Family Medicine and Community Health

Exploring conservative management for cervical intraepithelial neoplasia grade 2 in organised cervical cancer screening programmes: a multicentre study in Italy

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ABSTRACT

Cervical intraepithelial neoplasia grade 2 (CIN2) lesions may regress spontaneously, offering an alternative to immediate treatment, especially for women of childbearing age (15–45 years).

We conducted a prospective multicentre study on conservative CIN2 management, with semiannual follow-up visits over 24 months, biomarkers' investigation and treatment for progression to CIN3+ or CIN2 persistence for more than 12 months. Here, we assess women's willingness to participate and adherence to the study protocol.

The study was set in population-based organised cervical cancer screening.

From April 2019 to October 2021, 640 CIN2 cases were diagnosed in women aged 25–64 participating in the screening programmes.

According to our predefined inclusion and exclusion criteria, 228 (35.6%) women were not eligible; 93 (22.6%) of the 412 eligible refused, and 319 (77.4%) were enrolled. Refusal for personal reasons (ie, desire to become pregnant, anxiety, difficulty in complying with the study protocol) and external barriers (ie, residence elsewhere and language problems) accounted for 71% and 17%, respectively. Only 9% expressed a preference for treatment. The primary ineligibility factor was the upper age limit of 45 years. After enrolment, 12 (4%) women without evidence of progression requested treatment, 125 (39%) were lost to follow-up (mostly after 6–12 months) and 182 (57%) remained compliant. Remarkably, 40% of enrolees did not fully adhere to the protocol, whereas only 5% (20/412) of the eligible women desired treatment.

Our study demonstrates a good acceptance of conservative management for CIN2 lesions by the women, supporting its implementation within cervical screening programmes.

INTRODUCTION

Aims of the organised population-based screening are the detection and treatment of the high-grade lesions CIN2 and CIN3 (cervical intraepithelial neoplasia grades 2 and 3), and early detection of invasive cancers. CIN2 has a higher spontaneous regression rate (40%–60%, depending on age) and a lower progression capacity (around 15%) than CIN3 (30%–40% for both).[1] Excisional treatment (recommended for both lesions)[2] is highly effective in curing the lesions, but can pose risks such as preterm birth, premature rupture of membranes, low birth weight.[3 4] In the last decade, a few countries have developed specific guidelines for the conservative management of CIN2[5–8]; young age (below 25–30 years) is among the most used criteria for selecting suitable cases, as regression probability is higher in younger than older women,[5] the risk of progression after treatment is associated to older age at initial excision,[9] and women of childbearing age (15–45 years) benefit most. Active surveillance is performed also in countries lacking guidelines[6 7 10]; a recent Dutch nationwide survey disclosed that 41% of the women with a histological diagnosis of CIN2 did not undergo excision within 3 months after biopsy.[11] Lack of compliance to the follow-up visits and the long-term risk of cervical cancer might constitute barriers to the adoption of active surveillance.[7] In order to provide guidelines and recommendations, several studies are ongoing to evaluate the clinical outcomes of untreated CIN2 under active surveillance.[12 13]

Besides searching for factors and biomarkers[14–16] able to correctly stratify (at the time of diagnosis) the CIN2 lesions at higher probability of regression (or

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progression), it is very important also to understand the women's acceptability and the organisational impact on screening programmes.[7] Women's attitudes have been less frequently investigated; in Australia, active surveillance was preferred to surgery by 79% of women aged 25–40 years who were presented a hypothetical scenario of CIN2 diagnosis.[17]

In Italy, organised cervical cancer screening programmes started in the late 1990s, are performed according to national recommendations, by call–recall invitation of all women aged 25–64 years, and are operated at a regional level. HPV (human papillomavirus)-based testing is being implemented for women aged 30–64 years. Women negative for high-risk HPV (hrHPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68) are called for a new screening round 5 years later. In case of hrHPV positivity, cytology triage is performed on the same liquid-based sample. Women with cytological alterations (atypical squamous cells of undetermined significance or worse, ASC-US+) are referred to immediate colposcopy; those with normal cytology undergo 1 year recall for hrHPV testing repeat, with colposcopy in case of persistent hrHPV positivity, and return to screening in case of viral clearance. Women 25–29 years-old undergo cytology testing every 3 years, with immediate colposcopy for ASC-US+.[18–20] The aim of this paper is to describe the acceptability of conservative management by women with a CIN2 lesion for its implementation within organised cervical cancer screening programmes, by analysing the reasons of exclusion from or of refusal to participate to our study, and compliance to follow-up.

METHODS

Study population

The population under study is composed by all the women attending organised population-based cervical cancer screening programmes in four centres from 15 April 2019 to 31 October 2021 with a histological diagnosis of CIN2. They were evaluated for participation into a prospective multicentre study on the conservative management of CIN2 lesions, according to predefined inclusion and exclusion criteria. *Inclusion criteria* were histologically confirmed diagnosis of CIN2 (original diagnosis has been used); women 25–45 years of age; and transformation zone (TZ) fully visible at colposcopy. *Exclusion criteria* were ongoing pregnancy (women who became pregnant after enrolment into the study and after collecting one or more cervical samples for biomarkers were offered the possibility to remain within the study); previous treatment of a CIN2+ lesion; immunodeficiency; or presence of an endocervical lesion not completely visible at colposcopy. At the counselling visit for the communication of the CIN2 diagnosis to the patients, detailed information on the natural history of CIN2 lesions and the rationale of the study, on the routine treatment in use and its risks for subsequent pregnancies, and on the study protocol was given to those fulfilling the study criteria, by both oral and written form; women could give their acceptance/refusal decision immediately or within a couple of days. Reasons of exclusion and refusal were collected through personal interview (ad-hoc questions to disclose the reasons for the refusal) by professional operators (gynaecologist or midwife).

Women unwilling to enter the study underwent lesion excision, according to the routine practice, by large loop excision of transformation zone (LLETZ) procedure. Eligible and consenting women were enrolled after signing a written informed consent (a blank copy is provided as online supplemental material).

Women participating in the study underwent semiannual follow-up visits over a 24 months' period, during which colposcopy was performed (with biopsy in case of abnormal areas), and cervico-vaginal cells were collected for viral and cellular biomarkers analyses; that is, search of hrHPV-DNA sequences with reflex HPV16 and HPV18 partial genotyping, hrHPV extended genotyping of HPV-positive samples, p16/ki67 expression, methylation status for *FAM19A4* and *miR124-2* genes and for the L1 region of high-risk HPV types.

By protocol, surgical treatment was performed in case of progression to CIN3+ and after CIN2 persistence for 12–24 months.

Ethics approval was obtained by the Ethics Committees of the four areas involved in the study.

Statistical analysis

The number of cases to include in the study was based on estimates precision; 322 patients were necessary in order to detect a regression in at least 70% of CIN2 lesions with a precision of ±5%. We analysed the CIN2 distribution, the frequency of exclusion criteria, as well as the reasons for refusal of eligible women, by reason and age class (25–29, 30–34, 35–39, 40–45, 46+ years). For the women who exited the study, frequency and motivations were also analysed. Women not complying with the study protocol were considered as lost to follow-up. The χ^2 test was performed to determine the difference between the proportions. Statistical significance was considered with p value <0.05 (R-software).[21]

RESULTS

During the enrolment phase (April 2019–October 2021) of this prospective multicentre study, a total of 640 cases of CIN2 lesions were diagnosed among the women attending the four screening programmes, which contributed different numbers of cases to the study (range: 40–182, median: 48.5). The mean and median ages of the entire cohort were 37 and 35 years, respectively.

An overview of the entire cohort is provided in figure 1. The distribution of cases by age class, according to eligibility and acceptance to enter the study, is summarised in table 1.

Overall, according to the predefined criteria, 228 (35.6%) women (median age 46) were excluded and 412

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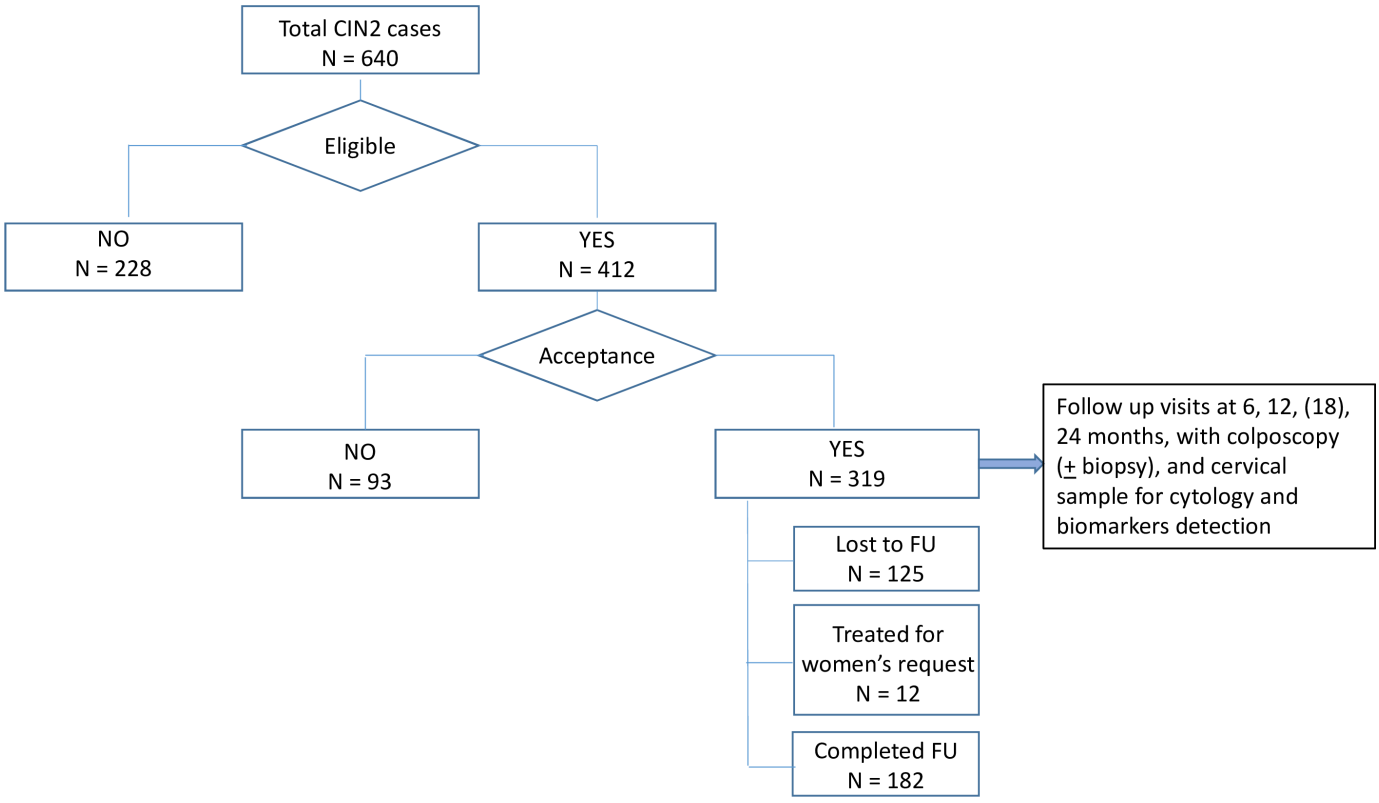

Figure 1 Flow chart of the distribution of women with a CIN2 lesion, according to inclusion/exclusion criteria and women's attitudes. CIN2, cervical intraepithelial neoplasia grade 2. FU, follow-up.

(64.4%) were eligible, with a statistically significant difference according to the age group (p<0.001); 93 eligible women refused to enter the study (median age 34). The reasons of exclusion and refusal to enter the study are reported in table 2.

Out of the 228 excluded women, 122 (53.5%) were older than 46 years, 90 (39.5%) had gynaecological characteristics deemed as 'high-risk' (ie, not visible TZ, previous high-grade lesion, pluricentric lesions, not completely visible lesion), while other reasons (ongoing pregnancy, other gynaecologic reasons, impossibility to comply with the study protocol, selection error) accounted for 7% (16 cases) only. The 45 years age limit, therefore, ranked first (53% of the cases) among the exclusion criteria, followed by a previous high-grade lesion (17.5%). A closer look at the characteristics of the women older than 45 years disclosed that 80.3% had age as the only exclusion criterion, while also other exclusion criteria were registered

Table 1 CIN2 distribution, overall rates of no eligibility and eligibility, refusal and acceptance rates among eligible women, by age class

	Age group					
CIN2 cases / n (%)**	**25–29**	**30–34**	**35–39**	**40–45**	**≥46**	**Total**
Diagnosed	140 (21.9)	150 (23.4)	130 (20.3)	98 (15.3)	122 (19.0)	640 (100)
Not eligible	21 (15.0)	22 (14.7)	28 (21.5)	35 (37.5)	122 (100)	228 (35.6)
Eligible	119 (85.0)	128 (85.3)	102 (78.5)	63 (64.3)	0 (0)	412 (64.4)
Eligible refused	26 (21.8)	26 (20.3)	26 (25.5)	15 (23.8)	0 (0)	93 (22.6)
Eligible accepted	93 (78.2)	102 (79.7)	76 (74.5)	48 (76.2)	0 (0)	319 (77.4)

*The columns include different groups; not eligible+eligible cases sum up to the total number of cases (228+412=640); eligible refused+eligible accepted sum up to the total eligible women (93+319=412).
CIN2, cervical intraepithelial neoplasia grade 2.

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Table 2 Baseline characteristics of women diagnosed with a CIN2 lesion not included in the study

Baseline characteristics	n (%)
Exclusion criteria	
Age >46 years (additional exclusion criteria in 24 of them)	122 (53.5)
Transformation zone not visible	7 (3.1)
Pluricentric lesion	20 (8.8)
Previously diagnosed high-grade lesion	40 (17.5)
Endocervical or not completely visible lesion	23 (10.1)
Ongoing pregnancy	5 (2.2)
Other causes (selection error; other gynaecological causes)	11 (4.8%)
Total	228 (100%)
Reasons for refusal	
Personal reasons	66 (71.0)
External barriers	16 (17.2)
Willingness to be treated	8 (8.6)
Other causes	3 (3.2)
Total	93 (100)

CIN2, cervical intraepithelial neoplasia grade 2.

in 24 (19.7%) cases; in particular, a not visible TZ and/or lesion were recorded in 17 (13.9%) cases, and a previous high-grade lesion in 7 (5.7%) cases.

Considering the whole cohort, the distribution by age class of the gynaecological reasons of exclusion was as follows. The squamo-columnar junction was not visible only in women older than 34 years, with a frequency of 8% (12/152) among women 35–55 years old and of 27.3% (9/33) after that age. A CIN2+ lesion had been previously diagnosed in 47 (7.3%) women, without significant differences by age. An endocervical lesion was recorded in 26 women, with the highest frequency (18/63, 28.5%) among those aged 35–45 years. Pluricentric lesions were found in 20 cases, with a decreasing frequency by age, from 38% (8/21) in the 25–29 age class to 0% in women older than 45 years.

Among the 93 eligible women not included in the study, the refusal was mostly motivated by personal reasons (66/93; 71%), followed by external causes (16/93; 17%). The most frequent personal reasons have been desire to become pregnant, anxiety, willingness to be managed by the personal gynaecologist, lack of interest in study participation, refusal to undergo the additional sampling for biomarkers' evaluation, difficulty in complying with the follow-up visits, fear due to the COVID-19 pandemic and serious concomitant extragenital morbidity. Residence elsewhere and language problems were the most frequently reported external causes. Willingness to be treated immediately within the screening programme accounted for less than 5% (20/412; 8 refused participation, 12 refused continuing active surveillance during follow-up). No feedback after the counselling visit occurred for 11 (3%) patients. Acceptance was (not significantly) higher among 25–34 years old than among older women.

The enrolment period, initially forecasted to last 12 months, was extended to 30 months, as a consequence of the COVID-19 pandemic that caused a 2 months' suspension (during March and April 2020) of the invitations to a new screening round, followed by a very slow recovery of the participation rates. The final cohort of cases included in the study is made up of 319 women, with mean and median ages of 34 and 33 years, respectively, and homogeneously distributed among age groups (p=0.8105). The follow-up ended in October 2023.

During the scheduled 24 months of follow-up, 125 (39%) of the enrolled women exited the study for personal reasons, the majority (77/125, 62%) after the 6/12 months' visit. These women were recalled to solicit their attendance; a large number declared they had referred to other gynaecological facilities, often accounting the COVID-19 pandemic as the cause. We compared these non-compliant women to the entire cohort. It emerged that 67% of the non-adherent women belonged to the three centres which cumulatively enrolled 43% of the cohort, while no difference by age was observed. We are actively searching additional information on these women, to understand their clinical outcome up to 24 months from enrolment (and correlate it to the biomarkers' results at baseline). Willingness to be treated for reasons other than protocol was expressed by 12 (4%) women (3 at baseline, 4 at 6 months, 3 at 12 months and 2 at 18 months, respectively); the histological diagnosis was CIN2 in 6, CIN3 in 3 and negative in 3 cases, respectively. The remaining 182 (57%) women fully adhered to the protocol.

In terms of workflow for the screening programme, the only additional activity performed is the sampling for the biomarkers' evaluation at the counselling visit, while all the follow-up visits have the same timing in use after excisional treatment. In terms of additional costs for the execution of the biomarkers' analyses, only the partial HPV 16/18 genotyping is actually routinely available, while all the others are not in routine use.

DISCUSSION

To evaluate the acceptability of CIN2 conservative management by the women and the impact of active surveillance on the screening programme, we analysed the age distribution of the study predefined criteria, the reasons of refusal to enter the study by eligible women and the adherence to the study protocol of those enrolled. This analysis was conducted within a multicentre prospective trial that involved 640 women with a diagnosis of CIN2 detected within organised cervical cancer screening programmes. On the basis of our predefined inclusion and exclusion criteria, that determined eligibility, and the

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refusal by eligible women, half of the cases could finally enter the study.

Almost one fifth (122/640, 19%) of the women were excluded because they were older than 46 years. This age limit was set by considering the benefit of avoiding the surgical treatment in women of childbearing age and the lower rate of spontaneous regression in older women. Indeed, most studies on the conservative management of CIN2 have been conducted in <45 years old women,[6 9 12 14 17] and less frequently[16 22] in women of all ages. The CIN2 regression rates recorded in these studies differed by gynaecological or viral (ie, HPV genotype) characteristics, but were not related to the woman's age. On the other hand, age limits have an impact on the proportion of women to whom active surveillance for CIN2 would finally be applied.

Among the women eligible to the study, 77.4% accepted the wait-and-see strategy. This figure is very close to the 79% acceptance rate observed among 1638 women residing in Australia given a diagnosis of CIN2 in a hypothetical scenario[23] and confronted with the choice between immediate surgical treatment or active surveillance. These women were randomised according to alternate terminology used to describe the regression of the lesion and the effects of the surgical procedure. Both the degree of understanding of the information provided and the perception of benefits and risks of surgery (overestimated and underestimated, respectively) had an influence on the final decision; this highlights the importance of communication and the need to assess patient understanding to close the loop of communication. It has been reported that a CIN2 diagnosis, as well as the indication to undergo a surgical procedure, can affect the psychosocial well-being of the affected woman. A cross-sectional study investigating the prevalence of depression/anxiety and the health-related quality of life in women with a CIN2 diagnosis who underwent either surgery or conservative management found that the conservative subgroup exhibited higher scores for health-related quality of life compared with women undergoing surgery, and that all CIN2 affected women showed a higher prevalence of depression/anxiety than those of the healthy group.[24]

To safely implement active surveillance and avoiding the risk of missing a progressive lesion, compliance is a critical aspect. In our study, full adherence to the 24 months' study protocol was recorded for less than 60% of the women. Nonetheless, we registered a higher adhesion (74%) in the largest centre than in the others (where the small numbers might have partly influenced the figures), and a 70% overall rate at 12 months. Indeed, since in a recent large study[22] 90% of regression and progression outcomes were recorded within 12 months of follow-up, this represents a positive finding. To effectively evaluate the likelihood of patients' compliance and their education about the importance of monitoring visits, training on communication should be provided to the dedicated healthcare personnel.

The follow-up protocol in use in our study for the CIN2 active surveillance has a number of visits comparable to that of the women treated as per routine practice. Therefore, no immediate impact on the screening programme's organisation occurred. After completion of the follow-up, the overall impact determined by the clinical outcome will be evaluated; women with a regressive CIN2 lesion would have spared the surgical treatment, while women who underwent delayed treatment would have had an increased number of visits. Moreover, the analysis of the timing of lesions' regression and the results of the biomarkers under study will allow the definition of protocols capable to balance the number of visits in relation to the woman's characteristics and the biomarkers' results, possibly taking into account also lifestyle factors that could reflect their cervical precancer risk.[25] To evaluate the cost-effectiveness of implementing a protocol for CIN2 active surveillance within an organised cervical cancer screening, the final data of our study will be analysed along with other similar studies, in order to formulate a national guideline. A recent analysis conducted in Germany on the healthcare costs for women 18–45 years old with CIN diagnosis, over a 2-year follow-up period, disclosed higher costs for those undergoing treatment (€ 1020) than for those under active surveillance (€ 328).[26]

In the future, the epidemiology of HPV infection and preneoplastic and invasive lesions will be modified by the combined protective effect of HPV vaccination in adolescent girls and cervical screening by primary HPV testing[27 28]; in particular, the women vaccinated before age 15 will not develop CIN2 lesions caused by HPV types prevented by vaccination (mainly HPV16 and HPV18). In our study, we could not evaluate whether a correlation between the vaccination status and the acceptance of conservative management could possibly exist since the vast majority (97.5%) of the women involved in our study were born before 1996 and only 1 of the 102 for whom the information is available had been vaccinated at 15 years of age.

Strengths and limitations

This multicentre study was carried out within four organised cervical cancer screening programmes based on the same protocol. The cohort of women included in the present analysis represents all the CIN2 cases diagnosed in a 30 months' period within a homogeneous geographical area. The results are therefore generalisable to the whole region, and to other similar areas.

The COVID-19 pandemic determined a 2 months' suspension of the screening programmes, and this affected the rate of CIN2 detection[29]; as a consequence, the study period was longer than initially determined. Moreover, while the pandemic only marginally affected the acceptance rate to enter the study, it might have negatively influenced the women's adherence to the follow-up. Sociodemographic data were available for a minority of women only and could not be analysed.

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CONCLUSIONS

Women are willing to accept a conservative management for CIN2 lesions within cervical screening programmes. Among eligible not enrolled women, refusal for personal reasons and willingness to be treated accounted for 71% and 9%, respectively. On the basis of our experience, careful selection of the patients with CIN2 lesions (with attention to communication for their commitment to adherence to follow-up) and specific training to all the healthcare operators (within and outside the screening programme) are key aspects to ensure a safe active surveillance.

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Contributors Conceptualisation: TM, ADM and MZ; methodology: HF, SG and LL; software: MM; validation: MZ; formal analysis: MM, SG, HF, MZ and ADM; investigation: AP, MS, CR, EI, GS and EB; resources, TM; data curation, MM; writing – original draft preparation: ADM, HF and SG; writing – review and editing: MZ, TM, MM, CR; supervision: TM and MS; project administration: ADM and TM; funding acquisition: TM and MS. All authors read and approved the final manuscript. All the members of the CIN2 study Working Group contributed to data generation.

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Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval Ethics approval was obtained by the Ethics Committee of the province of Venice and San Camillo Hospital (Venice, Italy, ethics ID 79A/CESC, 07/11/2017). Additional approvals were obtained from the participating centres (Ethics Committee of the provinces of Treviso and Belluno, ethics ID 595/CE Marca, 22/11/2018; Ethics Committee of the provinces of Verona and Rovigo, ethics ID 2062/CESC, 19/02/2019; Ethics Committee of the province of Padova, ethics ID 4723/AO/19, 27/06/2019). Written informed consent was obtained from each participant. The study was carried out in accordance with the Declaration of Helsinki. Participants gave informed consent to participate in the study before taking part.

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INFORMED CONSENT FORM

Study: "Conservative management of CIN2 lesions and evaluation of biomarkers for the identification of CIN2 lesions with a high probability of spontaneous regression"

I undersigned_____

born in_____on_____

resident in_____

telephone_____

I declare

- To have been informed that I have been diagnosed with a cervical lesion called CIN2 and that there is scientific evidence that this lesion can also regress spontaneously;
- To have received exhaustive explanations regarding the research project, which involves the non-immediate treatment of CIN2 lesions but a check-up every six months for two years, to which I declare that I am available;
- To have been informed that if the lesion is found to be persistent or evolving in one of the subsequent checks, the treatment will be carried out immediately;
- I have had sufficient time to carefully read, understand and eventually have additional information on the contents of the information leaflet;
- To be aware that participation is voluntary, with the assurance that refusal to participate will not affect receiving the most suitable treatment;
- To voluntarily participate in the Project and to adhere to the scheduled checks;
- That the biological material obtained with the biopsy or cytological sample can be stored and used subsequently to carry out exclusively tests relating to the purposes of the study in question, i.e. the prevention and treatment of cervical cancers;

- That the data concerning me are strictly confidential and will be used exclusively for the purposes indicated in the project (pursuant to Legislative Decree 196/2003, and subsequent amendments and additions as per the Guarantor's Guidelines for the processing of personal data within the scope of Clinical Trials - Official Journal 190 of 14 August 2008 and pursuant to the European Regulation for data protection no. 679/2016) and as per any other prescription/authorisation of the Guarantor itself, and which will be processed in such a way as to guarantee the confidentiality of my identity;
- That the data concerning me will only be disclosed in a strictly anonymous form, for example through scientific publications and scientific conferences;

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- That it is my right to have access to the documentation concerning me and to the evaluation expressed by the Provincial Ethics Committee, which I can contact if I deem it appropriate;

- That a copy of the informed consent and the documentation I have read will remain in my possession;

- That for any problem or further information I can contact the screening program secretariat by calling……..

Therefore,

I AGREE

FREELY, SPONTANEOUSLY AND IN FULL CONSCIENCE TO PARTICIPATE IN THE RESEARCH PROJECT PROPOSED TO ME and I consent to the processing of my personal data for the purposes of the project, within the limits and with the methods indicated in the information above, provided to me pursuant to art. 13 of Legislative Decree 196/2003 and pursuant to the European Data Protection Regulation no. 679/2016.

I also declare that I am aware of the possibility of revoking this consent at any time.

Date_____________ Legible signature of the participant _________________________

Colposcopist gynecologist (name, surname, legible signature):

____

OR

I DO NOT AGREE

FREELY, SPONTANEOUSLY AND IN FULL CONSCIENCE TO PARTICIPATE IN THE RESEARCH PROJECT PROPOSED TO ME.

Date_____________ Legible signature of the participant _________________________

Colposcopist gynecologist (name, surname, legible signature):

____

Participating Center:____