GynTect® DNA methylation marker - longitudinal observational study in patients with CIN2/3. Results from the GynTect-PRO trial*

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Talk FC05
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Objectives

Precancerous lesions of the cervix, depending on their grade of severity, are known to have a high potential to regress to normal. Especially among young women, only a few patients are at high risk to develop invasive cancer. DNA methylation markers such as ASTN1, DLX1, ITGA4, RXFP3, SOX17, ZNF671 comprising the diagnostic test GynTect® are a new class of biomarkers which are discussed to have prognostic potential. GynTect-PRO is a prospective, longitudinal and multi-centered trial which addressed the probability of regression in GynTect-negatively tested women having a CIN2 or CIN3 lesion (Negative Predictive Value, NPV). The study tests the null hypothesis NPV≤70% against the alternative hypothesis NPV≥90%.

Methods

77 women <25 years were included between December 2017 and February 2021, recruited from nine clinical centers in Germany. All patients had a histopathology confirmed CIN2 or CIN3 lesion at first visit. Follow-ups were planned for all patients every 6 months, CIN2 patients for up to 24 months (a max. of 5 visits) and CIN3 patients for up to 12 months (a max. of 3 visits). At all visits, colposcopy was done and, if indicated, a biopsy was taken. HPV testing, cytology and GynTect testing was also done at every timepoint. The outcome was defined as progression, persistence or regression with respect to the last biopsy, conization or colposcopy findings if no histopathology was done at the last visit.

Results

60 women fulfilled all inclusion criteria.

CIN2 GynTect V_0	Outcome						Total	
	Regression		Persistence		Progression			
	n	%	n	%	n	%	n	%
Invalid	2	100	0	0	0	0	2	100
negative	12	66.7	6	33.3	0	0	18	100
positive	3	75.0	1	25.0	0	0	4	100
All	17	70.8	7	29.2	0	0	24	100

CIN2 patient group: 24 patients were included (see Table 1); 18 were GynTect®-negative at Vo.

- 12 (66.7%) patients showed a regression
  → NPV = 0.67, 90% CI 0.44 – 0.85, p=0.53
- 6 (33.3%) showed a persistent lesion
- No patient showed a progression

Table 1: CIN2: Median outcome CIN2 patients after 1.8 years (range 0.5 – 2.6 years).

CIN3 GynTect V_0	Outcome						Total	
	Regression		Persistence		Progression			
	n	%	n	%	n	%	n	%
Invalid	3	100	0	0	0	0	3	100
negative	15	55.6	12	44.4	0	0	27	100
positive	2	33.3	4	66.7	0	0	6	100
All	20	55.6	16	44.4	0	0	36	100

CIN3 patient group: 36 patients were included (see Table 2); 27 were GynTect®-negative at Vo.

- 15 (55.6%) patients showed a regression
  → NPV =0.56, 90% CI 0.38 – 0.72, p=0.92
- 12 (44.4%) showed a persistent lesion
- No patient with status progression

Table 2: CIN3: median outcome CIN3 patients after 1 year (range 0.2 – 1.4 years).

Conclusion

Majority of CIN2 and CIN3 lesions in this study showed regression during follow-up, but the hypothesis (NPV ≥ 90%, CI=0.9: NPV ≥ 0.7, 80% power) could not be confirmed.

Some of the study participants terminated the study prematurely.
If in such a case a final persistence is detected, the probability of a final regression might be underestimated and that of a final persistence/progression might be overestimated.
In a sensitivity analysis in which regression is assumed for prematurely terminated cases with persistence (<1.5 years for CIN2, <0.8 years for CIN3) the negative predictive value would be:

- for CIN2 patients 0.78 (14/18) (90% CI 0.56 - 0.92, p right hand=0.33)
- for CIN3 patients 0.70 (19/27) (90% CI 0.52 - 0.85, p right hand=0.58).

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