Supplementary Figure 1:

Screening cohort

- n=587 non-metastatic, n=101 metastatic CRC patients from Heilbronn, Ludwigshafen, Mannheimand Speyer
 - → exclusion of neoadjuvant treated patients
 - → n=572 non-metastatic CRC patients available for analysis
- n=34 pairs of tumor and normal tissue samples (including non-metastatic and metastatic patients)
- n=269,306 CpGs included after preprocessing and filtering



Identification of candidate CpG sites

- variable screening for prognostic CpGs using Cox model adjusted for age as continuous covariate and gender, smoking behavior, MSI-status, tumor stage and tumor location as categorical covariates
- p-value adjustment via IHW using the difference between tumor and normal tissue as covariate (differences between tumor and normal tissues assessed by paired Wilcoxonsigned-rank test)



1000 CpGs with smallest p-values



20 CpGs with smallest Brier score for 3-year survival



ProMCol classifier

- multiplying the β-values of the 20 CpG sites with the respective weights of the first principal component
- score between 0.00 and 4.30
 score=0.00 → completely unmethylated status in all CpGs
 score=4.30 → fully methylated status in all CpGs

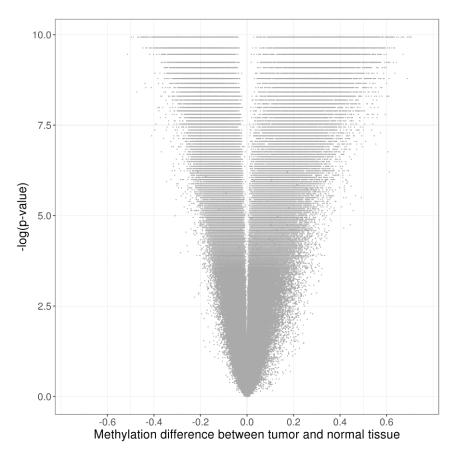


Validation cohort

n=274 non-metastatic CRC patients from Heidelberg

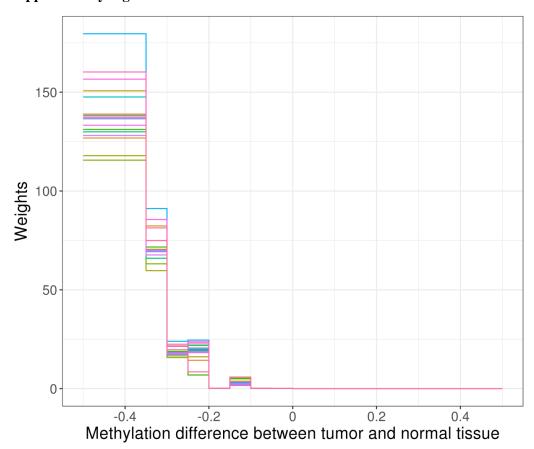
Supplementary Figure 1: Study design and analysis flowchart

Supplementary Figure 2:



Supplementary Figure 2: Volcano plot showing differentially methylated CpG sites across the genome comparing 34 pairs of tumor and normal mucosa tissue. On the x-axis the β -value difference between tumor (TU) and normal tissue (NT) is shown and on the y-axis the corresponding $-\log(p\text{-value})$.

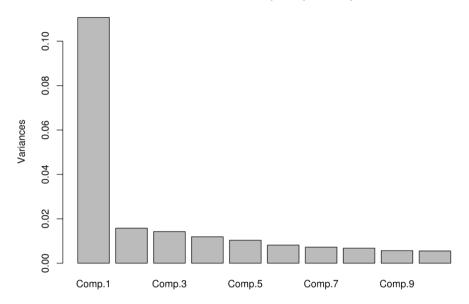
Supplementary Figure 3:



Supplementary Figure 3: Illustration of weighting in the IHW model. The left side of the plot, with β -value difference (x-axis) ranging between -0.5 and 0, represents the CpG sites with lower methylation in tumor than in normal mucosa tissue, the right side with β -value difference between 0 and 0.5, the CpG sites with higher methylation in tumor than in normal mucosa tissue. In all 20 folds, illustrated by the different colored lines, the highest weighting (y-axis) was given to CpG sites with clearly lower methylation levels in tumor than in normal mucosa tissue and no weight was given to CpG sites with higher methylation levels in tumor tissue.

Supplementary Figure 4:

Variances of the first 10 principal Components



Supplementary Figure 4: The depiction of the explained variance by the first 10 principal components of the 20 CpG sites included in our classifier shows that the usage of only the first component is sufficient for an appropriate presentation of their information value.