UNIVERSITÄTS KLINIKUM jena

**Frauenklinik**
Frauenheilkunde

# EUROGIN 2019 Congress in Monaco

## Performance of the GynTect® methylation assay in triage of HPV positive women

05. December 2019

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coi: MD is share-holder of oncgnostics GmbH

# Strategy for the identification of methylation markers for cervical cancer screening

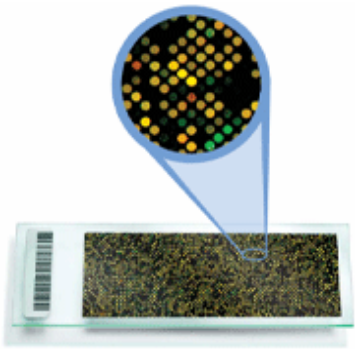
Tumor vs. HPV+ve/colpo-ve scrapes

Marker Identification

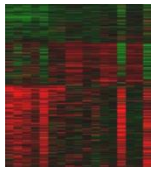
Marker Validation

Clinical Validation

Whole Genome CpG Microarrays covering 27.000 CpG islands



100 Candidate Marker Regions



12 Marker Regions


6 GynTect® marker panel

Special algorithm

PCR analyses

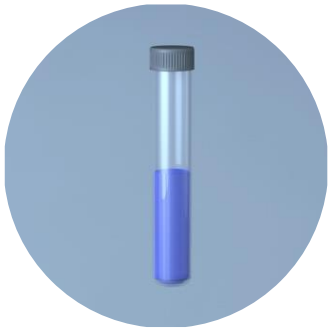
| 6 GynTect® markers | Controls used |
|---|---|
| ASTN1 | IDS-M |
| DLX1 | ACHE |
| ITGA4 | |
| RXFP3 | |
| SOX17 | |
| ZNF671 | |

CE-IVD certified 10/2015

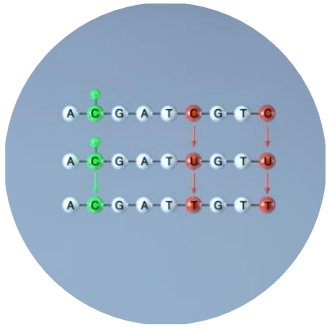
Hansel et al., 2014 PLoS ONE 9(3):e91905; Schmitz et al., 2017 Clinical Epigenetics 9:18

# GynTect® assay

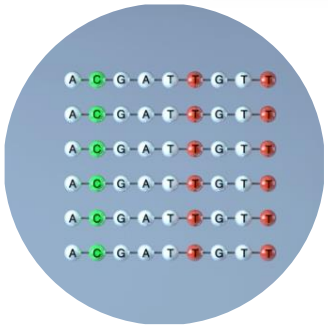
Special algorithm, resulting in a GynTect® Score from 0-15



Sample preparation



Bisulfite conversion allowing allowing „fixation“ of methylation status

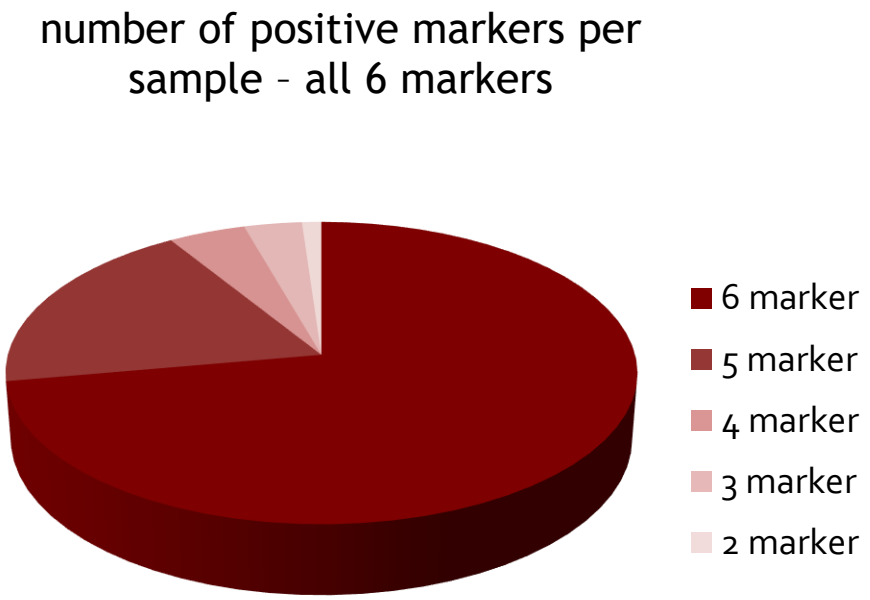


Detection of methylated DNA markers by PCR **MS-PCR**

Data analysis

Scoring algorithm:
DLX1=1, ASTN1=2, ITGA4=2, RXFP3=2, SOX17=2, ZNF671=6
Maximal score=15
Score ≥ 6 = GynTect® positive

# Marker validation in tissue

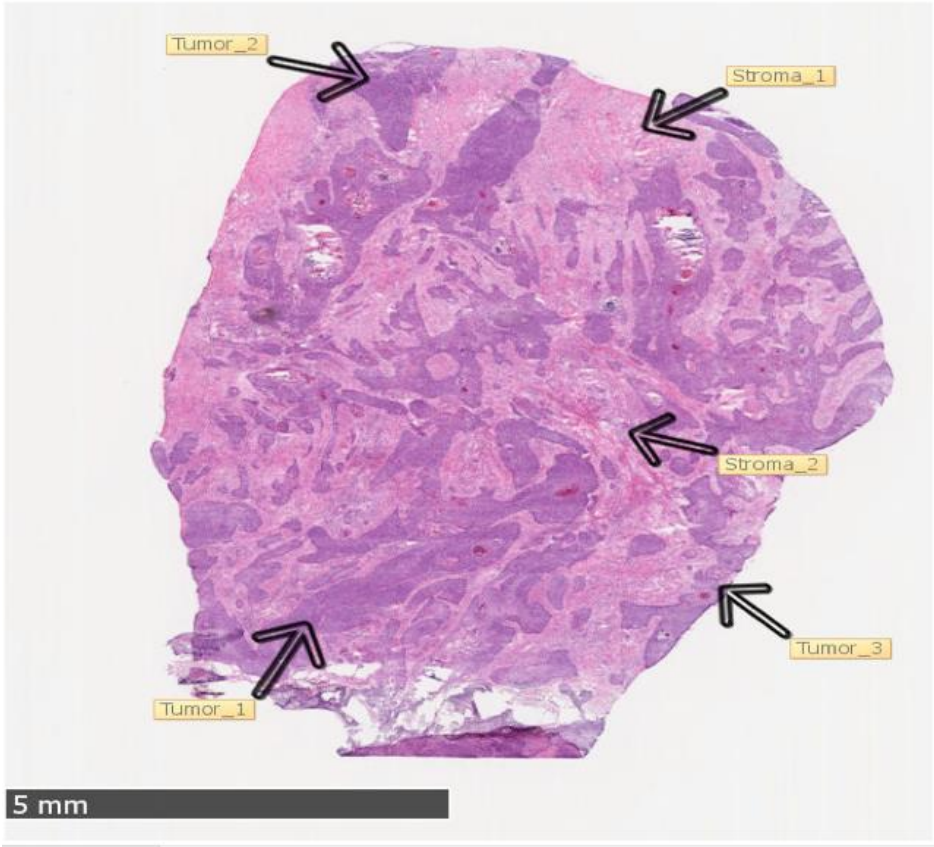



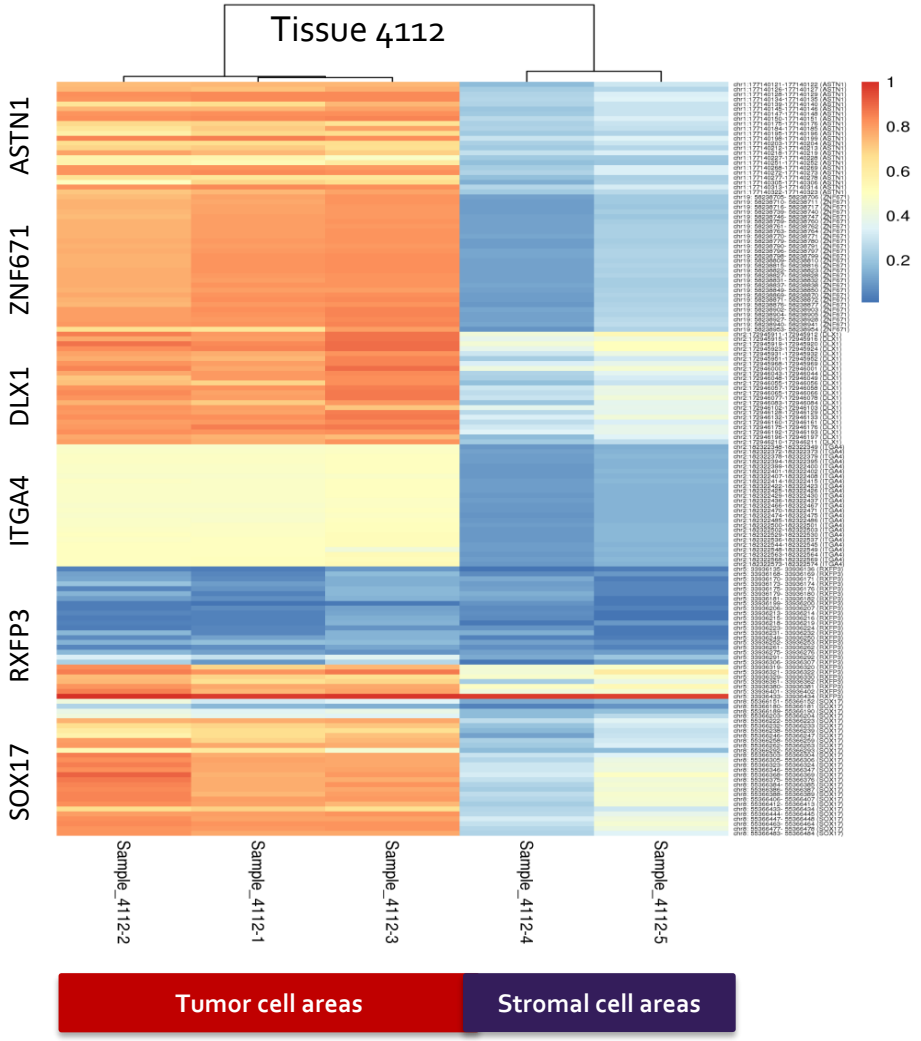

All 13 hrHPV types involved

Hansel et al., 2014 PLoS ONE 9(3):e91905; unpublished data

# Methylation status in microdissected tissue

## NGS-analyses of all markers




Carolin Dippmann, Friday FC 21/22 Methylation 16:15 – 18:45

# Summary GynTect® clinical evaluation studies

| Trial | Procedure | Sample material | Samples used | Reference |
|---|---|---|---|---|
| **A. VALIDATION OF MARKERS** | | | | |
| 1st marker validation study | preselected | Tissue sections | 205 | |
| 2nd marker validation study | preselected | Cervical scrapes (DNA) | 261 | Hansel et al., 2014 |
| **B: CASE CONTROL STUDIES** | | | | |
| 1st case control study | blinded | Cervical scrapes (DNA) | 218 | Hansel et al., 2014 |
| 2nd case control study CE IVD STM | blinded | Cervical scrapes (STM) | 306 | Schmitz et al., 2017 |
| 3rd case control study CE IVD LBC | blinded | Cervical scrapes (LBC) | 632 | Schmitz et al., 2018 |
| comparison HPV&CINtec Plus | blinded | Cervical scrapes (LBC) | 280 | Schmitz et al., 2018 |
| case control study Medirex | blinded | Cervical scrapes (LBC) | 100 | |
| 1st case control study UniLabs LAP, Porto | blinded | Cervical scrapes (LBC) | 103 | Sousa, Eurogin 2017 |
| comparison to Precursor-M (Self-Screen) | blinded | Cervical scrapes (LBC) | 105 | |
| 2nd case control study UniLabs LAP, Porto | blinded | Cervical scrapes (LBC) | 95 | Sousa, Eurogin 2018 |
| Comparison to QIAsure (QIAGEN) | blinded | Cervical scrapes (LBC) | 140 | Dippmann, Eurogin 2018 |
| Performance GynTect on Cobas Z480, CE IVD | blinded | Cervical scrapes (LBC) | 328 | Eichelkraut, Eurogin 2018 |
| 4th case control study clinical samples | blinded | Cervical scrapes (LBC) | 675 | Schmitz, Eurogin 2018 |
| **C. LONGITUDINAL TRIAL** | | | | |
| 1st longitudinal trial, retrospective | blinded | Cervical scrapes (DNA) | 336 | |

Total clinical samples used for GynTect® Validation in Europe **3784**

# Clinical validation study

## 2013 consecutive cervical scrapes; 217 with histopathology

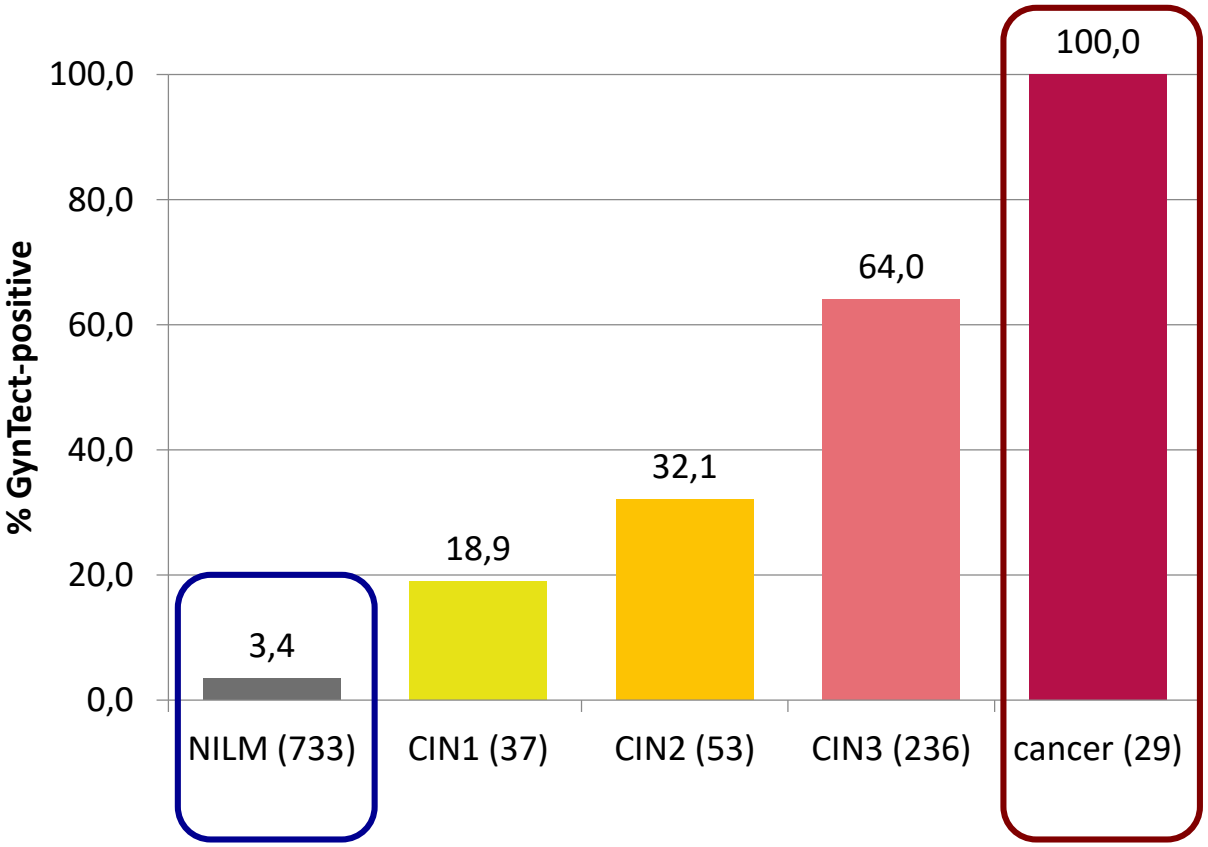
| | Women <30 (n = 114) | Women ≥30 (n = 103) |
|---|---|---|
| | Methylation-positive/total number n (% methylated; 95% CI) | |
| no CIN | 5/51 (9.8%; 3.3–21.4%) | 6/54 (11.1%; 4.2–22.6%) |
| CIN1 | 1/18 (5.6%; 0.1–27.3%) | 3/10 (30.0%; 6.7–65.3%) |
| CIN2 | 6/29 (20.7%; 8.0–39.7%) | 9/13 (69.2%; 38.6–90.9%) |
| CIN3 | 5/14 (35.7%; 12.8–64.9%) | 8/9 (88.9%; 51.8–99.7%) |
| CxCa | 2/2 (100%; 22.4–100%) | 17/17 (100%; 83.8–100%) |

➡ Significant differences in positivity between age groups correlates with the natural history of CIN

Methylation panel may be of prognostic significance!!!!

Hansel et al., 2014 PLoS ONE 9(3):e91905

# GynTect® performance in LBC medium




Schmitz et al., 2018 BMC Cancer 18:1192, unpublished data

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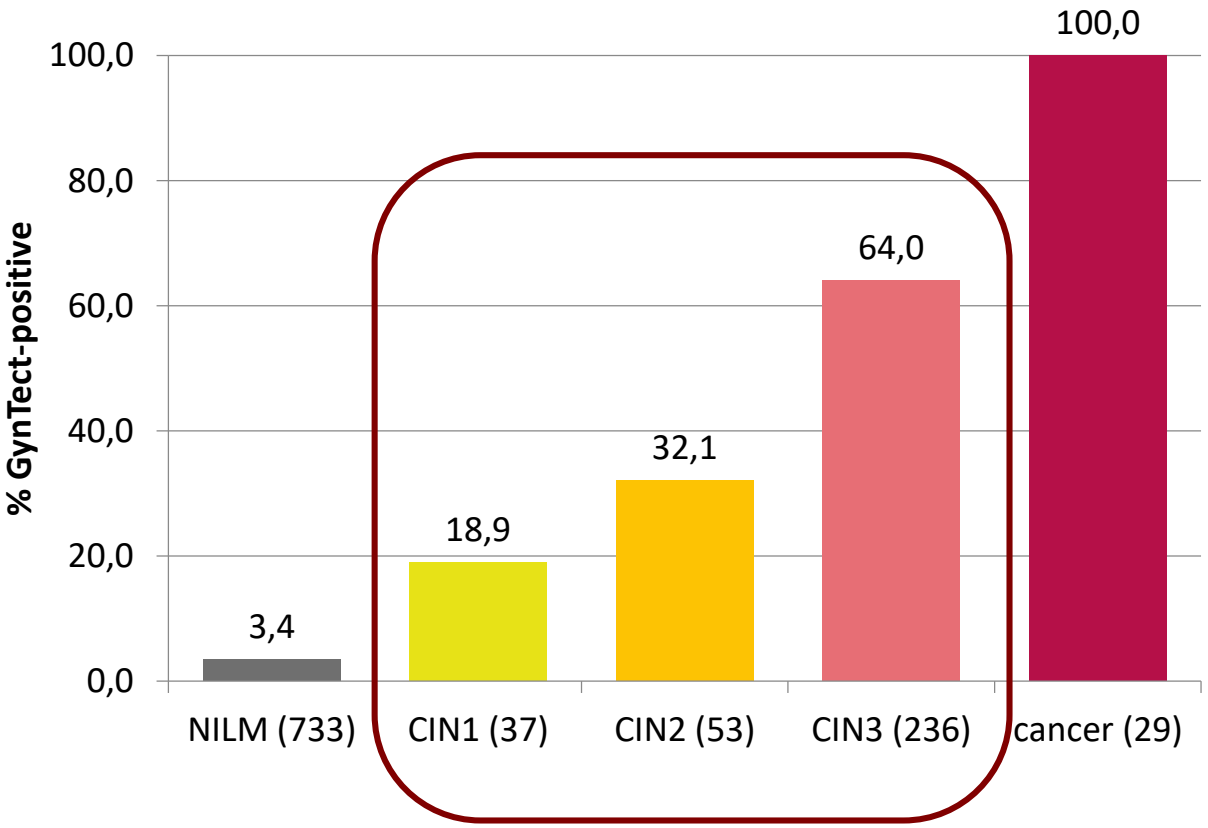
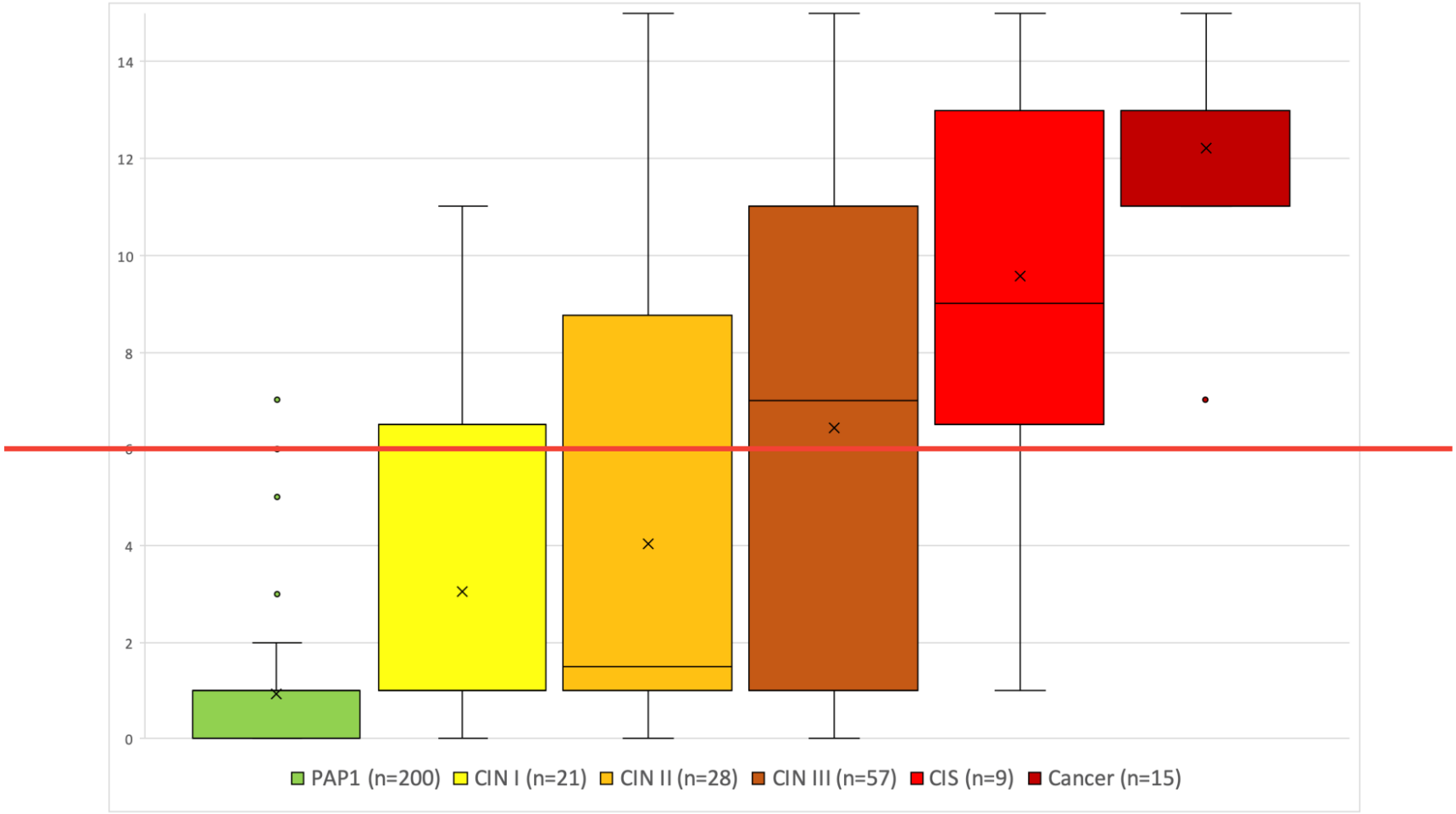



Increasing rate of positives within the CIN spectrum

Schmitz et al., 2018 BMC Cancer 18:1192, unpublished data

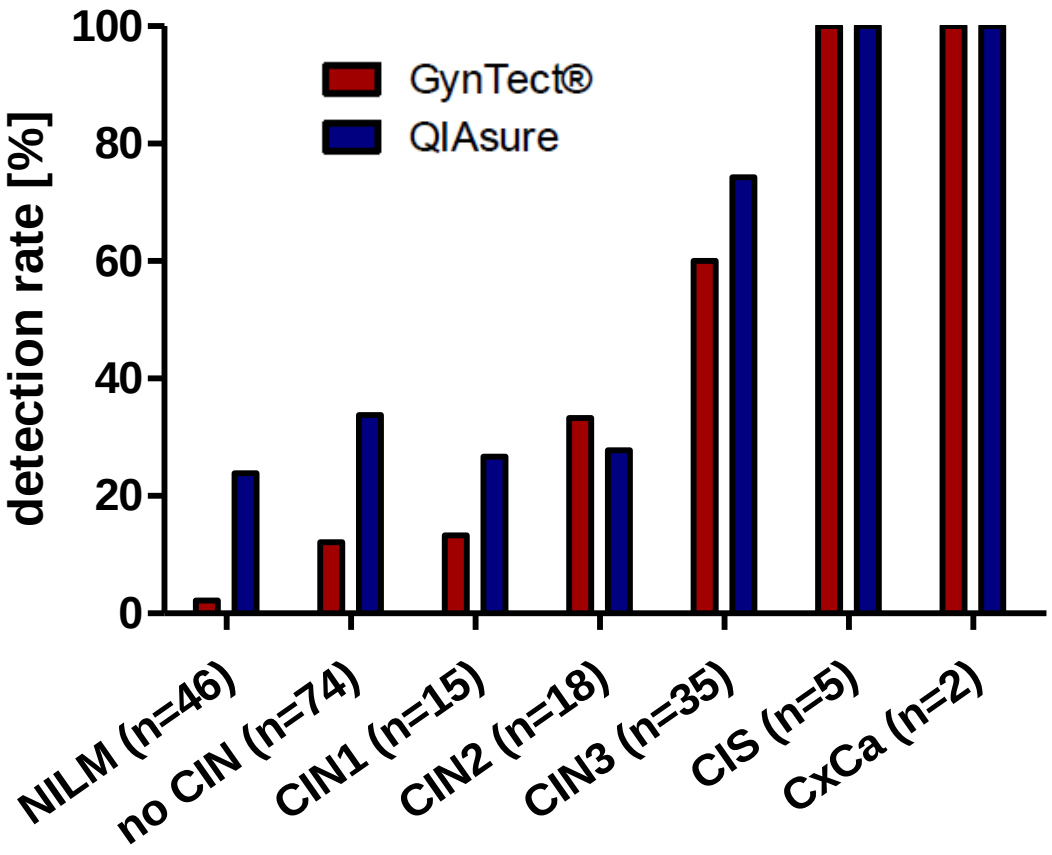
# GynTect® score in LBC medium

Overall score increases with disease severity




Schmitz et al., 2018 BMC Cancer 18:1192; unpublished data

# Comparison of 2 methylation triage tests




| | GynTect® | QIAsure |
|---|---|---|
| *Sensitivity* | | |
| CIN2+ | 56.7% | 63.3% |
| CIN3+ | 66.7% | 78.6% |
| *Specificity* | | |
| CIN2+ | 91.1% | 70.4% |
| CIN3+ | 88.2% | 70.6% |
| *PPV* | | |
| CIN2+ | 73.9% | 48.7% |
| CIN3+ | 60.9% | 42.3% |
| *NPV* | | |
| CIN2+ | 82.6% | 81.2% |
| CIN3+ | 90.6% | 92.3% |

195 HPV-positive samples were tested with QIAsure (QIAGEN) and GynTect®

Carolin Dippmann, manuscript in preparation

# GynTect® may be of prognostic significance

| | Women <30 (n = 114) | Women ≥30 (n = 103) |
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| | Methylation-positive/total number n (% methylated; 95% CI) | |
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➡ Significant differences in positivity between age groups correlates with the natural history of CIN

Hansel et al., 2014 PLoS ONE 9(3):e91905

# GynTect-Pro Study (DRKS-ID 00012571)

**Clinical aim:**

„**Proof-of-concept**“ for the validity of GynTect® as a prognostic marker at the time point of diagnosis for **women ≤ 24 years**

**Study design:**

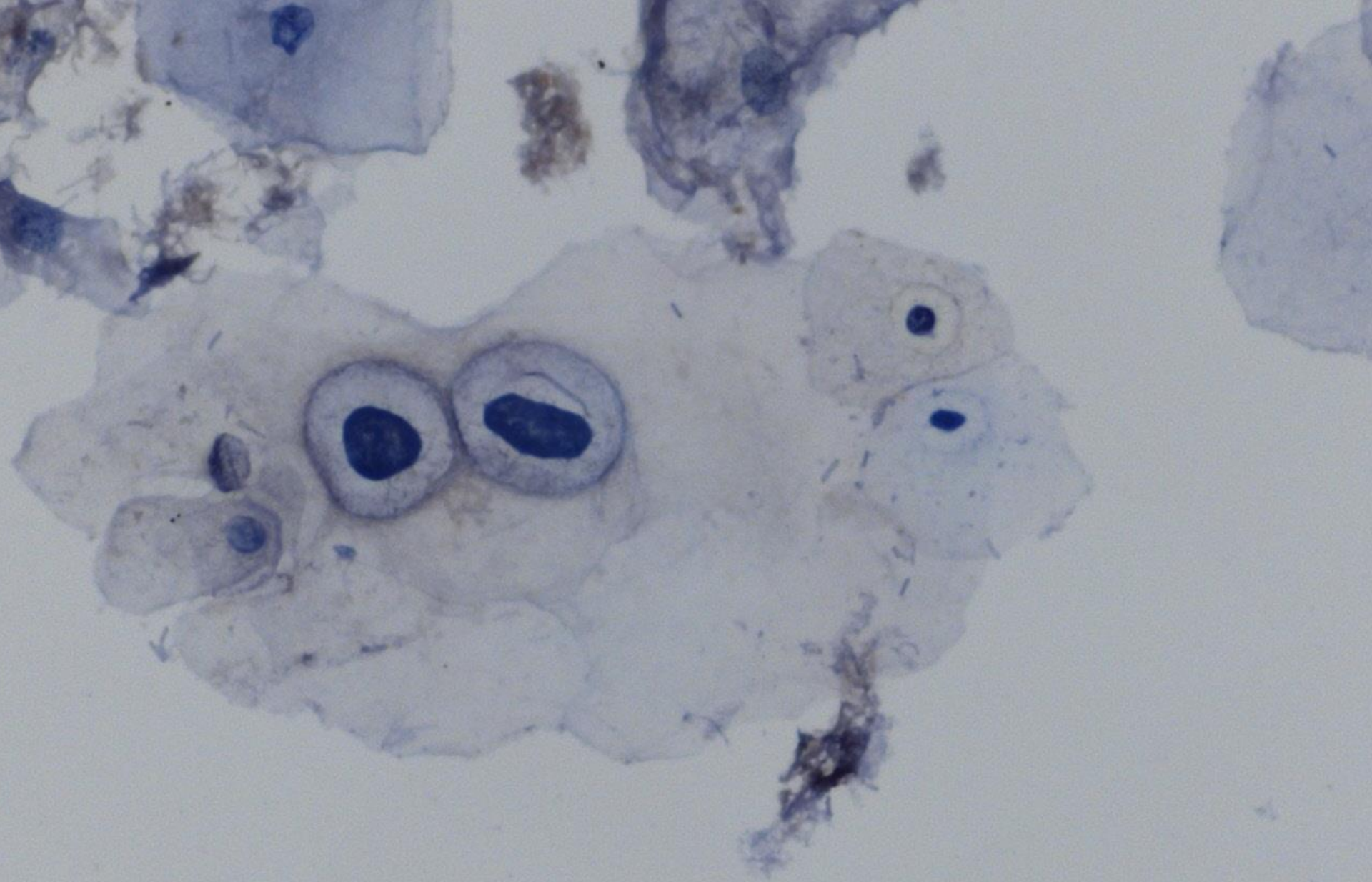
Prospective, multicentric cohort study in the context of „watchful waiting“

The GynTect® result does not influence treatment decision!!!

| | |
|---|---|
| **Patients:** | **CIN2** and **CIN3** |
| **Follow up:** | CIN2 max. 24 months (intervals 6, 12, 18 and 24 months) |
| | CIN3: max. 12 months (intervals 6 and 12 months) |
| **Primary end point :** | **Regression** (Predictive value of a GynTect® neg. test) |
| **Secondary end points:** | Persistence, progression |
| **Current status:** | 8 active centres, end of recruitment February 2020 |
| **Further info:** | matthias.duerst@med.uni-jena.de |

# Take home message

- GynTect® detects all cervical carcinoma and most likley all clinically relevant high grade lesions
- Extremely low number (3.4%) of positives among cytological normal scrapes
- The prognostic value of a GynTect® negative test result (NPV) is currently being investigated
- Two further talks on Friday FC21/22 16:15-18:45
- For further details please visit the **oncgnostic** booth



Thank you for your attention!