

Supplementary Information (online only)

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Survey questionnaire:

Understanding the WID test:

1) Please tick the types of cancer that the WID test targets. (One answer only).

- ovarian cancer, womb cancer, lung cancer, and pancreatic cancer
- colorectal cancer, breast cancer, cervical cancer, and liver cancer
- breast cancer, ovarian cancer, womb cancer, and cervical cancer

2) What can a woman do with a test result that tells her that she has a lower-than-average risk? (One answer only)

- Taking less intensive screening, what potentially reduces the risk of getting false alarms and unnecessary treatment.
- Taking more intensive screening, what potentially reduces the risk of dying of cancer.
- Have the certainty that she will definitely not get one of the tested types of cancer.

3) What could a woman do with a test result that tells her that she is at higher-than-average risk? (One answer only).

- Taking less intensive screening, what potentially reduces the risk of dying of cancer.
- Taking more intensive screening or preventive actions, what potentially reduces the risk of dying of cancer.
- Have the certainty that she will definitely get one of the tested types of cancer.

4) The WID test aims at predicting a woman's risk of developing female cancers by analyzing her epigenome.

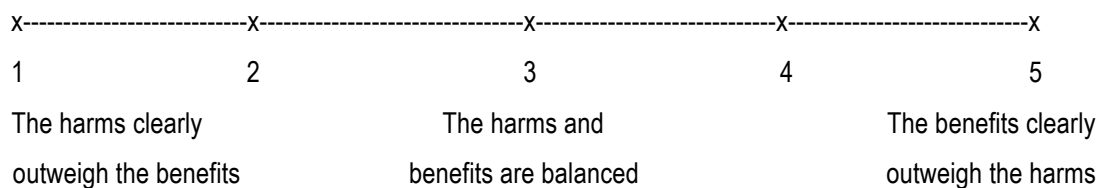
Which of the following statements about the epigenome is correct (please tick only one answer):

- Your environment and lifestyle is changing the epigenome of your cells
- The epigenome always stays the same during your lifetime
- The epigenome is a cell with cancerous mutations.

Attitude and intentions respecting the WID test:

The WID test is meant to predict your personal risks of getting one or more of the four female cancers: breast cancer, ovarian cancer, cervical cancer, womb cancer.

1) When thinking of the WID test, how do you feel about the balance between benefits and harms?



2) Whereas some women prefer to know their risks of getting a disease in the future, others prefer not to. Thinking of the WID test, do you want to know your risk of developing one or more of the following four female cancers within the next 10 years?

- | | |
|---------------------|--|
| For breast cancer | <input type="radio"/> yes <input type="radio"/> no |
| For womb cancer | <input type="radio"/> yes <input type="radio"/> no |
| For cervical cancer | <input type="radio"/> yes <input type="radio"/> no |
| For ovarian cancer | <input type="radio"/> yes <input type="radio"/> no |

3) If already easily and freely available now, would you do the WID test to predict your risk of developing any of the four female cancers?

- I would **definitely NOT** do the test.
- I would **probably NOT** do the test.
- I would **probably DO** the test.
- I would **definitely DO** the test.

4) In the past months we have interviewed several groups of women about their thoughts concerning the WID test.

The following list presents the main reasons of the interviewed women **in favour of** doing the WID test. Please tick all reasons that matter for you personally and number them in order of their importance to you. Please start with "1" for the most important reason. In case of an equal importance of two or more reasons you can give reasons the same number. In case one or more reasons do not matter for you, please do not tick or number it.

Having the test ...

- would reduce my concerns about getting cancer.
- would make me adopting a healthier lifestyle.

- would increase my perceived control of my life (e.g., to already discuss the options for a situation of being diagnosed with cancer before it develops).
- would help guide my medical strategy (e.g., individualize my screening uptake) to best prevent cancer or cancer death.
- would help me develop coping strategies early on in case of higher-than-average risk.

The following list presents the main reasons of the interviewed women **against** doing the WID test. Please tick all reasons that matter to you personally and number them in order of their importance to you. Please start with "1" for the most important reason. In case of an equal importance of two or more reasons you can give reasons the same number. In case one or more reasons do not matter for you, please do not tick or number them.

Having the test ...

- would be of no use to me because the test result is only an estimate that tells me nothing about whether I will be getting cancer for sure.
- may make me feel guilty or responsible, if I am shown to be at higher-than-average risk, because of the connection between this result and my lifestyle in the past.
- would unnecessarily worry me and my family and negatively affect my quality of life if I am shown to be at higher-than-average risk.
- may put pressure on me to adopt a lifestyle related to my risk or have more cancer screening tests in case I am at higher-than-average risk.
- would make me expect the onset of cancer permanently if I am at higher-than-average risk.

5) *[Screen presents ticked reasons automatically]* Here are the reasons you chose in **favour of** having the WID test. Looking at them, is there ONE reason that is so strong that it would outweigh all the other reasons for having the WID risk test?

Yes

- If yes, the decisive reason is: _____

No, I would definitely consider all of the reasons I ticked on the list.

6) *[Screen presents ticked reasons automatically]* Here are the reasons you chose **against** having the WID test. Looking at them, is there ONE reason that is so strong that it would outweigh all the other reasons for not having the WID risk test?

Yes

- If yes, the decisive reason is: _____

No, I would definitely consider all of the reasons I ticked on the list.

Table S1: Joint official distribution for age and education (ISCED levels) in base population per country and joint distribution within each of the national samples of the study.

Age	Education (ISCED)					
	Low		Medium		High	
	Population	Sample	Population	Sample	Population	Sample
Czech Republic						
40-49	10%	8%	32%	31%	40%	38%
50-59	22%	25%	27%	26%	30%	27%
60-69	41%	63%	29%	32%	20%	23%
70-75	27%	4%	12%	11%	10%	12%
Germany						
40-49	22%	21%	29%	29%	34%	35%
50-59	27%	27%	33%	34%	34%	34%
60-69	28%	29%	24%	24%	23%	22%
70-75	23%	24%	14%	13%	9%	9%
United Kingdom						
40-49	23%	22%	33%	32%	38%	38%
50-59	28%	29%	32%	33%	31%	31%
60-69	34%	34%	24%	23%	21%	21%
70-75	15%	15%	11%	12%	10%	10%
Italy						
40-49	23%	22%	42%	40%	48%	45%
50-59	26%	26%	35%	34%	28%	28%
60-69	31%	34%	18%	20%	19%	21%
70-75	19%	18%	5%	6%	5%	6%
Sweden						
40-49	16%	13%	32%	32%	39%	38%
50-59	23%	23%	31%	31%	29%	30%
60-69	39%	47%	26%	27%	24%	24%
70-75	22%	17%	10%	10%	8%	8%

*Field is marked red if official distribution and distribution within the sample differ by more than 3%.

Knowledge on core principals										
> 50% of answers correct	--	--	1	1.79 ^a	1.42 – 2.25	< .001	.87	0.69 – 1.10	.251	1
≤ 50% of answers correct	--	--	1	1.79 ^a	1.42 – 2.25	< .001	.87	0.69 – 1.10	.251	1
Evaluation of benefit-to-harm ratio										
Benefits clearly/probably outweigh harms	--	--	--	--	--	--	--	--	--	1
Harms clearly/probably outweigh benefits	--	--	--	--	--	--	--	--	--	0.31 ^a
										0.80 – 1.35
										0.25 – 0.40
										< .001

Abbreviations: OR = Odds Ratio, 95% CI = 95% confidence interval

^a Significant after Bonferroni correction



**The Women's Cancer Risk Identification (WID) Test
A test under development to identify a woman's risk of developing
breast cancer, ovarian cancer, cervical cancer, and womb cancer
Leaflet for women aged 50 years and above**



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Women’s cancer risk identification (WID) test

A test under development to identify a woman’s risk of developing breast cancer, ovarian cancer, cervical cancer, and womb cancer

Why this leaflet?

With this leaflet we would like to inform you about a new test – the **women’s cancer risk identification (WID) test** – that is currently under development. This new test is meant to predict a **healthy** woman’s risks of developing any of the following female cancers: breast cancer, ovarian cancer, cervical cancer, and womb cancer.

You can also learn more about your baseline risk of getting any of these female cancers, the current procedures to reduce the threat of these cancers, and the potential benefits and harms of taking the WID test, which is currently under development.

What is your baseline risk of developing female cancers?

In order to better evaluate the potential value of this new test, it is helpful for you to understand an average woman’s risk of developing any of these cancers. For the large majority of women, the risk of developing female cancers is fairly low. The following overview gives you an idea of how likely women at different ages will be diagnosed with each of the four female cancers.

Numbers of women who will develop cancer within the next 10 years...¹

	per 1,000 women aged 45 years	per 1,000 women aged 55 years	per 1,000 women aged 65 years	per 1,000 women aged 75 years
Breast cancer	21	30	35	33
Ovarian cancer	2	3	4	4
Cervical cancer	2	2	1	1
Womb cancer	2	5	6	6

¹All numbers refer to women from Germany; these are, however, comparable to the numbers of women from other European countries. German Centre for Cancer Registry Data within the Robert Koch Institute (2013). Database query: 1 August 2016, www.krebsdaten.de.



Women’s cancer risk identification (WID) test

A test under development to identify a woman’s risk of developing breast cancer, ovarian cancer, cervical cancer, and womb cancer

What are current approaches for healthy women to reduce the threat of these four female cancers?

Two approaches are currently used. The main approach – offered to all healthy women from a certain age on – is cancer screening such as mammography screening for breast cancer or ultrasound screening for ovarian cancer. Cancer screening is intended to detect cancer and precancerous lesions early. For the small proportion of women at very high risk another approach is preventive medication (e.g., with Tamoxifen®) and prophylactic surgery (e.g., removal of the breasts), which aim at preventing occurrence of cancer.

Currently used cancer screenings such as mammography can have benefits **AND** harms. The main benefit is defined as the number of women who will be saved from dying from cancer. The harms are defined by the number of women who experience false alarms, diagnoses of harmless forms of cancer (called overdiagnosis), and, as a consequence, unnecessary treatment (called overtreatment). The following table gives you the numbers for such a benefit-harm ratio for mammography. It shows that per 1,000 women aged 50 years or older who participated in mammography for 10 or more years, 1 woman would be saved from dying from breast cancer due to screening. At the same time, about 5 per 1,000 women who undergo screening would be wrongly diagnosed with progressive breast cancer and treated unnecessarily. Also, mammography has no effect on overall mortality from cancer.

Researchers assume that the benefit-harm ratio of screening would become more favorable if cancer screenings were tailored to a woman’s personal risk of getting cancer. Particularly for women at higher-than-average risk, the benefits of screening may outweigh its harms, whereas for women at average or lower-than-average risk, less screening could be more advantageous in terms of avoiding the potential harms of screening.

Breast Cancer Early Detection

by Mammography



Mammography screening may reduce the number of women who die from breast cancer but this has no effect on overall cancer deaths. Among all women taking part in screening, some women will be overdiagnosed with non-progressive cancer and unnecessarily treated.

Numbers for women aged 50 years or older who did or did not participate in screening for about 10 years.

	1000 women without screening	1000 women with screening
Benefits		
How many women died from breast cancer?	5	4
How many women died from all types of cancer?	21	21
Harms		
How many women without cancer experienced false alarms or biopsies?	–	about 100
How many women with non-progressive cancer had unnecessary partial or complete breast removal?	–	5

Source: Gøtzsche, Jørgensen (2013). *Cochrane Database of Systematic Reviews* (6): CD001877, pub5
 Numbers in the fact box are rounded. Where no data for women above 50 years of age are available, numbers refer to women above 40 years of age.
 Date last updated: 13 March, 2014

Women's cancer risk identification (WID) test

A test under development to identify a woman's risk of developing breast cancer, ovarian cancer, cervical cancer, and womb cancer

What is the rationale behind the currently developed WID test and what would it potentially change?

The rationale of the new WID test – currently under development – is to provide a woman with such a personalized risk prediction about getting certain female cancers **within the next 10 years**. The female cancers it targets are: breast cancer, ovarian cancer, cervical cancer, and womb cancer. In contrast to cancer screenings, the WID test is meant to predict the risk of these four female cancers **before** cancer is present. By using this test in the future, women may learn whether their personal risk is lower-than-average, at average, or higher-than-average.

To achieve this goal, the WID test will be based on the technology of epigenomics. Because each human being's *epigenome* records the life-time exposure to environmental cancer-triggering factors such as infections, diet, or smoking on an individual level, changes in our epigenome seem to be a promising target for predicting cancer risk. Not only may this technology assist in better predicting women's personal cancer risk in the future, but it may also make more information available on the relation between a woman's personal lifestyle and her cancer risk. The following figure illustrates the influence of some environmental factors on our epigenome.

If the WID test became available, it would be for women aged 50 years onwards. As the technology would use the epigenome of cervix cells, samples for the test would be obtained from cervix cells by a smear test. The test would be carried out by gynaecologists, general practitioners, and nurses who are qualified to perform smear tests. The test would take less than a minute and should not involve any pain. The cells taken from the smear test sample would be sent to a laboratory in order to test for your risk. When your results are made available, they would be discussed with your doctor at a follow-up meeting.

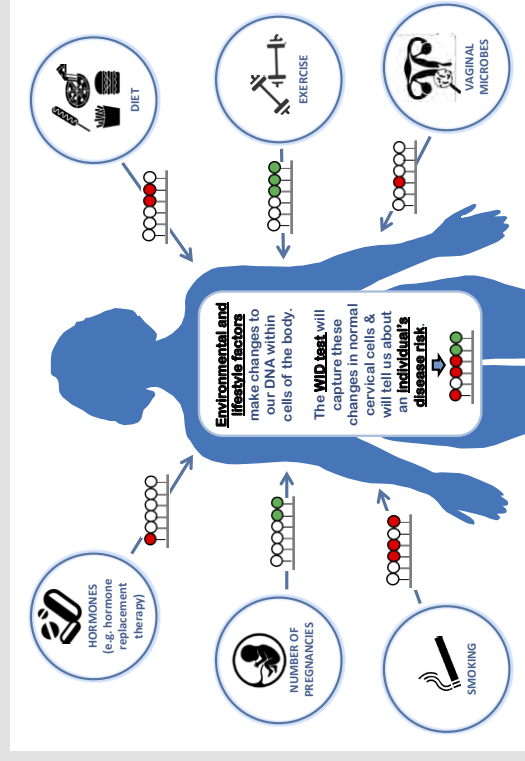


Figure: Various environmental factors trigger changes to our epigenome. The 'lollipops' next to each factor represent examples of potential epigenome changes that can happen in response to that factor. In the example these changes can be good (green) or bad (red) and can vary in strength – the more lollipops marked, the stronger the change. The WID test can measure these changes and so be used to predict the risks of developing certain diseases.



Women's cancer risk identification (WID) test

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What are the potential benefits of taking the test?

Currently, the WID test is under clinical investigation in order to identify appropriate risk groups and interventions that work best for each risk group. If these risk groups and interventions are eventually identified, the WID risk test may help women and their doctors in the future adjust a woman's health care to her personal risks, with the following advantages:

- Women who are predicted to have a higher-than-average risk of developing any of the female cancers could take preventive actions (e.g., adopting a healthier lifestyle if risk is slightly elevated, preventive medication or prophylactic surgery if risk is high) in order to control or to lower their risk. Also, they could do more frequent screening to detect a cancer as early as possible.
- Women who are predicted to have an average or lower-than-average risk may decide to maintain their current lifestyle and have less screenings that entail potential harms.
- Because the WID test will be able to record changes in the epigenome that are caused by environmental and life-style factors, the test may also allow for monitoring how effective preventive actions such as changes in life-style are on reducing the personal cancer risk over time.

What are potential harms of taking the test?

No test is perfect. The WID test may lead to an inaccurate prediction of your risk of developing cancer and could therefore lead to unnecessary anxiety, diagnostic procedures, or medical interventions, or to the illusion of being at low risk when one is actually at higher risk. Even if the prediction is accurate, it does not mean that a woman with a higher-than-average risk will get cancer for certain and a woman with a lower-than-average risk will not get cancer.

Because numerical information about the quality of the test is not available at the current developmental stage, the likelihood of its making inaccurate predictions is not yet known. Furthermore, whether the WID test will eventually help in further reducing the number of women dying from any of the four female cancers or in reducing the number of women experiencing wrong diagnoses needs to be demonstrated in a larger clinical study in the future.

Who will be able to access my test data if I have the WID test in the future?

If you did not consent to the permanent storage of your test sample and results, your sample would be destroyed after risk estimation. As with other diagnostic and predictive tests, your risk information falls under medical confidentiality, meaning that access would be restricted to you, the laboratory, and your doctor.

Are there any other considerations?

The technology of the test makes information available on the relation between a woman's personal lifestyle and her cancer risk. Receiving the result of a higher-than-average risk may make you feel personally responsible for this result. In addition, many people often take predictive tests to reassure themselves that everything is fine, which is not always the case. Before having the test you should therefore also think about how you would cope with receiving a higher-than-average result. It is recommended that you talk to your doctor and your family members about your thoughts and concerns before having such a test.



The FORECEE consortium with its following partners is responsible for the research and developmental work on the WID test

Who is responsible for the content of the leaflet?

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Where can you find more information about the test and the diseases?

www.forecee.eu
www.eveappeal.org.uk
www.cancerresearchuk.org

