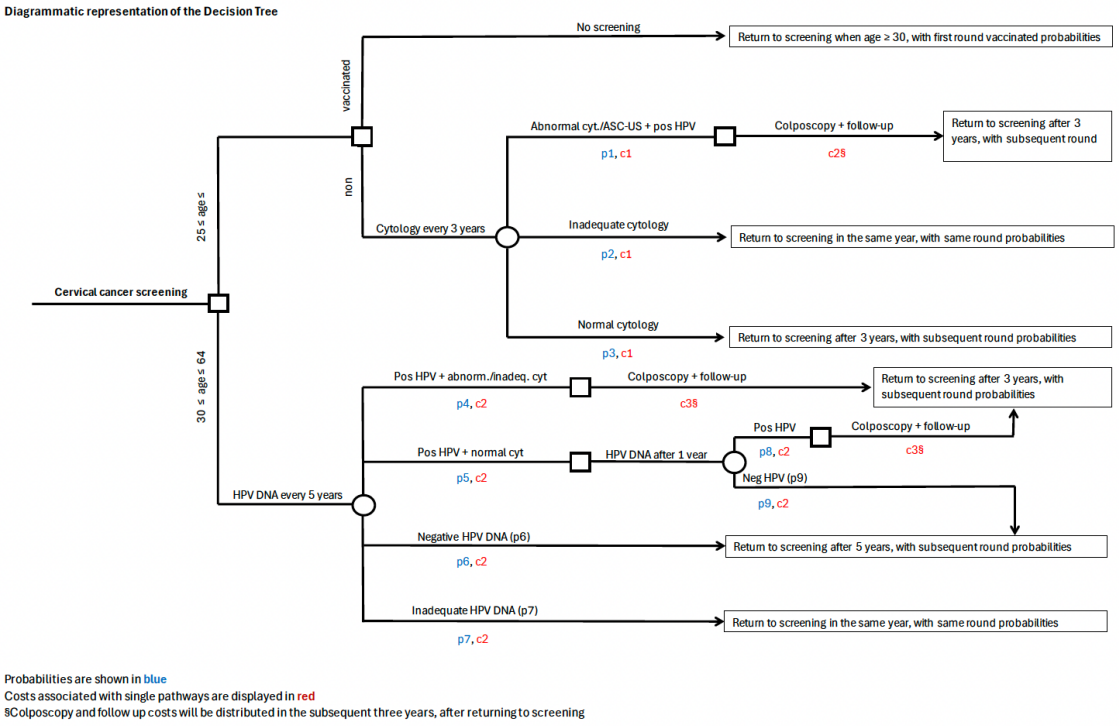


Figure 7. Decision tree diagram.

3.5 Time dependencies and discounting

Over the 10-year period covered by the BIA, several variables may change over time. For example, participation rates (uptake) are likely to increase, which would in turn affect the intervention mix. These aspects were addressed in the sensitivity and scenario analyses. Discounting was not applied, as it is not always recommended for BIAs(Sullivan *et al.*, 2014).

3.6 Data sources

To obtain the set of real-world parameters needed to run the BIM, we relied on two main data sources: the AHP Data Warehouse (DWH) and the screening database.

The DWH includes, among other information, data on outpatient tests and procedures performed under prescription in accredited institutions within the regional healthcare system. It aggregates data from multiple administrative health sources. For outpatient cervical cancer screening procedures, the main inputs are:

- *cons* data, which capture tests and procedures performed within the network of community reproductive health centers,
- *outpatient* data, which capture all other outpatient tests and procedures(Regional Council of Lombardy, 2019).

Each recorded procedure is classified by Tax Identification Number (TIN), registration date, registration center, the relevant code from the Regional reimbursement manual(Regional Council of Lombardy, 2023a), and reimbursement scheme (patient-paid, fully reimbursed, or partial reimbursed).

The screening database, hosted by the OSS -the Electronic Health Record (EHR) for screening- collects all data related to outpatient tests and procedures performed within organized screening(Regional Council of Lombardy, 2023a). For each test or procedure, the OSS records clinical details as well as administrative data already captured by the sources mentioned above. The OSS records first-level test data in a semi-automated and standardized manner, while second-level test data are standardized but entered manually. By contrast, administrative health data may be standardized or semi-automated only at the individual health facility level, and considerable differences in reporting can emerge across provinces. For these reasons, the screening database is preferred over administrative sources for monitoring organized screening test and procedures.

Since the HPV-based program had already been introduced, the first 16 months of roll-out provided real-world data (e.g., changes in the intervention mix, age-specific referral

colposcopy rates, age-specific participation rates, adherence to colposcopy, and CIN2+ detection rates) which were incorporated into the analysis. For parameters not covered by real-world observations from the first 16 months of implementation, we relied on published data. Where available, preference was given to large datasets, particularly those from Italian or European settings.

3.7 Target population

The target population for 2023, as estimated by the Italian National Institute of Statistics (Istat)(Italian Institute of Statistics, 2023), comprised 882,432 women aged 25-64 years, out of a total female population of 1,655,817 residents in the Metropolitan Area of Milan. These estimates were adjusted for historical fluctuations observed in monthly invitations during 2023, accounting for the dynamic nature of the population due to temporary and permanent migration. Specifically, adjustments were made by multiplying the Istat population by a correction factor, calculated as follows:

Numerator = (invited women in 2023 target cohorts) + (women yet to be invited in 2023 target cohorts) (source: screening database)

Denominator = (resident women in 2023 target cohorts) (source: Istat 2023)

The proportion of HPV-vaccinated women (defined as those who received at least two doses before age 15, in line with the Cervical Cancer Screening Italian Group recommendations(Giorgi Rossi *et al.*, 2017)) eligible for the tailored screening strategy was extracted from the Lombardy Region vaccine database when available, or estimated using Lombardy data reported by the National Ministry of Health(Italian Ministry of Health, 2025) when unavailable. For women born in 2010-2011, for whom National data were not available, vaccination coverage was assumed to be the same as that of the 2009 cohort. The AHP allows eligible women to provide vaccination certificates to switch to the tailored screening strategy. Conversely, women aged 25-29 years who were allocated to the tailored screening strategy may opt out and request a cytology test instead. According to the observed balance between these two phenomena (2022-23), a quote of the eligible population has been relocated in the vaccinated or unvaccinated groups. Adjustments were made by multiplying the unvaccinated population by a correction factor, calculated as follows:

Numerator = (vaccinated women born in 1997-98 actively requesting cytology in 2022-2023) - (women born in 1997-98 invited for cytology who disclosed vaccination status previously

unknown to the AHP, and requested the delayed screening strategy) (source: screening database)

Denominator = (women born in 1997-98) (source: Istat 2023) * (1-cohort-specific HPV vaccination coverage) (source: Regional vaccine database)

The actual number of registered invitations is shaped by the interaction between opt-out and opt-in screening policies. The proportion of the target population already invited in 2023 through opt-in was estimated at less than 4% of the total annual invitation (ca 7,500 first-level invitations: 2,500 primary HPV DNA and 5,000 cytology tests). Since these opt-in invitations were assumed to be homogenously distributed across time and age groups, they were not included in the analysis. As program roll-out progresses, the impact of opt-in invitations on projections will become negligible.

Entry and exit rates were assumed to remain in a steady state, given that permanent restrictions for gynaecologic cancers were negligible in the first 16 months of program activity (n=71) (source: screening database). Additionally, restrictions related to personal conditions (e.g., hysterectomy or chronic conditions) were inherently accounted for in the participation estimates.

3.8 Types of screening/diagnostic tests and costs

The AHP is the final payer for both screening and diagnostic tests performed within the organized program, as well as for opportunistic screening carried out within the Regional Health System. In the latter case, the payer is entitled to apply non-reimbursement lists to public or private accredited healthcare institutions. When the type and frequency of the test do not comply with the LEA indications, a copayment is applied over the 36.15 € threshold, while an out-of-pocket payment (ticket) is expected below the threshold(Italian Republic, 1993).

In opportunistic setting, however, monitoring individual coverage and enforcing restrictions requires significant time and resources, as most healthcare institutions rely on patient self-reports. Appropriateness criteria are similar inside and outside the program (cytology every 3 years for women aged 25-64, or HPV DNA test every 5 years starting at age 30). Consequently, outside the organized program, no first-level screening test is fully reimbursed for 3 years after a cytology test (5 years for an HPV DNA test). By contrast, in the organized program, women aged 30-64 receive free invitations for primary HPV DNA tests regardless of any additional ("interval") cytology performed outside the program(Regional Council of Lombardy, 2023a).

Importantly, in organized programs, appropriateness controls are performed systematically through automated workflows, making them more sustainable and efficient.

Cervical cancer screening and related outpatient diagnostic tests eligible for reimbursement, with their associated costs according to the regional reimbursement manual(Regional Council of Lombardy, 2023b), are reported in Table 2.

Because centralization and standardization of laboratory processes yield greater efficiency and cost-effectiveness for HPV DNA testing(Ronco *et al.*, 2012), the Regional Council set a reduced price for HPV DNA test performed within organized screening programs, coded as 91.24.D. The cost (€15) includes cytologic triage when required (Regional Council of Lombardy, 2023a). For the purpose of modeling the co-testing scenario, we assumed that the only HPV test prescribed for opportunistic co-testing was the one coded 91.24.B.

Type (level) of test	**Code**	**Descriptor**	**Price (€)**
Screening (I)	91.38.5	Cytology of the cervix (Pap test)	12.15
Screening (I)	91.48.4	Cervix sample collection	2.90
Screening (I)	91.24.9	HPV DNA, qualitative	68.58
Screening (I)	91.24.B	HPV, genomic typing	89.18
Screening (I)	91.24.C*	HPV, genomic typing with sequencing	89.18
Screening (I)	91.24.D	HPV DNA in organized program, incl. cytologic triage when needed	15.00
Diagnostic (II)	67.12	Endocervical biopsy	95.01
Diagnostic (II)	67.19.1	Endocervical biopsy, colposcopy-guided	27.45
Diagnostic (II)	67.32	LEEP	52.79
Diagnostic (II)	70.21	Colposcopy	10.55
Diagnostic (II)	91.44.3	Histopathology of the cervix and endometrium	66.50
Diagnostic (II)	91.46.3	Histopathology of the cervix, multiple samples	66.50
Diagnostic (II)	91.44.4	Histopathology of the cervix	15.65
Diagnostic (II)	91.46.4	Histopathology of endocervical polyp	15.65
Diagnostic (II)	91.46.6	Histopathology of cervical cone	66.50

Table 2. Cervical cancer screening and diagnostic tests performed in the outpatient setting and eligible for reimbursement. * Tests that are not currently reimbursed within the program may could soon be indicated as second-level follow-up tests. LEEP: Loop Electrosurgical Excision Procedure.

3.9 Previous interventions: opportunistic screening

Data on outpatient tests and procedures (Table 2) recorded by the AHP in 2018-2019 were extracted from the AHP's DWH. The DWH includes all registered outpatient tests and procedures, together with their administrative codes and the applied reimbursement scheme (out-of-pocket, copayment and full reimbursement). Annual volumes of test and procedures and cervical screening expenditure have been estimated by the average yearly tests and procedures, as well as cervical screening expenditure were estimated as the average annual figures observed in 2018-2019, and were used to define the reference scenario.

The overall average yearly expenditure for opportunistic screening was assumed to remain constant in the *reference* ("no organized screening") scenario.

The observation period was chosen because the province of Milan was severely affected by the COVID-19 pandemic in 2020 and 2021. Screening activity during those years was not representative of usual opportunistic screening behavior, as overall coverage had markedly declined, as highlighted by a national survey(Masocco and Gruppo Tecnico Nazionale Passi e Passi d'Argento, 2021).

It is important to note that the estimated expenditure included only the proportion of tests and procedures performed by public or private accredited health institutions, thus reimbursed by the AHP. The share of screening tests and procedures carried out in the private sector on a fully out-of-pocket basis could not be assessed. To our knowledge, overall cervical screening coverage in Lombardy has not been estimated by cross-sectional studies, since the Lombardy region does not participate in the national PASSI surveillance system(Network PASSI, 2021), which reports a nationwide coverage of 78% (47% within organized programs, 31% through opportunistic screening).

Consequently, our analysis considered only the proportion of cervical screening coverage reimbursed by the Regional Health System.

3.9.1 Estimate of pre-implementation screening coverage

Screening coverage reimbursed by the Regional Health System was calculated as follows:

Numerator = (annual average number of resident women aged 25-64 who had *at least one* cytology test during the observation period)*3 + (annual average number of women aged 30-64 who had *at least one* HPV DNA test during the observation period)*5 (source: DWH)

Denominator = (number of resident women aged 25-64) (source: Istat 2019)

3.9.2 Estimate of inappropriate cytology uptake

Within the same dataset, we identified the proportion of cytology tests performed in 2018-2019 that followed a previous test in the preceding 0-2 years. Deterministic record-linkage was performed using the TIN as a unique identifier. This proportion was used to estimate the overall rate of cytology beyond recommended intervals, i.e., "inappropriate" or leakage testing.

3.10 Uptake of the new intervention: first phase of implementation

The change in intervention mix following program implementation was investigated by retrospectively comparing two age-matched cohorts (25-28y + 57-64y) each from a different time period, before and after implementation: September 2018 - December 2019 (women born in 1991-1994 or 1954-1961) *vs* September 2022 - December 2023 (women born in 1995-1998 or 1958-1965). Data on outpatient tests and procedures reimbursed by the AHP were extracted from the AHP DWH.

Observation periods of equal duration and seasonal distribution were chosen to control for seasonality in screening behaviour. The pre-implementation period (2018-2019) was selected to avoid distortions caused by the COVID-19 pandemic. The post-implementation period corresponded to the first two years of active invitations of the organized program in the province of Milan and was therefore considered representative of opportunistic screening behaviour in the presence of organized screening.

From the extracted data, we estimated the parameters to fulfill Table 3. In detail, we calculated differences in the number of first-level tests performed under the opportunistic regime ("non screening", NS, light green) and their rates relative to the target population. The calculated rates served as parameters for the BIM.

In addition, we used deterministic record linkage (via TIN as a unique identifier) to identify inappropriate tests performed under the organized regime (S, green) during the first round of invitations, for which restrictions cannot yet be applied according to regional legislation(Regional Council of Lombardy, 2023a). HPV DNA tests performed within the program (S) were classified as inappropriate if the same woman had already undergone a fully or partially reimbursed HPV DNA within the previous 5 years. Cytology tests (S) were classified as inappropriate if the same woman had undergone a reimbursed cytology test within the prior 3 years. Since restrictions may only be applied starting with the second round of invitations(Regional Council of Lombardy, 2023a), the proportion of potentially inappropriate

tests was excluded from the model for all age cohort entering screening rounds beyond the first, as detailed in the next section.

Currently, restrictions cannot be applied to HPV DNA tests in women who had cytology within the previous 3 years (i.e. "interval cytology")(Regional Council of Lombardy, 2023a), even though this constitutes overscreening according to the Essential Assistance Levels. The estimated proportion of these tests (light blue) provided an indication of the potential savings in tests and cost should such restrictions be introduced.

Target age	Observation period	Cytology tests - S (n, rate)	Cytology tests – NS (n, rate)	HPV tests - S (n, rate)	HPV tests – NS (n, rate)	Inappropriate cytology tests (estimate) - S (n, rate)	Inappropriate HPV test - S (estimate) (n, rate)	Inappropriate HPV test due to interval cytology - S (estimate) (n, rate)
Cytology age	Pre-implementation	-		-		-	100%	-
	Post-implementation						100%	-
	Difference	-		-		-	0%	-
HPV age	Pre-implementation	-		-		-	-	-
	Post-implementation					-		
	Differential	-		-		-	-	-

Table 3. Comparison of screening tests before and after the implementation. S: test performed within the organized program; NS: test performed outside the organized program. Percentages were calculated using the number of eligible women as denominator (source: Istat). For NS test only, rates were divided by 1.33 to account for annual screening uptake. For organized tests, no correction was needed because distinct birth cohorts were actively invited in different years. Rates are expressed per 100 eligible women.

3.10.1 Estimate of post-implementation screening coverage

Yearly post-implementation cervical cancer screening coverage was estimated as follows:

Numerator = [(total cytology tests, S and NS) - (inappropriate cytology tests, S)]*3 + [(total HPV tests, S and NS) - (inappropriate HPV tests, S)]*5 (sources: screening database and DWH, record linkage performed using TIN as unique identifier)

Denominator = (number of resident women aged 25-64 years) (source: Istat 2023)

3.11 Uptake of the new intervention: estimates for the second phase of implementation

The proportion of invited cohorts who adhered to first-level tests (highlighted in yellow in Table 3) was used to calculate the participation rate of the organized program (S) (source: screening database). However, since we observed large differences in participation rates depending on age and the primary test offered, we used the overall participation rates observed in 2022-2023, stratified by the type of primary test, for the model calculations.

To simplify the analysis, we assumed that the change in screening behavior observed during the post-implementation period (light green in Table 3) would apply only to actively invited cohorts within the mixed screening offer. Cohorts not actively invited were assumed to behave as observed in the pre-implementation period.

The formulas used to project the future mix of interventions are detailed in section 3.13.

3.12 Cost of the previous and new intervention mix

The costs of both the previous and new intervention mix were determined by multiplying the price of each test and procedure (Table 2) by the total number of observed or expected tests and procedures. The cost of second-level or follow-up procedures other than colposcopies was estimated by adding the average ancillary costs per colposcopy, assuming these averages remains stable across age groups and screening rounds.

Specifically, we calculated the average costs of ancillary procedures (e.g., colposcopy-guided biopsies, pathology examinations and other related procedures) associated with second-level or follow-up colposcopies performed in 2022-2023 (organized setting) and overall colposcopies in the observed periods (opportunistic setting, see paragraph 3.13.2 for details). These average ancillary costs were then applied uniformly across rounds of invitations.

For the opportunistic scenario, we assumed that the proportion of reimbursement schemes observed in the pre-implementation period (out-of-pocket, copayment, and full reimbursement) would remain constant across all rounds of invitations.

3.13 Computing framework

The average annual number of tests and procedures, and the corresponding annual expenditures observed in 2018-2019, were used as the *reference scenario*. In this scenario, annual test volumes and expenditures were assumed to remain constant over the following years. No discount was applied.

The *intervention scenario* was simulated using a BIM implemented in Excel® (Figure 7). The BIM tracks each birth cohort across subsequent rounds of invitations for organized (S) screening and opportunistic (NS) screening, calculates the expected annual number of first-level tests and colposcopies, and incorporates a cost-calculator.

3.13.1 Organised screening (S)

First-level S test and procedures were estimated using the following formulas.

For each actively invited age cohort in the first round (according to the phased roll-out plan, Figure 5), the number of tests performed within the program (S) was calculated as follows:

Number of first-level S tests = (number of invited women)*(participation rate, proportion) for each primary test offered

For each actively invited age cohort in the second or subsequent rounds, the number of tests performed within the program (S) was calculated as:

Number of first-level S tests = [(number of invited women)* (1 - post-implementation inappropriate S tests, % of invited women)*(participation rate, proportion) for each primary test offered]

Participation rates were derived from the screening database. It was assumed that the proportion of women potentially subject to restriction (due to having undergone a screening test in the previous 3/5 years) would remain stable across consecutive rounds. Entry and exit rates were also assumed to be in steady state, since the number of permanent restrictions for gynaecologic cancer in the first 16 months of activity was negligible.

Participants to the program (S) were assumed to follow the protocols outlined in Figure 8. These protocols were applied to the annual age-specific phased invitation plan described above. Both attenders and non-attenders to a given invitation were scheduled for re-invitation after one round, with the length of the round determined by the type of the last screening test: 3 years after a normal Pap smear, and 5 years after a negative HPV DNA test. The cumulative duration of each round of second-level, including follow-up, was estimated at 3 years, consistent with previous literature(Ronco *et al.*, 2012).

Total expected first-level S tests also included recall or repetition tests:

- Inadequate tests requiring repetition: estimated from 2022-2023 data (screening database), using the proportion, attendance rate for repeated testing;
- HPV positive tests with normal cytology requiring recall after 12 months: estimated from 2022-2023 data (screening database), using the proportion, attendance rate for recall and viral clearance rate.

Four sets of probabilities were defined for the model parameters: first round, subsequent rounds, first round-vaccinated and subsequent rounds-vaccinated. Each set included probabilities p1-p9 (Figure 7), stratified by age group (25-29, 30-49, 50-64 years).

Age-, test- and round-specific referral rates to colposcopy were estimated from 2022-2023 screening database data when available, and from published literature when not(Pesola *et al.*, 2021), especially for age groups not covered by active invitations in that period and subsequent rounds tests. For simplification, probabilities p7-p9 were assumed to remain constant across age groups, rounds, and vaccination history. Other probabilities were estimated based on proportions between probabilities observed in prior studies(Pesola *et al.*, 2021). For vaccinated women, colposcopy referral rates were assumed to be reduced by 30%(Pesola *et al.*, 2021).

The attendance rate for colposcopy referrals was derived from 2022-2023 screening database data.

The average number of follow-up colposcopies was based on previous studies(Ronco *et al.*, 2012), assuming annual follow-up visits.

Until 2024, each second-level CC provided follow-up co-tests outside the organized program. The number of cytology and HPV DNA tests performed during follow-up was estimated according to averages reported in the literature(Ronco *et al.*, 2012). Follow-up colposcopies and co-test were assumed to occur annually, in line with regional guidelines for low-risk cytology, the most frequent category(Regional Council of Lombardy, 2023a).

The AHP had planned to include follow up co-testing within the program, performed in the first-level CCs. In this sub-scenario, the co-test price would equal the sum of HPV DNA test (S, code 91.24.D) + cervical sampling + cytology, representing a significant cost saving compared to the January 2024 setting. The cost difference with this sub-scenario was projected separately.

3.13.2 Opportunistic screening (NS)

First-level NS test and procedures were estimated using the following formulas.

For each actively invited age cohort (according to the phased roll-out plan, Figure 5):

- Number of NS first-level tests = (number of invited women)*(post-implementation NS annual rate, actively invited cohorts)
- Number of NS second-level tests = (number of invited women)*(post-implementation NS second-level annual rate, actively invited cohorts)

For each actively invited age cohort in the second or subsequent rounds:

- Number of NS first-level tests = (number of invited women)*(post-implementation NS annual rate, actively invited cohorts)
- Number of NS second-level tests = (number of invited women)*(post-implementation NS second level annual rate, actively invited cohorts)

For each non actively invited cohort:

- Number of NS first-level tests = (number of non-invited women)*(pre-implementation NS annual rate)
- Number of NS second-level tests = (number of invited women)*(pre-implementation NS second level annual rate)

A fully executable Budget Impact Model (BIM) is available on request to allow researchers and decision-makers to test alternative input parameters.

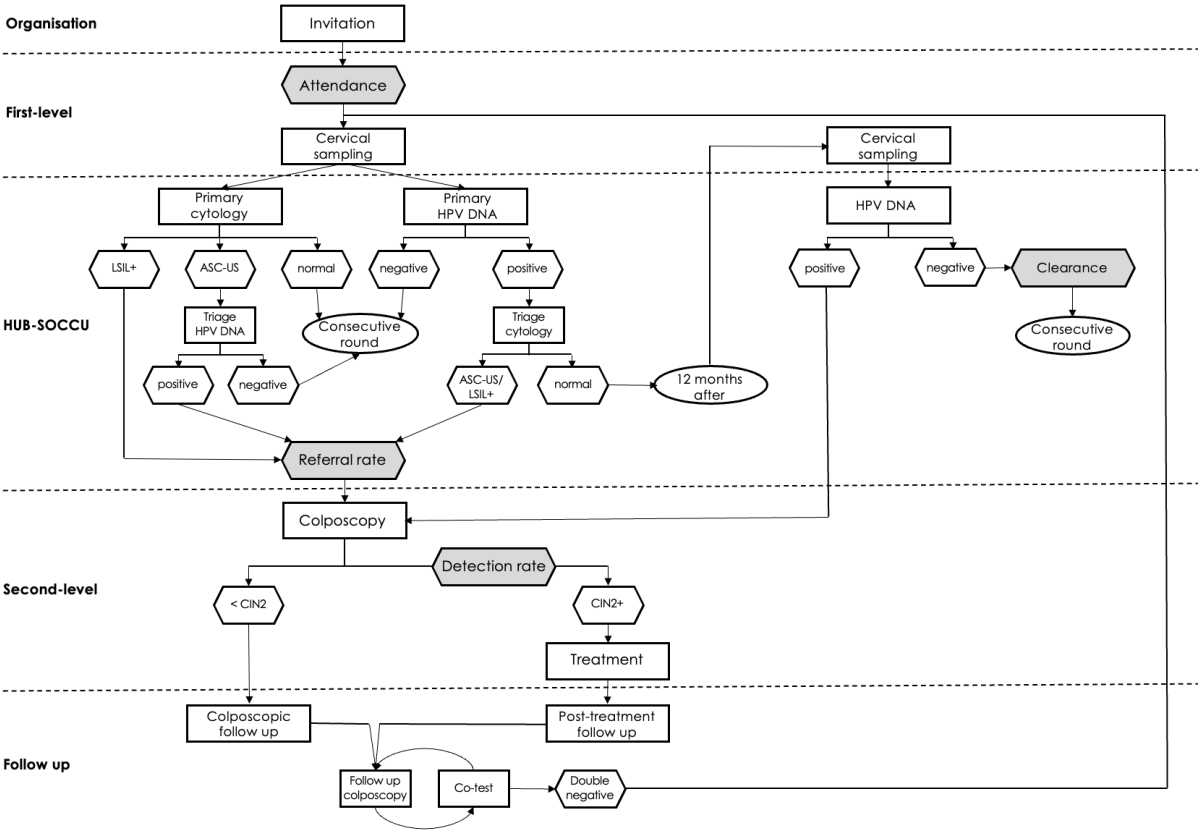


Figure 8. Flow diagram of the organized cervical cancer screening program. The figure illustrates the pathways followed by women attending the program, including first-level testing, triage, referral to colposcopy, and follow-up. The decision nodes reflect test results and subsequent management according to the regional protocols.

3.13.3 Input parameters

Most base-case clinical inputs mentioned above (e.g., participation rate, colposcopy attendance, inadequate test rate, clearance rate, and referral rates) were estimated from observed values in our study population or derived from Italian or European observational studies(Gori *et al.*, 2021; Pesola *et al.*, 2021).

For each base-case parameter, minimum and maximum values were defined according to previous literature(Ronco *et al.*, 2012) and expert opinion (Table 4). In some cases, minimum values were further adjusted downward in light of 2024 data from the AHP DWH, obtained during calibration analyses (see section 3.16).

Parameter	Base-case	Min	Max	Sources/Justification
Participation rate – primary HPV DNA (%)	35.5	23	70	The base-case value is the observed value during the first phase of implementation (2022-2023). The minimum and maximum values were set based on the lowest and highest regional values respectively observed in 2019 in Italy (Cervical Cancer Screening Italian Group -GISCI- survey 2019).
Participation rate – primary cytology (%)	24.3	23	70	The base-case value is the observed value during the first phase of implementation (2022-2023). The

				minimum and maximum values were set based on the lowest and highest regional values respectively observed in 2019 in Italy (Cervical Cancer Screening Italian Group -GISCI- survey 2019).
Referral rate – non-vaccinated, primary HPV DNA, 50-64 yo, first round (%)	3	1.2	3.1	The base-case value is the observed value during the first phase of implementation (2022-2023). The minimum and maximum values were set based on the 10th and 90th percentiles of the north Italian values observed in 2018 for women aged 45-64 years (Cervical Cancer Screening Italian Group –GISCI-survey 2018). Referral rate parameters for other age groups and rounds were derived proportionally from literature(Pesola *et al.*, 2021).
HPV DNA positivity with normal cytology – non-vaccinated, primary HPV DNA, 50-64 yo, first round (%)	2.4	2	5.7	The base-case value is the observed value during the first phase of implementation (2022-2023). The maximum value was set based on the 90th percentile of the north Italian values observed in 2018 for women aged 45-64 years (Cervical Cancer Screening Italian Group –GISCI- survey 2018). Since the 10th percentile was higher than the observed value, we rounded the minimum value to 2%. Parameters for other age groups and rounds were derived proportionally from literature(Pesola *et al.*, 2021).
Inadequate HPV DNA result – non-vaccinated, primary HPV DNA, 50-64 yo, first round (%)	0.6	0.5	2.4	The base-case value is the observed value during the first phase of implementation (2022-2023). The minimum value was set at - 10% of the reference value. The maximum value was that observed by a pilot study performed by the HUB-SOCCU in 2024, testing a different validity cut-off for cervical samples' cellularity assessment (unpublished data).
Referral rate – non-vaccinated, primary cytology, 25-29 yo, all rounds (%)	9.1	8.2	10	The base-case value is the observed value during the first phase of implementation (2022-2023). The minimum and maximum values were set at ±10% of the reference value.
Viral clearance at 12 months – HPV+/normal cytology (%)	48.6	34.9	56.4	The base-case value is the observed value during the first phase of implementation (2022-2023). The minimum and maximum values were set based on the 10th and 90th percentiles of the north Italian values observed in 2018 for women aged 45-64 years (Cervical Cancer Screening Italian Group –GISCI-survey 2018).
Colposcopy attendance rate (%)	80.6	75	98.3	The base-case value is the observed value during the first phase of implementation (2022-2023). The minimum and maximum values were set based on the 90th percentile of the north Italian values observed in 2018 for women aged 34-64 years, primary HPV DNA (Cervical Cancer Screening Italian Group –GISCI-survey 2018). Since the 10th percentile was higher than the observed value, we rounded the minimum value to 75%.
Follow up colposcopies, primary HPV DNA (n)	0.7	0.63	0.77	The base-case value was previously reported(Ronco *et al.*, 2012). The minimum and maximum values were set at ±10% of the base-case.
Follow up colposcopies, primary cytology (n)	0.6	0.54	0.66	The base-case value was previously reported(Ronco *et al.*, 2012). The minimum and maximum values were set at ±10% of the base-case.
Pre-implementation opportunistic cytology coverage, 25-29 yo (%)	6.45	5.8	7.1	The base-case value is the observed value before implementation (2018-2019). The minimum and maximum values were set at ±10% of the base-case.
Pre-implementation opportunistic cytology coverage, 30-64 yo (%)	6.02	5.4	6.6	The base-case value is the observed value before implementation (2018-2019). The minimum and maximum values were set at ±10% of the base-case.

Post-implementation opportunistic cytology coverage, 25-29 yo (%)	6.5	5.9	7.2	The base-case value is the observed value during the first phase of implementation (2022-2023). The minimum and maximum values were set at ±10% of the base-case, but the minimum value was lowered in light of calibration (2024 data).
Post-implementation opportunistic cytology coverage, 30-64 yo (%)	4.8	4.3	5.3	The base-case value is the observed value during the first phase of implementation (2022-2023). The minimum and maximum values were set at ±10% of the base-case, but the minimum value was lowered in light of calibration (2024 data).
Cost of a Pap smear (€)	12.15	10.94	17.00	The base-case value is the current tariff. The minimum value was set at -10% of the reference value. The maximum value is the newly introduced tariff (2025).
Cost of a colposcopy (€)	10.55	9.5	11.61	The base-case value is the current cost. The minimum and maximum values were set at ±10% of the base-case.
Mean cost added to a second level colposcopy (€)	28.07	25.26	30.88	The base-case value is the current cost. The minimum and maximum values were set at ±10% of the base-case.
Mean cost added to a follow up colposcopy, €	23.41	21.07	25.75	The base-case value is the current cost. The minimum and maximum values were set at ±10% of the base-case.

Table 4. Input parameters.

3.14 Uncertainty and scenario analyses

To address parameter uncertainty, we conducted a one-way sensitivity analysis (OWSA) on the variables with the greatest impact on the Budget Impact Model, including participation rates, referral rates for first and subsequent rounds, clearance rate, and the number of follow-up colposcopies and co-tests.

To explore structural uncertainty, we evaluated three different alternative scenarios:

1. Inclusion of follow-up Co-tests within the program compared to the pilot model, in which these tests -performed outside the program- were associated with higher costs;
2. Introduction of additional prescription restrictions, specifically excluding from reimbursement for previous “interval cytology tests”, compared with the current model in which such tests are still allowed.
3. Progressive reduction of opportunistic cytology combined with a gradual increase in participation to organized primary HPV testing, compared with the usual scenario.

3.15 Outcomes

The primary outcomes of the analyses were:

- the average total annual costs of screening;
- the annual test volumes (first- and second-level) for both organized and opportunistic screening.

Differentials were estimated with respect to the reference scenario. For the scenario analyses, additional comparisons were made against the usual (intervention) scenario, which better

reflects the current implementation phase in 2024. Furthermore, annual costs and test volumes were stratified by first- and second-level screening, to capture trends in both resource use and expenditure.

3.16 Calibration

External/predictive validation was performed using the observed 2024 data (sources: screening database and DWH). As a goodness-of-fit measure with observed 2024 data, we used the mean absolute percentage error (MAPE) for the relevant predicted endpoints(Moriña, De Sanjosé and DIaz, 2017). We compared the main outcomes predicted for 2024 (number of first-level tests and colposcopies, S+NS) with the real-world 2024 data on opportunistic screening (source: AHP DWH) and organized screening (source: screening database). The analysis aimed to re-calibrate the model parameters if a MAPE greater than 20% was found in at least one of the main outcomes. To put the larger observed MAPE deviations into context, the analysis was extended to the first four months of 2025 for organized screening only, as at the time of the analysis (May 2025) this was the only available source for 2025 data. Co-tests, introduced in november 2024, were also included in the analysis. The results are shown in Table 5.
All main outcomes (S+NS) fell within a variation of less than 10% of the MAPE.

Output parameter	**Predicted volumes, 2024**	**Observed volumes, 2024**	**MAE, 2024**	**MAPE, 2024**	**MAPE, 2025***	**MAPE, 2024-2025***
Pap test - S	1366	5069	3733	**73,6%**	-0,1%	**61,2%**
Pap test - NS	51180	43924	-7256	**-16,5%**		
Pap test - S+NS	52516	48933	-3523	-7,2%		
HPV DNA test - S	62231	59700	-2531	-4,2%	6,2%	-1%
HPV DNA test - NS	*3451*	*8821*	*5370*	***60,9%***		
HPV DNA - S+NS	*65682*	*68521*	*2839*	*4,1%*		
First-level tests - S	63567	64769	1202	1,9%	6%	3%
First-level tests - NS	54631	52745	-1886	-3,6%		

First-level tests – S+NS	118198	117514	-684	-0,6%		
Second-level colposcopies - S	2756	2709	-47	-1,7%	7,5%	1%
Follow up colposcopies - S	1748	730	-1018	**-139,5%**	**-258,6%**	**-174,9%**
Colposcopies - NS	*7533*	*9010*	*1477*	***16,4%***		
Colposcopies - S+NS	*12037*	*12449*	*412*	*3,3%*		
Co-test - S	458	29	-429	**-1480,5%**	**-13,5%**	**-41,4%**

Table 5. Calibration analysis. MAE: mean absolute error. MAPE: mean absolute percentage error. *The analysis was extended to the first 4 months of 2025 only for organized screening. MAPE values of above 10% are displayed in bold, while NS data at risk of miscoding are displayed in italics.

Some specific outcomes related to either organized or opportunistic screening showed MAPE deviations greater than 20%. These variations appear to be explained by the current implementation phase and therefore were not considered as indications for re-calibration, but were discussed further.

Specifically, regarding the number of cytologies performed in organized screening (Pap test – S), active invitations were extended to all women eligible for cytology during 2024 (Figure 5), including many women born in 1994. The model considered these women to be 30 years old in 2024 and therefore eligible for primary HPV DNA testing. However, since screening invitations are random, some (likely around 50%) of them were invited when they were still 29 years old and therefore underwent cytology. This event, which applies only to 2024 since this age group has already been covered by screening invitations, partly explains the positive deviation in Pap tests (S) and the negative deviation in HPV DNA tests (S) and was not considered a valid reason to re-calibrate the model. In fact, the deviation was resolved in the first four months of 2025 (Table 6).

By contrast, the negative deviation in opportunistic cytologies (Pap test – NS) was larger, although the MAPE deviation was less than 20%. Since this deviation is likely to represent a continuing trend, it was taken into account in the scenario analysis, leading to the introduction of two additional scenarios showing a 20% reduction in the uptake of opportunistic cytology.

As for second-level tests, while predicted values for second-level colposcopies were accurate (MAPE -1.7%), the deviation for follow-up colposcopies was quite large, with 1,018 fewer colposcopies performed in organized screening than expected (MAPE -139.5%). Conversely, a positive deviations of 1,477 colposcopies was observed in opportunistic screening, suggesting that the need for follow-up colposcopies was absorbed by the opportunistic market. During 2024, the program faced difficulties in organizing and delivering follow-up colposcopies, with delays in invitations and long waiting times. The colposcopy system was already under strain due to the expected peak in demand (see section 4.6.1).

The AHP Screening Unit implemented a quality improvement project to optimise colposcopy organization. Measures included:

- a semi-automatic inviation system with postal and SMS reminders;
- assessment of preliminary co-tests results, before deciding whether to refer patients for colposcopy or return to the first-level screening;
- increased available colposcopy slots in existing CCs;
- the introduction of four new colposcopy CCs into the screening network (three in 2023, one in 2025), with efforts ongoing to recruit further partners.

Nevertheless, regardless of the size and efficiency of the screening network, colposcopy capacity is likely to reach a threshold. In 2024, this was approximately set at 3,500 colposcopies/year. With the current network in 2025, the threshold is around 4,500/years -still below the required level- leading to longer waiting times. Indeed, the MAPE worsened in the first four months of 2025. Taking this into account, the model's predictions remain relevant for the AHP.

Of note, with regard to opportunistic (NS) screening HPV DNA tests and colposcopies, we found numerous anedoctal inconsistencies in coding, with many procedures coded as opportunistic while they should have been coded as organized screening. As already mentioned, the screening database is higly reliable, whereas the AHP DWH is subject to errors in coding, upcoding or lack of coding. For this reason, we performed record linkage to exclude the procedures already recorded in the screening database on the same date. However, we believe that NS data (displayed in italics in Table 5) are less reliable for total colposcopies and HPV DNA tests. The positive deviation in 2024 NS HPV DNA tests could at least partly reflect the need for co-testing, which was not met by the program until November. Similarly, the positive deviation in 2024 NS colposcopies may reflect the unmet demand for follow-up colposcopies among women diagnosed through the program.

Finally, the negative deviation in co-tests compared with expected values was significant in 2024, due to the novelty of the procedure and its initial underuse. In fact, the MAPE fell below 20% during the first four months of 2025.

3.17 Validation

Face validity was assessed by a group of public health physicians with expertise in cervical screening. The assessment(Hung *et al.*, 2019) covered the structure/conceptual model, the input data, and the results.

Computerized model consistency was assessed using extreme value analysis and "structured walk-throughs"(Eddy *et al.*, 2012).

To provide model users with a structured overview of the validation status, we used the Assessment of the Validation Status of Health-Economic decision models (AdViSHE) checklist(Vemer *et al.*, 2016). The checklist consists of 13 questions, grouped into different domains: the conceptual model, the input data, the implemented software, and the model outcomes. We completed the checklist to enable a sustainable and time-efficient validity assessment, reporting in a structured way the efforts undertaken to strenghten the validation status of the model and its ouctomes.

AdViSHE does not provide a validity score or threshold, in order to avoid "score overconfidence" and inappropriate comparisons between models, and because validation efforts should be tailored to the specific model.

The AdViSHE checklist is presented in Table 6. Out of 13 questions, one was marked as *not applicable*, while three were marked as *no*, since those specific validation efforts were either not performed or not feasible.

AdViSHE checklist	
Part A: Validation of the conceptual model (2 questions) Part A discusses techniques for validating the conceptual model. A conceptual model describes the underlying system (e.g., progression of disease) using a mathematical, logical, verbal, or graphical representation. Please indicate where the conceptual model and its underlying assumptions are described and justified.	
The conceptual model and its underlying assumptions are described in detail in the protocol and final report. A graphical representation is also available in the computing tool.	
A1) Face validity testing (conceptual model): Have experts been asked to judge the appropriateness of the conceptual model?	Yes
If yes, provide information on the following aspects: - Who are these experts? - What is your justification for considering them experts? - To what extent do they agree that the conceptual model is appropriate? If no, please indicate why not.	
The conceptual model was evaluated by AS and DI, former and current Director of the AHP Screening Unit, respectively. Both are Public Health physicians with experience in field epidemiology and in organizing population-based cancer screening in the Metropolitan Area of Milan. Both were involved in the roll-out of the AHP cervical cancer screening program and participated in the development of the regional guidelines for organizing cervical cancer screening. The experts agreed on the accuracy of the conceptual model. However, one pointed out that the chosen comparator (2018-2019 opportunistic screening) might not be fully representative of current opportunistic screening behaviour, as HPV testing was not yet fully established in the opportunistic market at the time. Nevertheless, the expert acknowledged that	

these were the best real-world data available for the Metropolitan Area of Milan, since the period 2020-2021 was exceptional for both opportunistic and organized screening and not representative of underlying screening trends. *The experts also noted that the BIA does not cover the organizational costs for the AHP (e.g., additional staff, printing and mailing invitations…). However, at the time of the evaluation, these aspects had already been addressed in prior research and had also clearly emerged from direct experience.*
Aspects to judge include: appropriateness to represent the underlying clinical process/disease (disease stages, physiological processes, etc.); and appropriateness for economic evaluation (comparators, perspective, costs covered, etc.).
A2) Cross validity testing (conceptual model): Has this model been compared to other conceptual models found in literature or clinical textbooks? — Yes
If yes, please indicate where this comparison is reported. If no, please indicate why not.
The conceptual model shown in Fig. 7 closely reflects the procedures outlined in the regional cervical cancer screening guidelines and in major multinational clinical and observational studies on HPV-based cervical cancer screening with cytologic triage. Other models are listed in Table 1 of the final report. The most similar model is the one described by Diaz et al(Diaz *et al.*, 2018)*, with the only difference being the age at which HPV DNA testing begins (30 years in our model, 33 years for Diaz et al)*(Diaz *et al.*, 2018)*.* *Regarding the time horizon and the budget impact of the increased CIN2+ detection rate, our conceptual model is unique in that it relies on annual costs based on a predefined annual implementation plan. Other models usually consider average annual costs and procedures.*
Part B: Input data validation (2 questions): Part B discusses techniques to validate the data serving as input in the model. These techniques are applicable to all types of models commonly used in HE modelling. Please indicate where the description and justification of the following aspects are given: - Search strategy; - Data sources, including descriptive statistics; - Reasons for inclusion of these data sources; - Reasons for exclusion of other available data sources; - Assumptions that have been made to assign values to parameters for which no data was available; - Distributions and parameters to represent uncertainty; - Data adjustments: mathematical transformations (e.g. logarithms, squares); treatment of outliers; treatment of missing data; data synthesis (indirect treatment comparison, network meta-analysis), calibration, etc.
All requested elements are described in detail in the protocol and in the methods, calibration, and sensitivity analysis sections of the final report.
B1) Face validity testing (input data): Have experts been asked to judge the appropriateness of the input data? — Yes
If yes, please provide information on the following aspects: - Who are these experts? - What is your justification for considering them experts? - To what extent do they agree that appropriate data have been used? If no, please indicate why not.
The experts are the same as those presented in point A1. In general, they agreed on the appropriateness of the selected data. However, one emphasized that some parameters (particularly the referral rate and the repetition rate) are strictly dependent on the quality of the analyses, and may vary based on potential future changes at the HUB-SOCCU, as well as on the age of the screened women. Assumptions were made for this latter aspect, but a certain degree of uncertainty remains. Similarly, costs may vary over time, but both experts were confident that the final budget differences would not be significant, as tariff changes are usually limited.
Aspects to judge may include but are not limited to: potential for bias; generalizability to the target population; availability of alternative data sources; any adjustment made to the data.
B2) Model fit testing: When input parameters are based on regression models, have statistical tests been performed? — NA
If yes, please indicate where the description, the justification and the outcomes of these tests are reported. If no, please indicate why not.
This item is not applicable since no input parameters were based on regression models.
Examples of regression models include but are not limited to: disease progression based on survival curves; risk profiles using regression analysis on a cohort; local cost estimates based on multi-level models; meta-regression; quality-of-life weights estimated using discrete choice analysis; mapping of disease-specific quality-of-life weight to utility values. Examples of tests include but are not limited to: comparing model fit parameters (R^2, Akaike information criterion (AIC), Bayesian information criterion (BIC)); comparing alternative model specifications (covariates, distributional assumptions); comparing alternative distributions for survival curves (Weibull, lognormal, logit); testing the numerical stability of the outcomes (sufficient number of iterations); testing the convergence of the regression model; visually testing model fit and/or regression residuals.
Part C: Validation of the computerized model (4 questions) Part C discusses various techniques for validating the model as it is implemented in a software program. If there are any differences between the conceptual model (Part A) and the final computerized model, please indicate where this differences are reported and justified.
There are no differences.
C1) External review: Has the computerized model been examined by modelling experts? — Yes
If yes, please provide information on the following aspects: - Who are these experts? - What is your justification for considering them experts? - Can these experts be qualified as independent? - Please indicate where the results of this review are reported, including a discussion of any unresolved issues. If no, please indicate why not.

The computerized model was examined by PC, a modelling expert at the University of Milan-Bicocca and President of the Italy-Milan Chapter of ISPOR. PC was not involved in the planning or implementation of the AHP's cervical cancer screening program. The discussion took place prior to the final version of the model and is therefore not included in the final report. The model was deemed appropriate with respect to both the conceptual model and the purpose of the HTA project.	
Aspects to judge may include but are not limited to: absence of apparent bugs; logical code structure optimized for speed and accuracy; appropriate translation of the conceptual model.	
C2) Extreme value testing: Has the model been run for specific, extreme sets of parameter values in order to detect any coding errors?	Yes
If yes, please indicate where these tests and their outcomes are reported. If no, please indicate why not.	
Extreme value testing was performed on all the parameters already included in the sensitivity analysis (both clinical and cost parameters), and the outcomes are available on request. No coding errors were detected.	
Examples include but are not limited to: zero and extremely high (background) mortality; extremely beneficial, extremely detrimental, or no treatment effect; zero or extremely high treatment or healthcare costs.	
C3) Testing of traces: Have patients been tracked through the model to determine whether its logic is correct?	Yes
If yes, please indicate where these tests and outcomes are reported. If no, please indicate why not.	
The computing model is available on request and is structured by listing the number of patients (procedures) in each stage of the screening process at all annual time points. The accuracy of traces at the 2024 time point has been tested against real-world data, and the results are reported in the calibration section of the final report.	
In cohort models, this would involve listing the number of patients in each disease stage at one, several, or all time points (e-g- Markov traces). In individual patient simulation models, this would involve following several patients throughout their natural disease progression.	
C4) Unit testing: Have individual sub-modules of the computerised model been tested?	Yes
If yes, please provide information on the following aspects: - Was a protocol that describes the tests, criteria and acceptance norms defined beforehand? - Please indicate where these tests and their outcomes are reported. If no, please indicate why not.	
Unit testing was not planned in advance, but some tests were performed, such as turning certain formulas on and off (e.g., in the 'population' sub-model) during sensitivity and scenario analyses.	
Examples include but are not limited to: turning sub-modules of the program on and off; altering global parameters; testing messages (e.g. warning against illegal or illogical inputs); drop-down menus; named areas; switches; labelling; formulas and macros; removing redundant elements.	
Part D: Operational validation (4 questions) Part D discusses techniques used to validate the model outcomes.	
D1) Face validity testing (model outcomes): Have experts been asked to judge the appropriateness of the model outcomes?	Yes
If yes, please provide information on the following aspects: - Who are these experts? - What is your justification for considering them experts? - To what extent did they conclude that the model outcomes are reasonable? If no, please indicate why not.	
The experts are the same as those presented in point A1. Main outcomes of this project were the volumes and costs of screening procedures. CIN2+ detection rate was a secondary outcome of the computerized model. Overall, and after verifying the calibration data, they agreed that they model main outcomes are reliable. *Regarding the CIN2+ detection rate, both the author and the experts agreed that the model projections are likely subject to overestimation, as formulas derived from literature do not produce results that match Italian official screening data. Conversely, official screening data are likely subject to underreporting, not only in Milan but across many Italian regions, according to official regional data, because of CIN2+ underreporting. For these reasons, this outcome was not reported in the final report.*	
Outcomes may include but are not limited to: (quality-adjusted) life years; deaths; hospitalizations; total costs.	
D2) Cross-validation testing (model outcomes): Have the model outcomes been compared to the outcomes of other models that address similar problems	No
If yes, please provide information on the following aspects: - Are these comparisons based on published outcomes only, or did you have access to the alternative model? - Can the differences in outcomes between your model and other models be explained? - Please indicate where this comparison is reported, including a discussion of the comparability with your model. If no, please indicate why not.	
The comparison was deemed not feasible because our conceptual model relies on annual costs linked to a predefined annual implementation plan. Other models usually consider average annual costs and procedures.	
Other models may include models that describe the same disease, the same intervention, and/or the same population.	
D3) Validation against outcomes using alternative input data: Have the model outcomes been compared to the outcomes obtained when using alternative input data?	No
If yes, please indicate where these tests and their outcomes are reported. If no, please indicate why not.	

The input parameters were specifically selected to represent the local epidemiology and costs of cervical cancer screening. Parameters were calculated directly or derived from local data. Alternative sources were not considered.	
Alternative input data can be obtained by using different literature sources or datasets, but can also be constructed by splitting the original data set in two parts, using one part to calculate the model outcomes and the other part to validate against.	
D4) Validation against empirical data: Have the model outcomes been compared to empirical data?	Yes
If yes, please provide information on the following aspects: - Are these comparisons based on summary statistics, or patient-level datasets? - Have you been able to explain any difference between the model outcomes and empirical data? - Please indicate where the comparison is reported. If no, please indicate why not.	
D4.A) Comparison against the data sources on which the model is based (dependent validation)	*Yes*
Validation was performed against empirical (2024 and first 4 months of 2025) screening data (organized and opportunistic), reported in the calibration section of the final report. The comparison is based on summary statistics. The author has been able to explain the main differences observed between modelled and observed outcomes.	
D4.B) Comparison against a data source that was not used to build the model (independent validation)	No
This was not feasible, since all possible alternative sources are based on the same original sources we used to develop the model.	
Part E: Other validation techniques (1 question)	
E1) Other validation techniques: Have any other validation techniques been performed?	Yes
If yes, indicate where the application and outcomes are reported, or else provide a short summary here.	
A short summary of other validation techniques performed is reported here and in the validation section of the final report. A structured walk-through of all the submodules of the computerized model was performed with the expert AS, which led to the identification and correction of some minor inconsistencies within the formulas.	
Example of other validation techniques: structured 'walk-throughs' (guiding others through the conceptual model or computerized program step-by-step); naïve benchmarking ('back-to-the-envelope' calculations); heterogeneity tests; double programming (two model developers program components independently and/or the model is programmed in two different software packages to determine if the same results are obtained).	

Table 6. AdViSHE checklist, completed by the model developers (filled text in italics).

4 RESULTS

4.1 Population

The overall target population for 2024, estimated using the Italian National Institute of Statistics (Istat) 2023 database(Italian Institute of Statistics, 2023), consisted of 877,482 women aged 25-64 years (born between 1960 and 1999): 79,618 women aged 25-29 years eligible for primary cytology, and 797,864 women aged 30-64 eligible for primary HPV DNA testing.

The modelled 10-year period starts in 2024. Two retrospective years (2022-2023) were included in the model, as the program's implementation had already begun and some birth cohorts had already been invited. To estimate each year's target population during the first ten years of implementation, we considered each birth cohort from 1958 to 2011. Each birth cohort was adjusted for age-specific historical migration trends and, for women born since 1997, for vaccination status, taking both previously published(Italian Ministry of Health, 2025) and updated vaccination data into account.

From the second round of invitations onward, each birth cohort was further adjusted by removing subgroups subject to current restrictions (see Paragraph 3.13.1), as well as potential future restrictions (interval cytology scenario, see Paragraph 3.14).

The adjusted target population for 2024 is reported in Table 7.

Protocol	**Birth cohorts**	**Istat population**	**Adjusted population (first round)**	**Adjusted population (subsequent rounds)**	**Adjusted population (subsequent rounds) (Interval cytology scenario)**
Primary Cytology (non-vaccinated)	1995-1999	54,746	52,808	52,484	52,484
Primary cytology (vaccinated)	1995-1999	24,872	24,154	24,091	24,091
Primary HPV DNA	1994-1960	797,864	842,704	840,513	806,383

Table 7. Overall target population for 2024. Istat: Italian Institute of Statistics (source: Istat 2023).

4.2 Previous interventions: opportunistic screening

Data on outpatient tests and procedures recorded by the AHP during 2018-2019 –representing the *reference scenario* - are reported in Table 8.

Before the program's implementation, opportunistic cervical cancer screening included an annual average of 59,301 first-level tests, the majority of which were Pap tests (n=54,142 per year), and 9,238 annual colposcopies. The total annual cost of opportunistic screening in the absence of organized program amounted to € 1,376,252.

Test/Procedure	**Annual volume (n)**	**Annual cost (€)**
Cytology	54,142	814,837
HPV DNA	5,165	232,838
Colposcopies	9,238	97,461
Ancillary tests to colposcopy	6,838	231,116
Overall	-	**1,376,252**

Table 8. Overall volumes and costs of screening tests before the program's implementation. Annual values represent the average for 2018-2019, the *reference scenario*.

4.2.1 Cytology inappropriate uptake

We investigated whether, among the average of 54,142 Pap tests performed in 2018-2019, the frequency of testing was inappropriate. Cervical cytology is in fact recommended every three years. The results are shown in Table 9.

Cytology by appropriateness	**n**	**%**
Overall cytology tests	54,142	100
Inappropriate – 0-1 years	6,320	11.7
Inappropriate – 1-2 years	10,899	20.1
Inappropriate – 2-3 years	6,902	12.7
Total inappropriate tests	24,121	44.6

Table 9. Opportunistic cytology inappropriate uptake in the pre-implementation period (2018-2019).

Of the 54,142 cytology tests fully reimbursed by the AHP, 24,121 (44.6%) were performed at inappropriate intervals and could potentially have been subject to reimbursement restrictions. The inappropriateness rate might be slightly overestimated, as the DWH does not distinguish between inappropriate first-level tests and follow-up tests, which are usually recommended every 6-12 months. However, the rate is far too high to be explained by follow-up alone, which

concerns only a minority of women.These data strongly suggest widespread inappropriate screening behavior.

The analysis was also performed for the province of Lodi, where an organized screening was already in place at the time, and showed an even higher rate of inappropriate opportunistic cytology uptake (62.3%). This suggests that public financial and organizational resources for opportunistic cervical cancer screening in the AHP area were invested in a limited group of women, likely subject to overtesting.

In the province of Milan, the most common inappropriate behavior was performing cytology 1-2 years after the last test (20.1%), followed by less than one year later (11.7%) and 2-3 years later (12.7%).

Applying financial restrictions to inappropriate cytology tests would have resulted in estimated annual savings of approximately € 363,014.

4.2.2 Pre-implementation screening coverage

In the *reference scenario*, the proportion of cervical cancer screening coverage attributable to publicly funded first-level tests was estimated at 19.5% in 2018 and 20.4% in 2019, for an average coverage of 19.9%.

This estimate is likely subject to overestimation, since the DWH does not distinguish between first-level and follow-up tests, and the formula does not account for inappropriate timing. When the formula was adjusted to include only appropriate tests, cervical cancer screening coverage dropped to 12.3%.

4.3 Uptake of the new intervention: first phase of implementation

The change in the intervention mix after the program's implementation was assessed by retrospectively comparing two cohorts of women with the same age (25-28 years and 57-64 years) in September 2018 - December 2019 *vs* September 2022 - December 2023.

From the extracted data (Table 10), the difference in first-level tests performed under the opportunistic regime ('non screening', NS) was calculated, along with the annual rates relative to the target population. The calculated rates were then used as parameters for the opportunistic module of the BIM, under the assumption that post-implementation opportunistic behavior would remain stable across age groups and over time.

The results, expressed as rates per 100 eligible women, are shown in Table 10. As expected, screening coverage of the target population increased after the program's introduction for

women aged 25-28 and for women aged 47-64 (+20.04 and 29.36 per 100 eligible women, respectively). Of the 9,168 cytology tests performed on women aged 25 to 28, 524 were found to be inappropriate (5.7%, 1.16 per 100 eligible women), meaning the same women had already undergone cytology in the previous three years. Among the 52,033 HPV DNA tests performed on women aged 47 to 64, 468 were found to be inappropriate because of an HPV test in the previous five years (0.9%, 0.26 per 100 eligible women), and 7,181 were inappropriate due to a cytology test in the previous three years ('interval cytology: 13.8%, 4.05 per 100 eligible women).

Following the program's implementation, the uptake of opportunistic screening shifted. Opportunistic cytology uptake remained stable among women under 30 years of age (+0.08 per 100 eligible women), while it showed a modest decrease among older women who were actively invited to primary HPV testing (-1.23 per 100 eligible women). These findings are consistent with the observed difference in participation rates, with younger women less likely to participate than older women. Conversely, opportunistic HPV DNA uptake slightly increased in both age groups (+0.37 and +0.18 per 100 eligible women, respectively). Given that during the first 16 months of implementation follow-up co-testing was not offered within the program, this increase may be explained by a higher demand for co-testing resulting from the increased detection rate following program implementation. Alternatively, it may reflect the gradual expansion of primary HPV testing, a relatively new technology that has only recently become widely available at affordable prices in the opportunistic network.

Opportunistic colposcopy uptake was calculated jointly for both age groups to simplify model computations. As with opportunistic HPV DNA, a modest increase in opportunistic colposcopy uptake was observed (+0.24 per 100 eligible women). This increase could be explained by a higher demand for colposcopy due to the growing availability of opportunistic primary HPV, which raised detection rates, and/or by cases detected within the program, with referred women choosing to undergo colposcopies in the private sector.

Age groups (years)	Observation period	Cytology tests - S (n, rate)	Cytology tests – NS (n, rate)	HPV tests - S (n, %)	HPV tests – NS (n, rate)	Inappropriate cytology tests (estimate) - S (n, rate)	Inappropriate HPV test - S (estimate) (n, rate)	Inappropriate HPV test due to interval cytology - S (estimate) (n, rate)	Colposcopies – NS* (n, rate)
25-28	Pre-implementation	-	5,283 (6.45)	-	780 (0.95)	-	-	-	-
	Post-implementation	9,168 (20.4)	3,911 (6.53)	-	793 (1.32)	524 (1.16)	-		-
	Difference	9,168 (20.4)	-1,372 (+0.08)	-	13 (0.37)	524 (1.16)	-		-
47-64	Pre-implementation	-	13,134 (6.02)	-	641 (0.29)	-	-		2,434 (0.81)
	Post-implementation	-	11,287 (4.79)	52,033 (29.36)	1,118 (0.47)	-	468 (0.26)	7,181 (4.05)	3,108 (1.05)
	Differential	-	-1,847 (-1.23)	52,033 (29.36)	477 (0.18)	-	468 (0.26)	7,181 (4.05)	674 (0.24)

Table 10. Comparison of the number of screening tests before and after the program's implementation. S: test performed within the organized program; NS: test performed outside the organized program. Rates are reported per 100 eligible women (%). *The NS colposcopy rate is the only parameter calculated for the entire screening population (25-28 and 47-64 years).

4.4 Post-implementation screening coverage

In 2023, the share of cervical cancer screening coverage attributable to publicly funded first-level tests was estimated at 51.3%, representing a 31.8% increase compared with 2018-2019. While the estimate attributable to organized screening (27.4%) is highly accurate, the estimate for opportunistic screening (19.5%) in subject to overestimation, for the same reasons discussed above for pre-implementation coverage. Assuming the rate of inappropriateness remais stable over time, adjusting the formula for appropriateness would decrease overall screening coverage to 39.7%.

4.5 Input parameters

The full set of parameters for the BIM is reported in Table 11. Some parameters were estimated from the screening database (Dynamic Population Calibration, Model Parameters, Attendance, colposcopies and follow up parameters), from the AHP DWH (intervention mix parameters), or from the Regional reimbursement manual (cost parameters), while others were estimated from published data (HPV vaccine coverage and detection parameters).

Name	Value	Description
HPV vaccine coverage by birth year, Lombardy Region		
Cov2003	0.7794	Proportion of HPV vaccine coverage for birth cohort 2003 reported by the Italian Ministry of Health (Lombardy Section), 2022
Cov2004	0.8034	Proportion of HPV vaccine coverage for birth cohort 2004 reported by the Italian Ministry of Health (Lombardy Section), 2022
Cov2005	0.8208	Proportion of HPV vaccine coverage for birth cohort 2005 reported by the Italian Ministry of Health (Lombardy Section), 2022
Cov2006	0.8280	Proportion of HPV vaccine coverage for birth cohort 2006 reported by the Italian Ministry of Health (Lombardy Section), 2022
Cov2007	0.8177	Proportion of HPV vaccine coverage for birth cohort 2007 reported by the Italian Ministry of Health (Lombardy Section), 2022
Cov2008	0.7776	Proportion of HPV vaccine coverage for birth cohort 2008 reported by the Italian Ministry of Health (Lombardy Section), 2022
Cov2009	0.6842	Proportion of HPV vaccine coverage for birth cohort 2009 reported by the Italian Ministry of Health (Lombardy Section), 2022
Cov2010	0.6842	Proportion of HPV vaccine coverage for birth cohort 2010, estimated from 2009 birth cohort data reported by the Italian Ministry of Health (Lombardy Section), 2022
Cov2011	0.6842	Proportion HPV vaccine coverage for birth cohort 2011, estimated from 2009 birth cohort data reported by the Italian Ministry of Health (Lombardy Section), 2022
Dynamic population calibration		
DynPopPap	-0.0334	Proportion of yearly dynamic fluctuation of the invited population for primary cytology estimated from historical (2023) data
DynPopHPV	0.0562	Proportion of yearly dynamic fluctuation of the invited population for primary HPV DNA estimated from historical (2023) data
DynVax	-0.0052	Proportion of yearly increase of Cytology invitations as a net result of the voluntary switch to cytology screening by 25-29 yo vaccinated women, and the voluntary switch to the delayed screening strategy by women whose vaccination status was previously unknow by the AHP
Intervention mix parameters		
PreNSPap	0.0602	Cytology tests in non screening regime during the pre-implementation period among women aged 30-64 y/women aged 30-64 y (annual rate)
PreNSPap_25-29	0.0645	Cytology tests in non screening regime during the pre-implementation period among women aged 25-29 y/women aged 25-29 y (annual rate)
PreNSHPV	0.0029	HPV DNA tests in non screening regime during the pre-implementation period among women aged 30-64 y/women aged 30-64 y (annual rate)
PreNSHPV_25-29	0.0095	HPV DNA tests in non screening regime during the pre-implementation period among women aged 25-29 y/women aged 25-29 y (annual rate)
PostNSPap	0.0479	Cytology tests in non screening regime during the post-implementation period among women aged 30-64 y/women aged 30-64 y (annual rate)

PostNSPap_25-29	0.0653			Cytology tests in non screening regime during the post-implementation period among women aged 25-29 y/women aged 25-29 y (annual rate)
PostNSHPV	0.0047			HPV DNA tests in non screening regime during the post-implementation period among women aged 30-64 y/women aged 30-64 y (annual rate)
PostNSHPV_25-29	0.0132			HPV DNA tests in non screening regime during the post-implementation period among women aged 25-29 y/women aged 25-29 y (annual rate)
InapSPap	0.0116			Proportion of screening cytology tests performed inappropriately during the post-implementation period (yearly estimate)
InapSHPV	0.0026			Proportion of screening HPV DNA tests performed inappropriately during the post-implementation period (yearly estimate)
IntervalSHPV	0.0405			Proportion of screening unnecessary HPV DNA tests during the post-implementation period, because of previous 'interval cytology' tests (yearly estimate)
PreNScolp	0.0081			Colposcopies in non screening regime during the pre-implementation period among women aged 25-64 y/women aged 25-64 y (annual rate)
PostNScolp	0.0105			Colposcopies in non screening regime during the post-implementation period among women aged 25-64 y/women aged 25-64 y (annual rate)
Model parameters				
First round, non vaccinated probability set				
age (y)	*25-29*	*30-49*	*50-64*	
p1	0.0914	-	-	Proportion of women who underwent primary cytology that were referred to colposcopy, by age (2022-2023 data)
p2	0.0119	-	-	Proportion of women who underwent primary cytology that were referred to repetition for inadequate result, by age (2022-2023 data)
p3	0.8967	-	-	Proportion of women who underwent primary cytology with normal result, by age (2022-2023 data)
p4	-	0.0754	0.0301	Proportion of women who underwent primary HPV DNA that were referred to colposcopy, by age (2022-2023 data)
p5	-	0.0596	0.0238	Proportion of women who underwent primary HPV DNA that turned out HPV positive with normal cytology, by age (2022-2023 data)
p6	-	0.8591	0.9400	Proportion of women who underwent primary HPV DNA with negative result, by age (2022-2023 data)
p7	-	0.0060	0.0060	Proportion of women who underwent primary HPV DNA that were referred to repetition for inadequate result, by age (2022-2023 data)
p8	-	0.5141	0.5141	Proportion of women who underwent 12-month recall of primary HPV DNA with positive result, by age (2022-2023 data)
p9	-	0.4859	0.4859	Proportion of women who underwent 12-month recall of primary HPV DNA with negative result, by age (2022-2023 data)
Subsequent rounds, non vaccinated probability set				
age (y)	*25-29*	*30-49*	*50-64*	
p1_2	0.0914	-	-	
p2_2	0.0119	-	-	
p3_2	0.8967	-	-	
p4_2	-	0.0283	0.0129	
p5_2	-	0.0255	0.0102	
p6_2	-	0.9402	0.9708	
p7_2	-	0.0060	0.0060	
p8_2	-	0.5141	0.5141	
p9_2	-	0.4859	0.4859	
First round, vaccinated probability set				
age (y)	*25-29*	*30-49*	*50-64*	
p4_vax	-	0.0475	0.0190	
p5_vax	-	0.0405	0.0162	
p6_vax	-	0.9060	0.9588	
p7_vax	-	0.0060	0.0060	
p8_vax	-	0.5141	0.5141	
p9_vax	-	0.4859	0.4859	
Subsequent rounds, vaccinated probability set				

age (y)	*25-29*	*30-49*	*50-64*	
p4_vax_2	-	0.0178	0.0081	
p5_vax_2	-	0.0174	0.0069	
p6_vax_2	-	0.9588	0.9789	
p7_vax_2	-	0.0060	0.0060	
p8_vax_2	-	0.5141	0.5141	
p9_vax_2	-	0.4859	0.4859	
Attendance parameters				
Particip_Pap	0.2432	Proportion of women invited for primary cytology who participated (estimated from 2022-2023 data)		
Particip_HPV	0.3551	Proportion of women invited for primary HPV DNA who participated (estimated from 2022-2023 data)		
Repet_Pap	0.6262	Proportion of women invited for repetition of primary cytology after an inadequate result who participated (estimated from 2022-2023 data)		
Repet_HPV	0.7908	Proportion of women invited for repetition of primary HPV DNA after an inadequate result who participated (estimated from 2022-2023 data)		
Recall_12	0.8000	Proportion of women invited for 12 months recall of primary HPV DNA who participated (estimated from 2022-2023 data)		
Colpo_att	0.8057	Proportion of women invited for colposcopy who attended (estimated from 2022-2023 data)		
Colposcopies and follow-up parameters				
FU_Pap	0.6000	Average yearly number of subsequent colposcopies after the first screening colposcopy - primary cytology (estimated from Ronco et al, 2012, assuming that the duration of follow up is 2 years)		
FU_HPV	0.7000	Average yearly number of subsequent colposcopies after the first screening colposcopy - primary HPV (estimated from Ronco et al, 2012, assuming that the duration of follow up is 2 years)		
Cotest_Pap	1.0500	Average yearly number of Co-tests after the first screening colposcopy - primary cytology (estimated from Ronco et al, 2012, assuming that the duration of follow up is 2 years)		
Cotest_HPV	1.0500	Average yearly number of Co-tests after the first screening colposcopy - primary cytology (estimated from Ronco et al, 2012, assuming that the duration of follow up is 2 years)		
Detection rate parameters				
age (y)	*25-29*	*30-49*	*50-64*	
PPV_Pap	0.5000			Positive predictive value for CIN2+ lesions of the first screening colposcopy referral - primary cytology (estimated from Pesola et al)
PPV		0.37	0.2500	Positive predictive value for CIN2+ lesions of the first screening colposcopy referral - primary HPV DNA (estimated from Pesola et al)
PPV12		0.32	0.2100	Positive predictive value for CIN2+ lesions of the first screening colposcopy referral after 12 month repetition - primary HPV DNA (estimated from Pesola et al)
PPV_2		0.3	0.2000	Positive predictive value for CIN2+ lesions of the first screening colposcopy referral - primary HPV DNA, subsequent rounds (estimated from Pesola et al)
PPV12_2		0.25	0.1700	Positive predictive value for CIN2+ lesions of the first screening colposcopy referral after 12 month repetition - primary HPV DNA, subsequent rounds (estimated from Pesola et al)
Cost parameters				
cCervSampl	2.90 €	Cervical sample collection, cost		
cHPVDNAscreening	15.0 €	HPV DNA in organized program, including cytologic triage when needed, cost		
cPapTest	12.150 €	Cytology of the cervix (Pap test), cost		
cColp	10.550 €	Colposcopy, cost		
cColpOther	28.070 €	Average costs added to a second level colposcopy, due to other exams performed during the exam (eg biopsy, histopathological exam…) (estimated from 2022-2023 data)		
cFUOther	23.410 €	Average costs added to a follow up colposcopy, due to other exams performed during the exam (eg biopsy, histopathological exam…) (estimated from 2022-2023 data)		
cCotest	27.150 €	HPV DNA + cytology of cervical sample (organized screening), cost		
cHPVDNANS	42.180 €	Average cost of a HPV DNA test performed out of the program (estimated from 2018-2019 data)		
cNSColpOther	16.580 €	Average costs added to a colposcopy performed out of the screening program, due to other exams performed during the exam (eg biopsy, histopathological exam…) (estimated average from the pre-implementation periods)		
cHPVDNAFU	44.590 €	HPV DNA, genomic typing, usually prescribed as a second level follow up test out of the screening program		

Table 11. Budget Impact Model: full set of parameters.

4.6 Uptake of the new intervention: Budget Impact analysis

For the reference scenario, total annual costs were estimated at €1,376,252 (€1,047,675 for first-level tests, and 328,577 for second-level tests) (Table 12). By comparison, the total annual costs of the current mix of interventions (usual scenario: coexisting organized and opportunistic screening) were estimated at €2,397,200 (€1,979,128 for first-level tests, primarily HPV DNA, and €418,072 for second-level tests). Regarding first-level cost, the share attributed to HPV DNA tests increased from 22% to 50%. Although annual expenditures for cervical cancer screening nearly doubled (+74%), publicly funded cervical cancer screening coverage more than tripled from 2019 to 2023 (+223%, excluding inappropriate opportunistic cytology from the calculation).

Considering opportunistic screening alone, a significant decrease in annual costs (-€293,512, -21%) was projected after the implementation of the program, with reductions across all budget categories: -€78,678 (-10%) for cytology, -€82,331 (-35%) for HPV DNA, and -€132,0503 (-40%) for second-level tests (Table 12).

Budget category	**Reference scenario**		**Intervention (usual) scenario**				**Differentials (intervention *vs* reference scenario)**	
	Opportunistic screening		**Opportunistic screening**		**Organised screening**			
	Volumes (n)	Cost (€)	Volumes (n)	Cost (€)	Volumes (n)	Cost (€)	Volumes (n)	Cost (€)
Cytology	54,142	814,837	48,914	736,159	1,862	28,018	-3,636	-50,660
HPV DNA	5,165	232,838	3,339	150,507	59,466	1,064,443	57,640	982,112
Total first-level	59,307	1,047,675	52,253	886,666	61,323	1,092,462	54,269	931,453
Colposcopies	9,238	97,461	7,227	76,247	6,182	65,217	4,171	44,003
Other 2nd-level tests	6,838	231,116	-	119,827	-	156,781	-	45,492
Total second-level	-	328,577	-	196,074	-	221,998	-	89,495
Total	-	1,376,252	-	1,082,740	-	1,314,460	-	1,020,948

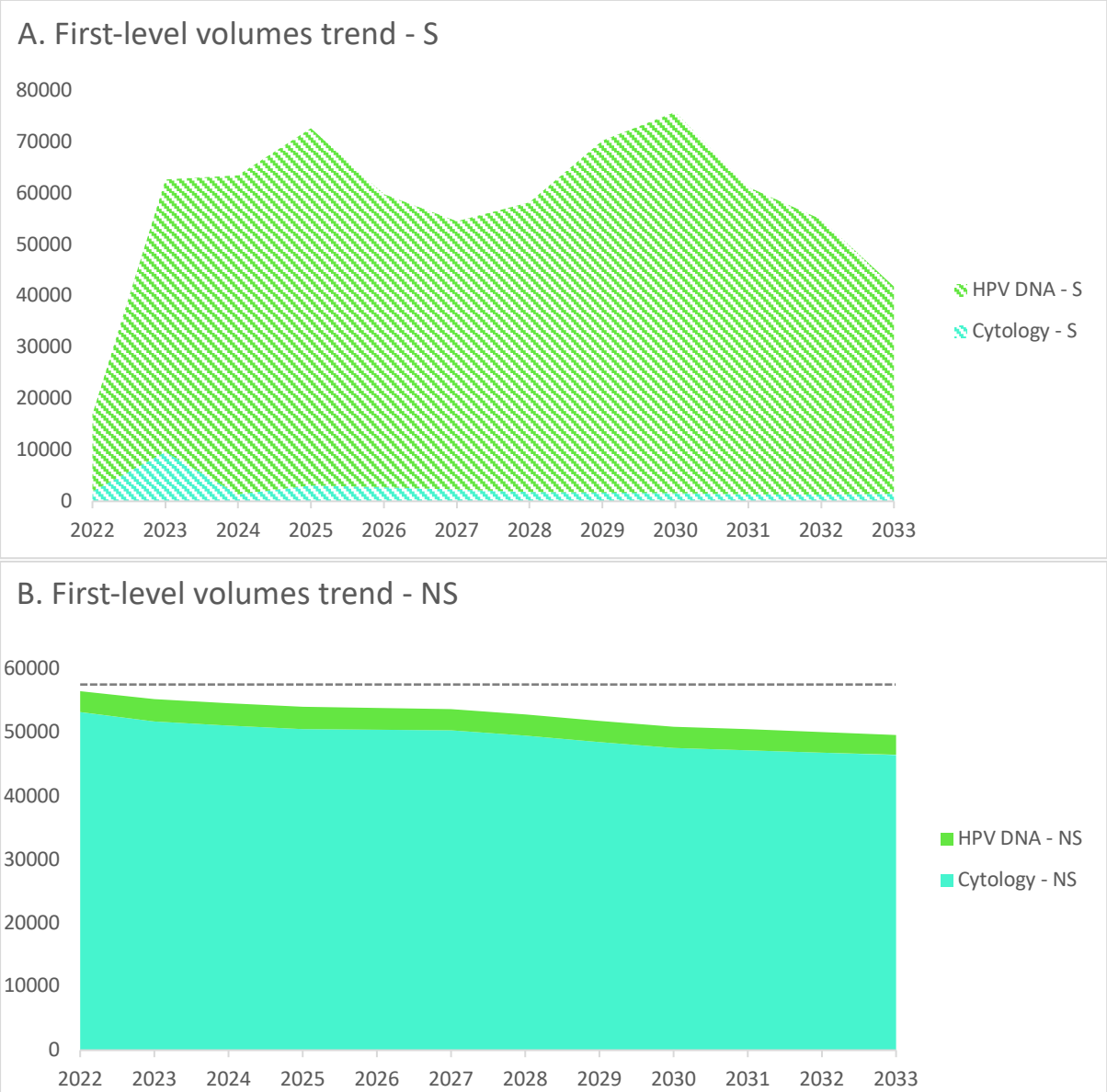
Table 12. Estimated average annual (2024-2033) volumes and cost (€) of previous opportunistic screening compared with the current mix of interventions: HPV-based organized program and opportunistic screening.

4.6.1 Annual trend: volumes

Regarding opportunistic screening, a slight and gradual decrease in both first- and second-level tests is predicted following the program's introduction (Figures 7B and 7C).

In contrast, organized screening is expected to show a rapid increase in the number of first-level tests, particularly HPV DNA tests, which are projected to reach two peaks (2025 and 2030) during the observation period. Cytology testing, on the other hand, is expected to gradually decline until reaching minimal volumes, with the exception of a modest peak in 2023 (Figure 7A).

As expected with the introduction of an organized program in a naïve population, the number of organized second-level colposcopies is estimated to peak in 2026, followed shortly thereafter by a peak in organized follow-up colposcopies in 2027 (Figure 7C). The slight and gradual decrease in opportunistic colposcopies will not offset this peak.



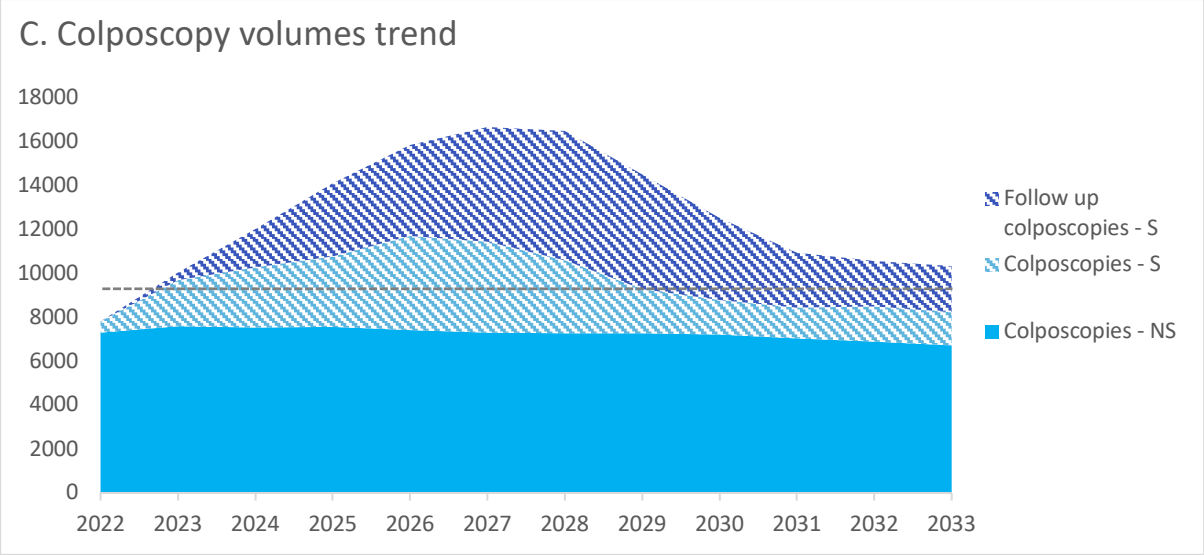


Figure 7. Annual trends in volumes (2022-2033) for organized first-level tests (A), opportunistic first-level tests (B) and overall colposcopies (C). The dotted grey line indicates the pre-intervention period, during which volumes and costs were assumed to be stable.

After this peak, the volume of organized colposcopies is predicted to rapidly decline to low levels.

4.6.2 Annual trend: costs

The overall costs of cervical cancer screening are expected to increase rapidly following the program's implementation, reaching two peaks: in 2025 (€2,654,984) and in 2030 (€2,606,122). With the introduction of organized screening, a shift from cytology to HPV DNA as the largest budget category is projected. Conversely, the costs of cytology and colposcopies are expected to gradually decrease over time. By 2023, the overall annual cost of organized screening was expected to exceed that of opportunistic screening.

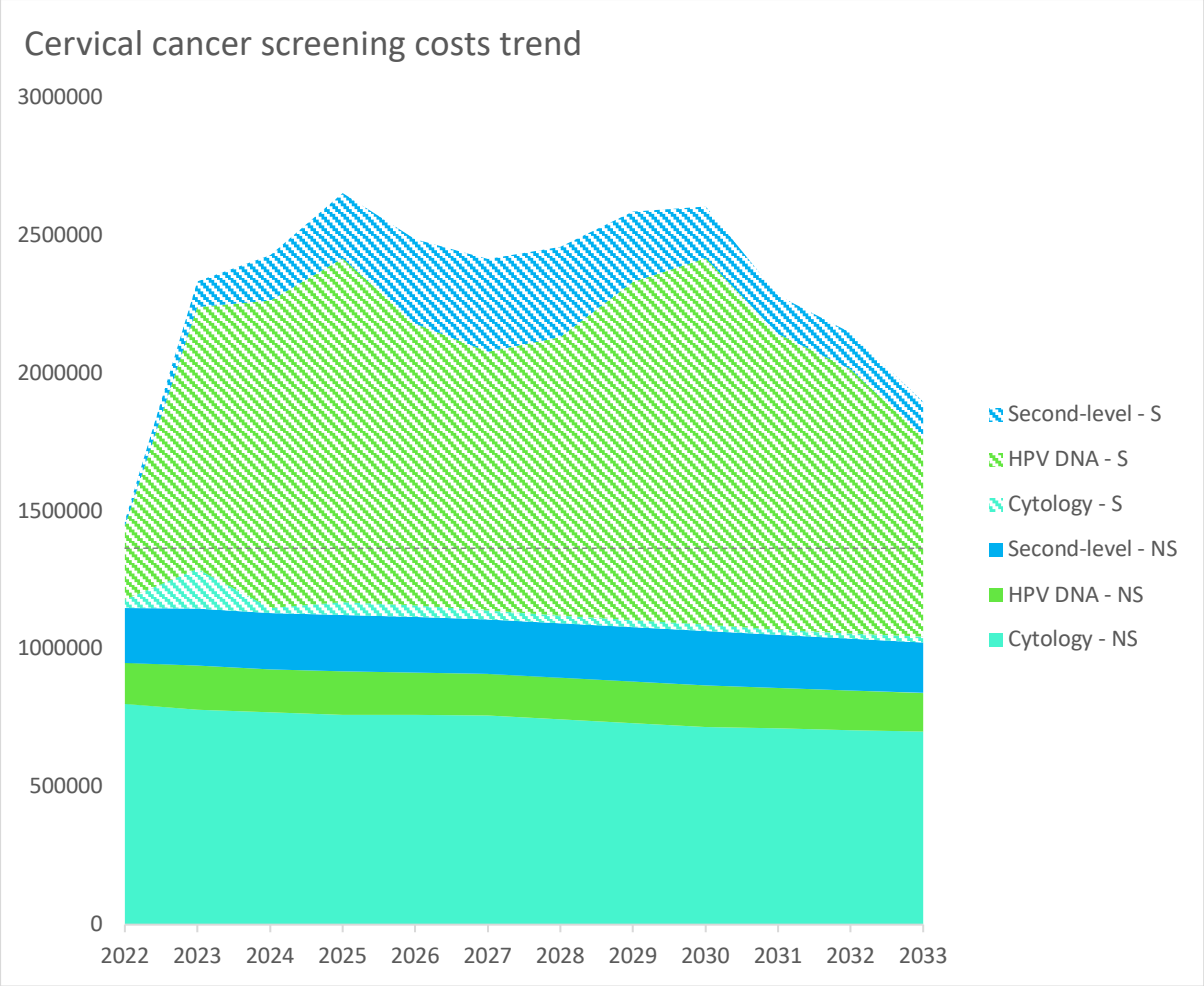


Figure 8. Annual trends in costs (2022-2033) for organized screening tests and opportunistic screening tests. The dotted grey line indicates the costs of the reference scenario, which are assumed to be stable over time.

4.7 Scenario analysis

Comparisons between different scenarios and the reference scenario for the first decade after the program's introduction are reported in Table 13 and Figure 9. Total annual expenditure on cervical cancer screening is estimated at €2,397,200 in the usual scenario (mixed interventions: opportunistic + organized screening with current participation rates), which is €1,141,375 higher than the cost associated with the reference scenario (opportunistic screening only, pre-implementation parameters: €1,255,825). The expected annual cost of organized screening per screened woman is €21.48. Since the usual scenario has already been implemented, additional scenarios were compared with the usual scenario.

In the usual scenario, the program does not include co-testing (a single sampling procedure for both cytology and HPV DNA). For comparison purposes, co-testing -the periodic test recommended for women undergoing follow-up after the first colposcopy- was assumed to be performed within the opportunistic network, with 50% reimbursement, and a fixed price based on code 91.24.B. (HPV DNA including genotyping), the best-performing test for follow-up due

to the prognostic value of genotyping. Under these assumptions, the annual cost associated with co-testing was estimated at €324,901, accounting for 30% of the cost of opportunistic screening (usual scenario). Consequently, we evaluated the budget impact of including co-testing within organized screening.

	Total costs per year – S (€)	**Total costs per year – NS (€)**	**Total costs per year- S+NS (€)**	**Screened women - S (n)**	**Cost per screened woman – S (€)**
Reference scenario	0	1,255,825	1,255,825	0	0
Usual scenario	1,314,460 *+1,314,460*	1,082,740 *-173,085*	2,397,200 *+1,141,375*	61,328 *+61,328*	21.48 *+21.48*
Co-test scenario	1,478,164 *+1,478,164*	757,839 *-497,986*	2,236,003 *+980,178*	61,328 *+61,328*	24.17 *+24.17*
Interval cytology restriction scenario	1,293,353 *+1,293,353*	1,082,740 *-173,085*	2,376,093 *+1,120,268*	60,231 *+60,231*	21.51 *+21.51*
Interval cytology restriction + Co-test scenario	1,456,152 *+1,456,152*	759,633 *-496,192*	2,215,785 *+959,960*	60,231 *+60,231*	24.23 *+24.23*
Switch opportunistic cytology>organised HPV (+5%) + Co-test scenario	1,608,474 *+1,608,474*	722,855 *-532,970*	2,331,329 *+1,075,504*	67,030 *+67,030*	24.038 *+24.038*
Switch opportunistic cytology>organised HPV (+10%) + Co-test scenario	1,747,062 *+1,747,062*	690,626 *-565,199*	2,437,687 *+1,181,862*	72,731 *+72,731*	24.035 *+24.035*

Table 13. Scenario analysis. Differentials in respect to the reference scenario are displayed in italics.

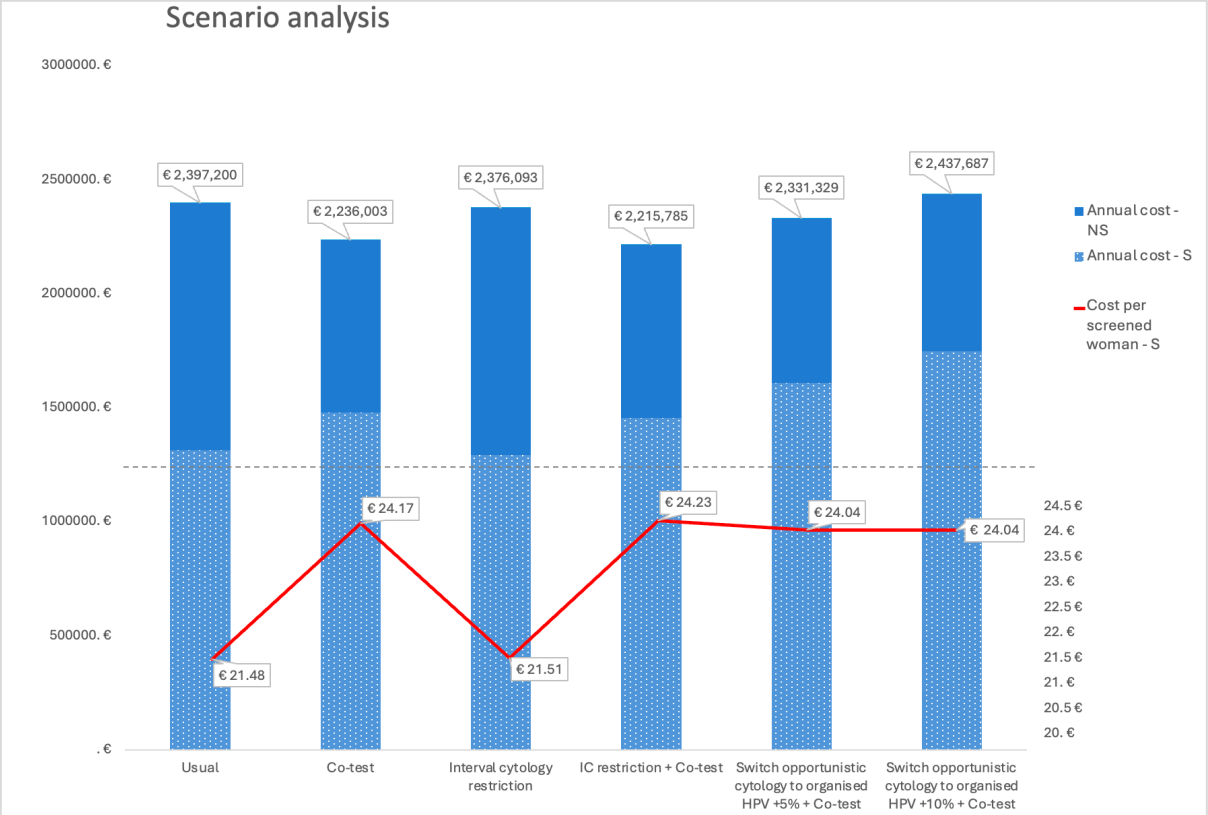


Figure 9. Total annual costs (2024-2033) for each scenario. The red line indicates the annual cost of the organized program per screened woman. The dotted grey line indicates the total costs of the reference scenario.

In addition to the reduction in opportunistic screening expenditure mentioned above, further cost savings derive from the lower price associated with the code 91.24.D (qualitative HPV DNA with partial genotyping), already adopted for first-level organized HPV testing (Table 2). The effect of including co-testing in organized screening is shown in Figure 9. The annual cost of organized screening is expected to increase by 12% (+€163,704), while the cost of opportunistic screening is projected to decrease by 30% (-€324,901). The net result is a reduction in overall annual cervical cancer screening expenditure of 7% (-€161,197). In the co-test scenario, the expected cost of organized screening per screened woman rises to €24.17 (+13%), while the overall cost (organized + opportunistic) per screened woman decreases by €2.65 (-7%) per year.

In the usual scenario, restrictions for recent cytology (within 3 years) are applied within the program only for women aged 25-29, although cytology remains an appropriate and effective screening strategy up to age 64. We investigated the budget impact of applying such restriction (so called "interval cytology" restrictions) also to women aged 30-64. Compared with the usual scenario, the total annual expenditure associated with interval cytology restrictions is projected to decrease by €21,107 (-1%), entirely due to reduced organized screening costs. A minimal

increase in the cost of organized screening per screened woman is also estimated (+€0.03, +0.2% per year), reflecting a slight decrease in organized screening coverage.

We also examined a third scenario combining co-testing and interval cytology restrictions, which proved less costly overall (€2,215,785 per year), with annual savings of €181,415 (-8%) compared to the usual scenario. In this scenario, the cost of organized screening per screened woman is estimated at €24.23 per year (+€2.75 per year, +13% compared with the usual scenario), while the overall cost of screening per screened woman decreases by €2.32 per year (-6%).

Of note, co-testing was gradually introduced into the program in November 2024 and has been an integral part of routine follow-up management since January 2025. Furthermore, during calibration analyses, we observed a disproportionate reduction in opportunistic cytology tests in 2024 compared with expectations, along with a slight increase in the participation in organized primary HPV (+2.5%). These changes may be explained by a growing enthusiasm for organized HPV screening, as well as by the gradual reduction in opportunistic test provision in healthcare facilities already implementing organized screening. For these reasons, we examined a fourth realistic scenario with the following features:

- inclusion of co-testing in organized screening starting in 2025;
- 20% reduction in opportunistic cytology uptake among women invited for organized HPV screening in the same year, starting in 2027;
- 5% increase in organized HPV DNA uptake starting in 2027.

In the fourth scenario, total annual costs are projected at €2,331,329, a 3% decrease (-€65,871 per year) compared with the usual scenario. Opportunistic screening expenditure is expected to decline substantially (-€359,885 per year, -33%), while organized screening expenditure increases due to higher screening coverage (+€294,014 per year, +22%).

We also explored a fifth scenario, identical to the fourth except for a 10% increase in participation in organized HPV DNA starting in 2027. In this case, the increase in the annual cost of organized screening (+€432,692 per year, +33%) would outweight opportunistic savings, raising total cervical cancer screening expenditure above the usual scenario (+€40,487 per year, +2%). These findings suggest that whenever participation in organized HPV DNA increases by 10% or more, the AHP should seek cost savings elsewhere -for example, by reducing the provision of opportunistic screening in public healthcare facilities while promoting the uptake of organized screening, or by applying restrictions on opportunistic screening more stringently. In the fourth and fifth scenarios, the expected cost of organized screening per screened woman increases to €24.04 (+11%), while the overall cost (organized

+ opportunistic) per screened woman decreases by €4.35 (-11%) and €5.53 (-14%) per year, respectively.

4.8 Sensitivity analysis

4.8.1 Total annual costs (usual scenario)

The OWSA results on total costs for the usual scenario are shown in Figure 10, where the largest bar represents the parameter with the greatest influence on the model's financial output. The x-axes represent the total annual cost of screening (S+NS) (A), the total cost of opportunistic screening (B) and the total cost of organized screening (C). For each panel, up to 10 inputs with the highest impact on total costs are displayed.

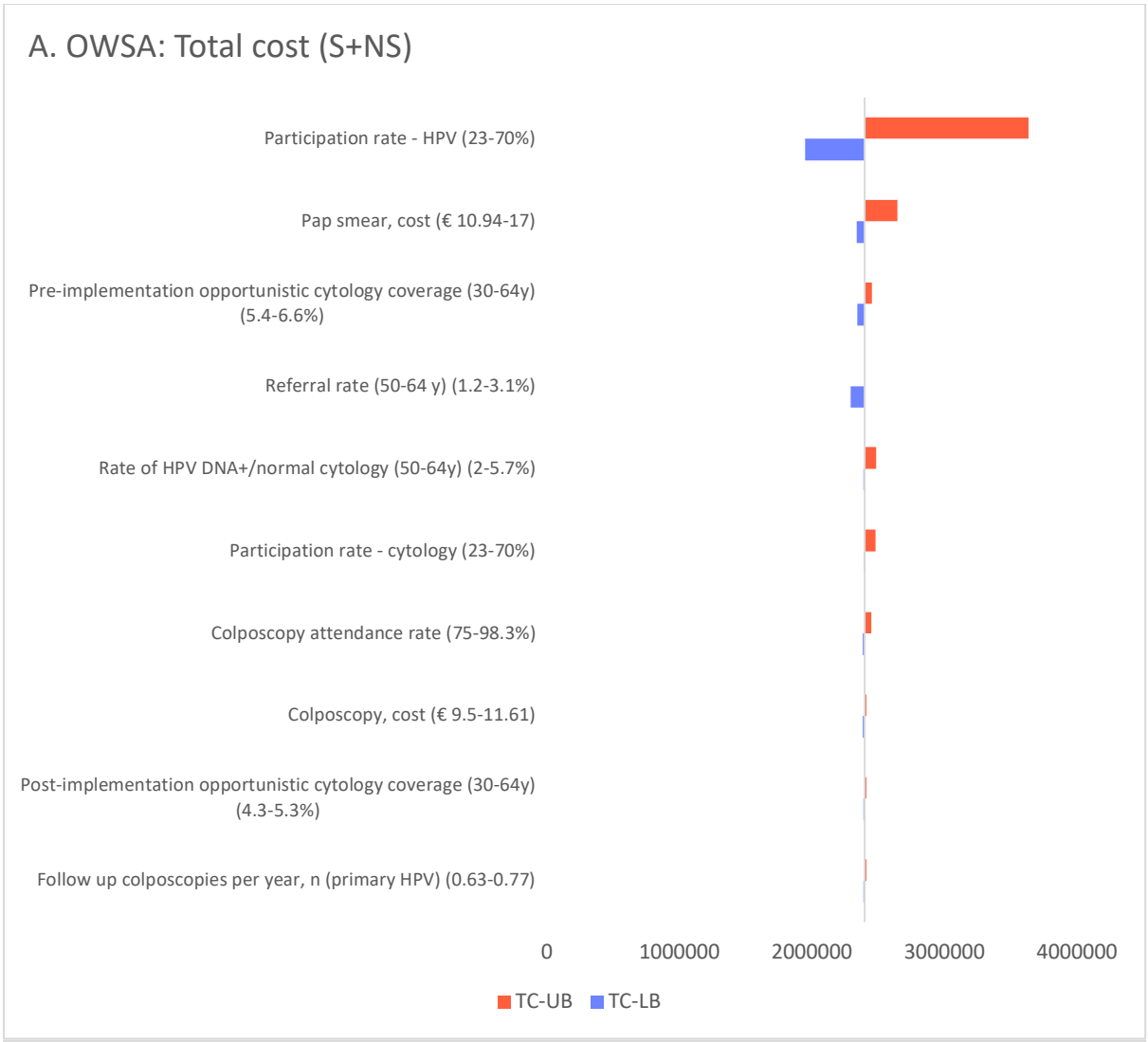
The OWSA showed that the participation rate for primary HPV screening (S), the cost of a cytology test, and pre-implementation cytology coverage among women aged 30-64 were the parameters with the greatest impact on total screening costs (S+NS) (Fig 10.A). In the base-case scenario, the primary HPV screening (S) participation rate was estimated at 35.51% based on values observed in 2022-2023, yielding total annual costs (S+NS) ranging from €2,215,785 to €2,437,687 across six different screening scenarios (Tab. 11). However, when the HPV participation rate was varied while performing the OWSA, using the lowest and highest values observed in the most recent survey (2019) by the Italian Cervical Cancer Screening Group(Italian Group on Cervical Cancer Screening, 2019), variability in total annual costs increased substantially, ranging from €1,948,808 to €3,634,611 (usual scenario).

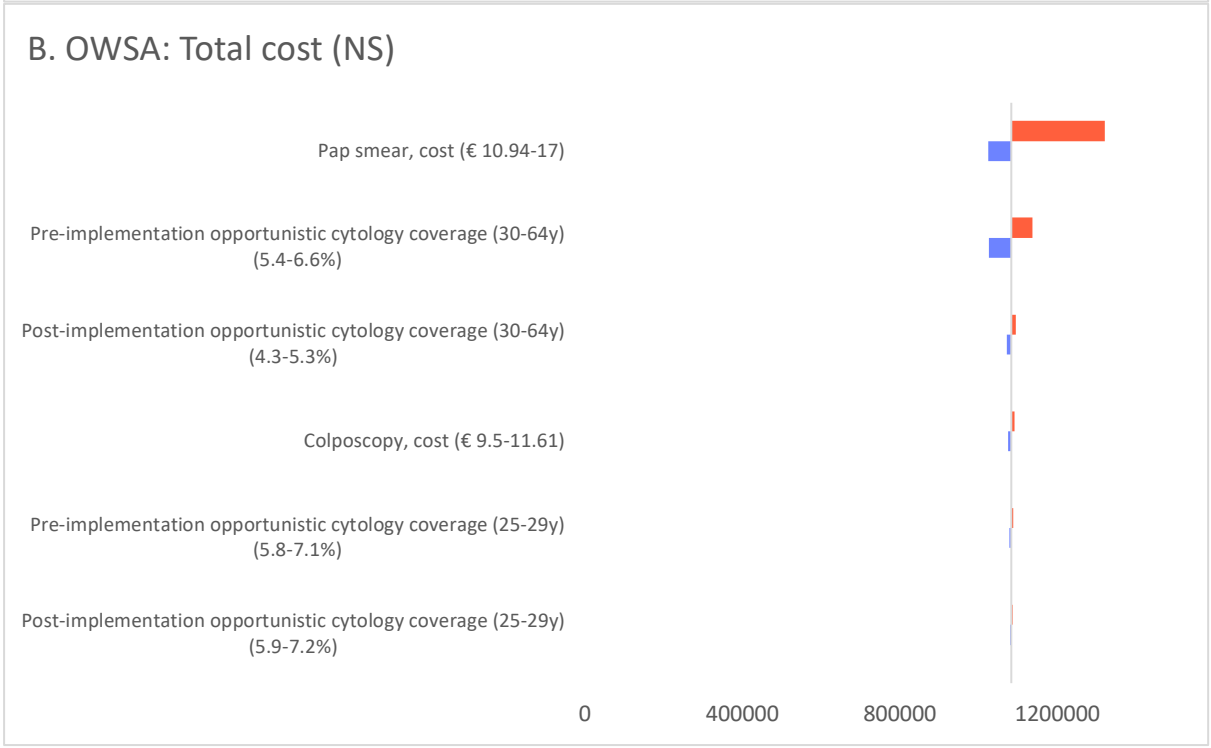
The cost of a Pap smear was the second most influential parameter. Varying this parameter between €10.94 and €17 resulted in total annual costs ranging from €2,335,762 to €2,643,463. Notably, while the lower bound for the Pap smear cost was set at -10% of the base-case, the upper bound was set at €17, based on the recently introduced tariff(Regional Council of Lombardy, 2024), thus reflecting a realistic scenario. Similarly, when pre-implementation opportunistic cytology coverage among women aged 30-64 (indicating the opportunistic screening behavior of women not actively invited to organized screening during the year) was varied ±10% (5.4% to 6.6%), total annual costs ranged between €2,340,340 and €2,450,392 (Figure 10A).

For opportunistic screening only, the cost of a Pap smear, pre-implementation opportunistic cytology coverage, and post-implementation opportunistic cytology coverage (indicating the behavior of women actively invited to organized screening during the year but still undergoing opportunistic testing) had the greatest impact on total NS costs in the usual scenario (Figure

10B). Varying these parameters increased variability in total annual NS costs from €1,023,553 to €1,319,974. Overall, NS costs showed less variability than organized screening costs in the usual scenario.

Regarding organized screening, OWSA results indicated that the parameters with the greatest influence on total annual costs (S) in the usual scenario were the participation rate in primary HPV screening (S), the primary HPV referral rate, and the HPV positivity rate with normal cytology. For the latter two parameters, the master parameter (primary HPV colposcopy referral rate/HPV positivity with normal cytology rate for women aged 50-64) was varied, with the rates for other age groups derived from it. When the participation rate in primary HPV screening was varied, total annual costs (S) ranged from €866,067 to €2,551,870 (Figure 10A). It is noteworthy that increasing participation rates in both primary cytology and primary HPV DNA (S) to 100% would result in total annual screening costs (only S) of €4,021,792, which is 62% higher than the total costs (S+NS) in the usual scenario. However, this would eliminate the need for opportunistic screening, resulting in very low NS costs, and would increase screening coverage by 96%. Varying the primary HPV referral rate by ±10% of the base-case increased variability in total annual S costs between €1,210,346 and €1,319,401. Similarly, varying the HPV positivity rate with normal cytology resulted in total annual S costs ranging from €1,304,595 to €1,400,114.


A. OWSA: Total cost (S+NS)
Participation rate - HPV (23-70%)
Pap smear, cost (€ 10.94-17)
Pre-implementation opportunistic cytology coverage (30-64y) (5.4-6.6%)
Referral rate (50-64 y) (1.2-3.1%)
Rate of HPV DNA+/normal cytology (50-64y) (2-5.7%)
Participation rate - cytology (23-70%)
Colposcopy attendance rate (75-98.3%)
Colposcopy, cost (€ 9.5-11.61)
Post-implementation opportunistic cytology coverage (30-64y) (4.3-5.3%)
Follow up colposcopies per year, n (primary HPV) (0.63-0.77)
0
1000000
2000000
3000000
4000000
TC-UB
TC-LB


B. OWSA: Total cost (NS)
Pap smear, cost (€ 10.94-17)
Pre-implementation opportunistic cytology coverage (30-64y) (5.4-6.6%)
Post-implementation opportunistic cytology coverage (30-64y) (4.3-5.3%)
Colposcopy, cost (€ 9.5-11.61)
Pre-implementation opportunistic cytology coverage (25-29y) (5.8-7.1%)
Post-implementation opportunistic cytology coverage (25-29y) (5.9-7.2%)
0
400000
800000
1200000

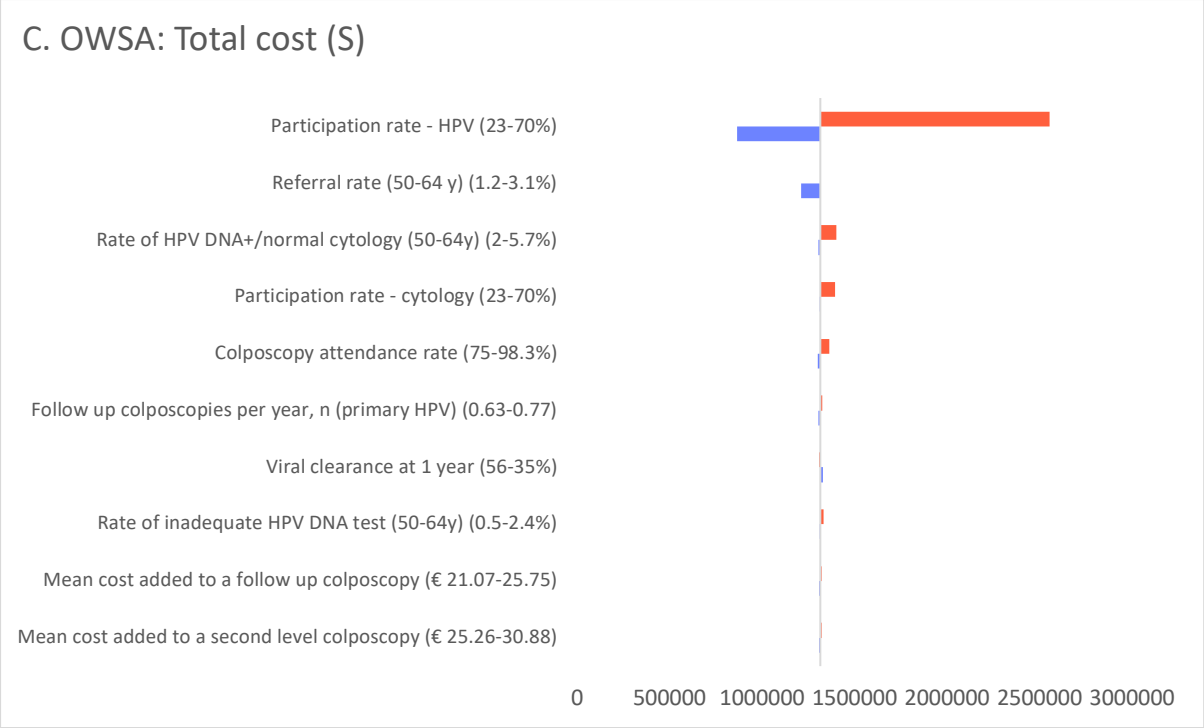


Figure 10. Tornado diagrams: one-way sensititivy analysis (OWSA) of overall costs (A), opportunistic screening costs (B), and organized screening costs (C) in the usual scenario. TC: total costs, LB: lower bound, UB: upper bound.

4.8.2 Colposcopy volumes (usual scenario)

Given that the predicted peak in colposcopy volumes (Figure 7C) could strain system capacity, we conducted an OWSA to identify the key parameters to prioritize for investment. The OWSA showed that the participation rate in primary HPV screening (S), the colposcopy referral rate after primary HPV, and the rate of HPV positivity with normal cytology after primary HPV were the parameters with the greatest impact on colposcopy volumes (Figure 11). All of these parameters, except the first, depend on the local epidemiology of HPV and related cytological abnormalities, as well as on the quality assurance of microbiological and pathology analyses at the HUB-SOCCU.

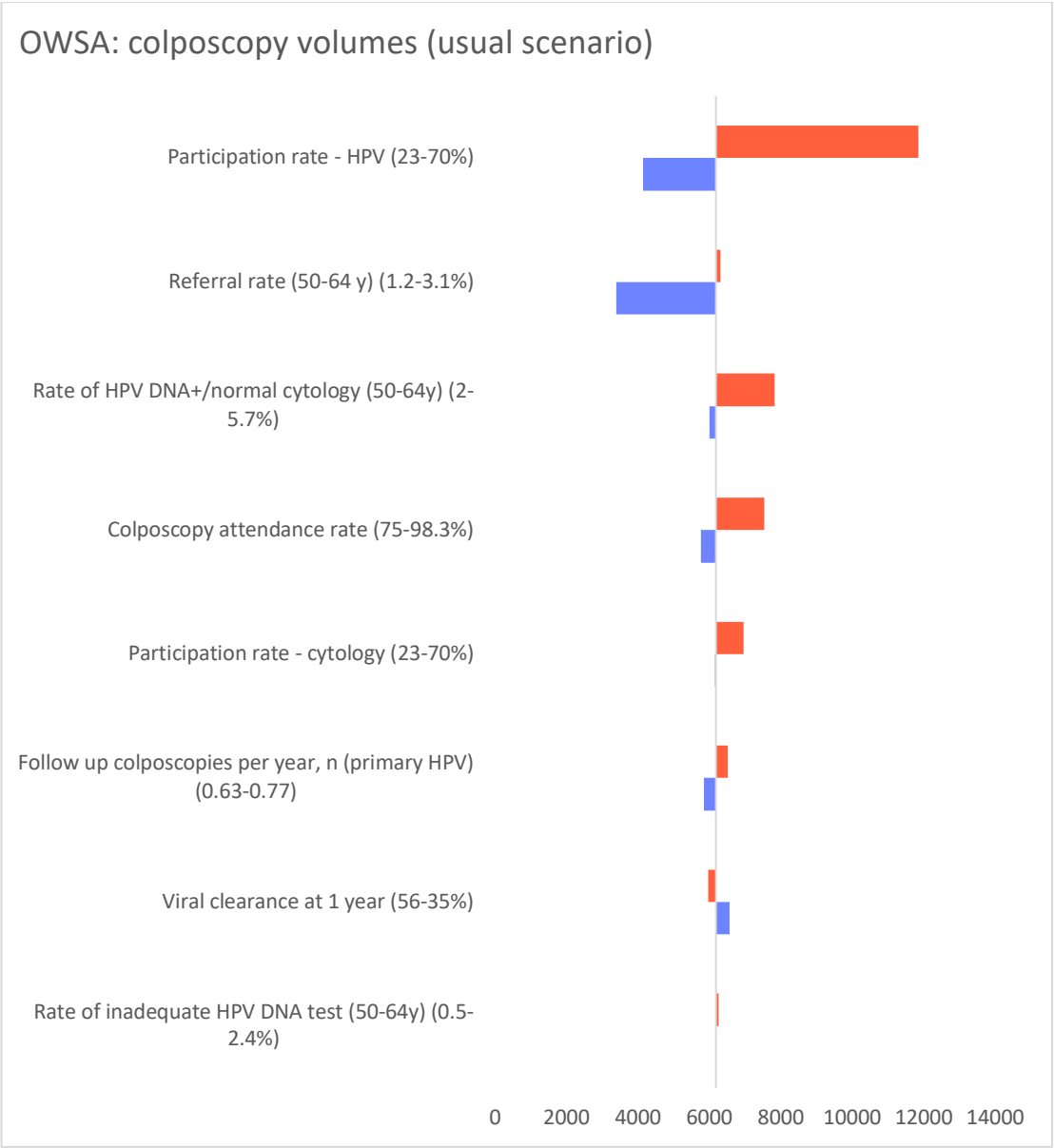


Figure 11. Tornado diagram: one-way sensititivy analysis (OWSA) of colposcopy volumes.

4.8.3 Cost per screened woman (usual vs alternative scenarios)(S)

For organized screening only, we conducted an OWSA of the cost per screened woman in the main alternative scenarios compared with the usual scenario. In Figure 12, the x-axes represent the cost differentials per screened woman (S) between the usual scenario and the alternative scenarios: the co-test scenario (Fig. 12A), the interval cytology restriction scenario (Fig. 12B), and the combined scenario (Fig 12C).

Notably, the magnitude of the impact on cost per screened woman was much greater for the co-test scenario compared with interval cytology restriction scenario. Consequently, the results for the co-test and combined scenarios were very similar (Fig. 12A and 12C).

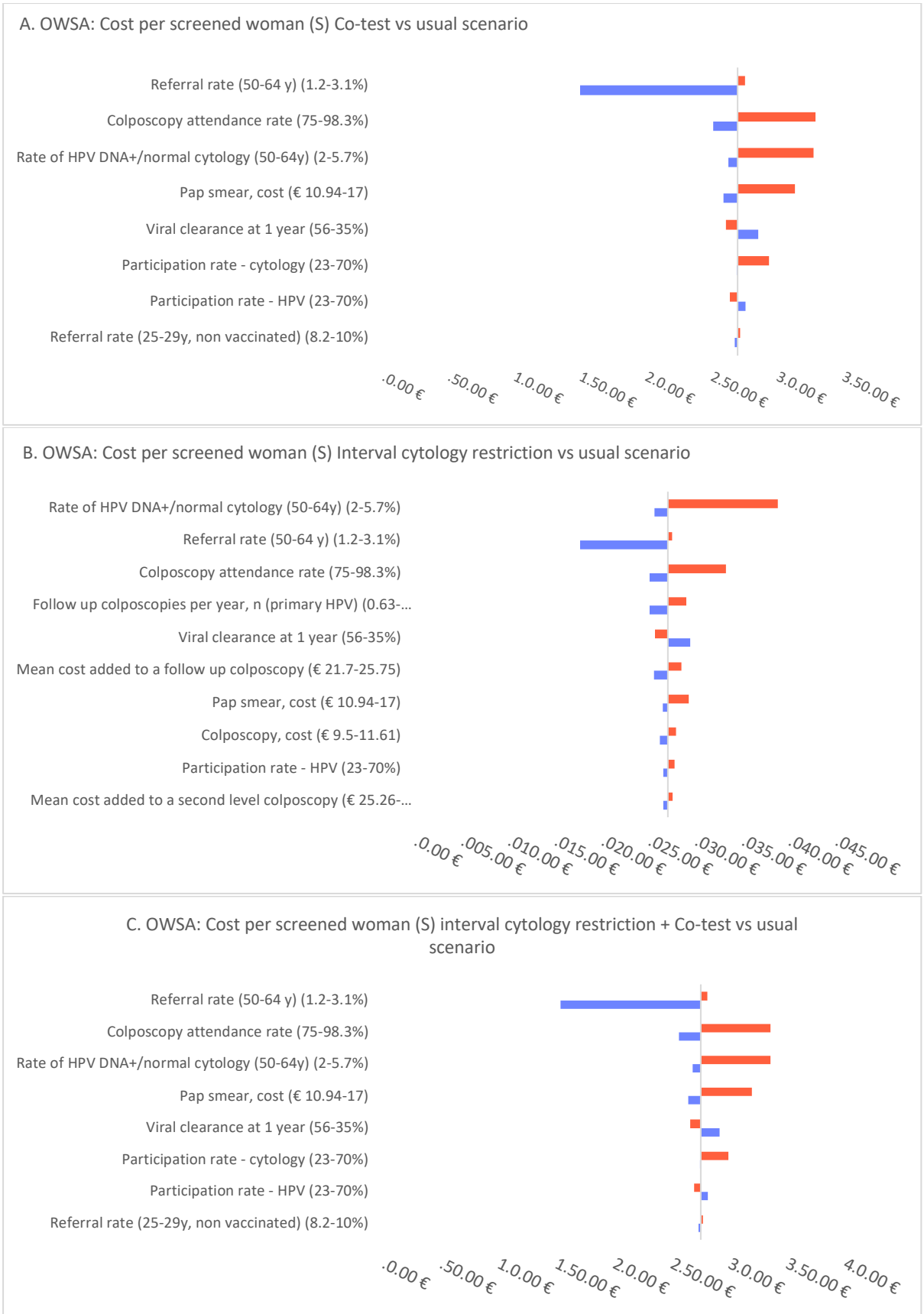


Figure 12. Tornado diagram: one-way sensititivy analysis (OWSA) of cost differentials per screened woman (S) across different scenarios compared with the usual scenario.

The OWSA showed that the cost differential per screened woman (S) between the usual scenario and both the co-test and the combined scenario was most sensitive to the colposcopy referral rate in primary HPV screening, the colposcopy attendance rate, and the rate of HPV positivity with normal cytology in primary HPV screening.

In the co-test scenario, setting the colposcopy referral rate to the 10th percentile of values observed in Northern Italy in 2018 for women aged 45-64 years(Italian Group on Cervical Cancer Screening, 2019) resulted in a budget impact of -€1.196 per screened woman, while the 90th percentile led to only a small increase of €0.057 compared with the usual scenario. This suggests that the local referral rate is very high, with significant budget implications. Similarly, setting the HPV positivity rate with normal cytology to the 90th percentile of the Northern Italy values(Italian Group on Cervical Cancer Screening, 2019) resulted in an increase of €0.579 in the cost differential per screened woman, while the 10th percentile led to only a €0.069 decrease, indicating that this parameter is relatively low. These two parameters are interdependent but ultimately depend on local HPV epidemiology and quality assurance at the HUB-SOCCU. Colposcopy attendance rate also influenced cost differentials per screened woman under the co-test policy compared with the usual scenario: lowering it to the 10th percentile of the observed attendance rate(Italian Group on Cervical Cancer Screening, 2019) yielded a decrease of €0.186, whereas increasing it to the 90th percentile produced an increase of €0.592.

When comparing the interval cytology restriction scenario with the usual scenario, the most impactful variables on the cost per screened woman differentials are the HPV positivity rate with normal cytology, the colposcopy referral rate with primary HPV testing, and the colposcopy attendance rate (Fig. 12B).

5 DISCUSSION

5.1 Main findings

This study evaluated the year-to-year economic impact of implementing an organized cervical cancer screening program based on primary HPV DNA testing in the province of Milan. Using a BIM and real-world data on test volumes, coverage and costs, the analysis demonstrated that transitioning from an opportunistic, cytology-based approach to an organized, HPV-based program markedly increased publicly funded coverage, altered test utilization patterns, and generated a significant though manageable rise in overall costs. Beyond the quantitative findings, this work offers valuable insights into the dynamics of implementing organized screening in a previously opportunistic context and provides policy-relevant implications for health systems.

Before the roll-out of the program, only one in eight eligible women received publicly funded first-level tests, all performed opportunistically. Following program implementation, screening coverage more than tripled, reaching nearly 40% of the target population, confirming that population-based invitation systems can effectively reach previously unscreened women(Cappelli *et al.*, 2018). This expansion represents a major public health achievement, as higher coverage rates have been consistently associated with declines in cervical cancer incidence within a few years(Serraino *et al.*, 2015). The shift was accompanied by a substantial increase in HPV DNA testing among first-level tests -from 9% to 55%- mostly within the organized setting. The temporary peak in colposcopy volumes projected for 2026-2027 reflects the expected short-term effect of introducing HPV-based screening in a naïve population, with a backlog of prevalent infections and lesions being detected and referred. Over time, volumes are expected to stabilize at sustainable levels.

From a financial perspective, overall expenditures nearly doubled relative to the pre-implementation scenario, primarily due to higher first-level testing volumes and, to a lesser extent, to the detection of more abnormalities requiring follow-up. However, the increase in cost was not proportional to the gain in coverage: publicly funded coverage more than tripled, suggesting that the investment yields significant population-level benefits in terms of equity and access. Sensitivity and scenario analyses identified participation in primary HPV screening as the single most influential determinant of both costs and colposcopy workload. For organized programs, sustained participation is essential for program effectiveness. Other influent factors, such as residual opportunistic coverage and quality assurance of first-level

analyses, should be key targets for policymakers seeking to enhance cervical cancer screening's economic efficiency and sustainability.

Our findings align with previous literature. Countries such as Australia(Machalek *et al.*, 2019), Canada(Ogilvie *et al.*, 2018), the Netherlands(Rijkaart *et al.*, 2012), and the United Kingdom(Pesola *et al.*, 2021) have all reported an initial rise in colposcopy referrals after switching from cytology-based to HPV-based primary organized screening, followed by stabilization as the prevalence of detectable lesions declines(Coldman *et al.*, 2015; Pesola *et al.*, 2021; Gottschlich *et al.*, 2023). To our knowledge, however, no previous study has examined the transition from a *no organized screening* policy to *HPV-based organized screening*. In such contexts, the initial increase in colposcopy referrals may be even higher than in countries where organized cytology screening was already established.

The increased program costs, compared with a cytology-based scenario, has also been documented elsewhere(Ronco *et al.*, 2012), although international cost-effectiveness analyses consistently demonstrate that HPV-based screening is more efficient in the long term in diverse settings, due to its higher sensitivity, lower frequency of testing, and improved prevention of advanced disease(Jansen *et al.*, 2021; Simms *et al.*, 2023; Harasani *et al.*, 2025). Our study differs, however, in that the baseline context was dominated by opportunistic testing. Opportunistic screening can lead to both overtesting in some groups and undertesting in others(Palencia *et al.*, 2010). Transitioning to a free, organized program thus has not only clinical and economic implications, but also important equity consequences by reducing variability in access(Audiger *et al.*, 2022)(Spadea *et al.*, 2010). Although the progressive decline in opportunistic cytology indicates an encouraging trend toward standardization and quality assurance within screening pathways, it remains a substantial component of the screening budget. Opportunistic testing, usually initiated by the woman herself or by her general practitioner, has been previously observed in regions with mature organized programs(Nieminen *et al.*, 1999; Bos *et al.*, 2002; Blanks *et al.*, 2007; Tranberg *et al.*, 2015). However, we observed that opportunistic tests still accounted for over half (52%) of total tests, and that 46% were performed at inappropriate intervals. Reducing this overlap requires targeted communication campaigns, integration between private and public services, and engagement of general practitioners and gynecologists to encourage adherence to organized pathways.

5.2 Interpretation

From a health economics standpoint, implementing organized HPV-based screening represents a shift from fragmented, demand-driven resource use to a coordinated, evidence-based model. The observed cost increase is justified, as it allows more equitable access to effective prevention, while reducing inappropriate testing. Nonetheless, ensuring long-term sustainability will require complementary measures such as stricter regulation of opportunistic screening, tariff policies favoring organized pathways, quality assurance, and ongoing monitoring of referral practices to avoid unnecessary colposcopies.

Scenario analyses suggest that integrating co-testing within organized screening leads to an increase in organized screening costs that could be balanced by savings in opportunistic screening. In addition, integrating co-testing within organized programs could potentially enhance patient retention in follow-up pathways. The budget impact of integrating co-testing withing organized programs was highly sensitive to local referral rates and HPV positivity patterns, emphasizing the importance of maintain strict microbiological and cytological quality assurance systems.

The temporary surge in colposcopy demand is a critical finding. Without adequate planning, this peak could strain diagnostic capacity and delay case management, potentially undermining both program efficiency and public confidence. The sensitivity analysis identified the main drivers of colposcopy volumes as participation rate, referral rate, and HPV positivity with normal cytology. These findings emphasize the importance of robust quality assurance systems, particularly for microbiological and cytological testing and colposcopy referral management, as also emphasized in European quality assurance guidelines(European Commission, 2015). Local HPV epidemiology, laboratory performance, and adherence to guidelines can substantially affect both volumes and costs, underscoring the need for continuous monitoring and adaptive governance as screening coverage expands.

5.3 Strengths and limitations

The strengths of the study include the integration of real-world administrative and screening program data, linkage between multiple databases, and flexible modeling framework that allows exploration of multiple scenarios and sensitivity analyses. Year-by-year projections of test volumes and costs, according to a pre-defined implementation plan, were designed to support adaptive governance and inform resource allocation throughout program roll-out. Calibration with empirical data confirmed that the model effectively captured key cost drivers,

making it transferable to other real-world settings preparing to adopt an HPV-based cervical cancer screening with cytologic triage.

Among the study limitations, the use of a retrospective observational design limits causal inference regarding changes in intervention mix after the program's implementation. The selected periods (2018-2019 *vs* 2022-2023) and age groups (25-28 and 47-64 years old) may not fully represent the screening behavior trends of the full target population before the implementation, and for the whole post-implementation projected period (2024-2033). The potential impact of HPV vaccination in reducing colposcopy referrals is likely underestimated, as data on catch-up(Canfell *et al.*, 2017) or single dose schedule vaccinations(Kamani *et al.*, 2023) were unavailable, and we did not take herd immunity(Drolet *et al.*, 2019), including that due to male vaccination, into account. Ideally, data for all screening parameters would derive from the Italian setting, but some had to be derived from those from England, where HPV positivity rates appeared to be similar(Pesola *et al.*, 2021). However, the English pilot used different assays and the local epidemiology differed, leading to possibly biased results. Furthermore, estimates of inappropriate testing rely on the assumption that all the observed tests were first-level tests, although individual screening histories and results were not accessible. By contrast, as already pointed out, all tests performed in the private sector were unknown. Overall, the estimate of inappropriate testing is likely subject to underestimation. We excluded broader outcomes such as quality-adjusted life years or cancer incidence reduction, which would require cost-effectiveness analyses rather than a BIA. The analysis focused on direct medical costs and excluded non-medical, programmatic and indirect costs in our BIA, adopting a conservative approach that exclude the positive benefits on non-medical and indirect costs associated to HPV-based screening. The impact of HPV-based organized cervical cancer screening on non-medical and indirect costs, compared with cytology alone, has been previously described in the literature(Ronco et al., 2012;). Specifically, direct non-medical costs related to patient transportation are nearly halved with HPV-based screening due to the longer screening intervals(Diaz *et al.*, 2018). Indirect costs are moderately reduced with HPV-based screening compared to opportunistic cytology, decreasing progressively as coverage increases(Diaz *et al.*, 2018). This is because productivity loss costs are correlated with morbidity and mortality: the higher the screening coverage, the lower the number of incident cases of cervical cancer. Conversely, programmatic costs increase with greater coverage(Diaz et al., 2018) although they remain significantly lower for HPV-based compared with cytology-based organized screening(Ronco *et al.*, 2012). Programmatic costs are highly context-dependent. In Lombardy, the costs associated with the Screening Unit's staff, telephone

contracts, communications campaigns, and screening software implementation depend on the AHPs, and most cost increases already occurred during the pilot phase. Conversely, programmatic expenditure related to screening clinical staff, medical devices, and consumable kits for first- and second-level tests are largely managed at the CC level, outside the AHP's perspective. Therefore, caution should be exercised when extrapolating our findings to other healthcare systems. Despite these limitations, the study provides robust, policy-relevant evidence to guide regional decision-making.

5.4 Future perspectives

Since the introduction of HPV-based cervical cancer screening, research has focused on refining screening protocols and triage strategies to address both the colposcopy overload and the reduced disease prevalence in vaccinated cohorts, while maintaining a high screening performance. Emerging innovations that will be likely integrated soon by national and regional guidelines include a precision approach based on high risk HPV extended genotyping and p16/Ki-67 dual staining triage(Benevolo *et al.*, 2024), lengthened intervals for vaccinated women(Choi *et al.*, 2023), and extending primary HPV testing to 25-29 age group(European Commission, 2025). These developments aim to achieve a more risk-stratified, cost-effective, and sustainable screening system.

Looking forward, our BIM can be adapted to include these upcoming innovations, supporting policymakers in planning future transitions, optimizing resource allocation, and maintain equitable, evidence-based cervical cancer prevention.

6 CONCLUSIONS

The implementation of an organized HPV-based cervical cancer screening program in the province of Milan substantially increased screening coverage, shifted testing practices from primary cytology to primary HPV DNA testing, and improved equity of access -albeit with higher but sustainable expenditures. The program also generated an initial peak in colposcopy referrals, which is expected to decline as the prevalence of detectable lesions decreases.

From a policy perspective, these results emphasize the importance of careful planning during transitional phases, with particular attention to managing temporary increases in colposcopy demand and ensuring adequate laboratory and human resources. The findings also support continued investment in organized HPV-based screening, coupled with measures to regulate opportunistic testing, strengthen quality assurance, and enhance communication and data integration across health services.

Compared with international experience, the case of Milan metropolitan area illustrates the specific challenges of transitioning from opportunistic to organized models, but also the potential for rapid improvement in population coverage and access.

Overall, the findings underline that HPV-based screening represents a valuable and sustainable public health innovation. Ensuring high participation, careful cost management, and integration with vaccination and follow-up policies will be essential to maximize its long-term benefits for women's health.

7 BIBLIOGRAPHY

Accetta, G. *et al.* (2010) 'Is human papillomavirus screening preferable to current policies in vaccinated and unvaccinated women? A cost-effectiveness analysis', *Journal of Medical Screening*, 17(4), pp. 181–189. doi:10.1258/jms.2010.010019.

Amézquita, M. *et al.* (2022) 'Budget impact analysis of primary screening with the HPV test and genotyping against conventional cytology in Colombia', *Biomedica*, 42(2), pp. 290–301. doi:10.7705/biomedica.6016.

Andermann, A. *et al.* (2008) 'Revisiting Wilson and Jungner in the genomic age: A review of screening criteria over the past 40 years', *Bulletin of the World Health Organization*, pp. 317–319. doi:10.2471/BLT.07.050112.

Audiger, C. *et al.* (2022) 'Social Inequalities in Participation in Cervical Cancer Screening in a Metropolitan Area Implementing a Pilot Organised Screening Programme (Paris Region, France).', *International journal of public health*, 67, p. 1604562. doi:10.3389/ijph.2022.1604562.

Bechini, A. *et al.* (2024) 'Human Papilloma Virus Vaccination and Cervical Screening in the Italian Regions: An Overview of the Current State of the Art', *Vaccines*, 12(5). doi:10.3390/vaccines12050504.

Benevolo, M. *et al.* (2024) 'Comparison of HPV-positive triage strategies combining extended genotyping with cytology or p16/ki67 dual staining in the Italian NTCC2 study.', *EBioMedicine*, 104, p. 105149. doi:10.1016/j.ebiom.2024.105149.

Berkhof, J. *et al.* (2010) 'The health and economic effects of HPV DNA screening in the Netherlands', *International Journal of Cancer*, 127(9), pp. 2147–2158. doi:10.1002/ijc.25211.

Blanks, R. *et al.* (2007) 'An examination of the role of opportunistic smear taking in the NHS cervical screening programme using data from the CSEU cervical screening cohort study', *BJOG: An International Journal of Obstetrics & Gynaecology*, 114(11), pp. 1408–1413. doi:10.1111/j.1471-0528.2007.01467.x.

Bos, A.B. *et al.* (2002) 'Women who participate in spontaneous screening are not at higher risk for cervical cancer than women who attend programme screening', *European Journal of Cancer*, 38(6), pp. 827–831. doi:10.1016/S0959-8049(02)00026-6.

Bray, F. *et al.* (2024) 'Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries', *CA: A Cancer Journal for Clinicians*, 74(3), pp. 229–263. doi:10.3322/caac.21834.

Canfell, K. *et al.* (2017) 'Cervical screening with primary HPV testing or cytology in a population of women in which those aged 33 years or younger had previously been offered HPV vaccination: Results of the Compass pilot randomised trial.', *PLoS medicine*, 14(9), p. e1002388. doi:10.1371/journal.pmed.1002388.

Cappelli, M.G. *et al.* (2018) 'Cervical cancer prevention: An Italian scenario between organised screening and human papillomaviruses vaccination', *European Journal of Cancer Care*, 27(5). doi:10.1111/ecc.12905.

Choi, H.C.W. *et al.* (2023) 'Maximizing the cost-effectiveness of cervical screening in the context of routine HPV vaccination by optimizing screening strategies with respect to vaccine uptake: a modeling analysis', *BMC Medicine*, 21(1). doi:10.1186/s12916-023-02748-3.

Chugh, Y., De Francesco, M. and Prinja, S. (2021) 'Systematic Literature Review of Guidelines on Budget Impact Analysis for Health Technology Assessment', *Applied Health Economics and Health Policy*. Adis, pp. 825–838. doi:10.1007/s40258-021-00652-6.

Coldman, A.J. *et al.* (2015) 'Projected Impact of HPV and LBC Primary Testing on Rates of Referral for Colposcopy in a Canadian Cervical Cancer Screening Program', *Journal of Obstetrics and Gynaecology Canada*, 37(5), pp. 412–420. doi:10.1016/S1701-2163(15)30255-3.

Crosbie, E.J. *et al.* (2013) 'Human papillomavirus and cervical cancer', *The Lancet*. Elsevier B.V., pp. 889–899. doi:10.1016/S0140-6736(13)60022-7.

Deandrea, S. and Schivardi, M.R. (2020) *Gli screening oncologici in Lombardia. Report dei dati di attività 2018*. Milan. Available at: https://www.regione.lombardia.it (Accessed: 19 July 2025).

Diaz, M. *et al.* (2018) 'Moving towards an organized cervical cancer screening: costs and impact', *European journal of public health*, 28(6), pp. 1132–1138. doi:10.1093/eurpub/cky061.

Dreyer, G., Maske, C. and Stander, M. (2019) 'Clinical evaluation and budget impact analysis of cervical cancer screening using cobas 4800 HPV screening technology in the public sector of South Africa', *PLoS ONE*, 14(9). doi:10.1371/journal.pone.0221495.

Drolet, M. *et al.* (2019) 'Population-level impact and herd effects following the introduction of human papillomavirus vaccination programmes: updated systematic review and meta-analysis', *The Lancet*, 394(10197), pp. 497–509. doi:10.1016/S0140-6736(19)30298-3.

Eddy, D.M. *et al.* (2012) 'Model transparency and validation: A report of the ISPOR-SMDM modeling good research practices task force-7', *Medical Decision Making*, 32(5), pp. 733–743. doi:10.1177/0272989X12454579.

European Commission (2015) *European guidelines for quality assurance in cervical cancer screening Second edition-Supplements*. Luxembourg. doi:10.2875/93363.
European Commission (2025) *European guidelines on cervical cancer screening and diagnosis*. Available at: https://cancer-screening-and-care.jrc.ec.europa.eu/en/ec-cvc/european-cervical-cancer-guidelines (Accessed: 5 October 2025).
Garay, O.U. *et al.* (2021) 'Cost-Effectiveness and Budget Impact Analysis of Primary Screening With Human Papillomavirus Test With Genotyping in Argentina', *Value in Health Regional Issues*, 26, pp. 160–168. doi:10.1016/j.vhri.2021.07.004.
Giorgi Rossi, P. *et al.* (2017) 'Cervical cancer screening in women vaccinated against human papillomavirus infection: Recommendations from a consensus conference', *Preventive Medicine*, 98, pp. 21–30. doi:10.1016/j.ypmed.2016.11.020.
Goldhaber-Fiebert, J.D. *et al.* (2008) 'Cost-Effectiveness of Cervical Cancer Screening With Human Papillomavirus DNA Testing and HPV-16,18 Vaccination', *JNCI Journal of the National Cancer Institute*, 100(5), pp. 308–320. doi:10.1093/jnci/djn019.
Gori, S. *et al.* (2021) 'Clinical relevance of partial HPV16/18 genotyping in stratifying HPV-positive women attending routine cervical cancer screening: a population-based cohort study', *BJOG: An International Journal of Obstetrics & Gynaecology*, 128(8), pp. 1353–1362. doi:10.1111/1471-0528.16631.
Gottschlich, A. *et al.* (2023) 'Colposcopy referral rates post-introduction of primary screening with human papillomavirus testing: evidence from a large British Columbia cohort study.', *Lancet regional health. Americas*, 26, p. 100598. doi:10.1016/j.lana.2023.100598.
Hafidz, F. *et al.* (2024) 'Economic Evaluation of Cervical Cancer Screening by HPV DNA, VIA, and Pap smear Methods in Indonesia', *Asian Pacific Journal of Cancer Prevention*, 25(9), pp. 3015–3022. doi:10.31557/APJCP.2024.25.9.3015.
Harasani, K. *et al.* (2025) 'Systematic review of cost-effectiveness studies on cervical cancer screening across Europe', *European Journal of Surgical Oncology*, 51(4). doi:10.1016/j.ejso.2024.108742.
HPV Information Centre, I. (2023) *Human Papillomavirus and Related Diseases, Summary Report: Italy*. Barcelona. Available at: www.hpvcentre.net.
Hung, A. *et al.* (2019) *Validating a Budget Impact Model Using Payer Insight and Claims Data: A Framework and Case Study*, *JMCP Journal of Managed Care & Specialty Pharmacy*. Available at: www.jmcp.org.
Italian Association of Medical Oncology (2019) *I numeri del cancro in Italia: 2019*. Brescia.
Italian Association of Medical Oncology (2020) *I numeri del cancro in Italia: 2020*. Brescia.

Italian Group on Cervical Cancer Screening (2019) *Survey 2019 - Estensione e adesione*. Available at: https://gisci.it/index.php/tutti-documenti/survey/136-survey-2019 (Accessed: 24 August 2025).
Italian Institute of Statistics (2022) *Istat demo - demografia in cifre*. Available at: https://demo.istat.it/ (Accessed: 20 July 2025).
Italian Institute of Statistics (2023) *Istat demo - demografia in cifre*. Available at: https://demo.istat.it/app (Accessed: 14 January 2024).
Italian Ministry of Health (2017) *D.P.C.M 12 gennaio 2017 Definizione e aggiornamento dei livelli essenziali di assistenza*. Rome, Italy.
Italian Ministry of Health (2020) *Piano Nazionale della Prevenzione 2020-2025*. Rome.
Italian Ministry of Health (2023) *Piano Nazionale di Prevenzione Vaccinale (PNPV) 2023-2025*. Rome.
Italian Ministry oh Health (2025) *HPV vaccine coverage to december 31, 2023*. Rome. Available at: https://www.salute.gov.it/imgs/C_17_bancheDati_39_0_2_file.pdf (Accessed: 16 July 2025).
Italian National Screening Observatory (2022) *Rapporto sul 2021*. Available at: https://www.osservatorionazionalescreening.it/content/rapporto (Accessed: 7 October 2025).
Italian Republic (1993) *Legge 24 Dicembre 1993, n. 537: Interventi correttivi di finanza pubblica*. Rome.
Italian Republic (2000) *Legge 23 Dicembre 2000, n 388: Disposizioni per la formazione del bilancio annual e pluriennale dello Stato (Legge finanziaria 2001)*. Rome: capo XIV, art. 85, comma 4.
Jahn, B. *et al.* (2019) 'Budget Impact Analysis of Cancer Screening: A Methodological Review', *Applied Health Economics and Health Policy*. Springer International Publishing, pp. 493–511. doi:10.1007/s40258-019-00475-6.
Jansen, E. *et al.* (2021) 'Cost-effectiveness of HPV-based cervical screening based on first year results in the Netherlands: a modelling study.', *BJOG : an international journal of obstetrics and gynaecology*, 128(3), pp. 573–582. doi:10.1111/1471-0528.16400.
Jit, M. *et al.* (2014) 'Cost-effectiveness of female human papillomavirus vaccination in 179 countries: A PRIME modelling study', *The Lancet Global Health*, 2(7), pp. e406–e414. doi:10.1016/S2214-109X(14)70237-2.
Kamani, M.O. *et al.* (2023) 'ESGO Prevention Committee opinion: Is a single dose of HPV vaccine good enough?', *International Journal of Gynecological Cancer*, 33(4), pp. 462–464. doi:10.1136/ijgc-2023-004295.

Kositamongkol, C. *et al.* (2023) 'Cost-utility and budget impact analyses of cervical cancer screening using self-collected samples for HPV DNA testing in Thailand', *BMC Public Health*, 23(1). doi:10.1186/s12889-023-17358-0.

Lew, J. Bin *et al.* (2016) 'Effectiveness modelling and economic evaluation of primary HPV screening for cervical cancer prevention in New Zealand', *PLoS ONE*, 11(5). doi:10.1371/journal.pone.0151619.

Li, Z. *et al.* (2025) 'Global landscape of cervical cancer incidence and mortality in 2022 and predictions to 2030: The urgent need to address inequalities in cervical cancer', *International Journal of Cancer*, 157(2), pp. 288–297. doi:10.1002/ijc.35369.

Lynge, E. *et al.* (2012) 'Determinants of successful implementation of population-based cancer screening programmes', *European Journal of Cancer*, 48(5), pp. 743–748. doi:10.1016/j.ejca.2011.06.051.

Machalek, D.A. *et al.* (2019) 'Routine cervical screening by primary HPV testing: early findings in the renewed National Cervical Screening Program', *Medical Journal of Australia*, 211(3), pp. 113–119. doi:10.5694/mja2.50223.

Martello, G. *et al.* (2023) 'Acceptability of deferring the start of cervical cancer screening to age 30 for women vaccinated against human papillomavirus', *Preventive Medicine Reports*, 36. doi:10.1016/j.pmedr.2023.102438.

Masocco, M. and Gruppo Tecnico Nazionale Passi e Passi d'Argento (2021) *PASSI e PASSI d'Argento e la pandemia COVID-19*.

Mauskopf, J. (1998) 'Prevalence-Based Economic Evaluation', *Value in Health*, 1(4), pp. 251–259. doi:10.1046/j.1524-4733.1998.140251.x.

Mauskopf, J.A. *et al.* (2007) 'Principles of good practice for budget impact analysis: Report of the ISPOR Task Force on Good Research Practices - Budget Impact Analysis', *Value in Health*, 10(5), pp. 336–347. doi:10.1111/j.1524-4733.2007.00187.x.

Mezei, A.K. *et al.* (2017) 'Cost-effectiveness of cervical cancer screening methods in low- and middle-income countries: A systematic review', *International Journal of Cancer*. Wiley-Liss Inc., pp. 437–446. doi:10.1002/ijc.30695.

Moriña, D., De Sanjosé, S. and DIaz, M. (2017) 'Impact of model calibration on cost-effectiveness analysis of cervical cancer prevention', *Scientific Reports*, 7(1). doi:10.1038/s41598-017-17215-2.

Naber, S.K. *et al.* (2016) 'Cervical Cancer Screening in Partly HPV Vaccinated Cohorts – A Cost-Effectiveness Analysis', *PLOS ONE*, 11(1), p. e0145548. doi:10.1371/journal.pone.0145548.

Network PASSI (2021) *Il programma di screening cervicale - l'evoluzione degli ultimi anni*, *Istituto Superiore di Sanità*. Available at: https://www.epicentro.iss.it/passi/infoPassi/archivio2021 (Accessed: 7 October 2025).

Nieminen, P. *et al.* (1999) 'Organised vs. spontaneous pap-smear screening for cervical cancer: A case-control study', *International Journal of Cancer*, 83(1), pp. 55–58. doi:10.1002/(SICI)1097-0215(19990924)83:1<55::AID-IJC11>3.0.CO;2-U.

Ogilvie, G.S. *et al.* (2018) 'Effect of Screening With Primary Cervical HPV Testing vs Cytology Testing on High-grade Cervical Intraepithelial Neoplasia at 48 Months', *JAMA*, 320(1), p. 43. doi:10.1001/jama.2018.7464.

Orlewska, E. and Gulácsi, L. (no date) *Budget-Impact Analyses A Critical Review of Published Studies*.

Palencia, L. *et al.* (2010) 'Socio-economic inequalities in breast and cervical cancer screening practices in Europe: influence of the type of screening program', *International Journal of Epidemiology*, 39(3), pp. 757–765. doi:10.1093/ije/dyq003.

Parra, U. *et al.* (2018) 'Clinical and Budget Impact of Primary HPV Genotyping for Cervical Cancer Screening in Peru', *SOJ Gynecology , Obstetrics & Women's Health*, 4(1), pp. 1–8. doi:10.15226/2381-2915/4/1/00133.

Pedersen, K. *et al.* (2018) 'Adapting cervical cancer screening for women vaccinated against human papillomavirus infections: The value of stratifying guidelines', *European Journal of Cancer*, 91, pp. 68–75. doi:10.1016/j.ejca.2017.12.018.

Pesola, F. *et al.* (2021) 'Introducing human papillomavirus (HPV) primary testing in the age of HPV vaccination: projected impact on colposcopy services in Wales', *BJOG: An International Journal of Obstetrics and Gynaecology*, 128(7), pp. 1226–1235. doi:10.1111/1471-0528.16610.

Petry, K.U. *et al.* (2017) 'A model to evaluate the costs and clinical effectiveness of human papilloma virus screening compared with annual papanicolaou cytology in Germany', *European Journal of Obstetrics and Gynecology and Reproductive Biology*, 212, pp. 132–139. doi:10.1016/j.ejogrb.2017.03.029.

Pista, A. *et al.* (2019) 'Budget impact analysis of cervical cancer screening in Portugal: Comparison of cytology and primary HPV screening strategies', *BMC Public Health*, 19(1). doi:10.1186/s12889-019-6536-4.

Regional Council of Lombardy (2015) *Regional law n. 23, august 11, 2015: Evoluzione del sistema sociosanitario lombardo: modifiche al Titolo I e al Titolo II della legge regionale 30 dicembre 2009, n. 33 (Testo unico delle leggi regionali in materia di sanità)*.

Regional Council of Lombardy (2017) *Regional law n. 7013, July 31, 2017: Aggiornamento ed estensione del programma di screening organizzato del tumore della cervice uterina*.
Regional Council of Lombardy (2021) *Regional law n. 22, december 14, 2021: Modifiche al Titolo I e al Titolo II della legge regionale 30 dicembre 2009, n. 33 (Testo Unico delle leggi regionali in materia di sanità)*. Available at: https://www.polis.lombardia.it/wps/wcm/connect/2e9dd0ca-14e4-437e-93ce-2418c892c9c4/Legge+Regionale+14+dicembre+2021+%2C+n.+22_SUP50_15-12-2021.pdf?MOD=AJPERES&CACHEID=ROOTWORKSPACE-2e9dd0ca-14e4-437e-93ce-2418c892c9c4-nVOFlWw (Accessed: 20 January 2024).
Regional Council of Lombardy (2023a) *Regional law n. 48, march 23, 2023: Prevenzione del tumore della cervice uterina: aggiornamento delle indicazioni regionali*. Milan.
Regional Council of Lombardy (2023b) *Regional law n. 1239, october 30, 2023: Approvazione del nomenclatore regionale dell'assistenza specialistica ambulatoriale ai sensi del DPCM 12 gennaio 2017 'Definizione e aggiornamento dei Livelli Essenziali di Assistenza'*.
Regional Council of Lombardy (2024) 'Regional Law n. 3630, december 16, 2024: Approvazione del nomenclatore tariffario regionale dell'assistenza specialistica ambulatoriale e protesica ai sensi dello schema di decreto di cui all'intesa Stato Regioni del 14 novembre 2024'.
Regional Council of Lombardy (no date) *Manuale Rilevazione*, *Bollettino Ufficiale Serie Ordinaria*.
Rijkaart, D.C. *et al.* (2012) 'Human papillomavirus testing for the detection of high-grade cervical intraepithelial neoplasia and cancer: final results of the POBASCAM randomised controlled trial', *The Lancet Oncology*, 13(1), pp. 78–88. doi:10.1016/S1470-2045(11)70296-0.
Ronco, G. *et al.* (2012) 'Health technology assessment report: HPV DNA based primary screening for cervical cancer precursors', *Epidemiol Prev*, 36, pp. e1–e72. Available at: www.epiprev.it.
Ronco, G. *et al.* (2014) 'Efficacy of HPV-based screening for prevention of invasive cervical cancer: follow-up of four European randomised controlled trials', *The Lancet*, 383(9916), pp. 524–532. doi:10.1016/S0140-6736(13)62218-7.
Sefuthi, T. and Nkonki, L. (2022) 'A systematic review of economic evaluations of cervical cancer screening methods', *Systematic Reviews*, 11(1). doi:10.1186/s13643-022-02017-z.

Serraino, D. *et al.* (2015) ‘Changes in cervical cancer incidence following the introduction of organized screening in Italy’, *Preventive Medicine*, 75, pp. 56–63. doi:10.1016/j.ypmed.2015.01.034.

Shen, J. *et al.* (2018) ‘Cost of HPV screening at community health campaigns (CHCs) and health clinics in rural Kenya’, *BMC Health Services Research*, 18(1). doi:10.1186/s12913-018-3195-6.

Shi, J.F. *et al.* (2012) ‘Estimation of the costs of cervical cancer screening, diagnosis and treatment in rural Shanxi Province, China: A micro-costing study’, *BMC Health Services Research*, 12(1). doi:10.1186/1472-6963-12-123.

Simms, K.T. *et al.* (2023) ‘Benefits, harms and cost-effectiveness of cervical screening, triage and treatment strategies for women in the general population’, *Nature Medicine*, 29(12), pp. 3050–3058. doi:10.1038/s41591-023-02600-4.

Skroumpelos, A. *et al.* (2015) ‘Budget Impact Analysis Of High-Risk Hpv Dna (Hrhpv) Test With 16/18 Genotyping As A Primary Screening Method For Cervical Cancer In Greece’, *Value in Health*, 18(7), p. A349. doi:10.1016/j.jval.2015.09.631.

Spadea, T. *et al.* (2010) ‘The impact of interventions to improve attendance in female cancer screening among lower socioeconomic groups: A review’, *Preventive Medicine*, pp. 159–164. doi:10.1016/j.ypmed.2010.01.007.

Sullivan, S.D. *et al.* (2014) ‘Budget impact analysis - Principles of good practice: Report of the ISPOR 2012 budget impact analysis good practice II task force’, *Value in Health*, 17(1), pp. 5–14. doi:10.1016/j.jval.2013.08.2291.

Tessandri, L. *et al.* (2023) *Gli screening oncologici in Lombardia. Report dei dati di attività 2020-2021*. Available at: https://www.regione.lombardia.it/wps/wcm/connect/cfcfaed2-b4c7-4b2e-b5f6-a4433e870fba/Screening+report+2023+su+dati+2020-2021.pdf?MOD=AJPERES&CACHEID=ROOTWORKSPACE-cfcfaed2-b4c7-4b2e-b5f6-a4433e870fba-pnNZLud (Accessed: 19 July 2025).

The Lancet Infectious Diseases (2024) ‘A blueprint for elimination of cervical cancer’, *The Lancet Infectious Diseases*. Elsevier Ltd, p. 1. doi:10.1016/S1473-3099(23)00764-8.

Tjalma, W.A.A., Kim, E. and Vandeweyer, K. (2017) ‘The impact on women’s health and the cervical cancer screening budget of primary HPV screening with dual-stain cytology triage in Belgium’, *European Journal of Obstetrics and Gynecology and Reproductive Biology*, 212, pp. 171–181. doi:10.1016/j.ejogrb.2017.01.010.

Tranberg, M. *et al.* (2015) 'Impact of opportunistic testing in a systematic cervical cancer screening program: A nationwide registry study Health behavior, health promotion and society', *BMC Public Health*, 15(1). doi:10.1186/s12889-015-2039-0.

Trueman, P., Drummond, M. and Hutton, J. (2001) *Developing Guidance for Budget Impact Analysis*, *Pharmacoeconomics*.

Vemer, P. *et al.* (2016) 'AdViSHE: A Validation-Assessment Tool of Health-Economic Models for Decision Makers and Model Users', *PharmacoEconomics*, 34(4), pp. 349–361. doi:10.1007/s40273-015-0327-2.

Willis, M. *et al.* (2024) *Budget impact models for lung cancer interventions: A systematic literature review*, *JMCP.org*.

World Health Organisation (2020) *Global strategy to accelerate the elimination of cervical cancer as a public health problem*. World Health Organization. Available at: https://www.who.int/publications/i/item/9789240014107 (Accessed: 16 July 2025).

Wright, T. *et al.* (2016) 'The budget impact of cervical cancer screening using HPV primary screening', *Am J Manag Care*, 22(3), pp. e95–e105.

Yagudina, R.I. *et al.* (2017) 'Concept of Combining Cost-Effectiveness Analysis and Budget Impact Analysis in Health Care Decision Making', *Value in Health Regional Issues*, 13, pp. 61–66. doi:10.1016/j.vhri.2017.07.006.