

Claims

1. A method for detecting HPV-induced high-grade precancerous lesions and HPV-induced invasive cancers and nonHPV-induced gynaecological and anogenital cancers, said method comprising detection of hypermethylation in the GHSR and/or ZIC1 gene in a cell whereby such
5 hypermethylation indicates the presence of HPV-induced precursor lesions with invasive potential, HPV-induced invasive cancers and nonHPV-induced gynaecological and anogenital cancers.
2. Method according to claim 1, wherein said HPV-induced high-grade precancerous lesion or HPV-induced invasive carcinoma is a high-
10 grade premalignant cervical lesion or invasive cervical cancer.
3. Method according to claim 1 or 2, wherein said HPV-induced invasive cancer is a high-risk HPV-induced invasive cancer.
4. Method according to claim 1, wherein said nonHPV-induced gynaecological cancers is an endometrial cancer.
- 15 5. Method according to any one of the preceding claims, wherein said hypermethylation is detected in the CpG rich sequences as indicated in Figures 1 and 2.
6. A method of detecting HPV-induced high-grade precancerous lesion and HPV-induced invasive cancers and nonHPV-induced
20 gynaecological or anogenital cancer according to any of claims 1-5, wherein said hypermethylation is an increased methylation of GHSR and/or ZIC1 CpG rich promoter and/or gene sequences in the test cell as compared to the comparable normal cell
7. Method according to any of claims 1-6, wherein the reagent is a
25 methylation sensitive restriction endonuclease, chosen from the group consisting of BssHII, MspI, NotI and HpaII.

8. Method according to any of claims 1-6 wherein the method involves nanotechnology, preferably lab on a chip technology.
9. Method according to claim any of claims 1-6, wherein a methylation specific PCR is performed, which is based on bisulfite
5 modification of DNA, followed by specific PCR reactions that target CpG rich sequences
10. Method according to claim 9, wherein the reagent is a nucleic acid probe or primer that binds to the nucleic acid as indicated in Figure 1 or 2.
11. Method according to claim 10, wherein said nucleic acid probe or
10 primer has a detectable label.
- 12 Method according to claim 9, 10 or 11, wherein the nucleic acid probe has a nucleotide sequence selected from the group consisting of:
- a) a polynucleotide sequence capable of hybridizing under stringent conditions to the sequence ZIC1 as set forth in Figure 1
15 or to the sequence GHSR as set forth in Figure 2;
 - b) a polynucleotide having at least 70% identity to one of the polynucleotides of a);
 - c) a polynucleotide complementary to one of the polynucleotides of a); and
 - 20 d) a polynucleotide comprising at least 15 bases of one of the polynucleotides of a) or b).
13. Method according to any of claims 1 -12, wherein the methylation of both the GHSR and the ZIC1 gene is determined
14. Use of GHSR and/or ZIC1 as a molecular diagnostic marker for
25 the detection of HPV-induced high-grade precancerous lesion or HPV-induced invasive carcinoma or nonHPV-induced gynaecological or anogenital cancer, preferably wherein the methylation of said marker is predictive for the occurrence of said lesion, carcinoma or cancer.
15. Method according to any of claims 1 – 14, wherein the cell is
30 derived from a urine sample or a cervical sample.

16. Method according to claim 15, wherein the cervical sample is a self-sample.
17. Kit of parts for use in a method of detecting HPV-induced high-grade precancerous lesion or HPV-induced invasive carcinoma or nonHPV-induced gynaecological or anogenital cancer, said kit comprising
- 5 -means for the detection of GHSR and/or ZIC1 methylation wherein said means comprise probes and/or primers specific for the ZIC1 nucleotide sequence of Figure 1 and/or the GHSR nucleotide sequence of Figure 2.
- 10 -means for the detection of HPV infection, wherein said means comprise probes and primers specific for HPV.