MASTER THESIS

Designing a strategy to implement methylation tests in the Dutch cervical cancer prevention and diagnostics market

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Colophon

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ACKNOWLEDGEMENTS

Dear reader,

Thank you for taking the time to read my master thesis, which focuses on designing a strategy to implement methylation tests in the Dutch cervical cancer prevention and diagnostics market. This graduation project presents the final project of my MSc Strategic Product Design and concludes my time as a student.

During my studies at the faculty of Industrial Design Engineering, my interest in designing for healthcare gradually developed. I am grateful to have had the opportunity to do my graduation project in collaboration with Self-screen, which allowed me to dive deeper into designing for healthcare. At the start of the project, I had to familiarize myself with this specific healthcare context. This proved to be an interesting challenge from which I learned a lot throughout the process.

There are a few people I would like to thank for supporting me during this project. Firstly, I would like to thank my academic supervisors, Valeria and Brechtje, for all their valuable feedback, and support throughout the entire project. Valeria, thank you for your always honest feedback and your experience and suggestions, which consistently helped me improve my work.

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I would also like to thank everyone who contributed to this project and shared their time and knowledge with me. Especially the gynaecologists and other experts who made time in their busy schedules for the interviews and validation sessions. Additionally, I am grateful for the students and colleagues who supported me throughout the process.

Lastly, thanks to my friends and family for the support and advice during the entire project.

I am proud of the results of this project, and I hope you enjoy reading my thesis!

RIVA

EXECUTIVE SUMMARY

Cervical cancer is a cancer that is largely preventable, which is already addressed through screening programmes and diagnostic pathways. However, current programmes and pathways have their limitations. The current test is subjective, labour intensive, and contributes to unnecessary referrals and overtreatment, which creates an extra burden on patients and the healthcare system. These limitations create a need for an improved test which addresses these limitations. A solution is the methylation test, however, implementing a new test in the healthcare system is not simple.

This graduation project explored how the methylation tests could be positioned and implemented in the cervical cancer prevention and diagnostics market. This is explored in collaboration with Self-screen, that develops the methylation tests. Methylation tests are a promising alternative since they are objective, support better risk stratification, can reduce unnecessary referrals and treatments and are effective on self-samples.

Although the scientific evidence for methylation is strong, its adoption is still slow. The key challenge was how and where to position methylation in an already well-established healthcare system. Existing routines, limited awareness among gynaecologists, clinical guidelines, reimbursement and laboratory capacity all affect adoption.

This project followed a Double Diamond design approach and combined a literature review, stakeholder analysis, competitor analysis and interviews with different stakeholders. The findings from this research show that methylation tests are especially valuable in situations where the current test leaves uncertainty in the diagnostics of cervical cancer. Specifically in the situations where treatment should be avoided, such as younger women with a child wish and pregnant women. In addition, the research showed that the strategy should focus on increasing awareness, building trust and communicating the clinical added value of methylation tests to gynaecologists.

Based on these insights, a strategic and tactical roadmap for the gradual implementation of methylation tests is developed. Instead of implementation in the national screening programme, the proposed strategy focuses on implementation in cervical cancer diagnostics. This can be implemented more easily in the short-term and can help to create value earlier and build acceptance for later implementation in the screening programme. The designed roadmap is structured in three horizons. The first horizon focuses on creating awareness and identifying gynaecologist spokespersons. The second horizon focuses on sharing information with other gynaecologists through webinars and articles. The third horizon focuses on evaluating the use of methylation tests, improving the process and scaling the adoption by sharing results with more gynaecologists.

This strategy contributes to the implementation of methylation tests in the screening programme for cervical cancer, by first positioning methylation as a tool to support clinical decision-making in the diagnostics for cervical cancer. This strategy is effective since it supports clinical needs and decision-making processes, it fits within existing diagnostic workflows and enables the use of the test in practice. By first introducing the methylation tests in diagnostics, awareness and trust among gynaecologists can be built. This way, a strong foundation can be created for the long-term integration into the Dutch cervical cancer screening programme.

TERMINOLOGY

List of abbreviations

AMC	Amsterdams Medisch Centrum
ASCUS/LSIL	Atypical Squamous Cells of Undetermined Significance/ Low-Grade Squamous Intraepithelial Lesion
CE-IVD	Conformité Européenne – In Vitro Diagnostic
CIN	Cervical Intraepithelial Neoplasia
EMC	Erasmus Medisch Centrum
ESGO	European Society of Gynaecological Oncology
GMH	Gedragscodes Medische Hulpmiddelen
HPV	Human Papillomavirus
hrHPV	high-risk Human Papillomavirus
IVD UKCA	In Vitro Diagnostic UK Conformity Assessed
NTOG	Nederlands Tijdschrift voor Obstetrie en Gynaecologie (Dutch Journal of Obstetrics and Gynaecology)
NVOG	Nederlandse Vereniging voor Obstetrie en Gynaecologie (Dutch Society of Obstetrics and Gynecology)
Pap smear	Papanicolaou smear (a screening procedure used to detect precancerous or cancerous cells on the cervix)
VIA	Visual Inspection with Acetic Acid

List of definitions

Colposcopy
"A medical examination of the cervix (= the lower part of the womb that leads into the vagina) using a special instrument" (Cambridge Dictionary, 2026)

Cytology
"The study of the appearance of cells, usually with the aid of a microscope, to diagnose diseases" (EBSCO Research, n.d.)

Diagnostics
"Identifying a particular illness using a combination of signs and symptoms" (Cambridge Dictionary, 2026)

Methylation
"A chemical reaction in the body in which a small molecule called a methyl group gets added to DNA, proteins, or other molecules. Changes in the methylation patterns of genes or proteins can affect a person's risk of developing a disease, such as cancer" (NCI Dictionary of Cancer Terms, n.d.)

Risk stratification
"The ability of a test or model to separate those at high absolute risk of disease from those at low absolute risk" (Katki, 2019)

Screening
"Identify people in an apparently healthy population who are at higher risk of a health problem or a condition, so that an early treatment or intervention can be offered and thereby reduce the incidence and/or mortality of the health problem or condition within the population" (WHO, 2020)

Triage test
"Triage is a process by which patients are assessed, classified, and sorted based on their presenting complaint and clinical urgency, providing assurance for timely access to emergency care" (De Lemos Martíns, 2005)

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INTRODUCTION

1.1 PROJECT INFORMATION

1.1.1 Problem introduction

Cervical cancer is the fourth most common cancer in women, and in 99% of the cases, this is caused by an infection of the oncogenic types of the human papillomavirus (HPV). HPV is a sexually transmitted infection, which almost all sexually active people will get at some point. HPV is sexually transmittable and it can affect genital area, anal area, skin and throat. In most of the cases, HPV does not cause a problem, and the immune system clears the infection. However, it can also lead to abnormal cell changes, which eventually may develop into cervical cancer (WHO, 2025).

Cervical cancer is a cancer that can be prevented. There are several measures that can reduce the risk of an HPV infection or stop the HPV or precancerous lesions from progressing to cervical cancer. Firstly, vaccinations can protect women against the most common types of HPV that are associated with the development to cervical cancer. Secondly, there are screening programmes to detect women with HPV infections and/or precancerous lesions. The last important measure is the treatment of precancerous lesions to prevent progression to cervical cancer (WHO, 2025).

The second measure, screening for precancerous lesions, is currently done with different types of primary tests around the world. These primary tests are the HPV, cytology and the VIA test. In 2021 the guidelines from the WHO (2021) recommended the HPV test as the primary test for the screening. However, cytology is still used in a lot of countries as primary or triage test. Over the years, cytology has shown several disadvantages, and other tests have been researched to find better alternatives. One of those tests is a methylation test. A methylation test can detect the relevant lesions that need to be referred for colposcopy or treatment.

It can distinguish the difference between lesions with a high and low risk on short-term progression to cervical cancer. This is relevant since with the other tests there is a possibility of overtreatment, which can lead to cervical morbidity and preterm birth (Loopik et al., 2021). With methylation tests you only treat relevant lesions whereby health costs can be reduced. Additionally, there is an increase in false negatives with cytology, which means precancerous lesions can be missed (Kärrberg et al., 2026). Unfortunately, new medical tests are difficult to implement for multiple reasons such as scientific validity, clinical usefulness and regulatory hurdles (Ivanov, 2013).

This graduation project aims to address the challenge of the implementation of the methylation test in the prevention and diagnostics of cervical cancer.

1.1.2 Self-screen

This graduation project is in collaboration with Self-screen. They are one of the companies that have developed methylation tests. The company was founded in 2008 as an Amsterdam University spin-off and is an independent company since 2012. Self-screen is a Dutch molecular diagnostics company focused on HPV related cancer screening. They develop, produce and sell diagnostic tests, including HPV tests and methylation-based follow-up tests for cervical cancer. In addition, they also develop methylation tests for other anogenital cancer types.

Self-screen initiated this project because the translation from test development to the implementation in real practice is complex.

market introduction not only depends on the availability of the methylation test but also on the positioning in the existing market.

1.1.3 Problem statement

Despite the scientific evidence and strong publications supporting the use of methylation tests in cervical cancer screening and diagnostics, their adoption in practice remains slow. The validation of the test alone is not enough to ensure implementation. There is a challenge in positioning the test within an already established screening and diagnostic landscape. Barriers such as existing screening routines and limited awareness among gynaecologists contribute to this slow adoption. As a result, the value of methylation tests is not yet fully recognised and communicated to be embedded in the clinical practice.

1.1.4 Project goal

The goal of this project is to develop an implementation plan and strategic roadmap for the use of methylation testing in cervical cancer screening and diagnostics. This project will assess how methylation tests can be introduced into the market.

This will be achieved by identifying the important factors for implementation. Factors that, for example, currently limit awareness and acceptance of methylation tests. In addition, clinical, regulatory, organisational and economic requirements for the implementation will be identified.

1.1.5 Project approach

This project followed a Double Diamond approach, designed by the British Design Council (2004). The Double Diamond approach alternates between divergent and convergent thinking and consists of four phases: discover, define, develop and deliver, see figure 1.

In the first phase, discover, the focus was on exploring the context of methylation tests in cervical cancer prevention, screening and diagnostics. The aim was to look into the current situation and what and who can influence the implementation of methylation. Desk research, literature research, competitor analysis and stakeholder analysis were conducted in this phase. In addition, different stakeholders were interviewed.

In the define phase, the collected insights were analysed to define the main challenges and opportunities. All the findings were used to redefine the problem statement and to define the scope and to translate them into design criteria.

In the develop phase, different directions and ideas for implementation were explored and generated. The aim was to generate a wide variety of concepts for how methylation tests can be implemented. Different options were developed and discussed with different stakeholders.

In the deliver phase, the implementation strategy is evaluated in collaboration with different stakeholders and the strategy is refined.

Although the double diamond seems linear, multiple iterations took place throughout the process.

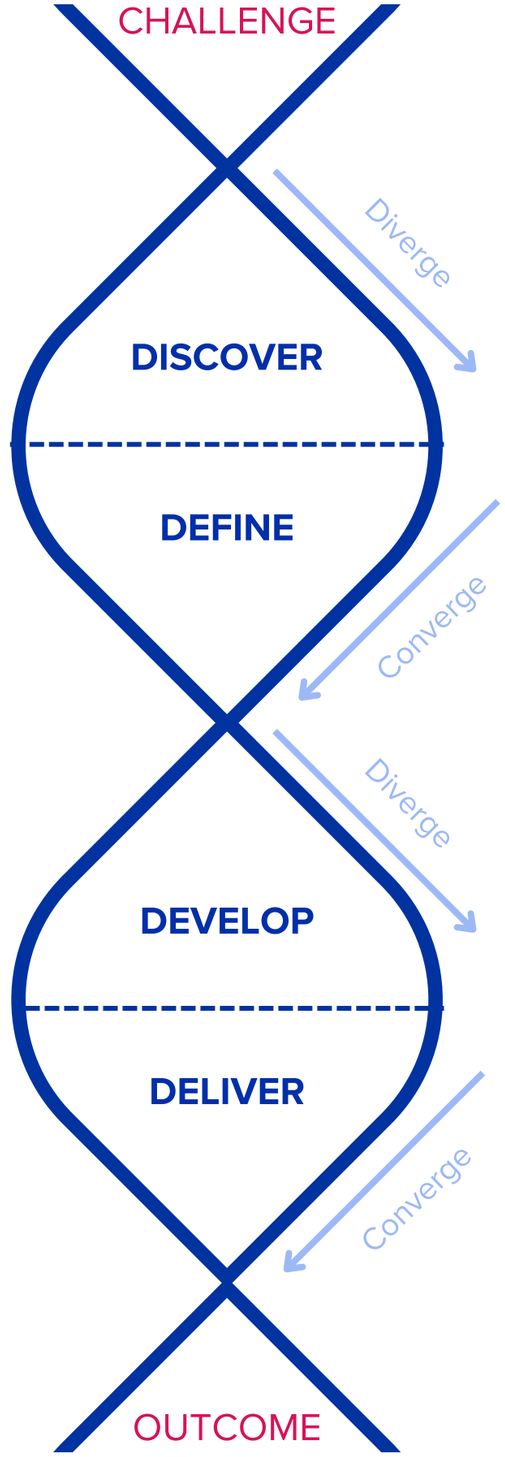


Figure 1: Double diamond approach

1.2 BACKGROUND INFORMATION

1.2.1 From HPV infection to cervical cancer

Cervical cancer is the fourth most common cancer worldwide. Yearly there are around 660 000 new cases, and 350 000 deaths from cervical cancer. Most of these incidents and deaths, 94%, are in low- and middle-income countries. In 99% of the cases, cervical cancer is caused by HPV (WHO, 2025).

How HPV develops to cervical cancer is shown in figure 2 (HPV Self Sampling, n.d.). After an HPV infection, most of the time, the infection clears, however it can also be persistent. A persistent infection can cause changes in cells and can progress to mild abnormalities, such as CIN 1, which often clear on their own. Or it can progress into more severe abnormalities, such as CIN 2 and CIN 3, also called high-grade lesions. Those have a higher risk of progressing to cervical cancer. These cells change slowly, over a time of 5 to 20 years. If high-grade lesions are untreated, these can progress to cervical cancer (HPV Self Sampling, n.d.).

The flowchart in figure 3, which is based on literature, shows that HPV is very common among sexually active women, but that in a lot of cases, it does not progress to cervical cancer. Most infections regress spontaneously and even if they do develop to CIN 1, they still have a high chance of regression. Even if the HPV does progress to CIN 2 or CIN 3, there is still a chance of spontaneous regression. Concluding, the flowchart shows that cervical cancer only develops after progression through several precancerous stages. Overall, this shows that although HPV infection is common, progression to cervical cancer is relatively rare (WHO, 2025).

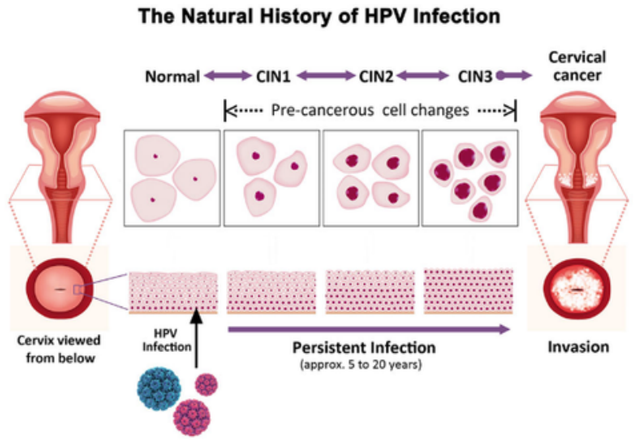


Figure 2: The natural history of HPV infection

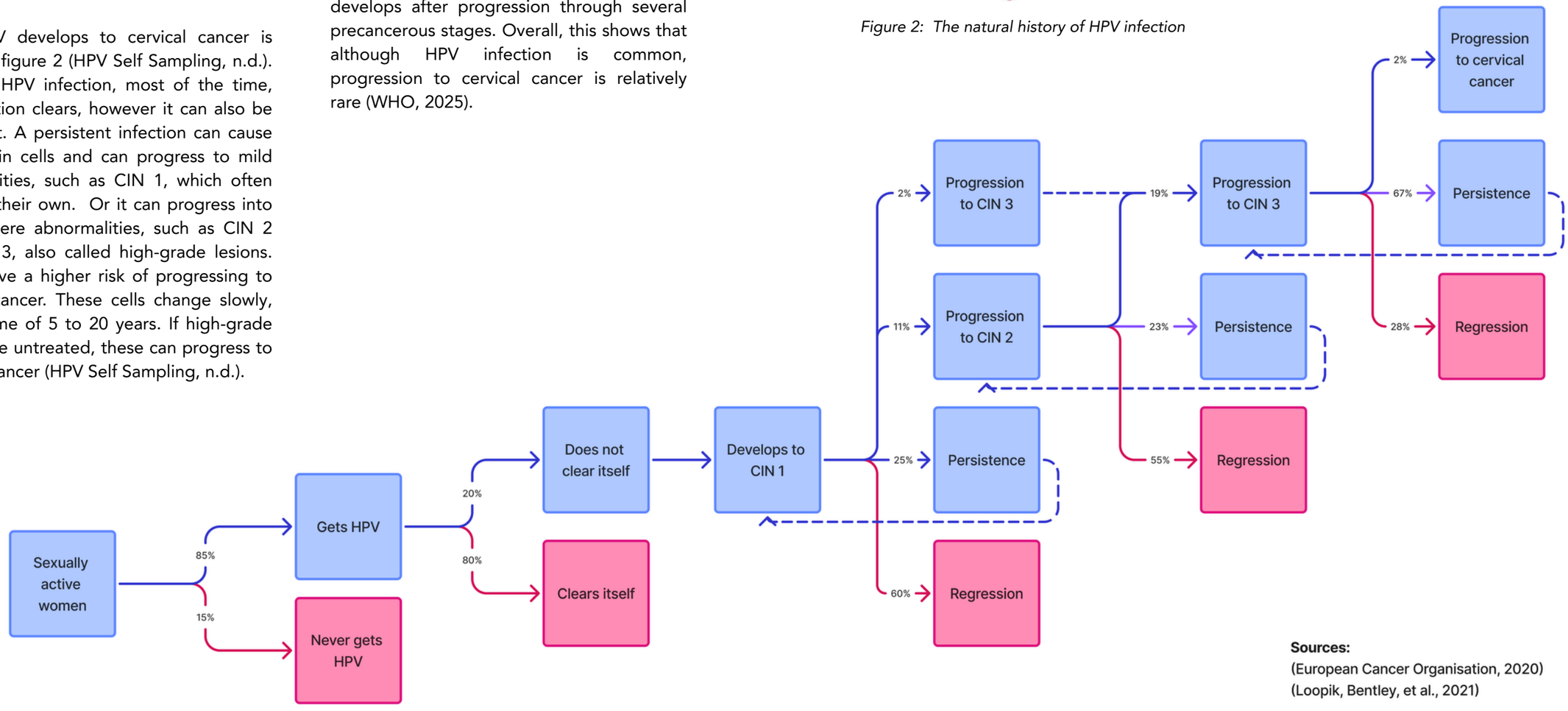


Figure 3: Flowchart progression and regression HPV to cervical cancer

1.2.2 Prevention of cervical cancer

Cervical cancer is a cancer that can be prevented. The WHO showed with the 90-70-90 plan and modelling estimates that they could prevent 62 million deaths by 2120. The rules are as follows (WHO, 2025):

- "90% of girls vaccinated with the HPV vaccine by age 15;
- 70% of women screened with a high-performance test by 35 years of age and again by 45 years of age; and
- 90% of women with cervical precancer or cancer receiving treatment."

The first step to prevent cervical cancer are vaccinations against HPV. However, vaccinations are only for certain HPV types and do not cover all types. Which means you can still get HPV, even when you are vaccinated. There are fourteen types of HPV that have been identified as hrHPV types for cervical cancer and among these different types, the risk of getting cervical cancer varies. There are two types of hrHPV, namely HPV16 and HPV18 that cause most of the cervical cancers. Namely, 50-60% of the cervical cancers are caused by HPV16 and 10-15% is caused by HPV18 (Cuzick et al., 2021).

There are three different types of vaccines, a bivalent, quadrivalent and a nonavelent vaccine. All three of the vaccines protect against HPV 16 and 18. The quadrivalent also protects against HPV 6 and 11 and the nonavelent vaccine also protects against five other hrHPV types (Duijster et al., 2024).

Another step in cervical cancer prevention is screening, there are different tests that can be used for this, such as cytology, HPV and VIA. It depends per country which test is used for the screening. With this screening, precancerous lesions can be detected and treated before it develops to cervical cancer (Banerjee et al., 2022).

The last step to prevent cervical cancer would be to treat the precancer and cancer. Treatment of precancerous lesions most of the times involves limited discomfort compared to other medical procedures. However, it is not preferred for pregnant women or women with a child wish (WHO, 2025).

Within this three-step prevention strategy, this report focuses specifically on the screening and diagnostics, since it researches the implementation of the methylation test. This test is used to detect progression from an HPV infection to cervical cancer, which is relevant in the step of the screening process.

1.2.3 Current screening process cervical cancer

To implement a new test into cervical cancer screening, it is important to understand the current screening and diagnostics process. Therefore, the screening programmes in the Netherlands and in other high-income countries are researched to assess if the test could be implemented in a similar way, or if different countries would require different implementation approaches.

The Netherlands

Since 2010 the HPV vaccination is part of the national vaccination programme in the Netherlands. However, there are multiple reasons why screening is still very important. Namely, not all women in the Netherlands have been vaccinated against HPV, especially older women, or younger women who did not participate in the HPV vaccinations, since the vaccination rate for women is only between 62-75% (RIVM, 2023). A second reason is that the development from an HPV infection to cervical cancer takes 10-15 years. As a result, older women who are not vaccinated may still develop cervical cancer in the coming years.

Lastly, HPV vaccinations do not protect against all types of HPV and the Netherlands use bivalent vaccinations, which covers less of the hrHPV types. They will switch to nonavalant vaccines from September 2026 (Rijksvaccinatieprogramma, n.d.).

Therefore, cervical cancer screening is still an important method for the detection and prevention of cervical cancer. Figure 4 (RIVM, n.d.) shows the ages at which women are invited to participate in the Dutch cervical cancer screening programme. Women receive an invitation from the Dutch national screening programme for cervical cancer. They receive an invitation at the ages of 30, 35, 40, 50, and 60.

In addition, women who test HPV-positive at the ages of 40, 50, or 60 receive an extra invitation five years later instead of after ten years. Women who are invited can choose if they want to participate. Those who decide to participate can do so either by using a self-sampling kit or by having a smear test performed at their general practice (RIVM, n.d.). To make it more accessible to join the programme, the women who get invited for the first time at the age of 30, automatically get a self-sampling kit sent to them. Women between 35 and 60 who do not respond to their invitation get a self-sampling kit sent to them after 12 weeks (Bevolkingsonderzoek Nederland, n.d.).

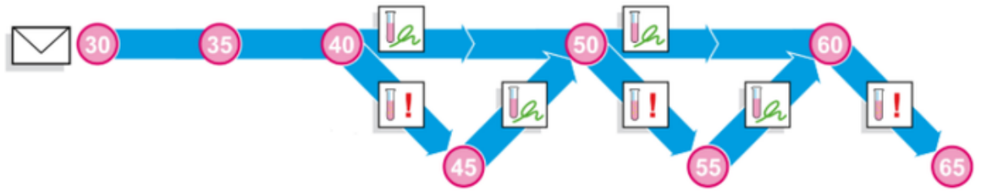
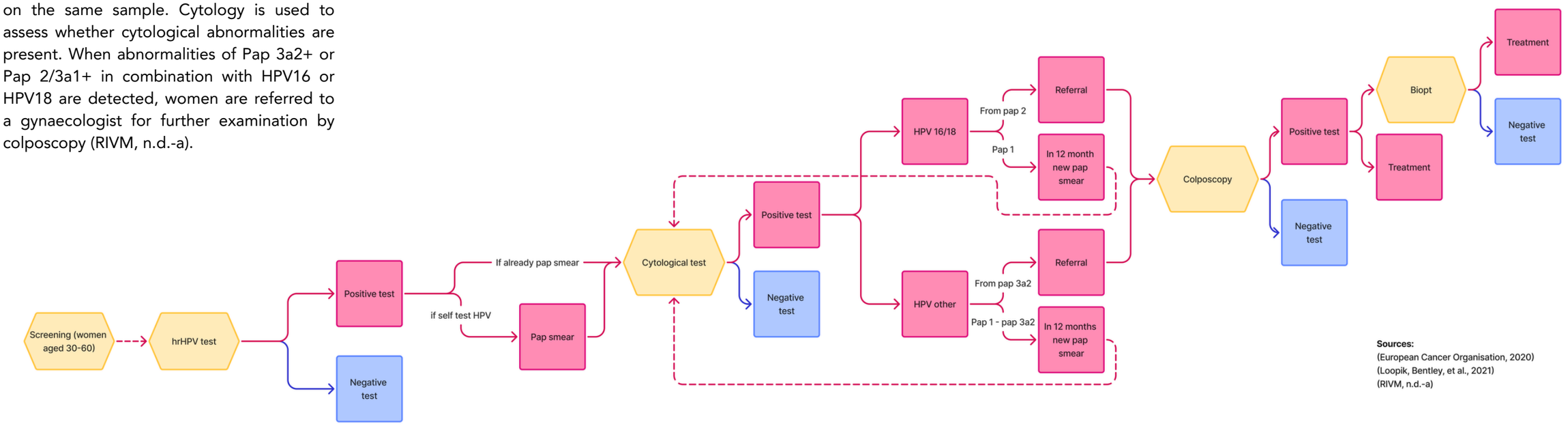


Figure 4: Invitation scheme for cervical cancer in the Netherlands (RIVM,nd)

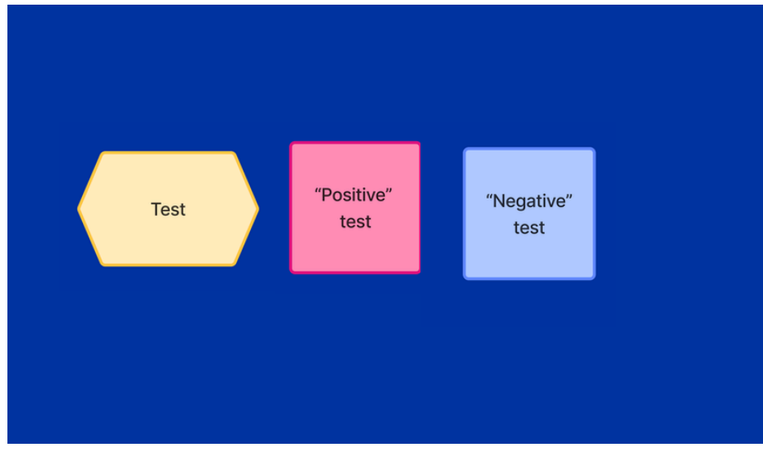
After an hrHPV-positive result, additional follow-up tests are performed to determine whether the infection has already progressed, as shown in figure 5. When a woman has used a self-sampling test and receives an HPV-positive result, she is advised to visit her general practitioner for a Pap smear. A cytology test is then performed. If a Pap smear was already taken initially, this cytology test can be performed on the same sample. Cytology is used to assess whether cytological abnormalities are present. When abnormalities of Pap 3a2+ or Pap 2/3a1+ in combination with HPV16 or HPV18 are detected, women are referred to a gynaecologist for further examination by colposcopy (RIVM, n.d.-a).

If the gynaecologist identifies abnormal cells during the colposcopy, a biopsy is also performed. During a biopsy, a small piece of tissue is removed for further examination. The results of this examination can show if cervical cancer is present, whether there is a precancerous stage that may require treatment, or whether no abnormalities are found (Stichting kanker.nl, 2024).



Sources:
(European Cancer Organisation, 2020)
(Loopik, Bentley, et al., 2021)
(RIVM, n.d.-a)

Figure 5: Flowchart of tests in cervical screening programme



Comparison cervical cancer screening in high-income countries

The number of women who are screened for cervical cancer is relatively the highest in high-income countries, such as, Sweden, Australia and the Netherlands, see figure 6 (Bruni et al., 2022).

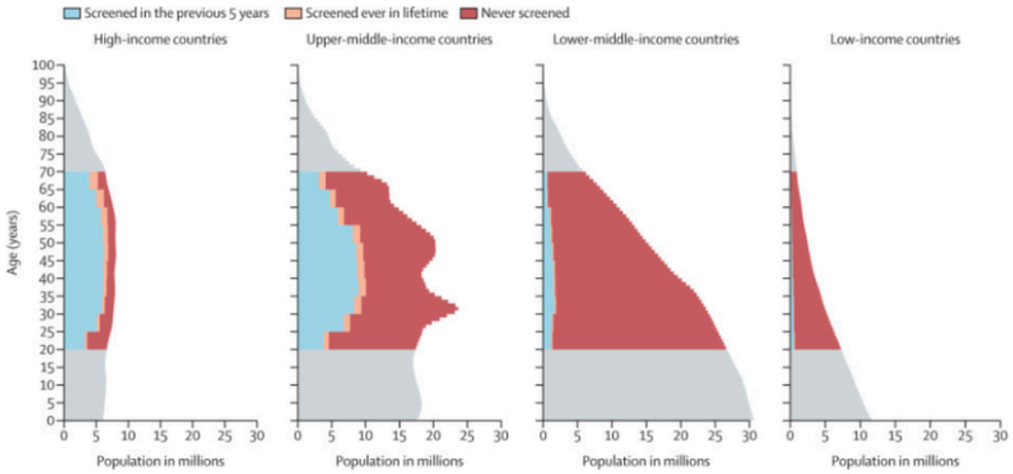


Figure 6: Female population pyramid by cervical cancer screening status and income level

This is because, across different high-income countries, most of them offer a screening programme. The kind of screening programme that is offered still differs between HPV, cytology an VIA, see figure 7 (Bruni et al., 2022).

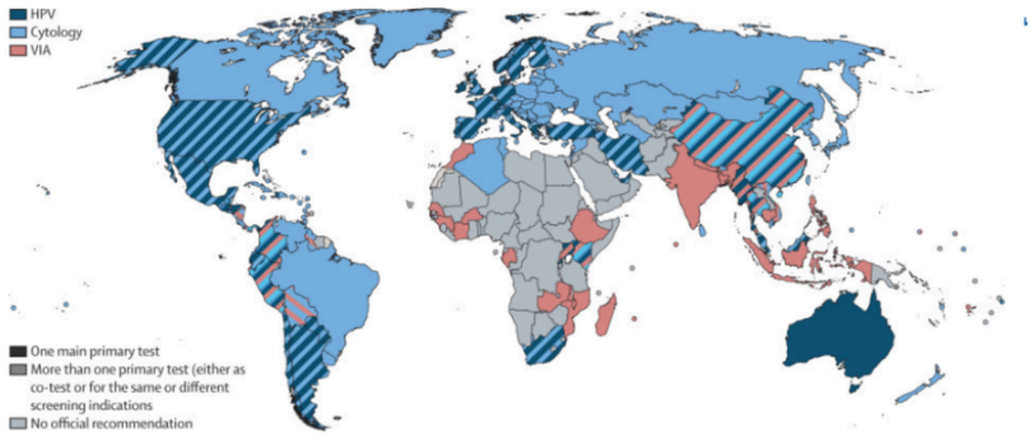


Figure 7: Screening programmes for cervical cancer worldwide

In most of the high-income countries, there is an organised screening programme. Table 1 below shows the different programmes in some high-income countries. Across high-income countries, cervical screening is mostly organised around HPV testing and/or cytology. Countries such as the Netherlands, the UK, Sweden and Australia have largely adopted HPV-based screening, and some have already integrated self-sampling as routine a option. In contrast, others still do not have an option for self-sampling or still rely on cytology-based testing. Self-sampling is becoming more established and multiple countries are researching the possibility to implement this.

Country	Program Type	Primary Strategy	Target Population (age)	Screening Interval	Most Recent Participation/ Coverage	Self-Sampling	Sources
Netherlands	Organized screening program (invitation based)	Primary HPV screening with triage	30–60	Standard at ages 30, 35, 40, 50 and 60	54.4%	Yes	(RIVM, n.d.-b) (RIVM, 2025) (RIVM, n.d.-c)
Belgium	Organized screening program (invitation based)	-Age 25–29: cytology -Age 30–64: HPV testing with cytology triage	25–64	-Age 25–29: every 3 years -Age 30–64: every 5 years	65.9%	Feasibility studies ongoing	(Bevolkingsonderzoek Baarmoederhalskanker, n.d.)
United Kingdom	Organized screening program (invitation based)	Primary HPV screening with triage	25–64	Every 3–5 years	68.8% (2023/24)	Feasibility studies ongoing	(Cervical Screening: Programme Overview, 2026) (England, 2024)
Sweden	Organized screening program (invitation based)	Primary HPV screening with triage	23–70	-Age 23-50: every 5 years -Age 51-70: every 7 years	82.9% (2024)	Yes	(Dillner et al., 2025)
Finland	Organized screening program (invitation based) (regional variation)	-Age 25-30: cytology -Age 30+: HPV with triage	30–65 (some regions 25–65)	Every 5 years	73.1% (2023)	Feasibility studies ongoing	(OECD & European Commission, 2025) (Finnish cancer registry, 2026)
Austria	Opportunistic screening system (no organized national programme)	Cytology	–	–	Self-reported coverage ~85%	–	(European Cancer Inequalities Registry, 2025) (MTRC, 2019)
Germany	Organized screening program (informed through health insurance)	-Age 20–34: cytology -Age ≥35: co-testing (HPV + cytology)	20–65	-Age 20–34: annually -Age ≥35: every 3 years	47%	Feasibility studies ongoing	(European Cancer Inequalities Registry et al., 2025) (Eurostat, 2025)
France	Organized screening program (invitation based)	-Age 25–29: cytology -Age 30–65: HPV testing with triage	25–65	-Age 25–29: every 3 years -Age 30–65: every 5 years	59.5% (2020–2022 coverage)	Feasibility studies ongoing	(ARS, n.d.)
Canada	Organized screening program (provincial/ territorial) (some invitation and some opportunistic)	Cytology with transition toward primary HPV screening	Typically 25–69 (varies by province)	Pap testing every 2–3 years; HPV screening every 5 years	69% (2024)	Implemented in British Columbia; expansion under evaluation	(CPAC, 2026) (CPAC, 2018)
Australia	Organized screening program (invitation based)	Primary HPV screening	25–74	Every 5 years	78% over 5.5 years (2020–June 2025)	Yes	(AIHW, 2025)
New Zealand	Organized screening program (invitation based)	Primary HPV screening with triage	25–69	Every 5 years	72.7% (2024)	Yes	(Cancer Society NZ, 2021)

Table 1: Screening programmes in different high-income countries

1.2.4 Current diagnostics cervical cancer

In addition to the organised screening there is also a diagnostics market for cervical cancer. The patient flow for the diagnostics market works differently. In diagnostics, patients with symptoms go to the doctor to get checked. The patient flow differs considerably because symptoms can be different. Patients might go to the doctor first and could get a referral to a gynaecologist. A cytology test will probably be done to determine the next steps. The aim is to determine whether cervical abnormalities are present, how severe they are, and if treatment or a follow-up is needed.

Compared to the screening, the diagnostics focus more on the individual situation of the patient and the judgement of the gynaecologist. This makes the diagnostics market also relevant for methylation tests, since it can provide additional information in cases where there is no clear decision-making. In these cases, methylation tests can help with decision-making.

1.2.5 What is methylation

Methylation is an epigenetic change in DNA where a methyl group is added to CpG sites (Cytosine–Guanine regions). When this happens in certain promoter regions, it can reduce the activity of tumour suppressor genes and contribute to the development of cervical cancer.

A methylation test measures how much hypermethylation is present in these promoter regions. Higher methylation levels are linked to more advanced disease grades and can therefore be used as a marker for disease progression. A methylation test provides a positive or negative result. Methylation can asses the risk on short-term progression to cervical cancer. Methylation can offer better risk stratification and support clinical decision-making. It can help to better identify which women are at increased risk and need treatment and to identify women with a lower risk, who can follow a wait-and-see policy. Figure 8 (Self-screen, 2025) shows how methylation tests can identify the difference between lesions with a different progression risk.

A methylation test can be used as a replacement of cytology or as an add-on to get better insights in the diagnostic situation. A study from Bonde et al. (2020) showed that methylation tests performed at least as well, if not even better compared to cytology for identifying which hrHPV-positive women should be referred for colposcopy.

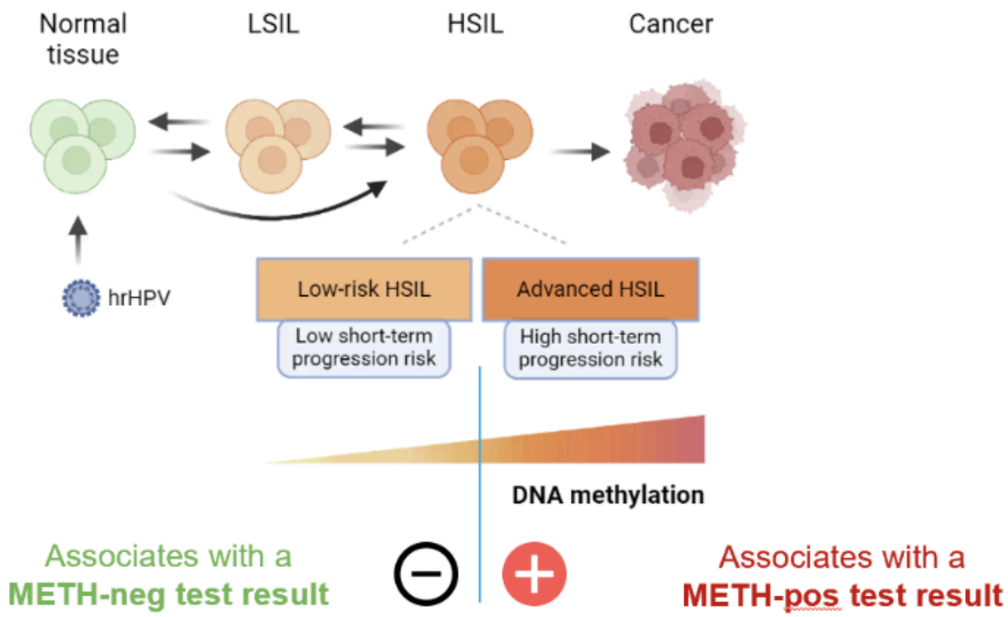


Figure 8: Results methylation test in HPV progression to high-grade lesions

The flowchart in figure 10 shows how the current process would be changed if a methylation test would replace the current cytology test. In this new pathway, the methylation test would be implemented as a triage test directly after a positive hrHPV test. A negative methylation test would support a wait and see trail with a follow-up. A positive methylation test would lead to a referral to a gynaecologist. This can simplify the decision-making and reduce the number of steps in the process, which is an advantage of using methylation.

A methylation test can also be used as an additional test to cytology in the current screening process. For example, when women prefer to avoid treatment, a methylation test can help assess the risk that the HPV infection will progress to cervical cancer. This is especially relevant for women who are pregnant or still wish to have children, since the treatment is preferably avoided because it can lead to complications during childbirth.

1.2.6 Conclusion

To understand how a new test can be implemented into cervical cancer screening and diagnostics, it is important to first understand the current screening process. The screening programmes in the Netherlands and other high-income countries were addressed to see if similar approaches could be implemented in different countries. Based on the background research, a methylation test would be easier to implement in countries where HPV testing is already used as the primary screening method, because an important part of the screening process is already in place. In those countries, only the triage test would need to be adapted. The potential benefits may be even greater where HPV self-sampling is already available, since methylation tests can also be applied to self-collected samples. Since this would mean that women who got a positive HPV result on a self-sample, do not have to come back for a Pap smear at the General Practitioner (GP).

For this research, the Netherlands was chosen as the main focus, for researching and developing a strong strategic plan. There are a few reasons for this choice, firstly, the Netherlands has already implemented HPV as a primary test, which is recommended for implementing methylation as a triage test, which makes the change smaller, and it can be easier to implement. In addition, the Netherlands already offers self-sampling, and methylation tests could provide added value in this context, because women would not need to visit the GP for an additional smear.

The Netherlands also evaluates its screening programme regularly and wants to provide the best screening and diagnostics. Lastly, the interviews that will be conducted for this research will be held with Dutch experts, so the best insights can be gathered about the Netherlands. However, because several other high-income countries have similar cervical screening and diagnostics systems, the findings could also be relevant for those countries.

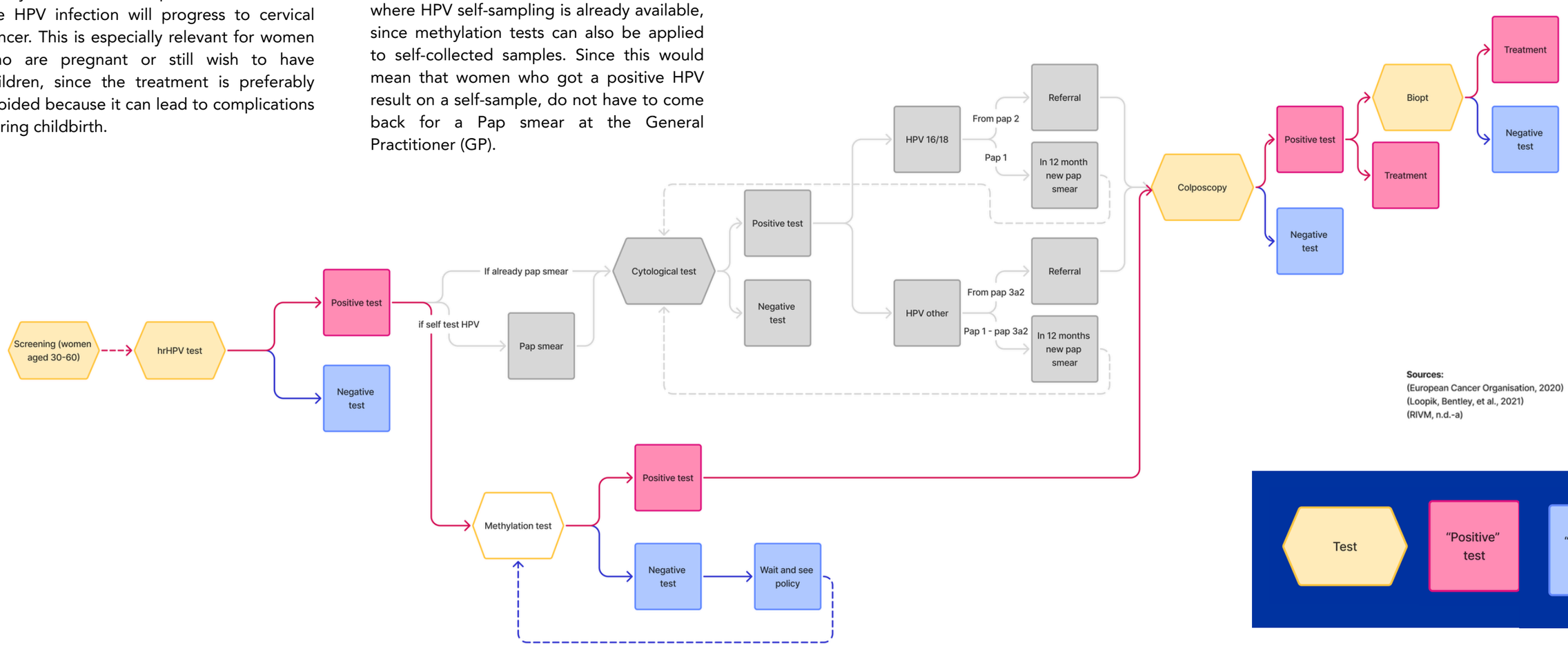


Figure 9: Flowchart when methylation would be used as triage test

02

LITERATURE REVIEW

2.1 LITERATURE REVIEW

2.1.1 Introduction

To understand why and how methylation tests could be implemented in the Dutch cervical cancer screening programme, a literature review is conducted. First, the limitations of the current triage test, cytology, are examined. Second, the advantages of methylation tests are researched to assess if it could improve the current screening process. Finally, there is investigated how the screening programme previously has been revised to understand how a new test can be implemented and what steps are required. Together, these topics provide the basis for analysing if and how methylation tests can be implemented in the Dutch cervical cancer screening programme.

To examine the disadvantages of cytology and the advantages of methylation, a literature review is conducted. Scientific literature was mainly collected through PubMed, using combinations of the terms "cervical cancer (screening)", "HPV", "methylation", "triage", "self-sampling", "implementation" and "Netherlands". In addition, relevant scientific articles provided by Self-screen were used for the research. For the information about how a test can be implemented in the current screening programme, desk research and document analysis were conducted. For this analysis, official policy documents, reports and guidelines were used.

2.1.2 Limitations of cytology as triage test

In the Netherlands, cytology is used as a triage test for women who test positive for hrHPV. Although cytology is good in detecting cervical abnormalities, it also has its limitations. One of the key issues is that with the current triage process, there are a lot of unnecessary referrals to gynaecologists. Since the implementation of the HPV-based screening programme in the Netherlands, the referral rates to gynaecologists for colposcopy have increased. This can lead to higher healthcare costs and more pressure on the colposcopy capacity (Aitken et al., 2019).

Many women who get referred for a colposcopy, do not have a clinically relevant cervical lesion. Research shows that this accounts for around 50% of women who get referred. This means there is overdiagnosis and over-referral and this could lead to overtreatment (Korfage et al., 2013). These unnecessary colposcopy referrals can also cause psychological distress and anxiety among women who participate in the screening programme (Korfage et al., 2013).
In addition, unnecessary treatment can lead to physical complications such as pain, bleeding, discharge and risks with pregnancy such as preterm birth (Arbyn et al., 2008). This affects the well-being of the patients and creates higher healthcare costs, for the patients or health insurers, which should be prevented (RIVM, 2025a).

Another limitation of the current triage with cytology is that follow-ups are needed. When women use a self-sampling kit for testing for HPV and they test positive, they need to get a Pap smear at the general practitioner for a cytology test. However, research about the Dutch screening programme showed that approximately 10-20% of women who were invited for a Pap smear did not show up (IKNL, 2021). This means that some cervical cancers might be missed and this creates a less effective screening programme.

Next to the clinical implications, there is also

an operational challenge concerning cytology. For cytological analysis, specialised personnel and constant quality control is needed. These are not available everywhere, and in addition, cytology is a subjective test. Which means that it can lead to inconsistency and wrong diagnostic outcomes. Also, high quality cytology can be expensive, so it is not always the most cost-effective triage method, especially in countries with a higher disease rate (Almonte et al., 2011).

Additionally, cytology as a triage test after an HPV positive test might miss relevant abnormalities. The incidence of cervical cancer after a negative cytology has increased over time, which suggests that the protective effect of cytology is declining. This shows that there is a need for improved or alternative triage methods (Kärrberg et al., 2026).

In summary, cytology as a triage test has several important limitations. These include unnecessary colposcopy referrals, overdiagnosis and overtreatment, and psychological and physical burden for the patients. In addition, there is loss to follow-up after self-sampling, the test is subjective, needs specialised personnel and there is a risk of missing relevant abnormalities. Together, these points show that there is a need to explore improved or alternative triage methods in the Dutch cervical cancer screening programme.

2.1.3 Advantages of methylation tests

Triage for cervical cancer could also be tested with other tests than cytology, such as methylation tests. These can address some of the limitations that cytology has. Methylation can detect the difference between the high-grade lesions with a higher risk for cervical cancer and the lower grade lesions with a lower risk. This test provides an objective result compared to the subjective result from cytology (Overmeer et al., 2010; Eijsink et al., 2011). This improves the reproducibility and variability between different labs.

Another advantage is that methylation tests can be automated. This can improve the laboratory scalability and efficiency, especially in population-based screening programmes (Stark et al., 2022). Automation can also lower the workload and can increase the consistency of the results of the tests. However, automated workflows are not yet available in labs, which could limit the current applicability.

In addition, the methylation test can be performed on a self-collected sample. This is mostly relevant for the countries that have implemented self-sampling as an option in the screening programme. In the Netherlands the participation in the cervical screening programme is still quite low (EMC, 2024). Since methylation tests can be applied directly onto self-samples, it could improve the participation since patients do not need to go for additional visits to a GP.

Also, methylation-based triage can reduce the number of unnecessary colposcopy referrals. Studies have shown that methylation tests could reduce the direct colposcopy rates by 60% (Dick et al., 2021). Methylation tests can identify women at higher risk for cervical cancer more accurately. This way it can lower the amount of unnecessary referrals, lower healthcare costs and minimize unnecessary medical procedures.

In summary, methylation-based triage offers multiple advantages compared to cytology. Such as giving objective results, the possibility of automation, the compatibility with self-samples and an improved risk stratification.

Altogether, this can contribute to a better and more efficient screening programme, where patients get less unnecessary referrals and overtreatment and where healthcare costs could be lowered.

2.1.4 Implementing a new test in the Dutch screening programme

To understand how a screening programme can be updated with a new test, it helps to look at how this process has gone before. For example, the cervical cancer screening programme was changed in 2017, from primary cytology to primary HPV testing. Implementing a new test involves multiple stages of different people and organisations for approval.

Foundational science

The science behind a new test creates the foundation for implementation. In the case of the HPV test it starts with the discovery by Harald zur Hausen, that HPV causes the development of cervical cancer (NCI, n.d.).
After this, laboratory tests that could detect hrHPV accurately and reliably were developed. Over the years different tests and methods were studied to make it suitable for testing and screening. After some time, there was enough evidence to show that HPV tests were better than cytology and VIA in detecting cervical cancer and precancer. Only after this the scientific foundation for HPV testing could be considered for screening programmes (IARC, n.d.). For this consideration other aspects such as technical and economic factors play a role and need to be researched.

Health council (gezondheidsraad)

The Netherlands was one of the first countries to implement HPV tests as primary test in the screening for cervical cancer. In 2011 the Health council sent an advisory letter to the Minister of Health, Welfare and Sports. This letter included the advice to switch to HPV as primary screening test (Gezondheidsraad, 2011).

POBASCAM trial

This Dutch trial was used to show that HPV tests could detect relevant lesions earlier compared to cytology. The study was published in 2011 and important as evidence for the shift to HPV as primary test (Rijkaart et al., 2011).

Implementation test (uitvoeringstest)

An implementation test was done to see if the new programme would be feasible. RIVM concluded that it was organisable and executable and worked out the plan to organise this. They mentioned that they needed two years to prepare for this plan (RIVM, n.d.-d).

Decision minister of health, welfare and sport

At the end of 2013 the minister officially decided to implement the new screening programme. It was stated that it makes the cervical screening more effective, more future-proof, cheaper and more user-friendly. In 2017 the new screening programme officially started (Overheid.nl, 2013).

WHO guideline

The WHO issued its first formal guideline on screening and treatment of cervical pre-cancer lesions in 2013.This was the first time an authoritative international organization recommended HPV-based testing as a screening method. They recommended, where resources permit, that the screening should be done with an HPV test. However, they also suggested cytology or VIA when resources were not available (Guidelines Review Committee, 2013).

In 2021, the WHO updated its guideline

about cervical cancer screening. They recommended HPV testing as the preferred primary screening method for women in the general population from the age of 30. They recommended this as a test instead of screening based on cytology or visual inspection methods, because the HPV test offers a stronger performance for early detection of cervical cancer risk (WHO, 2021).

European council recommendation

In 2017 The European council and the European guide on quality improvement in comprehensive cancer control recommended to look into the validated alternatives for screening (Albreht et al., 2017).

In March 2022, the commission's group of chief scientific advisors recommended to update the current methodology and test for cervical cancer screening to HPV as primary test. In December 2022, the new recommendation was formally adopted by the council of the EU (European Commission, 2022).

IARC scientific guidelines

The European Commission and IARC developed the EC Initiative on Cervical Cancer (EC-CvC). These are specific European guidelines for cervical cancer screening that recommend HPV testing as the primary screening method for people with a cervix aged 30–64. Cytology and co-testing are no longer recommended as primary methods, and existing programmes are advised to transition to HPV-based screening (EC-CVC, n.d.).

Conclusion

When looking at the implementation of primary HPV testing, the Netherlands was ahead of the international guidelines from the WHO and the IARC. It can be concluded that changes in the screening programme in the Netherlands can be initiated at a national level, even without international guidance. At the same time, international guidelines can still play an important role in guiding new implementations. In a lot of other countries, they do only act when international guidelines are suggested. This makes international guidelines in most countries an important step when implementing a new screening test.

03

MARKET ANALYSIS

3.1 STRATEGIC ANALYSIS

3.1.1 Introduction

This section has been removed from the public version, as it contains confidential information.

3.1.2 Stakeholder analysis

This section has been removed from the public version, as it contains confidential information.

3.1.3 Competitor analysis

This section has been removed from the public version, as it contains confidential information.

3.2 INTERVIEWS: STAKEHOLDER PERSPECTIVES ON METHYLATION

3.2.1 Introduction

To get a better understanding of the entire context and the different perspectives of stakeholders, interviews were conducted. The interviews provided insights into how stakeholders view the current screening process, challenges they might experience and what they expect to see in the future developments of cervical screening.

3.2.2 Method

For the selection of the participants, a purposive sampling strategy is used. The participants were selected based on different stakeholder groups that could influence the implementation of methylation tests. Six experts were interviewed: three gynaecologists, one epidemiologist, one distributor and one researcher specialised in methylation tests. The gynaecologists who were interviewed currently receive women referred from the cervical cancer screening programme and can be the ones to request a methylation test. They all work at different hospitals or medical centres, which provides broad insights. The epidemiologist has a lot of knowledge about the current screening programme and how a screening programme is analysed to be effective for screening. The distributor of the methylation tests could offer knowledge about the promotional approaches and what is effective. Lastly, the researcher could offer expertise about the advantages and current status of methylation.

The interviews that were conducted followed a semi-structured approach. This ensured a clear structure in which the most important questions were asked, while still allowing to follow the flow of the conversation and ask additional questions. Because of the different stakeholder perspectives, separate interview questions were developed for the different stakeholders. The interviews were conducted online through Microsoft Teams and by phone. To follow a structured interview process, an interview guide was developed. The introduction of the interview guide was the same for each interview, appendix B. This guide was used to ensure that everything was ready for the interview beforehand and to not forget important steps. Participants received the consent form (appendix C) in advance, so they had time to review it beforehand. At the beginning of the interview any questions about the consent form could be asked. Once it was confirmed that there were no further questions about the consent form and it had been signed, the interview began. Each interview started with a short introduction from both parties and after that the main interview questions started. These questions for the interviews differed per stakeholder, the questions can be found in appendix D.

3.2.3 Results

The interviews were recorded and notes were taken during each interview. Afterwards the interviews were transcribed, and the data was familiarized trough repeated review and summarising of the transcripts. After the familiarisation of the data, the interviews were imported into ATLAS.ti and analysed through coding. The codes were linked to the quotes of the participants and analysed through thematic content analysis (Ahmed et al., 2025). Several iterations were done on the thematic analysis to refine and strengthen

Themes	Subthemes
1. The current screening programme and the role of cytology	1.1 Positivity about current screening programme (with cytology as triage)
	1.2 Awareness about limitations of the current pathway
	1.3 Continuous optimisation of the Dutch programme
	1.4 Uncertainty about knowledge and accessibility methylation tests
2. Caution and risk aversion in treatment decisions	2.1 Treatment decisions differ by patient profile
	2.2 Fear for development to cervical cancer, preference for treatment
	2.3 Caring about the patients and what they want
3. Clinical value of methylation testing in decision-making	3.1 Usefulness in uncertain or complex cases
	3.2 Added value for younger women and women with a child wish
	3.3 Positive aspects of methylation as triage test
4. Requirements and barriers for implementation	4.1 Need for evidence, guidelines, and professional support
	4.2 Challenge of practical and organisational barriers
	4.3 Considerations for adoption and implementation strategy
5. Ethical and research considerations	5.1 Ethical concerns and hesitancy about withholding treatment
	5.2 Need for certainty in research and practice
	5.3 Challenges in study design and participation
6. Improving the screening programme	6.1 Importance of improving effectiveness while reducing harm
	6.2 Reducing burden and loss to follow-up
	6.3 Necessity of evaluation on feasibility, costs, and stakeholder coordination

Table 2: Themes and subthemes

the themes. In the first iteration, the codes were grouped on the initial interpretations. After this, it became clear that many of the themes were closely related, several themes were merged and subthemes were created. This thematic analysis resulted in six main themes with subthemes, shown in table 2. A more elaborate thematic analysis can be found in appendix E.

3.2.4 Key themes from the interviews

1. The current screening programme and the role of cytology

The first theme reflects the positive perception of the current Dutch screening system. The experts described the programme as well organised and effective. Cytology as triage test is well trusted and supported by guidelines. However, there were also a few limitations explained, such as a lot of unnecessary referrals, stress for women, loss to follow-up and the workload that comes with cytology. In addition, the Dutch screening programme is always monitored and can always be revised, since the Netherlands strives for the most effective screening programme. However, this can only be done in a structured and evidence-based process.

Methylation is not a part of the standard pathway of the screening. Currently, methylation is not a part of the routine practice and in most of the hospitals it is not requested or it is unavailable.

"Of course, a big group is screened and very little comes out of it, and for women it is, of course, a burdensome examination."

"Het is natuurlijk zo dat er een heleboel wordt gescreend en dat er heel weinig uitkomt, en het is voor vrouwen natuurlijk een belastend onderzoek."

2. Caution and risk aversion in treatment decisions

The second theme shows that decisions that are made about the treatment of the patient are mostly based on the characteristics of the patient. Factors such as age, pregnancy and a child wish play an important role in advising the patient a treatment or a follow-up. Especially with CIN 2, the younger women with a child wish are often considered for a follow-up instead of treatment, since treatment can bring complications with childbirth. On the other hand, older women with CIN 2 are almost always treated. Experts acknowledge that treatment can have physical or emotional consequences, however, treatment is still viewed as the safest and quickest option to prevent progression to cervical cancer. At the same time, the interviews also showed the importance of shared decision-making with women with CIN 2. With CIN 3, experts explained that there is almost always a preference for treatment instead of follow-up.

"We treat CIN2 and CIN3, CIN2 in people who have completed their childwish, and CIN3 also in people who still wish to have children."

"CIN2 en CIN3 behandelen we, CIN 2 bij mensen met een voltooide kinderwens. En CIN3 ook bij mensen die nog wel een kinderwens hebben."

3. Clinical value of methylation testing in decision-making

The third theme reflects the situations in which the experts believe methylation tests can add value. Methylation tests are seen as useful in complex or uncertain cases, such as persistent HPV infection, abnormal cells after treatment or unclear management of CIN 2. In these cases, methylation can be used as an extra tool to support decision-making.

Methylation can also have value for younger women, women with a child wish and pregnant women, since treatment preferably is avoided for these groups.

Instead of only using methylation tests as an add-on, it can also be used as a triage test instead of cytology. Experts explained that the compatibility with self-sampling is an important advantage. In addition, less unnecessary referrals, colposcopies, overtreatment and lowering the burden on the healthcare system, can be advantages.

"You see it for example very specifically for the pregnant women, they will already look for a more conservative approach, or for young women who still wish to have children."

"Je ziet het ja heel specifiek voor voor zwangere vrouwen bijvoorbeeld zullen ze sowieso al op zoek gaan naar een meer conservatieve aanpak of bij onge vrouwen die nog een kinderwens hebben"

4. Requirements and barriers for implementation

The fourth theme highlights the requirements and barriers for the implementation of methylation. That the methylation test can add clinical value is not enough for it to be implemented. Implementation requires strong evidence, effectiveness, reliability and cost effectiveness. Including the test in the guidelines and support from the NVOG are described as essential for implementation for gynaecologists. There can also be practical and organisational barriers, for example, that at this moment, the test cannot be requested everywhere and there might be limited laboratory capacity. Additionally, reimbursement is an important aspect, just as feasibility and the automation for large-scale implementation.

Implementation is a gradual process and takes time and a strong evidence base to be considered. Experts mentioned that things such as local awareness, national studies, education, publications, congresses and alignment between stakeholders can help the implementation process.

"I think the guidelines are very important now."

"Ik denk dat de guidelines heel belangrijk zijn nu"

5. Ethical and research considerations

The fifth theme explains the ethical concerns of the experts about methylation tests. Since gynaecologists are used to treating CIN 3, it would be difficult to step away from that when a methylation test is negative. Even if this would be done in a study, there are still some concerns, it is emphasised that strong confidence in the test is needed to support a wait-and-see policy. It is also mentioned that it would be difficult to justify such a study and there is uncertainty whether enough women would be willing to participate in a study like this.

"Because I do wonder how many women would be willing to participate if you explain it that way."

"Omdat ik me wel afvraag hoeveel vrouwen mee zouden willen doen als je dat dan uitlegt"

6. Improving the screening programme

The sixth theme explains the optimisations of screening programmes. The experts explained that a good screening programme not only reduces cervical cancer incidents and mortality but also looks at the possible negative sides of a screening programme.

These can consist of false positives, unnecessary referrals and procedures, patient anxiety or high costs. Methylation can be valuable but the balance between the benefits and harms need to be assessed to know the net effectiveness. Positive aspects are to reduce the burden on women and preventing loss to follow-up, since each step in the pathway can create inconvenience. Therefore, a simpler pathway, especially one that works with self-sampling, can improve the participation for women. Another aspect of changing the screening programme is the feasibility, acceptable costs and coordination between stakeholders.

"Not having to go to the general practitioner for a Pap smear anymore is an additional advantage, which means you have less dropout along the way."

"Niet meer naar de huisarts hoeven voor een uitstrijkje is een extra voordeel waarmee je dus minder uitval hebt tussendoor"

Conclusion

Overall, the thematic analysis shows that methylation tests are promising, however, it is not an innovation that can be implemented easily or quickly. Different stakeholders do recognise the possible advantages, but there are also barriers and there could be negative effects. The role of methylation tests does not only depend on its clinical performance, but also on how it fits in the current screening programme and the screening infrastructure in the Netherlands.

Although the different stakeholders have the same end goal, namely, to have the best test to prevent cervical cancer, different stakeholders consider different aspects to be important. The strategic roadmap should therefore account for these differing interests and explain how they can be brought together.

04

REDEFINE DESIGN BRIEF

4.1 REDEFINE DESIGN BRIEF

4.1.1 Introduction

To bring together all the key insights from the literature research and analysis, the limitations and opportunities are summarized. With these insights, the scope is defined, product positioning is created and design criteria are made.

4.1.2 Limitations and opportunities

Limitations

- **Awareness of methylation is low:** methylation is currently not a part of the cervical screening and the awareness about it is still limited
- **Need for strong evidence:** it is emphasised that strong evidence is needed before the test can be adopted
- **Practical implementation barriers**: reimbursement, laboratory capacity and feasibility are important barriers that need to be addressed
- **Guideline dependency:** for professionals to accept a new test, the inclusion in the guidelines and support from organisations such as the NVOG is very important
- **Need for education and promotion**: before it can be adopted, aspects such as local awareness, education, publications and congresses are important.
- **Clinical and ethical considerations:** stakeholders are careful about changing treatment decisions
- **Complex implementation process:** the implementation depends on many stakeholders, such as clinicians, laboratories, screening programmes, insurers, etc., which makes adoption complex.
- **Implementation in the screening takes time:** screening programmes are difficult to change quickly, implementation depends on ongoing research that takes several years.

Opportunities

- **Objective triage test:** methylation offers an objective test to assess the progression risk to cervical cancer
- **Better risk stratification:** the test can distinguish between lesions with a high short-term progression risk and lesions with a lower risk
- **Reduction of unnecessary steps:** it can reduce referrals, colposcopies and overtreatment, which can lower the burden on patients and the entire healthcare process
- **Works well with self-sampling:** methylation works on self-samples, which can help simplify the pathway and make it more accessible for women.
- **Added value for certain groups**: methylation can especially be useful for younger women, pregnant women and women with a child wish, when avoiding treatment is important.
- **Support decision-making:** methylation can help gynaecologists decide whether treatment or a more conservative follow-up approach is needed in uncertain cases
- **Start for implementation:** already multiple things are started to evaluate the implementation of methylation tests, such as the revision of the guidelines and the research for the revision of the screening

4.1.3 Scope

The final goal for the position of the methylation test would be to use it as a triage test within the cervical cancer screening. However, the revisions of a screening programme are very structured and difficult to influence directly. The first steps of the current cervical cancer screening revisions have already started, but the testing and evaluation will take time.

For Self-screen it is also not desirable to just wait for the outcomes of the research for revision of the screening process. Implementation in the national screening will remain the long-term goal, however, a short-term implementation strategy can already create value. By focusing on implementing methylation in diagnostics first, Self-screen can already increase awareness among gynaecologists to build trust. This way the test can be more accepted, and this could add value for broader implementation.

Therefore, methylation tests can offer value within the diagnostics for cervical cancer. The scope of this project will focus on the implementation of methylation tests in diagnostics for cervical cancer. Specifically on how regional gynaecologists can be reached, informed and engaged. This is especially relevant in situations where methylation can support the decision-making. For example, in cases of women with ASCUS/LSIL results, younger women with a child wish and pregnant women, where treatment should be avoided.

The focus will be on how the awareness of the test can be implemented, how trust in the test can be established and how the added value of the test can be communicated so that clinicians are willing to request the test in practice.

The problem can therefore be redefined in the following question:

How can methylation tests be implemented in Dutch cervical cancer diagnostics by increasing awareness, building trust, and communicating the clinical added value to gynaecologists?

4.1.4 Product positioning

With the scope in mind, the methylation test should not be positioned as a replacement for the current screening, but as a test that can help gynaecologists with decision-making in cervical cancer diagnostics. The long-term potential of methylation tests does lie in the triage for the cervical screening programme. However, the current positioning should focus on the value in the diagnostics pathway, which can also help for the adoption in the screening programme.

Methylation tests should be positioned as an objective test that can support risk stratification. This can help gynaecologists to identify if women are at a higher short-term risk for cervical cancer, or a lower short-term risk. The test can contribute to reducing unnecessary treatment in situations where treatment should be avoided. It can be positioned as a tool to help in decision-making in specific situations, these include cases with ASCUS/LSIL, younger women with a child wish and pregnant women.

The focus with the positioning should be on the awareness, trust and clinical relevance of the methylation test. Gynaecologists should be informed about what methylation is and when it can be helpful. By positioning methylation this way for diagnostics, a stronger foundation for the implementation in the screening can be created.

4.1.5 Design requirements

Based on the scope, product positioning and research, the following design requirements have been created.

1. The strategy should position methylation tests as a support tool for decision-making in cervical cancer diagnostics.

2. The design should clearly communicate in which situations methylation tests can add value.

3. The design should communicate the value of methylation tests in a scientifically credible way.

4. The strategy should focus on trust through evidence and experiences.

5. The strategy should be transparent about the role of Self-screen to prevent problems with conflict of interest.

6. The strategy should increase the awareness of methylation among gynaecologists.

7. The strategy should increase the requests of methylation tests among gynaecologists.

8. The design should provide clear information about methylation tests.

9. The design should focus on the information that is important to gynaecologists.

10. The strategy should also take the accessibility of requesting methylation tests into account.

11. The strategy should support gradual adoption.

12. The strategy should contribute to the long-term goals of the implementation of methylation tests in the national screening.

05

DESIGNING CONCEPTS

5.1 IDEA GENERATION

5.1.1 Method introduction

With the scope as a foundation, the process of concept creation started. It started with the creative ideation, which was done with individual brainstorming to generate a wide range of ideas. After this, collaborative creative sessions were held together with three other industrial design students to generate different ideas using various creativity methods. The insights for the individual and collaborative creative sessions were used to create an initial roadmap.

To ensure that the ideas for the implementation of the methylation test were also feasible and aligned with reaching gynaecologists, a gynaecologist was interviewed. This interview was conducted by phone, took around 45 minutes, and was recorded. The focus in this interview was on which ideas and approaches would be most effective. The insights gathered from this interview were used to refine the ideas and strategic roadmap. In addition, the concept roadmap is also evaluated with Self-screen to assess if it is realistic and aligns with the value of the company.

In the end, this iterative process resulted in a strategic roadmap, supported by a tactical roadmap, that can be used for the implementation of methylation tests. A strategic roadmap defines the goals and a tactical roadmap translates these goals into concrete actions.

5.1.2 Creative ideation

The first step of the creative ideation started individually, with all the findings in mind. With different methods ideas were generated. It started with brainwriting, writing down every idea that came to mind. To generate more and different ideas, the ''How can you...'' method was used. This helped to generate a broader range of ideas, see appendix F.

However, because individual ideation was influenced by existing knowledge about the subject, a creative session with other students was organised. In this session different methods were used for generating ideas. The focus of the creative session was to generate ideas on how to reach gynaecologists with the right information to increase awareness of methylation tests. The creative session started with an explanation and a few illustrative visuals, about the subject and an explanation of what should be solved. Secondly, a warm-up exercise was executed to start creative flow. After the warming up exercise, multiple methods were used for idea generation. It started with open brainstorming to think of the initial ideas that came up after the introduction of the topic. Then, the starbursting method was used to come up with all the questions related to the implementation of methylation tests. The third way to generate ideas was with the random input method. Lastly, every person chose one of the ideas to ideate further on with SCAMPER.

These ideas mostly focused on how gynaecologists could be informed and activated to learn about the use of methylation tests in their practice. However, this is not something that can simply be solved with one simple solution. The final goal is that many gynaecologists will request a methylation test, but to reach this, smaller steps of change need to be made first. It is a gradual process that takes time for adaptation and acceptance among gynaecologists. When integrating new tests, gynaecologists differ in their willingness to adopt new technologies. Some gynaecologists are more innovation driven and others prefer to rely on the established practice.

5.1.3 Diffusion of innovation

These differences in adoption can be understood with the diffusion of innovations theory by Everett Rogers, see figure 13. This theory describes how a new product or practice goes through different stages of adoption within a social system over time. It shows that adoption is not simultaneous but follows different categories of adopters. These groups range from innovators to more conservative users.

With the development of the strategic roadmap, these different stages of adoption were taken into account. With the roadmap, the different stages of different groups will be addressed, since early adopters require a different approach compared to laggards. To design the roadmap to support a more effective and realistic implementation plan, these different stages of adoption were considered in the horizons.

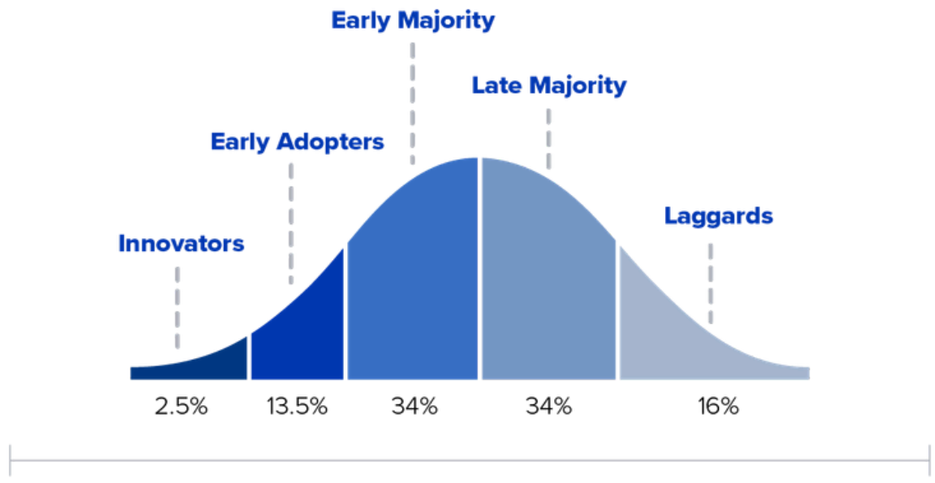


Figure 13: Diffusion of innovation (Recchia, 2022)

5.1.4 Roadmapping as implementation method

A roadmap can be used as a strategic design method to work towards a future vision. The steps to reach that vision are described in different horizons. Simonse (2024) describes design roadmapping as a combination of design, strategy, innovation and foresight. With roadmapping a future vision can be created and the way towards it can be mapped. A roadmap can be created by foresight techniques, trends, technologies, values and ideas that are translated in an overview. This makes roadmapping useful for strategic challenges over a period of time.

5.2 CONCEPT CREATION

5.2.1 Introduction

For this research, a roadmap is developed to define the horizons for the implementation of methylation tests in the diagnostics for cervical cancer. Each horizon has different key activities and challenges that show the different steps in the roadmap. This way the roadmap does not only show a future vision but also translates into concrete steps.

5.2.2 First iteration roadmapping

With the ideas from the ideation, the diffusion of innovation theory and the roadmapping theory in mind, multiple sketches of strategic roadmaps were developed, appendix G. One roadmap focused more on what gynaecologists could do for the implementation and one roadmap more focused on what actions Self-screen could take for the implementation. While sketching these roadmaps it became clear that they could work together and that Self-screen could use the help of gynaecologists for informing others.

The final and ideal goal of the implementation of methylation would be to implement it in the Dutch screening programme. However, research for this has already started, and this study needs to be completed before methylation can be implemented in the national screening programme. In the meantime, methylation can be used in diagnostics and with the results from the use of methylation and more clinicians who try it this can add to the probability of implementation in the screening.

The future vision of the roadmap should focus on methylation tests being the standard option for gynaecologists to consider when applicable.

To get to this future vision there are multiple steps to take which are divided into three horizons. Each horizon represents one year of implementation. The focus of the first horizon will be on the innovators from the diffusion of innovation theory. These innovators should be found so they can become spokespersons for the use of methylation. Examples of ways that they can be found or contacted would be at congresses, direct contact through researchers, flyers or brochures, a website or through NVOG.

In the second horizon the focus will be on targeting the early adopters among the gynaecologists. The spokespersons would work together with Self-screen to reach this group. This could be done through case studies, a podcast, local awareness or training evenings. For this horizon there is also a choice to make about where to start the awareness, ideas for this are educational hospitals, STZ hospitals, private clinics or locally.

In the third horizon the focus will be on the early majority. To reach the late majority the same methods as in the second horizon could be used. However, it is also essential to evaluate the results from the gynaecologists that now use methylation. With good results, this can show the effectiveness of methylation which could help to convince the early majority.

5.3 CONCEPT ITERATIONS

5.3.1 Iteration with gynaecologist

The roadmap still included multiple options per horizon, for example on how gynaecologists can be informed or where implementation should start. To get a better understanding of what would be the best way to implement methylation, an interview was conducted. The interviewee is a gynaecologist who is also a researcher on the topic methylation. Since the interviewee understands both the clinical value of methylation and the perspective of gynaecologists, the interview provided very valuable insights.

The interview was a phone call from around 45 minutes which was recorded. The questions were semi-structered and written down beforehand, however the interview followed the flow of the conversation. During the interview, the gynaecologist was asked open questions about how other gynaecologists could be reached with information about new tests. Later, ideas of communicating information with gynaecologists that were considered in the idea generation were also discussed, appendix D. The gynaecologist suggested that others can be reached through the NTOG, a magazine for gynaecologists.

"Actually, by writing an article in the NTOG, because then you reach Dutch gynaecologists."

"Eigenlijk door een stuk te schrijven in het NTOG, want dan bereik je de Nederlandse gynaecologen"

In addition, he mentioned that webinars are a very suitable way of sharing new information with gynaecologists and that those also have good attendance.

"They also occasionally have a webinar about cervical abnormalities."

"Die hebben ook een nog wel eens en webinar over cervix afwijkingen."

The gynaecologist agreed that congresses are also valuable places to reach other gynaecologists and increase awareness.

"Yes, undoubtedly. Especially for the cervix, there are conferences as well."

"Ja ongetwijfeld, je hebt zeker voor de cervix zijn er wel congressen ook"

The interview also confirmed that the clear information about methylation is currently missing.

"That is due to a lack of clear information or some kind of guideline-like document."

"Dat is dus de door gebrek toch aan een duidelijke informatie of een soort richtlijn, achtig iets"

Regarding where to reach the early adopters, it was concluded that Amsterdam could be an interesting starting point, since the methylation test can be processed at the AMC lab. This could make it more accessible for labs in Amsterdam to send it there. In addition, protocols are easier to change locally than nationally.

"This is something that you can simply decide on together as a group."

"Dit is wel iets waar je dan gewoon onderling als club een beslissing en besluit over kan nemen''

5.3.2 Iteration with Self-screen

To improve the roadmap even further, the concept was discussed with an employee from Self-screen to understand their perspective on the concept. The goal was to see if this roadmap would also be realistic for them as a company. During this, it became clear which elements were good and which ones could be adjusted to add more value for Self-screen. Since they work with distributors, the key activities for the distributors were also added to the roadmap. In addition, the explanation about the webinars was specified further and the same is done for the articles. This helped to align the roadmap more with Self-screen's role and the possibilities for implementation. For the design of the flyer, multiple iterations were done and evaluated with Self-screen to improve the flyer.

06

VALIDATION OF THE STRATEGY WITH STAKEHOLDERS

6.1 VALIDATION SESSIONS

6.1.1 Introduction

To evaluate the concepts of the roadmaps and the flyer, three validation sessions were held. The concepts of the roadmaps and flyer used for the validation session can be found in appendix H. These validation sessions were held to evaluate if the strategic plan is feasible and realistic and to improve the roadmaps and flyer to have the most effect. For the strategic and tactical roadmap, the validation sessions were to answer the questions about whether it would be feasible to implement in these horizons. For the validation of the flyer it was discussed if it contained the right information for the most effective communication. These validation sessions were aimed on having a good and validated final roadmap and a flyer that can be used in the communication of methylation.

6.1.2 Set-up validation sessions

The validation sessions were conducted with three different stakeholders, a distributor, a gynaecologist and with someone from Self-screen. One of the sessions was online and two were in person, they took around 45 minutes. The validation sessions started by an explanation of the goal of the project. After this introduction, the roadmaps were presented and explained. The participants were asked about their opinions and if they thought it was a realistic and feasible roadmap. In addition, the flyer from the first horizon was shown to evaluate if it conveys the right message and to see if important information was missing.

6.1.3 Validation with distributor

The evaluation with the distributor confirmed that working together with gynaecologists is a good direction for the strategic roadmap. It was suggested to already incorporate experiences of gynaecologists in the flyer or refer to it on the flyer. Since gynaecologists often listen more to the experiences from other gynaecologists compared to information they get from a commercial company.

It was clear that a QR code has added value but that it can be used in different ways. Such as referring to use cases or to go to a web page to download a PDF. With referring to the download of a PDF, it could be possible to get information from people to follow up and contact the gynaecologists.

It was also addressed to add the source of the guideline explanation so gynaecologists would be able to find this as well. This flyer is now focused on gynaecologists which was seen as a positive aspect since other information is mostly focused on everything together. It was seen as a good approach to split this up so the flyer can really be focused on the target audience.

Lastly, it was mentioned to make the subtitle a bit bigger to really grasp the attention from gynaecologists, so they want to read further. It was also said that it is a bit much text but that there was not really any information that could be left out.

6.1.4 Validation with Self-screen

From the feedback from Self-screen, it was suggested that more activities could be delegated to the distributor. During the feedback session it was discussed what kind of activities could go more to the distributor, however, there was not a clear answer to this. The balance between Self-screen and the distributor is difficult to establish. It is recommended in the strategy to maintain close contact with the distributor about this to make a clear division of activities between Self-screen and the distributor.

The flyer was initially made in the style of the report for the first version. However, to facilitate easier implementation for Self-screen, the flyer should be adapted to the style of Self-screen.

Something missing from the strategy were the opportunities that could arise outside from the planned strategy. These include things that can happen in the meantime that could have a positive effect on the implementation of methylation. Since these opportunities can occur in each horizon, this will be incorporated in the explanation about the horizons.

6.1.5 Validation with gynaecologist

The feedback session with the gynaecologist was conducted with a gynaecologist who could also take on the role of a spokesperson within the proposed strategy. The overall strategy is explained and discussed. The gynaecologist supported the concept to let experienced gynaecologists explain the value to other gynaecologists. The gynaecologist considered the activities in the second horizon, namely webinars and sharing scientific articles as relevant and feasible activities. The gynaecologist was also open to explore collaboration with Self-screen as a spokesperson. However, there was a key point that the gynaecologist highlighted that could make implementation more difficult. It was mentioned that if gynaecologists do not know enough about methylation themselves it would be difficult how to act on a positive or negative result from a methylation test. This highlights that gynaecologists would need to strengthen their knowledge about methylation or that there should be a clear protocol with easily accessible information to support the decision-making of gynaecologists.

The flyer was also evaluated. Overall, the gynaecologist was positive about both the design and the content. The data used from the studies was also well received and aligned with the gynaecologist's views. A key improvement was that the flyer should more clearly communicate when and how the methylation test should be used in the process. Making this more explicit could improve the usability of the flyer and support more consistent information.

6.1.6 Conclusion

Overall, the validation with different stakeholders provided valuable insights that confirmed the feasibility and desirability of the roadmap. The different stakeholder perspectives, all agreed that it is an appropriate direction for the strategy and that it aligns within the current practice.

In addition, there was also important feedback and possibilities for improvement. Coordination of the division of activities between Self-screen and the distributor requires a bit more information. Furthermore, for gynaecologists a clearer protocol for the interpretation of the results of the methylation tests is necessary. The flyer needed an extra source, and it should communicate more explicit information about when to use a methylation test.

In conclusion, the stakeholders supported the overall strategy while also identifying a few points for refinement.

6.2 STRATEGY EVALUATION

6.2.1 Design requirements

The design requirements that were formulated in this project in chapter 4.1.5 served as principles to develop a strategy for the implementation of methylation tests in the diagnostics for cervical cancer. To validate the design, each design requirement is assessed against the final strategy. Overall, the majority of the requirements have been met, although a few requirements are not fully addressed.

Two requirements (six and seven) are only partially met because they also depend on behavioural changes. The strategy does include communication and awareness about methylation tests. However, actual adoption and use of the test in their practice cannot be guaranteed and remains uncertain.

nr.	Design requirement	
1	The strategy should position methylation tests as a support tool for decision-making in cervical cancer diagnostics.	
2	The design should clearly communicate in which situations methylation test can add value.	
3	The design should communicate the value of methylation tests in a scientifically credible way.	
4	The strategy should focus on trust through evidence and experiences.	
5	The strategy should be transparent about the role of Self-screen to prevent problems with conflict of interest.	
6	The strategy should increase the awareness of methylation among gynaecologists.	
7	The strategy should increase the requests of methylation tests among gynaecologists.	
8	The design should provide clear information about methylation tests.	
9	The design should focus on the information that is important to gynaecologists.	
10	The strategy should also take the possibility of requesting methylation tests into account.	
11	The strategy should support gradual adoption.	
12	The strategy should contribute to the long-term goals of the implementation of methylation tests in the national screening.	

6.2.2 Feasibility, desirability and viability.

Feasibility

The feasibility of the strategy for the implementation of methylation tests is supported by the compatibility within the existing workflows. The steps in the strategy are activities that are already often executed and does not require fundamental changes. In addition, several laboratories can already process the test, which lowers the barrier for initial implementation. However, the number of labs where the methylation tests can be processed is low. Within the strategy, this is addressed through the gradual implementation in additional laboratories and developing a protocol for consistent information.

Most of the activities defined in the strategy are considered operationally feasible, since the align with the existing activities in the Dutch healthcare system. Validation with stakeholders confirmed that these activities are realistic and that gynaecologists likely would contribute or join a webinar and read an article.

Overall, the feasiblity is good for the phased implementation strategy, there are some small constraints, but these can be mitigated with the designed strategy.

Desirability

The desirability of implementing methylation tests in the diagnostics for cervical cancer is generally positive among different stakeholders. Especially in situations where the current tests leave clinical uncertainty. Gynaecologists recognise the added value in cases where overtreatment should be prevented, such as pregnant women or women with a child wish.

Additionally, methylation tests are also seen as valuable in the cervical cancer screening to improve the risk stratification and reduce referrals, overtreatment and loss to follow-up. This can contribute to reducing the burden on the patients and the healthcare pathway.

The desirability is strong, but the existing established pathways make implementation more challenging. The existing pathways are preferred since they are familiar and based on long-term evidence.

Viability

The viability of the designed strategy is high, with a roadmap structured in three horizons. These horizons enable a phased adoption, which allows the implementation to progress with stakeholder and organisational readiness.

Validation with stakeholders, including the company Self-screen, indicates that the strategy is feasible to execute for the company and within the current healthcare pathway. The roadmap was perceived as a realistic approach to introducing a new test into an established healthcare system.

However, the viability is also dependent on external stakeholders, such as the involvement of gynaecologists as spokespersons. Their position is essential to spread awareness and build credibility. Their role is important across all three horizons, from building awareness to supporting broader adoption into practice.

Overall, the strategy is viable with the phased strategy and validation confirms that it is realistic for the company and within the healthcare pathway. However, the viability also depends on the gynaecologists as spokespersons since their involvement is essential.

07

FINAL STRATEGY

7.1 ROADMAPS

7.1.1 Strategic and tactical

For the final strategy, the roadmap is split into two connected roadmaps. A strategic and a tactical roadmap, shown on the next pages. With both a strategic and a tactical roadmap, there is a combination of outlined goals and their translation into practical actions.

The strategic roadmap focuses on a clear direction and outlines of the goals to be reached over time. This gives an overview of the goals to reach in each horizon for the implementation of methylation tests. These horizons go from creating awareness and building trust to use in real practice. The strategic roadmap shows the overall directions and the desired outcomes.

The tactical roadmap translates the strategic roadmap into more concrete actions. It shows when activities need to take place and which actors are involved. While the strategic roadmap shows what should be achieved, the tactical roadmap focuses on how this can be achieved.

To give a clear explanation of the roadmap a description per horizon is written. For every horizon, the focus, goals, key activities and challenges are explained. This can help to get a better understanding of the roadmap and explains how every horizon contributes to the implementation of methylation tests in diagnostics for cervical cancer.

	2026	2027	2028	2029
	HORIZON 1	**HORIZON 2**	**HORIZON 3**	**FUTURE VISION**
	PROMOTION AND FINDING SPOKESPERSONS	**SHARING INFORMATION**	**EVALUATING AND IMPROVING**	**THE NEW STANDARD**
	Build awareness by engaging gynaecologists through congresses and collaboration with them as spokespersons.	**Increase adoption of methylation in diagnostics for cervical cancer in collaboration with spokespersons through webinars and articles.**	**Scale methylation adoption in diagnostics for cervical cancer through evaluation, improvement, and shared clinical insights.**	**Methylation tests being a standard action for gynaecologists to take.**
				
GOAL	The goal of Horizon 1 is to create awareness among gynaecologists who are already interested in methylation tests or who currently use it in their practice. Self-screen should identify and engage them and assess their willingness to support the wider communication of methylation tests. These gynaecologists will be credible spokespersons who can share their experience and advocate for the use of methylation. These spokesperson will be valuable for a strong foundation for clinical credibility, visibility, and future adoption of methylation.	In Horizon 2, the goal is to get active clinical engagement and education. Self-screen should work closely with the spokespersons to promote the value and use of methylation tests among other gynaecologists. By involving respected gynaecologists, Self-screen can build stronger credibility, enthusiasm, and trust for a bigger group of gynaecologists. The spokesperson should help to communicate a clear protocol for methylation tests, to support consistent and correct implementation.	The goal of Horizon 3 is to evaluate the use of methylation tests in clinical practice and optimise the this where needed. Gynaecologists who already use methylation should monitor how implementation is going. These findings can be shared with other gynaecologists to show the value, build confidence, and convince more clinicians to adopt methylation tests in diagnostics.	All gynaecologists use a methylation test in the diagnostics for cervical cancer when this can provide added value. This can be when there is an unclear decision to make especially with younger or pregnant women. By embedding methylation tests into the process, it can support the decision-making of gynaecologists and it can improve the women's health outcomes.
TARGET AUDIENCE	• Gynaecologists (innovators)	• Gynaecologists (early adopters) with an initial focus on Amsterdam	• Gynaecologists who use methylation • Gynaecologists (early majority) • Labs	
KEY ACTIVITIES SELF-SCREEN	• Promotion methylation tests at relevant congresses • Spreading flyer with relevant information • Direct contact with enthousiast gynaecologists to explore spokespersons	• Co-design a webinar with gynaecologists • Write article for in the NTOG about methylation • Explore additional labs for implementation in Horizon 3	• Collect feedback about using methylation • Evaluate and improve where necessary • Reaching more gynaecologists through webinars, using learnings and early results to convince the early majority	
KEY ACTIVITIES GYNAECOLOGIST	• Attending congresses	• Actively promote methylation through webinars to inform and activate others • Write clear protocol for methylation tests	• Monitoring results of using methylation • Act actively on these findings	
KEY ACTIVITIES DISTRIBUTOR	*This section has been removed from the public version, as it contains confidential information.*	*This section has been removed from the public version, as it contains confidential information.*	*This section has been removed from the public version, as it contains confidential information.*	

HORIZON 1

2026 – 2027

PROMOTION AND FINDING SPOKESPERSONS

Build awareness by engaging gynaecologists through congresses and collaboration with them as spokespersons.

HORIZON 2

2027 – 2028

SHARING INFORMATION

Increase adoption of methylation in diagnostics for cervical cancer in collaboration with spokespersons through webinars and articles.

HORIZON 3

2028 – 2029

EVALUATING AND IMPROVING

Scale methylation adoption in diagnostics for cervical cancer through evaluation, improvement, and shared clinical insights.

FUTURE VISION

THE NEW STANDARD

Methylation tests being a standard action for gynaecologists to take

All gynaecologists use a methylation test in the diagnostics for cervical cancer when this can provide added value. This can be when there is an unclear decision to make especially with younger or pregnant women. By embedding methylation tests into the process, it can support the decision-making of gynaecologists and it can improve the women's health outcomes.

ACTIONS

- Promotion methylation to gynaecologists
- Search and contact interested gynaecologists
- Co-design webinar & article
- Start looking for other labs
- Inspire other gynaecologists about methylation
- Understanding and using methylation tests
- Evaluation of the use of methylation
- Take role of spokesperson
- Writing protocol for requesting and using methylation
- Improve process of methylation
- Actively promote methylation
- Monitoring results of methylation testing
- Act on findings of the evaluation

ACTORS

- Self-screen
- Gynaecologists (innovators)
- Gynaecologists (early adopters)
- Labs
- Gynaecologists (early majority)

TOUCHPOINTS

- National and international congresses
- Direct contact gynaecologists (mail or in person)
- distributors

- Webinars to inform and activate
- NTOG article about methylation
- Local awareness in hospitals and clinical centres

- Direct contact by sending evaluation form
- Webinars/NTOG

COSTS

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CHALLENGES

- Finding gynaecologists with an interest in or experience with methylation tests
- Managing potential conflict-of-interest for gynaecologists related to collaboration with a commercial company

- Strong collaboration with spokespersons
- Engaging gynaecologists with educational content such as articles and webinars
- Making sure that gynaecologists convert knowledge about methylation into implementation

- Reaching labs and convincing them to process methylation tests
- Making sure gynaecologists take the time to evaluate the process and findings

DECISION GATE

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7.2 HORIZON 1: PROMOTION AND FINDING SPOKESPERSONS

Build awareness by engaging gynaecologists through congresses and collaboration.

(This image is generated with ChatGPT)

Focus

The first horizon focuses on creating awareness and building the initial foundation for the broader adoption of methylation tests among gynaecologists. The gynaecologists that already use methylation or who are innovative and interested in methylation should be identified. By actively finding these gynaecologists, possibilities for a collaboration and for them to become a spokesperson for methylation can be identified.

Goal

The goal of this horizon is to create awareness among gynaecologists who are interested in methylation and find gynaecologists who already use methylation and are enthusiastic about it.

This way gynaecologists who are interested in methylation and want to engage with it can be identified.

From these gynaecologists it is important to find potential spokespersons. These spokespersons should not only understand and use methylation but should also be willing to share their experiences with other gynaecologists. This is essential since it is often more credible to learn from other gynaecologists compared to learning from a commercial company.

The goal at the end of the horizon is that there is a small and engaged group of gynaecologists who believe in methylation testing and are willing to share their experiences with other gynaecologists to build more awareness for methylation.

Key activities

The actions in the horizons are in different colours. The actions in light blue are actions that can be taken by Self-screen themselves and the actions in dark pink, require other stakeholders. The other stakeholders that are needed are gynaecologists who are spokespersons. They are essential for this strategy.

The key activities of the first horizon are all about promotion, engagement and building relationships with innovator gynaecologists. The promotion of methylation tests should be done at congresses where gynaecologists who are interested can be reached. At congresses, the gynaecologists who are really interested in methylation can be found. Congresses are an important touchpoint since they provide the opportunity to present the information, answer any questions and identify gynaecologists who show interest. The promotion can be done with a stand that includes flyers with the most essential information. What information is formulated in the flyer is discussed with gynaecologists. Congresses they could attend could include Eurogin, ESGO, ESCMID and IPVC.

Next to promotion at congresses, Self-screen can also initiate direct contact to gynaecologists who have done research about methylation, since they are probably interested in methylation. Direct contact can also be established with gynaecologists who were interested at the congress.

The next step is to identify which gynaecologists would be interested in being a spokesperson about methylation and would want to work together with Self-screen on this. These spokespersons should be supported by Self-screen with clear and relevant information about methylation and the scientific background so they can feel confident in sharing the right information with others in the next horizon.

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Challenges

Finding the right spokespersons for methylation tests is one of the biggest overarching challenges of the first horizon. Firstly, there is probably only a limited pool of gynaecologists that is enthusiastic to be spokespersons. Not all gynaecologists are that enthusiastic about innovative methods and even less might be willing to advocate for the test. Identifying the right spokespersons is difficult and crucial. To find the right gynaecologist, good observation and congresses is important and the use of existing professional networks could help. In addition, when a first spokesperson has been found it can help to ask them to reach out in their network as well.

A second challenge is the credibility of the spokespersons, since it is important that they are perceived as trustworthy. Especially in healthcare, evidence-based information and professional reputation can influence the trustworthiness and adoption. Selecting the right gynaecologists as spokespersons is key, to verify the trustworthiness of

gynaecologists there can be looked at what they have done in the field of gynaecology.

Another challenge is that gynaecologists often have limited time and availability. This could reduce the number of possible spokespersons and how much time they might have. This might not motivate gynaecologists to put more time into something extra. To get gynaecologists who are enthusiastic to collaborate, a compensation could be offered.

In addition, it is a challenge to manage the potential conflict of interest. Since the promotion of the test would be in collaboration with a commercial company, gynaecologists might be cautious. It is very important that the communication about methylation is transparent, credible and scientifically grounded. To manage this, agreements can be made that gynaecologists are free to communicate their real experiences and cannot be biased by working with a commercial company. This way the focus is on the clinical value instead of the commercial aspect.

A recurring challenge in all the horizons is the division of activities for which Self-screen is responsible and for which distributors are responsible. It can be difficult to define which activities are better to be handled by Self-screen and which are the responsibility of distributors. To make sure that this is divided correctly, regular meetings and communication are essential. This communication can help to align expectations and clarify roles and responsibilities.

Especially the challenge of finding spokespersons is critical. However, even with only one gynaecologist as spokesperson, the strategy can still proceed to work. Since there is already one potential spokesperson identified, the overall risk is reduced.

Costs

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Flyer

As part of the first horizon, a flyer should be used for the communication of methylation tests towards gynaecologists. This flyer is designed and can be found on the next pages. The aim for the flyer is to translate the scientific findings into a clear and accessible format. Since awareness about methylation is not very high yet, the focus is on what methylation is and in which situation it can be used.

The front side of the flyer provides information about methylation tests in cervical cancer diagnostics. It also shows the numbers of methylation that support the scientific evidence. In addition, the cases in which methylation is useful in diagnostics are described. Lastly, there is a small text about Self-screen as a company.

In addition to informing the gynaecologists, the back of the flyer is designed to activate the gynaecologists. It includes a step-by-step guide that shows gynaecologists when they could consider a methylation test. In addition, a section about the guideline is included to show that according to the guidelines, methylation can be considered in specific cases.

The QR code is included to make the next step for the gynaecologists more accessible. Where the QR code leads to can depend on the context of when and where the flyer is used. Options could include a website with FAQs about methylation, the Self-screen website, patient case examples, or a downloadable PDF with more detailed information. If a PDF download is provided, it could also include a part asking if their email can be shared, allowing follow-up to them later.

Opportunities

Besides the planned activities in each horizon, there are also several opportunities that can appear, which can support the implementation of methylation tests. These are opportunities that Self-screen cannot directly control and can happen during any of the horizons. These opportunities can help to increase awareness and strengthen the trust about methylation tests. The first one is that unpublished study results where the methylation test from Self-screen is used might become available. In addition, there can also be studies in other countries that might get published in the meantime that can support the scientific evidence of methylation.

Another opportunity is the presence of healthcare professionals, especially gynaecologists at congresses. These are places that they share knowledge with each other and discuss the developments in healthcare. Especially when a gynaecologist would have done a study about methylation this can be an interesting opportunity.

In addition, the revision of the guidelines can be a very interesting opportunity. If methylation tests would be included more as an advice to be used, this can help with formal recognition. Since gynaecologists follow the guidelines this can make the implementation easier.

Lastly, there is the opportunity of the development of methylation tests for anal cancer. If this progresses, laboratories might adapt their workflows for processing methylation tests already. This could lower the barrier for broader implementation since the infrastructure is then already in place.

All these opportunities should be monitored, so when they occur, Self-screen can react and adjust to this. Self-screen can use these changes by connecting them to relevant activities in the horizon, for example to strengthen the communication and to support broader implementation.

METHYLATION TESTING IN CERVICAL (PRE-) CANCER DIAGNOSTICS

Objective molecular risk stratification when cytology leaves clinical uncertainty

Premalignant cervical lesions are heterogeneous, which means that some lesions may progress while others regress. This can make it difficult to determine whether patients require treatment or can be safely monitored. Therefore, there is a clinical need for markers that can distinguish CIN lesions with a high short-term risk of progression to cervical cancer from those with a low risk. Methylation assays allow objective clinical decision-making about patient treatment or conservative management.

What is methylation?

Methylation is an epigenetic change in the DNA. Hypermethylation impacts the tumour surpressing functionality of the DNA.
Increased methylation levels therefore are a powerful indicator for progression or regression of pre-cancer stages.

Methylation test

The PreCursor-M test detects hypermethylation of two disease related genes, FAM19A4 and mir124-2. Extensive studies, including cross-sectional, longitudinal and prospective studies, provide evidence on the performance of the test in relation to progression and regression of pre-cancer lesions. As a result PreCursor-M distinguishes patients with a high risk on short-term progression versus a low risk on short-term progression

Numbers behind methylation

- **98.3%** Sensitivity cancer [1]
- **78.6%** Sensitivity CIN3+ [2]
- **76.8%** Specificity CIN 3+ [2]
- **96.9%** NPV[2]
- **28.2%** PPV[2]

When to use methylation?

Next to its primary use as triage marker after a positive HPV test, specific useful cases in diagnostics are:

- **ASC-US/LSIL cases:** To support decision-making for women with low-grade abnormalities. [3]
- **Pregnant women:** To help assess risk while avoiding unnecessary treatment.
- **Younger women with a child wish:** To support a more conservative approach and reduce the risk of overtreatment and complexities with pregnancy

Self-screen

Self-screen was founded in 2008 as a spin-off from Amsterdam University and is an independent company since 2012. The company is built on scientific expertise in HPV-induced cancers, qPCR, DNA methylation, and CE-IVD diagnostic assays. By translating molecular research into clinically applicable tests, Self-screen contributes to more accurate risk assessment in HPV-related disease.

[1] Vink et al, Int J Cancer 2020 – FAM19A4/miR124-2 methylation in invasive cervical cancer: A retrospective cross-sectional worldwide study. https://pubmed.ncbi.nlm.nih.gov/31390052/
[2] Bonde et al, Int J Cancer 2020 – Methylation markers FAM19A4 and miR124-2 as triage strategy for primary human papillomavirus screen positive women: A large European multicenter study. https://pubmed.ncbi.nlm.nih.gov/32997803/
[3] Dick et al, BMJ 2021 – Risk-stratification of HPV-positive women with low-grade cytology by FAM19A4/miR124-2 methylation and HPV genotyping. https://www.nature.com/articles/s41416-021-01614-4
Kremer et al, J Clinical Oncology 2022 – Clinical regression of high-grade cervical intraepitehelial neoplasia is associated with absence of FAM19A4/miR124-2 DNA methylation (Concerve Study) https://ascopubs.org/doi/full/10.1200/JCO.21.02433

WHEN SHOULD YOU USE METHYLATION?

Step-by-step guide

1 Identify the patient context
hrHPV-positive patient with cytological abnormalities or clinical uncertainty

2 Assess clinical risk factors
When methylation should be considered:
- ASC-US/LSIL cases
- Pregnant women
- Younger women with a child wish

3 Request a methylation test (PreCursor-M)
Use PreCursor-M to support risk stratification and clinical decision-making

- **+ Positive**
  High risk on short-term progression
- **- Negative**
  Low risk on short-term progression

Position in current Dutch guidelines

According to the cervixtology and hrHPV guidelines gynaecologists are allowed to consider methylation tests in specific cases where it can support clinical decision-making [5]

Want to learn more about the use of methylation tests?

Scan the QR code for additional background information, scientific papers and requesting the test.

Self-screen
INNOVATIVE | MOLECULAR | DIAGNOSTICS

[5] Cervixcytologie en hrHPV. (n.d.). https://richtlijnendatabase.nl/richtlijn/cervixcytologie/diagnostiek/cervixcytologie_keuze_voor_test_test_traject/nieuwe_moleculare_en_cytologische_technieken_detectie_cin2/moleculare_technieken_detectie_cin2.html

7.3 HORIZON 2: SHARING INFORMATION

Increase adoption of methylation with spokespersons through webinars and articles

(This image is generated with ChatGPT)

Focus

The focus in the second horizon is on increasing awareness and active education about methylation. The spokespersons can share their expertise with the early adopter gynaecologists. They will share their knowledge and experience about methylation through webinars and articles.

Goal

The goal is to increase the awareness and implementation of methylation among more gynaecologists through the spokespersons. A lot of gynaecologists already know methylation exists, but in this horizon, this should shift to understanding what value it can add and how and when it can be applied.

The goal is to educate mostly the early adopters, with a focus on the ones in Amsterdam. The focus on this group is because after the innovators, the early adopters follow. Since they can adapt relatively quickly but do need the innovators to move first. Amsterdam is chosen as the initial focus since this is the most accessible for methylation tests, since the tests can be processed in the AMC. Hospitals and medical centres near the AMC can send methylation tests more easily, which makes the implementation of the tests in this region more accessible.

Key activities

The first activity in this horizon is to co-design webinars with gynaecologists. These webinars should consist of scientific facts which show the advantages of methylation and real cases and experiences from the gynaecologist to support this. The collaboration between Self-screen and the spokespersons is important since Self-screen can contribute scientific evidence and gynaecologists can make the information relevant and trustworthy with real examples.

These co-designed webinars should be held by the spokespersons so they can share the information with other gynaecologists. The promotion of the webinars will focus on the clinical centres in Amsterdam, however, any gynaecologist who is interested can join. These webinars should explain when methylation can be used and what advantages it can bring to convince other gynaecologists to see this value as well.

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A webinar can be organised with or without accreditation points. A webinar without points is easier to organise, but a webinar with accreditation points can attract more gynaecologists. Gynaecologists need to get a certain amount of accreditation points every five years, so this could motivate gynaecologists to join the webinar. In addition, the webinar speaker can also get accreditation points. However, to get the webinar approved for accreditation points there are some required conditions. A few of these aspects are especially important since it is in collaboration with a commercial company:

- The content should be objective
- Promotional programmes will not be accredited
- Brand names of the test cannot be mentioned
- A personal disclosure page at the beginning of the presentation

Another important activity is to publish an article in the NTOG about methylation, this can also help increase the awareness among gynaecologists. An article can also help to clearly explain the scientific findings in one place. It is also a source of information that gynaecologists can easily revisit and share with each other. In the NTOG there are two different types of articles, the first one is a scientific article which must be approved by the NTOG. This is a free but more complicated option. The second option is to publish an article as an advertorial. This is an easier option but costs money, depending on the size this can cost up to 6850 euros.

A clear protocol is also an important aspect of this horizon. To be able to implement methylation in places where this is not yet possible or used, a clear protocol for gynaecologists is needed. This protocol should explain when methylation can be considered and how to interpret the results.

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Challenges

In this horizon, the challenges are mostly about sharing information effectively and engaging gynaecologists. The first challenge is the strong collaboration with spokespersons that is required. Their involvement is very valuable, and it is important that they take an active role in promoting and explaining methylation. They must be able to communicate the value of methylation tests very well to other gynaecologists. Some people might be better at presenting and sharing their stories than others. To tackle this challenge the spokespersons could discuss who is good at this. Otherwise practising the presentation or a short course about presenting can be considered.

Another challenge is to ensure the participation of other gynaecologists, namely the early adopters, to go to webinars or read the article. They might not prioritize going to webinars if they are not sure if it is relevant. They must be encouraged to learn more about methylation and the value it has to offer. To address this, accreditation points for a webinar could help motivate the participation. Invitations, promotion and/or reminders can also help to increase participation. For the article, it could get more attention when it is published as a real article compared to an advertorial.

The next challenge is that the communication of the information should be clear. Next to understanding how a methylation tests works, it should also be clear when to apply them and what advantages they can offer. The webinars and the article should be carefully designed and written. The use of scientific data and real-life examples can help to improve the understanding and engagement.

A further challenge can be the logistics of a webinar, it could for example face scheduling conflicts. Because of this, not all the gynaecologists that might want to join the webinar can be there at that moment. An option could be to record the webinar or organise multiple webinars.

The last challenge is to ensure that knowledge about methylation actually translates into the implementation and use of the test. To facilitate this, it should be easy for gynaecologists to request the test, and a clear protocol should be in place. If the test is not easily accessible or if there is no established protocol, gynaecologists may not request it. The protocol should be developed in advance by the spokesperson to support smooth implementation. A clear protocol ensures that when a gynaecologist requests a methylation test for the first time, the process runs smoothly and avoids negative experiences. It is difficult to fully control the requests made by gynaecologists. This challenge remains the most significant and may be difficult to tackle.

Costs

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7.4 HORIZON 3: EVALUATING AND IMPROVING

Scale methylation adoption through evaluation, improvement and shared clinical insights.

(This image is generated with ChatGPT)

Focus

The third horizon focuses on scaling the implementation of methylation throughout the Netherlands with a focus on the early majority. The feedback from the gynaecologists that already use methylation tests is essential to improve the process and show the positive outcomes to other gynaecologists to convince them.

Goal

The goal of the third horizon is to evaluate the use of the methylation tests with the gynaecologists that already use them. This feedback is essential to improve the implementation and optimize the process. A goal with the feedback from the results is also to convince other gynaecologists, the early majority. The findings can help to show the positive sides and results of methylation to gynaecologists who are still a bit hesitant about methylation tests.

Key activities

The key activities from horizon 3 focus on evaluation, improvement and communication to the early majority. First, feedback should be collected from the gynaecologists who already use methylation tests. The gynaecologists need to monitor their findings to communicate them with Self-screen. This includes when methylation tests are used and what the results are and how they are acted upon.

To gather this feedback in a structured way, short surveys will be sent to gynaecologists who use methylation tests. These surveys would include questions in the direction of when methylation tests are used, what the results are and how they are acted upon. In addition, a few short interviews should be conducted to get more in-depth insights. In these interviews the gynaecologists can share their reflections of the use of the test, areas of improvement and experiences about working with methylation tests. These experiences can then be shared with other gynaecologists. The combination of surveys and interviews can provide a good understanding of the implementation of methylation tests. It can provide valuable insights to improve and share the experiences of methylation with other gynaecologists.

These findings should be used for improvement of the process and protocols, but also for the communication of the findings to the early majority. The results can be shared in the webinars to make them more tangible and credible for the gynaecologists who do not use methylation tests yet. With this, it can be shown that methylation is not only scientifically proven but also useful and feasible in their practice.

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To make broader implementation possible, more laboratories should be included in this horizon. For more gynaecologists to be able to request the test, it also has to be possible to do the test in a laboratory. In this horizon there should be looked at possibilities for sending methylation tests to certain laboratories or ensuring that more laboratories are able to process the test

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Challenges

One of the key challenges of the third horizon is that the feedback should be collected in a structured and useful way. This is needed for clear insights and to ensure that they can be translated into concrete improvements. To ensure that the feedback is collected in a structured way, a clear survey should be designed and sent out. For the interviews the questions have to be set up with a clear interview guide. With a good and structured preparation, there will be clear evaluation results to analyse and improve.

The second challenge is to encourage the gynaecologists to act on the results from the evaluation. Most importantly, translating the findings and knowledge to webinars and/or an article or sharing this with other gynaecologists in other ways would be helpful. This is also something that needs to be done by the gynaecologists themselves and might be more difficult to have effect on as a company. However, the gynaecologists who are also spokespersons who get a compensation might be more open to share their findings with others.

The third challenge is to find and convince more labs to process methylation tests. Labs will need to adjust, and before they change their workflow, they need to be encouraged to invest in this. If the labs are not convinced, adoption can be slowed down, even if gynaecologists are enthusiastic about methylation. This is a more complicated

challenge to tackle. If the labs would not want to cooperate it will be difficult to expand methylation tests to more places. It is important to show that gynaecologists do want to request the test, so the labs want to start with it as well. If this proves to be difficult, there can also be looked at improving the infrastructure to send the test to the labs that do want to incorporate methylation tests.

Costs

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08

DISCUSSION

8 DISCUSSION

8.1 General discussion

This graduation project explored the implementation of methylation test in the cervical cancer screening and diagnostics. The findings show that despite the scientific evidence, the adoption of methylation remains slow. The main barrier is not the effectiveness of the test itself, but the integration into an established screening programme and into a system where the awareness about methylation is low.

To understand the current system, research is done to compare current screening programmes and diagnostics in different high- income countries. This highlighted the differences in the organisation of healthcare, guidelines and decision-making and that this can have an effect on the adoption of a new test. For the development of the strategy, it was chosen to focus on the implementation of methylation test in the diagnostics of cervical cancer, since this showed the most promising opportunities in the next years.

The awareness of methylation tests is important for the implementation together with alignment between stakeholders and the implementation in the guidelines. Based on these insights a strategic and tactical roadmap are developed with a focus on reaching gynaecologists to support gradual implementation of methylation into practice.

The strategic roadmap translates the findings into three horizons for gradual implementation with the goals of each horizon. The tactical roadmap translates these goals into concrete actions in each horizon. The strategy outlines how methylation can be positioned and identifies key steps needed to increase awareness and use of methylation tests. The roadmap is designed in different horizons as a phased approach since an implementation in a healthcare system does not happen in a single step.

Overall, this graduation project shows that the implementation of methylation in diagnostics for cervical cancer in the Netherlands depends on the awareness of methylation among gynaecologists. To address this, a strategy is developed for this implementation. The roadmaps provide a structured pathway to support this implementation of methylation tests in cervical cancer diagnostics in the Netherlands.

8.2 Limitations and recommendations

Laboratory perspectives and scalability

One of the limitations from this graduation project is that not all the different stakeholders were included in the interviews. Especially the laboratories are an important stakeholder, since they need to be able to process the test. To address this, it is recommended for future research to involve laboratories in interviews even before the second horizon, as described in the strategy. This could provide insights about the possible bottlenecks for broader implementation of methylation tests in the Netherlands. If some laboratories are not willing to adapt, other options such as infrastructures to send samples to the labs who do have the capacity to process the test could be explored.

International applicability

This graduation project focused on the implementation of methylation tests in the Netherlands. While the same strategy could potentially be applied in other countries,

some adaptation might be required to account for the differences in healthcare systems. Future research could examine the structure of other countries to find out whether the strategy is compatible in other countries or how it could be adjusted for international implementation.

Roadmap improvements

The proposed strategy consists of activities in three horizons. However, unanticipated challenges or changes can arise during the implementation that can affect on the adoption. To address this, the roadmap can be seen as adaptive instead of a fixed plan. Continuous monitoring of the roadmap and changes is important to make iterative adjustments on the strategy to remain relevant.

Uncertainty results interpretation

A critical limitation is that there is no clear and officially established clinical protocol that describes how gynaecologists should act on a negative or positive result of a methylation test. This might be confusing for gynaecologists who want to request the test. Future research should focus on the clinical pathways after a positive and negative methylation test to ensure clear and consistent decision-making when methylation is implemented on a bigger scale.

Broader adoption guidelines

Although methylation tests are already mentioned in the guidelines, the presence is very limited. If the implementation of methylation tests could be implemented broader in the guidelines, this could improve the adoption. Advising the methylation test in the guidelines and recommending when and how the test should be used, would help gynaecologists with how to interpret the results. This can increase the confidence in requesting the test. Future research should look into the possibilities of the broader implementation of methylation tests in the guidelines.

Introducing methylation earlier

Another recommendation is to explore the opportunities to incorporate the information about methylation into the training and education of gynaecologists. It might be easier to introduce methylation from the start instead of changing their knowledge and behavior later, when they already have established routines.

8.3 Reflection design approach and methods

During this project, different research and design methods were used to understand the context, different stakeholder perspectives and the challenges around the implementation of methylation tests. This section reflects on the methods that were used and how they contributed to the project, what was learned from it and what can be improved for future projects.

Designing for healthcare was different from more open design projects. Multiple stakeholders are involved, gynaecologists, researchers, epidemiologists, laboratories and guideline committees have different kinds of interests and influence. This made it difficult to align these insights into one strategy.

Before conducting the interviews, it was required to get approval from the Human Research Ethics Committee, to ensure the study followed the ethical standards for research. An advantage of this study was that there were no patients involved in the research. This reduced the ethical complexity since there was no vulnerable data included about patients. However, it takes time to get everything approved so it is important to start this process as one of the first steps.

Another challenge was the limited time and availability of healthcare professionals. When reaching out to different gynaecologists, the response rate was very low, even sometimes when they did answer, after a few messages they went silent. The gynaecologists that were interviewed did this during their lunch break or got calls in between. One of the interviews was even conducted in three different moments since they needed to be somewhere, this made it more difficult to go in-depth in certain subjects.

Systems in healthcare are also highly regulated and based on evidence and safety, which made the freedom of creativity in design more limited. Solutions must not only be innovative but also scientificically based and believable. The more common used design methods could not always be applied in healthcare context. Most methods are based on encouraging creativity, however, idea generation for healthcare has its limitations and needs to be evidence-based and trustworthy. Research from Groeneveld et al. (2018) also showed that the balance between the structured clinical requirements and more flexible and creative design methods are complex.

This project required an approach that combined the elements of design with a more structured and evidence-based strategy. While the design methods were still relevant and valuable to use, they must be adapted to fit within the constraints of healthcare systems.

8.4 Use of AI

In this thesis, artificial intelligence, specifically ChatGPT was used as a supportive tool in the writing process. It was used to help with reformulating and improving certain parts of text to enhance the clarity and readability. After the use of AI, the text was rewritten again and reviewed to ensure that the text reflected the intended meaning.

AI was also used to generate a few images to support the communication of the concepts. The visuals were adapted where necessary until they were relevant and appropriate for the context they were meant for.

Overall, AI was used as an aid to strengthen the communication. Careful and critical evaluation of the output is maintained throughout the process. In this project the use of AI mainly contributed to improve readability and supporting visual elements. While always staying critical about the output of AI.

09

CONCLUSION

9 CONCLUSION

In conclusion, this graduation project addressed the gap between the strong scientific literature about methylation tests in cervical cancer prevention and diagnostics and the slow adoption of methylation in the real practice. Existing screening programmes and limited awareness among gynaecologists contribute to the fact that methylation is barely embedded in practice.

Based on this problem and after research, the question was redefined as: How can methylation tests be implemented in the Dutch cervical cancer diagnostics by increasing awareness, building trust and clearly communicating the clinical added value to gynaecologists?

The answer to this question is translated into a strategy, which consists of a strategic and a tactical roadmap. Both are structured within three horizons for the implementation of methylation tests in diagnostics in the Netherlands. In horizon 1, the focus is on building awareness and introducing methylation tests to gynaecologists and finding gynaecologists who are enthusiastic about methylation.

The second horizon is focused on sharing the information about methylation with even more gynaecologists through webinars and articles created by gynaecologists who believe in methylation. In horizon 3, the use of methylation tests is evaluated, and these findings are shared with an even bigger group of gynaecologists to convince them to use methylation as well.

The strategy is validated with different stakeholders and assessed as feasible in the Dutch diagnostics market for cervical cancer. This supports the strategy and a realistic implementation.

A broader implementation of methylation tests in the cervical cancer screening programme is considered as a future vision. The proposed strategy contributes to this future vision by supporting the adoption and future scalability to the screening programme.

10

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10 REFERENCES

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11

APPENDIX

11 APPENDIX

A. Competitor analysis

This section has been removed from the public version, as it contains confidential information.

B. Interview guide

Interviewgoal: Understand the current screening and diagnostics process of cervical cancer and the knowledge of methylation tests and how these could be implemented.

Planned date: dd-03-2026
Method: Physical or teams call, in Dutch

Checklist for start
- Werkt de teams call en het opname systeem
- Geopende interview guide en eventueel geprint
- Presentatie methylering en richtlijnen open op laptop
- Notitieboekje en papier

Persoonlijke introductie
Hi, dank u wel dat u tijd kon maken voor deze meeting. Ik ben Riva en ik ben bezig met de masteropleiding Strategic Product Design aan de TU Delft. Op dit moment ben ik bezig met mijn afstudeerproject in samenwerking met Self-screen.

I**ntroductie afstudeerproject**
Voor mijn masterthesis doe ik onderzoek naar de mogelijke implementatie van methyleringstesten binnen het huidige traject van de screening voor baarmoederhalskanker. Dit onderzoek voer ik uit in samenwerking met Self-screen, een bedrijf dat deze methyleringstesten ontwikkelt.

De test zou kunnen bijdragen aan een betere inschatting van het risico op baarmoederhalskanker waar voordelen bij komen kijken ten opzichte van het huidige traject. Voor mijn onderzoek kijk ik naar de mogelijke implementatie van deze test binnen het bestaande screenings- en vervolgtraject.

Consent form
Voordat we gaan beginnen, wil ik graag controleren of het oké is als ik dit gesprek opneem en notities meeschrijf. Ik heb U ook al eerder een consent form gestuurd voor dit onderzoek, heeft u hier al naar kunnen kijken en heeft u hier misschien nog verdere vragen over?

Zoals ook beschreven zou ik resultaten van dit gesprek graag anoniem verwerken in mijn afstudeerproject. Als u hier akkoord mee bent zou ik graag de opname starten.

Start opname!!

C. Informed consent form

U wordt uitgenodigd om deel te nemen aan een onderzoek genaamd "Marktintroductie strategie voor methyleringstesten in HPV-screening, detectering en preventie''. Dit onderzoek wordt uitgevoerd door master student Riva Hoogveld van de TU Delft in samenwerking met het bedrijf Self-screen.

Het doel van dit onderzoek is het ontwikkelen van een strategische roadmap voor de implementatie en marktintroductie van een methylerings-triagetest voor HPV-positieve testen.
De data zal gebruikt worden voor de volgende onderdelen:
- Masterthesis (TU Delft)
- Academische publicatie(s) (geanonimiseerd)
- Praktische toepassing: het opstellen van een implementatie roadmap voor de methyleringstest

U wordt gevraagd om vragen te beantwoorden in een interview over onderwerpen zoals de huidige processen op het gebied van HPV-screening, detectie en preventie, en de eventuele toepassing van de methyleringstest binnen dit systeem.

Zoals bij elke onlineactiviteit is het risico van een databreuk aanwezig. Wij doen ons best om uw antwoorden vertrouwelijk te houden. We minimaliseren de risico’s door:
- Uw naam en contactgegevens gescheiden van de interviewdata te bewaren.
- Audio-opnames, transcripties en aantekeningen op te slaan in de beveiligde TU Delft Onedrive met beperkte toegang (alleen onderzoeker).
- In de uitwerking identificerende details te verwijderen en citaten alleen te gebruiken in geanonimiseerde vorm.

Uw deelname aan dit onderzoek is volledig vrijwillig, en u kunt zich elk moment terugtrekken zonder reden op te geven. U bent vrij om vragen niet te beantwoorden. De data zal worden verwijderd binnen 3 maanden na afronding van de thesis.

Uitvoerende onderzoeker:
Riva Hoogveld

Verantwoordelijke onderzoeker:
Valeria Pannunzio

PLEASE TICK THE APPROPRIATE BOXES	Yes	No
A: GENERAL AGREEMENT – RESEARCH GOALS, PARTICPANT TASKS AND VOLUNTARY PARTICIPATION		
1. Ik heb de informatie over het onderzoek gedateerd [04/02/2026] gelezen en begrepen, of deze is aan mij voorgelezen. Ik heb de mogelijkheid gehad om vragen te stellen over het onderzoek en mijn vragen zijn naar tevredenheid beantwoord.	☐	☐
2. Ik doe vrijwillig mee aan dit onderzoek, en ik begrijp dat ik kan weigeren vragen te beantwoorden en mij op elk moment kan terugtrekken uit de studie, zonder een reden op te hoeven geven.	☐	☐
3. Ik begrijp dat mijn deelname aan het onderzoek de volgende punten betekent - Een met audio opgenomen interview - De audio zal getranscribeerd worden als tekst en daarna worden vernietigd.	☐	☐
4. Ik begrijp dat mijn deelname aan het onderzoek niet wordt gecompenseerd	☐	☐
5. Ik begrijp dat de studie naar verwachting in juli 2026 eindigt.	☐	☐
B: POTENTIAL RISKS OF PARTICIPATING (INCLUDING DATA PROTECTION)		
6. Ik begrijp dat mijn deelname het risico meebrengt dat ik onbedoeld gevoelige informatie kan vrijgeven. Ik begrijp dat deze risico's worden geminimaliseerd door dat ik de content in zou kunnen zien voor publicatie.	☐	☐
7. Ik begrijp dat mijn deelname betekent dat er persoonlijke identificeerbare informatie en onderzoeksdata worden verzameld, met het risico dat ik hieruit geïdentificeerd kan worden. Dit kan eventueel effect hebben op mijn publieke reputatie.	☐	☐
8. Ik begrijp dat de volgende stappen worden ondernomen om het risico van een databreuk te minimaliseren, en dat mijn identiteit op de volgende manieren wordt beschermd in het geval van een databreuk: - Door geanonimiseerde data collectie - Veilige data opslag	☐	☐
9. Ik begrijp dat de persoonlijke informatie die over mij verzameld wordt en mij kan identificeren, zoals naam en email, niet gedeeld worden buiten het studieteam.	☐	☐

10. Ik begrijp dat de persoonlijke data die over mij verzameld wordt, vernietigd wordt eind juli.	☐	☐
C: RESEARCH PUBLICATION, DISSEMINATION AND APPLICATION		
11. Ik begrijp dat na het onderzoek de geanonimiseerde informatie gebruikt zal worden voor een master thesis en het ontwerpen van een strategie.	☐	☐
12. Ik geef toestemming om mijn antwoorden, ideeën of andere bijdrages anoniem te quoten in resulterende producten.	☐	☐
D: (LONGTERM) DATA STORAGE, ACCESS AND REUSE		
13. Ik geef toestemming om de geanonimiseerde data, verwerkt in de masterthesis gearchiveerd wordt in de TU Delft repository opdat deze gebruikt kunnen worden voor toekomstig onderzoek en onderwijs.	☐	☐

Signatures

_____	_____	_____
Naam deelnemer	Handtekening	Datum

Ik, **de onderzoeker**, verklaar dat ik de informatie en het instemmingsformulier correct aan de potentiële deelnemer heb voorgelezen of laten lezen en, naar het beste van mijn vermogen, heb verzekerd dat de deelnemer begrijpt waar hij/zij vrijwillig mee instemt.

_____	_____	_____
Naam onderzoeker	Handtekening	Datum

Contactgegevens van de onderzoeker voor verdere informatie:

- Riva Hoogveld

D. Interview questions

Interview gynaecologists

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Interview distributor

This section has been removed from the public version, as it contains confidential information.

Interview epidemiologist

This section has been removed from the public version, as it contains confidential information.

Interview researcher

This section has been removed from the public version, as it contains confidential information.

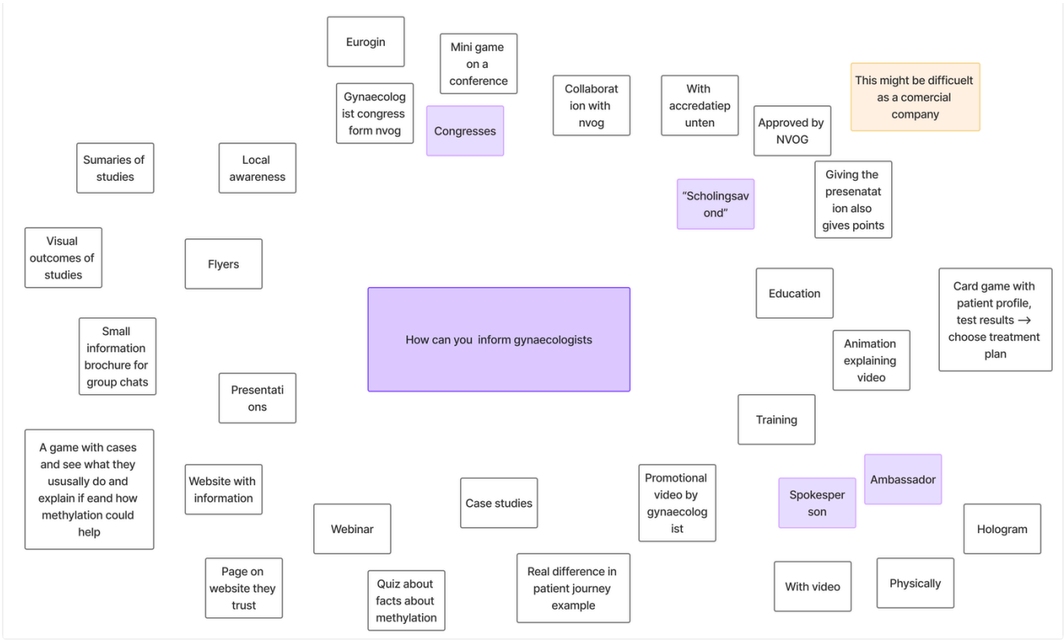
Interview gynaecoloog & researcher

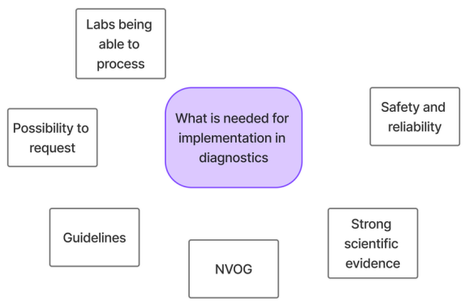
This section has been removed from the public version, as it contains confidential information.

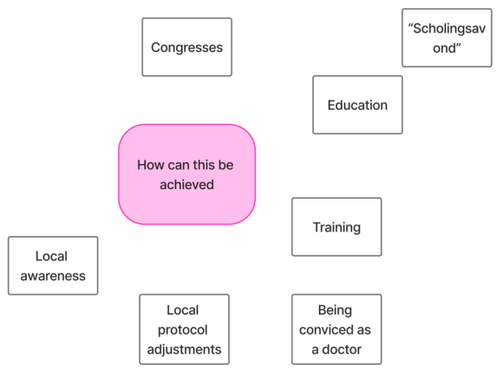
E. Thematic analysis

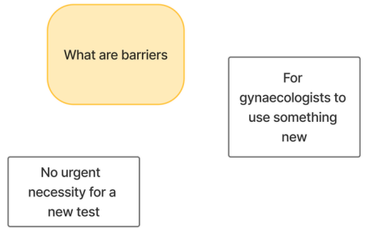
This section has been removed from the public version, as it contains confidential information.

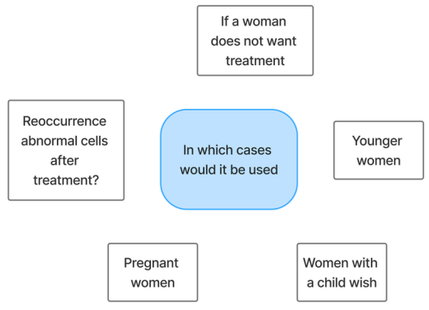
F. Individual ideation

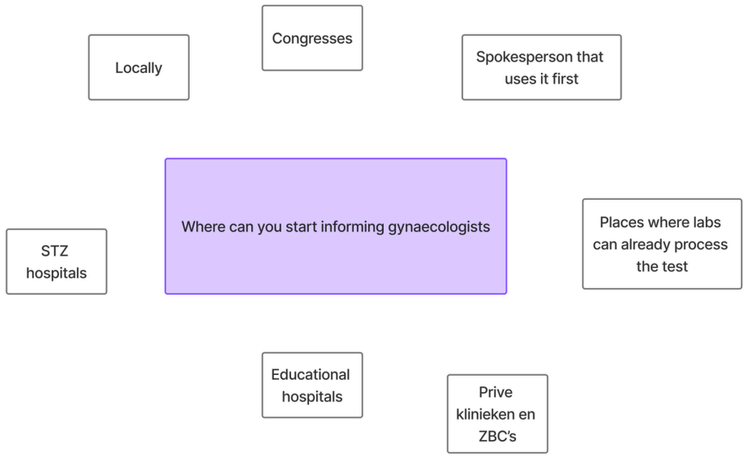




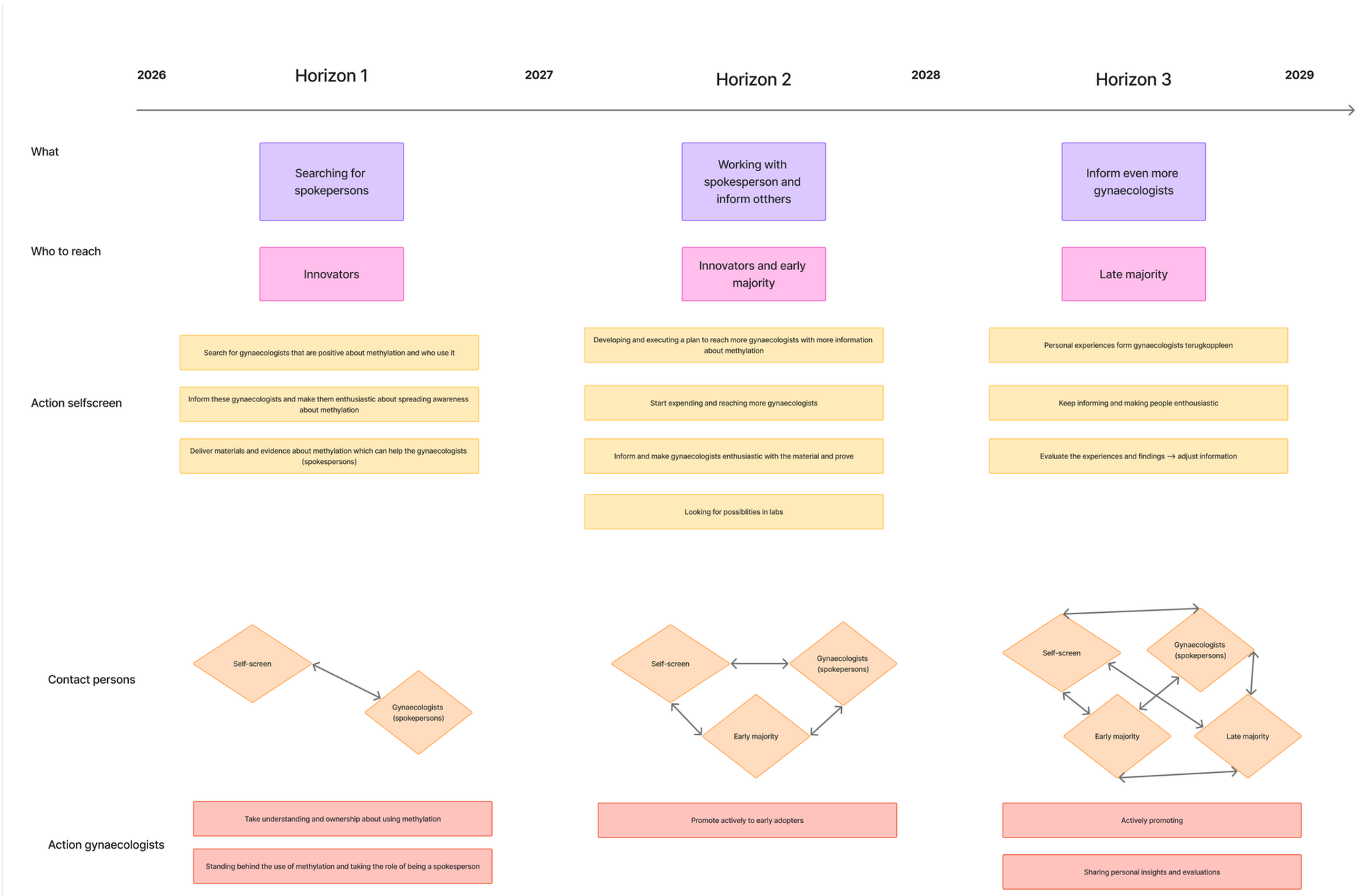


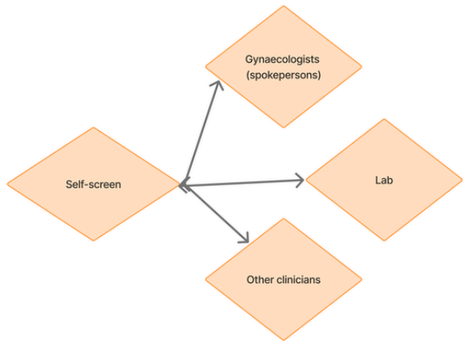
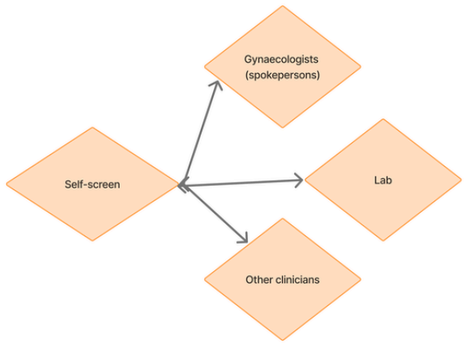
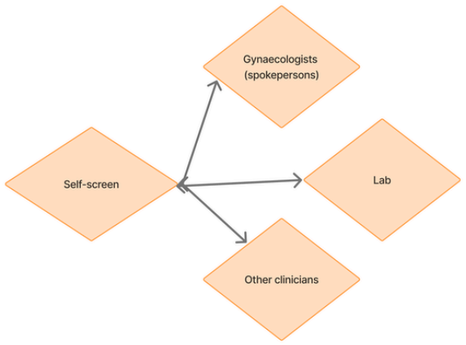






G. First concept roadmaps



	2026	2027	2028	2029
	Horizon 1	Horizon 2	Horizon 3	
What	Promotion of methylation	Organizing a way to spread information to gynaecolgists	Feedback on what is working and evaluating and improving	
Who to reach	Innovators	Early majority	Early/late majority	
Action selfscreen	Promotion on places where gynaecologists go to such as congresses Self promotion, also focus on what they stand for, not typical commercial company Create publicity of the company and the methylation test	Organzing an evening to spread information about methylation Invite different users of hte methylation test Add active element for giving a better feeling and more action points	Feedback/evaluation of the use→ what can we improve/how much is it used Setting up the possibilities of the use	
Contact persons				
Action gynaecologists	Create interest and curiosity in methylation	Setting up the possibilities of the use of methylation Finding out where it is and is not possible → how to make it possible	Monitoring what the results are Looking out for what works and what does not work Act actively on these results	

H. Concept roadmaps and flyer

	2026	2027	2028	2029
	HORIZON 1	**HORIZON 2**	**HORIZON 3**	**FUTURE VISION**
	PROMOTION AND FINDING SPOKESPERSONS	**SHARING INFORMATION**	**EVALUATING AND IMPROVING**	**THE NEW STANDARD**
	Build awareness by engaging a gynaecologists through congresses and collaboration with them as spokespersons.	**Increase adoption of methylation in diagnostics for cervical cancer in collaboration with spokespersons through webinars and articles.**	**Scale methylation adoption in diagnostics for cervical cancer through evaluation, improvement, and shared clinical insights.**	**Methylation tests being a standard action for gynaecologists to take.**
				
GOAL	The goal of Horizon 1 is to create awareness among gynaecologists who are already interested in methylation testing or who currently use it in their practice. Self-screen should identify and engage them and assess their willingness to support the wider communication of methylation testing. These gynaecologists will be credible spokespersons who can share their experience and advocate for the use of methylation. These spokesperson will be valueable for a strong foundation for clinical credibility, visibility, and future adoption of methylation.	In Horizon 2, the goal is to get active clinical engagement and education. Self-screen should work closely with the spokespersons to promote the value and use of methylation tests among other gynaecologists. By involving respected gynaecologists, Self-screen can build stronger credibility, enthusiasm, and trust for a bigger group of gynaecologists. The spokesperson should help to communicate a clear protocol for methylation tests, to support consistent and correct implementation.	The goal of Horizon 3 is to evaluate the use of methylation tests in clinical practice and optimise the this where needed. Gynaecologists who already use methylation should monitor how implementation is going. These findings can be shared with other gynaecologists to show the value, build confidence, and convince more clinicians to adopt methylation tests in diagnostics.	All gynaecologists use a methylation test in the diagnostics for cervical cancer when this can provide added value. This can for example be when there is an unclear decision to make especially with younger or pregnant women. By embedding methylation tests into the process, it can support the decision-making of gynaecologists and it can improve the women's health outcomes.
TARGET AUDIENCE	• Gynaecologists (innovators)	• Gynaecologists (early adopters) with an initial focus on Amsterdam	• Gynaecologists who use methylation • Gynaecologists (early majority) • Labs	
KEY ACTIVITIES SELF-SCREEN	• Promotion methylation tests at relevant congresses • Spreading flyer with relevant information • Direct contact with enthousiast gynaecologists to explore spokepersons	• Co-design a webinar with gynaecologists • Write article for in the NTOG about methylation • Explore additional labs for implementation in Horizon 3	• Collect feedback about the using methylation • Evaluate and improve where neccesary • Reaching more gynaecologists through webinars, using learnings and early results to convince the early majority	
KEY ACTIVITIES GYNAECOLOGIST	• Attending congresses	• Actively promote methylation through webinars to inform and activate others • Write clear protocol for methylation tests	• Monitoring results of using methylation • Act actively on these findings	
KEY ACTIVITIES DISTRIBUTOR	*This section has been removed from the public version, as it contains confidential information.*	*This section has been removed from the public version, as it contains confidential information.*	*This section has been removed from the public version, as it contains confidential information.*	

HORIZON 1

2026

PROMOTION AND FINDING SPOKESPERSONS

Build awareness by engaging a gynaecologists through congresses and collaboration with them as spokespersons.

HORIZON 2

2027

SHARING INFORMATION

Increase adoption of methylation in diagnostics for cervical cancer in collaboration with spokespersons through webinars and articles.

HORIZON 3

2028

2029

EVALUATING AND IMPROVING

Scale methylation adoption in diagnostics for cervical cancer through evaluation, improvement, and shared clinical insights.

FUTURE VISION

THE NEW STANDARD

Methylation tests being a standard action for gynaecologists to take

All gynaecologists use a methylation test in the diagnostics for cervical cancer when this can provide added value. This can for example be when there is an unclear decision to make especially with younger or pregnant women. By embedding methylation tests into the process, it can support the decision-making of gynaecologists and it can improve the women's health outcomes.

ACTIONS

- Promotion methylation to gynaecologists
- Search and contact interested gynaecologists
- Co-design webinar & article
- Start looking for other labs
- Inspire other gynaecologists about methylation
- Understanding and using methylation tests
- Evaluation of the use of methylation
- Take role of spokesperson
- Writing protocol for requesting and using methylation
- Improve process of methylation
- Actively promote methylation
- Monitoring results of methylation testing
- Act on findings of the evaluation

ACTORS

- Self-screen
- Gynaecologists (innovators)
- Gynaecologists (early adopters)
- Labs
- Gynaecologists (early majority)

TOUCHPOINTS

HORIZON 1	HORIZON 2	HORIZON 3
• National and international congresses • Direct contact gynaecologists (mail or in person) • distributors	• Webinars to inform and activate • NTOG article about methylation • Local awareness in hospitals and clinical centres	• Direct contact by sending evaluation form • Webinars/NTOG

COSTS

HORIZON 1	HORIZON 2	HORIZON 3
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CHALLENGES

HORIZON 1	HORIZON 2	HORIZON 3
• Finding gynaecologists with an interest in or experience with methylation tests • Managing potential conflict-of-interest for gynaecologists related to collaboration with a commercial company	• Strong collaboration with spokespersons • Engaging gynaecologists with educational content such as articles and webinars • Making sure that gynaecologists convert knowledge about methylation into implementation	• Reaching labs and convincing them to process methylation tests • Making sure gynaecologists taking the time to evaluate the process and findings

DECISION GATE

HORIZON 1	HORIZON 2	HORIZON 3
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METHYLATION TESTING IN CERVICAL (PRE-) CANCER DIAGNOSTICS

Objective molecular risk stratification when cytology leaves clinical uncertainty

Premalignant cervical lesions are heterogeneous, which means that some lesions may progress while others regress. This can make it difficult to determine whether patients require treatment or can be safely monitored. Therefore, there is a clinical need for markers that can distinguish CIN lesions with a high short-term risk of progression to cervical cancer from those with a low risk. Methylation assays allow objective clinical decision-making about patient treatment or conservative management.

What is methylation?

Methylation is an epigenetic change in the DNA. Hypermethylation impacts the tumor surpressing functionality of the DNA.
Increased methylation levels therefore are a powerful indicator for progression or regression of pre-cancer stages.

Methylation test

The PreCursor-M test detects hypermethylation of two disease related genes, FAM19A4 and mir124-2. Extensive studies, including cross-sectional, longitudinal and prospective studies, provide evidence on the performance of the test in relation to progression and regression of pre-cancer lesions.As a result PreCursor-M distinguishes patients with a high risk on short-term progression versus a low risk on short-term progression

Numbers behind methylation

- **98.3%** Sensitivity cancer [1]
- **78.6%** Sensitivity CIN3+ [2]
- **76.8%** Specificity CIN 3+ [2]
- **96.9%** NPV[2]
- **28.2%** PPV[2]

When to use methylation?

Next to its primary use as triage marker after a positive HPV test, specific useful cases in diagnostics are:

- **ASC-US/LSIL cases:** To support decision-making for women with low-grade abnormalities. [3]
- **Pregnant women:** To help assess risk while avoiding unnecessary treatment.
- **Younger women with a child wish:** To support a more conservative approach and reduce the risk of overtreatment and complexities with pregnancy

Self-screen

Self-screen was founded in 2008 as a spin-off from Amsterdam University and is an independent company since 2012. The company is built on scientific expertise in HPV-induced cancers, qPCR, DNA methylation, and CE-IVD diagnostic assays. By translating molecular research into clinically applicable tests, Self-screen contributes to more accurate risk assessment in HPV-related disease.

[1] Vink et al, Int J Cancer 2020 – FAM19A4/miR124-2 methylation in invasive cervical cancer: A retrospective cross-sectional worldwide study. https://pubmed.ncbi.nlm.nih.gov/31390052/
[2] Bonde et al, Int J Cancer 2020 – Methylation markers FAM19A4 and miR124-2 as triage strategy for primary human papillomavirus screen positive women: A large European multicenter study. https://pubmed.ncbi.nlm.nih.gov/32997803/
[3] Dick et al, BMJ 2021 – Risk-stratification of HPV-positive women with low-grade cytology by FAM19A4/miR124-2 methylation and HPV genotyping. https://www.nature.com/articles/s41416-021-01614-4
Kremer et al, J Clinical Oncology 2022 – Clinical regression of high-grade cervical intraepitehelial neoplasia is associated with absence of FAM19A4/miR124-2 DNA methylation (Concerve Study) https://ascopubs.org/doi/full/10.1200/JCO.21.02433

WHEN SHOULD YOU USE METHYLATION?

Step-by-step guide

1. **Identify the patient context**
   hrHPV-positive patient with cytological abnormalities or clinical uncertainty
2. **Assess clinical risk factors**
   Consider age, pregnancy status, wish for future pregnancy, cytology and colposcopy findings
3. **Request a methylation test (PreCursor-M)**
   Use PreCursor-M to support risk stratification and clinical decision-making

- **+ Positive**
  High risk on short-term progression
- **- Negative**
  Low risk on short-term progression

Position in current Dutch guidelines

According to the cervixtology and hrHPV guidelines gynaecologists are allowed to consider methylation tests in specific cases where it can support clinical decision-making.

Want to learn more about the use of methylation tests?

Scan the qr code for additional background information, scientific papers and requesting the test.