VIPER Supplementary Materials

This document was created using R markdown. The source document and data are available in the "viperData" R package (1). There are three sections:

- Study Designs
- Sizing
- Histograms of reader scores and ROC curves.

Study Designs

In Fig. S1A through Fig. S1E we graphically show the reader and case sampling of the five VIPER reader studies. Each (row, column) pixel corresponds to a reader/radiologist (row) and a case/patient (column). The readers may be different from study to study. The cases are organized by type: BIRADS 0 by full-field digital mammography (FFDM), BIRADS 0 by screen-film mammography (SFM), BIRADS 1-2 by FFDM, BIRADS 1-2 by SFM, and cancer. If the pixel is white, the corresponding reader evaluated the corresponding case. If the pixel is gray, the corresponding reader did not read the corresponding case. These "missing" observations were either by design or were accidentally skipped by readers during data collection. On average readers missed less than one case per modality and sub-study; there was a total of 138 missing observations out of 20,520 planned.

For example, in the cancer block of Fig. S1B we see the prototypical split-plot design with two missing cases. Readers 1-5 read the first 30 cases, readers 6-10 read the next 31 cases, readers 11-15 read the next 29 cases, and readers 16-20 read the last 25 cases. In the "BIRADS 0 by FFDM" block of Fig. S1B, every reader read 4 cases. During the study, these four cases were split into two case sets so that each reading session had two cases. For readers 1-5, these cases appear sequentially in Fig. S1B. For the other readers, the cases appear separated into two locations.

We could reorder each block to show the prototypical split-plot design, but the order would be different for each reader study. Instead, we wanted to keep the same order for all the study designs, even if that meant some blocks didn't appear as the prototypical split-plot design. Using the same order for all the study designs shows how the studies fit together. For example, most readers that participated in the screeningLowP reader study also participated in the screeningMedP and challengeMedP studies. If you trace any line down through these study designs, you will find that no reader group read the same case more than once.

Lastly, we can distinguish the screening studies (Figs. S1A-S1C) from the challenge studies (Figs. S1D-S1E) by the sparse inclusion of BIRADS 0 cases and heavy inclusion of BIRADS 1-2 cases. We can also see changes in prevalence as the number of non-cancer cases decreases from Fig. S1A to Fig. S1C and from Fig. S1D to Fig. S1E.

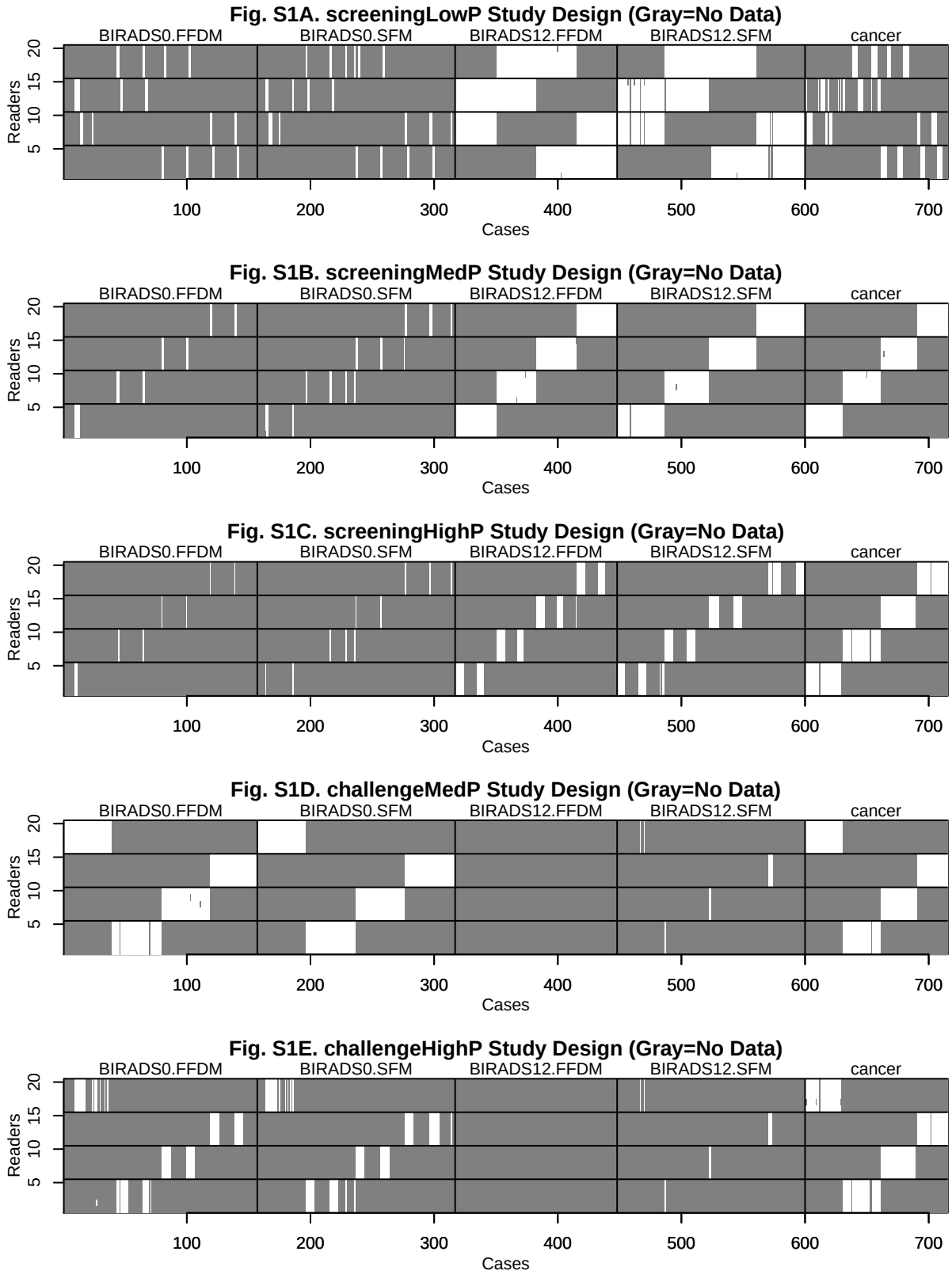


Figure 1: Figure S1: Graphical depiction of VIPER reader study designs.

Sizing

In what follows, we sketch out the steps we took to size the VIPER reader studies. We targeted a standard error of 0.03, believing that would allow ample precision for testing an effect size of 0.11, the difference between the area under the receiver operating characteristic curves (AUCs, ROCs) from FFDM and SFM observed in DMIST (2). The power for a significance level of 0.01 (0.05 split evenly among 5 reader studies) is 0.86 under a normal approximation.

The process to size VIPER started with DMIST reader study data:

- Hendrick2008_Radiology_v247p38 (3): 'Accuracy of soft-copy digital mammography versus that of screen-film mammography according to digital manufacturer: ACRIN DMIST retrospective multi-reader study.'
  - There were four machines studied, labeled below as hendrick2008.GE, hendrick2008.Fuji, hendrick2008.Fischer, and hendrick2008.Hologic. The Hologic data is not inclucded since only a few cancer cases were available.
- An unpublished study evaluating the effect of breast density on diagnostic accuracy of FFDM and SFM.
  - There were four density levels studied, corresponding to the four BIRADS density levels, labeled as breastDensity.A, breastDensity.B, breastDensity.C, breastDensity.D. The study included 320 women (109 cancers) stratified by original SFM breast density determination, 8 readers reading FFDM, and 8 readers reading SFM.
- An unpublished study evaluating performance in a reader study at 50% prevalence. The scope of the study has been described as including 30 readers assigned to read a total of 300 cases by FFDM and SFM.
  - There was one data set, labeled below as prevalence50.
- Nishikawa2009_Radiology_v251p41, 'Comparison of Soft-Copy and Hard-Copy Reading for Full-Field Digital Mammography.' This data was not used here since it did not compare FFDM to SFM.

Tables S1 and S2 show the U-statistics-based performance results as calculated by version 4.0 of the iMRMC application developed at the FDA (4).

Table S1: Performance Results for DMIST Reader Studies

	NR	N0	N1	AUC.FFDM	SE(AUC.FFDM)	AUC.SFM	SE(AUC.SFM)
hendrick2008.GE	12	72	48	0.773	0.030	0.805	0.030
hendrick2008.Fuji	12	71	27	0.720	0.047	0.762	0.047
hendrick2008.Fischer	6	73	42	0.718	0.041	0.742	0.041
breastDensity.A	16	61	19	0.852	0.042	0.890	0.042
breastDensity.B	16	40	39	0.767	0.036	0.758	0.036
breastDensity.C	16	41	39	0.828	0.030	0.818	0.030
breastDensity.D	16	69	12	0.548	0.051	0.672	0.051
prevalence50	29	156	144	0.765	0.019	0.788	0.019

Table S1 footnote: NR is the number of readers, N0 is the number of non-cancers, N1 is the number of cancers, AUC.FFDM and AUC.SFM are the AUCs for FFDM and SFM evaluations, and SE is the standard error.

Table S2: Performance Differences for DMIST Reader Studies

	NR	N0	N1	AUC.FFDM minus AUC.SFM	SE(AUC.FFDM minus AUC.SFM)
hendrick2008.GE	12	72	48	-0.032	0.024
hendrick2008.Fuji	12	71	27	-0.042	0.026
hendrick2008.Fischer	6	73	42	-0.025	0.024
breastDensity.A	16	61	19	-0.037	0.033

	NR	N0	N1	AUC.FFDM minus AUC.SFM	SE(AUC.FFDM minus AUC.SFM)
breastDensity.B	16	40	39	0.009	0.026
breastDensity.C	16	41	39	0.010	0.028
breastDensity.D	16	69	12	-0.123	0.055
prevalence50	29	156	144	-0.022	0.017

Table S2 footnote: NR is the number of readers, N0 is the number of non-cancers, N1 is the number of cancers, AUC.FFDM and AUC.SFM are the AUCs for FFDM and SFM evaluations, and SE is the standard error.

The total variance of AUCs or differences in AUCs from a fully-crossed study can be expressed as (5,6)

Equation 1

$$V = \frac{var_0^2}{N_0} + \frac{var_1^2}{N_1} + \frac{var_{01}^2}{N_0 N_1} + \frac{var_R^2}{N_R} + \frac{var_{0R}^2}{N_0 N_R} + \frac{var_{1R}^2}{N_1 N_R} + \frac{var_{01R}^2}{N_0 N_1 N_R},$$

where N_0, N_1, N_R are the number of normal (non-cancer) cases, diseased (cancer) cases, and readers, var_0^2, var_1^2, and var_R^2 are the variances due to the normal cases (non-cancers), the diseased cases (cancers), and the readers. The other variance components correspond to variances arising from interactions between the main variance components.

When the study is not fully crossed, the weights for each variance component are different and calculable (7). In particular, we can calculate the weights for a split-plot study design. For example, consider a split-plot study with N_G groups that have the same number of readers and cases (N_0, N_1, and N_R are all divisible by N_G). Assuming a study with readers and cases paired across the modalities, the variance of the difference in AUCs is given by

Equation 2

$$V = \frac{var_0^2}{N_0} + \frac{var_1^2}{N_1} + \frac{N_G var_{01}^2}{N_0 N_1} + \frac{var_R^2}{N_R} + \frac{N_G var_{0R}^2}{N_0 N_R} + \frac{N_G var_{1R}^2}{N_1 N_R} + \frac{N_G^2 var_{01R}^2}{N_0 N_1 N_R}.$$

In addition to performance results, the DMIST reader studies provide estimates of the MRMC variance components for the AUC differences. We can use these to size a study to compare FFDM to SFM for women with dense breasts.

Table S3: Variance Components of AUC Differences for DMIST Reader Studies

	var_0	var_1	var_{01}	var_R	var_{0R}	var_{1R}	var_{01R}
machA	0.0082	0.0186	0.0029	-0.0009	0.0287	0.0583	0.0437
machB	0.0019	0.0102	0.0012	0.0004	0.0315	0.0573	0.0470
machC	0.0025	0.0141	0.0016	-0.0017	0.0541	0.0869	0.0616
mach4	0.0039	0.0111	0.0011	0.0012	0.0136	0.0385	0.0329
densityA	0.0060	0.0096	0.0018	-0.0005	0.0425	0.0620	0.0453
densityB	0.0014	0.0097	0.0018	0.0016	0.0258	0.0609	0.0402
densityC	0.0080	0.0299	0.0018	-0.0067	0.0561	0.1083	0.0426
prevalence50	0.0019	0.0108	0.0019	0.0020	0.0435	0.0684	0.0515
sizingModel	0.0100	0.0300	0.0050	0.0010	0.0550	0.0900	0.0650

The last row of Table S3 shows the variance components in the model that we used to size VIPER. We generally took round numbers that were between the mean of the variance components observed or higher. This can be seen in Figure S2 where the circles show the variance components from the DMIST reader studies. The "x" symbols connected by lines show the variance components in the model that we used to size VIPER.

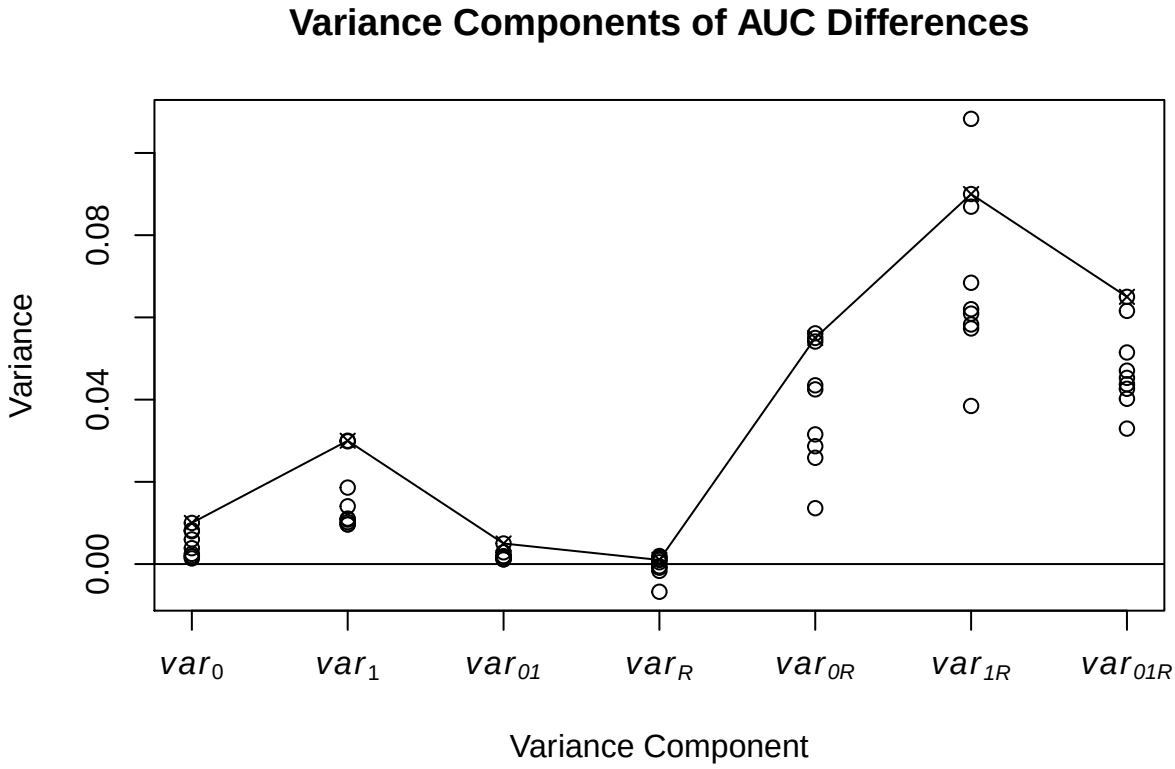


Figure 2: Figure S2: Variance components from DMIST reader studies (circles) and for the model to size the VIPER studies (x's connected by lines).

The original plan for VIPER included a large fully-crossed study (N_0=400, N_1=100, N_R=20). Given the model parameters discussed above and Eq. 1, we get the following estimates of uncertainty:

```
#> Total variance: 0.0004270812
#> Standard error: 0.02066594
#> Half width of 95% CI: 0.04133189
```

Before VIPER data collection started, a paper about split-plot study designs was published (8), and we decided to design split-plot studies for VIPER. Given the model parameters discussed above and Eq. 2, we get the following estimates of uncertainty for a split-plot study with four groups (N_G=4):

```
#> Total variance: 0.0005843
#> Standard error: 0.0241723
#> Half width of 95% CI: 0.0483446
```

The split-plot design was going to save about 75% of the reading time (75% of our costs) and with a moderate impact on precision. With this savings, we wanted to explore more study conditions (prevalence levels and types of non-cancers). We decided to design a split-plot study at ~10% prevalence per reader in which each reader would read N_1=20 cancers and N_0=160 non cancers. Given the model parameters discussed above and Eq. 2, we get the following estimates of uncertainty for a split-plot study with four groups (N_G=4):

```
#> Total variance: 0.0006842188
#> Standard error: 0.02615758
#> Half width of 95% CI: 0.05231515
```

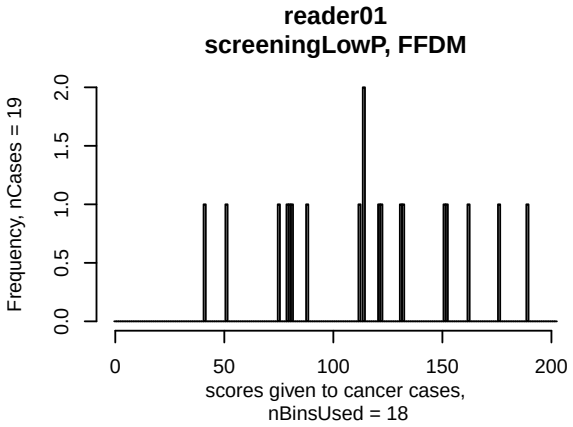
This study design was acceptable except that it required 50% more non-cancer cases than we had originally considered. This increase could not be accommodated by the available cases. After some consideration, we decided that we would split the non-cancer cases into four *overlapping* groups instead of four *independent* groups (See blocks "BIRADS12.FFDM" and "BIRADS12.SFM" in Fig. S1A). Such a study would only require 320 cases instead of 640, and the impact on the uncertainty is negligible. The standard error of the difference in AUCs is insensitive to the number of non-cancers because there are so many non-cancers. The standard error is driven by the number of readers and cancers.

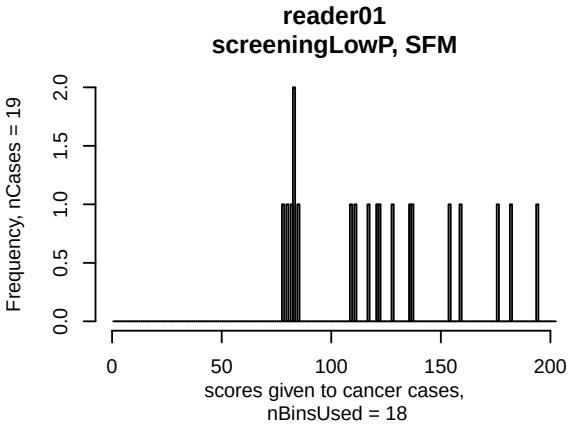
Given our initial budget and the precision achievable by a study at approximately 11% prevalence, we determined that we could conduct five reader studies in total. After splitting our significance level by five (Bonferroni Correction), the power to detect a difference between FFDM and SFM was 0.86. This was acceptable.

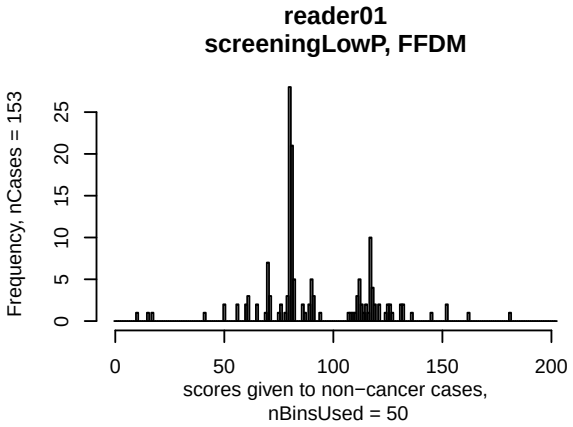
Reader Scores and ROC Curves

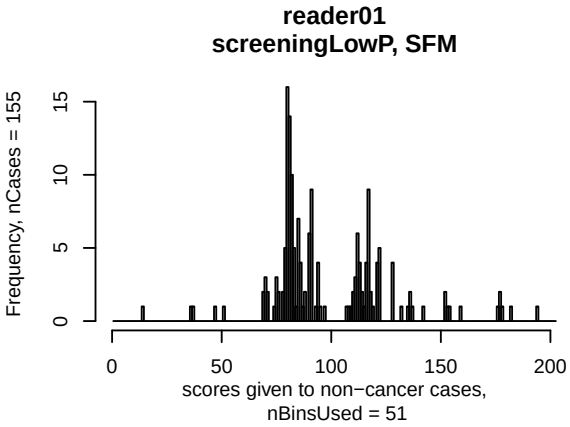
In the following pages we give histograms of the reader scores and the corresponding ROC curves and operating points. They are organized by reader study (screeningLowP, screeningMedP, screeningHighP, challengeMedP, and challengeHighP). Then for each reader study, we show the figures for each reader. In the histograms (one for FFDM and one for SFM), the scores from cancer and non-cancer cases are combined, and we indicate the number of cases (nCases) and the number bins used by each reader (nBinsUsed). The ROC curves are the empirical ROC curves obtained by considering all possible thresholds from 0 to 202. To these curves we add the operating points based on the readers' binary recall decision. The operating points fall on the ROC curves as a result of the two step scoring method summarized in the main paper.

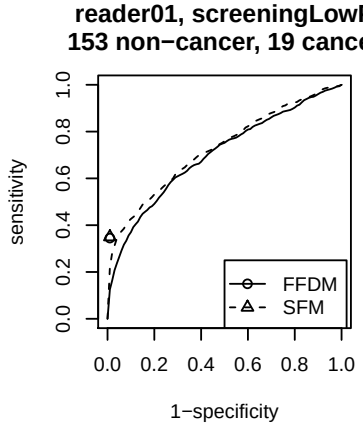
screeningLowP







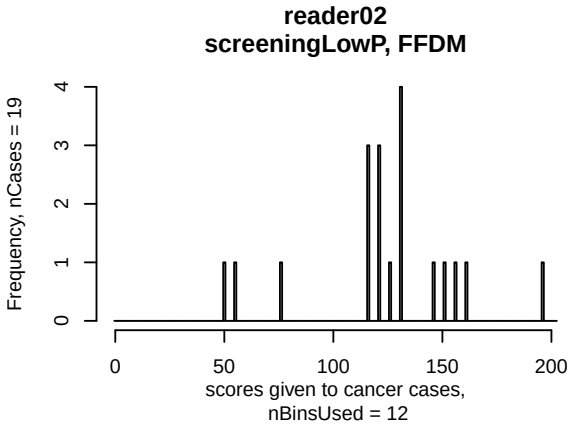


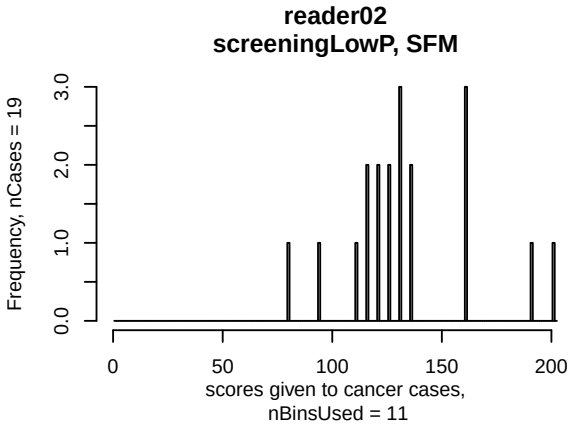


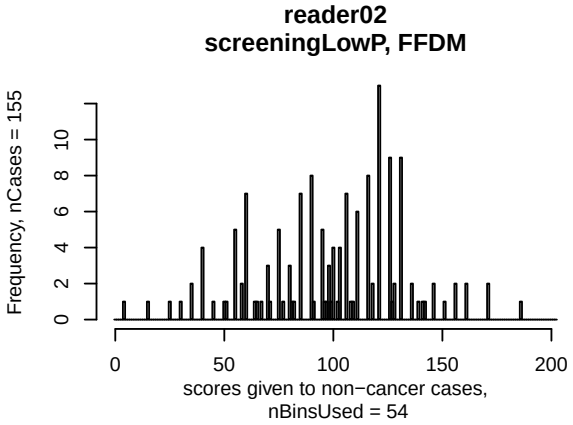
	AUC	se
FFDM	0.666	0.082
SFM	0.721	0.07
FFDM−SFM	−0.055	0.053

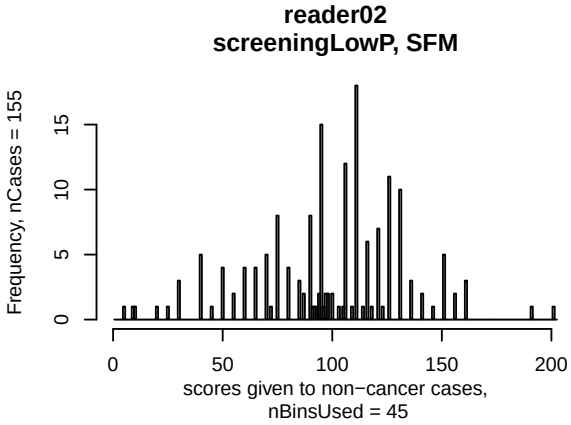
	Sens.	se
FFDM	0.666	0.082
SFM	0.721	0.07
FFDM−SFM	−0.055	0.053

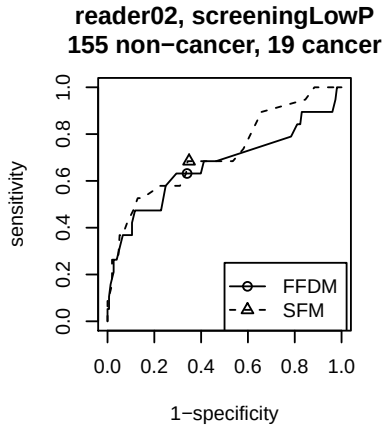
	Spec.	se
FFDM	0.666	0.082
SFM	0.721	0.07
FFDM−SFM	−0.055	0.053











	AUC	se
FFDM	0.719	0.068
SFM	0.832	0.048
FFDM−SFM	−0.113	0.076

	Sens.	se
FFDM	0.719	0.068
SFM	0.832	0.048
FFDM−SFM	−0.113	0.076

	Spec.	se
FFDM	0.719	0.068
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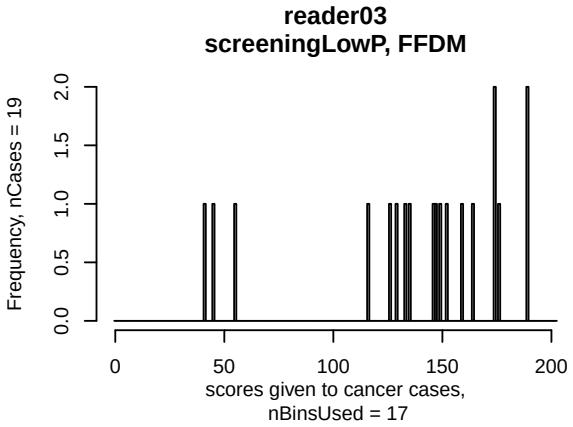

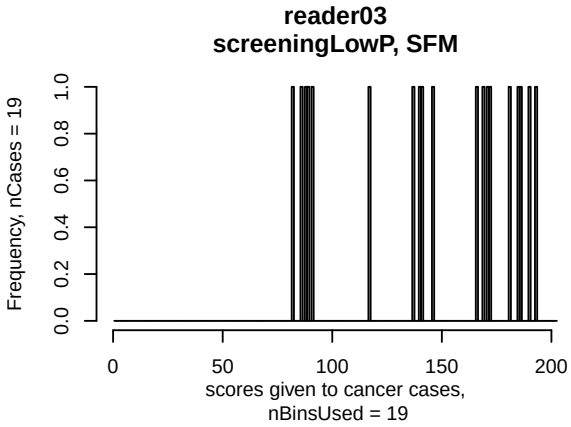

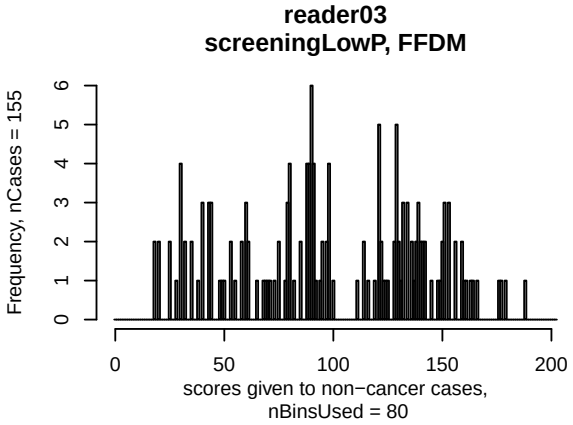

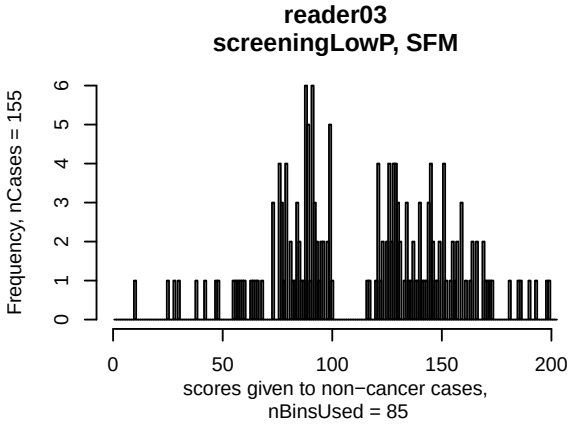

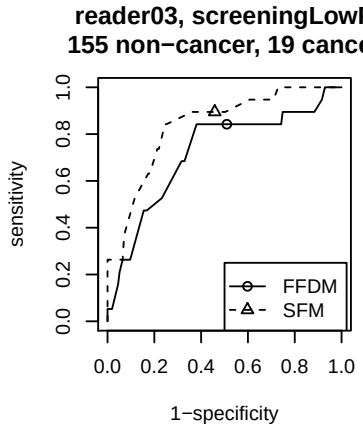

	AUC	se
FFDM	0.746	0.068
SFM	0.729	0.07
FFDM−SFM	0.017	0.087

	Sens.	se
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SFM	0.729	0.07
FFDM−SFM	0.017	0.087

	Spec.	se
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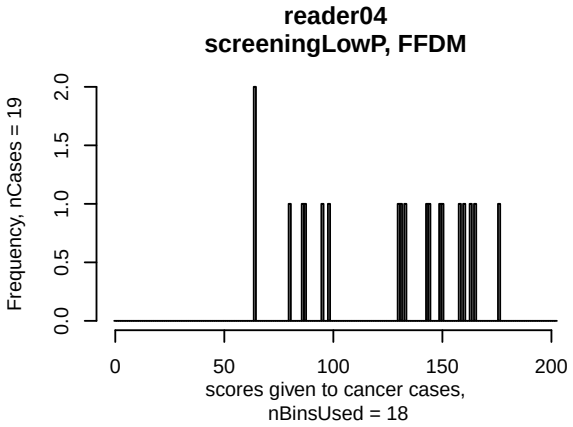

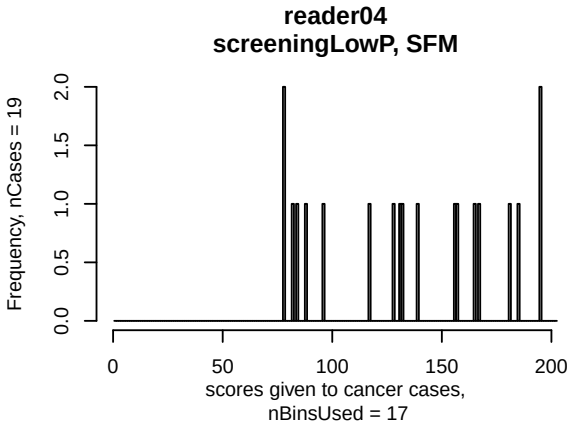

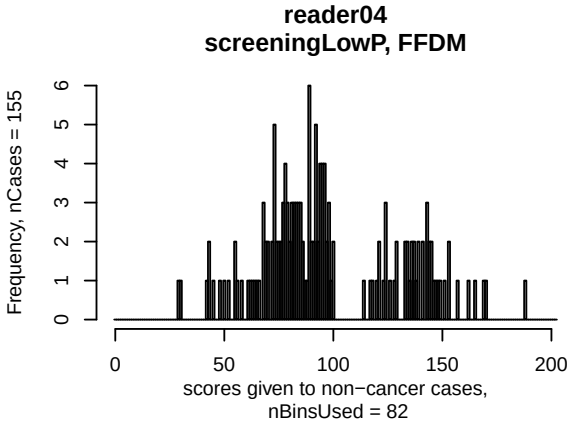

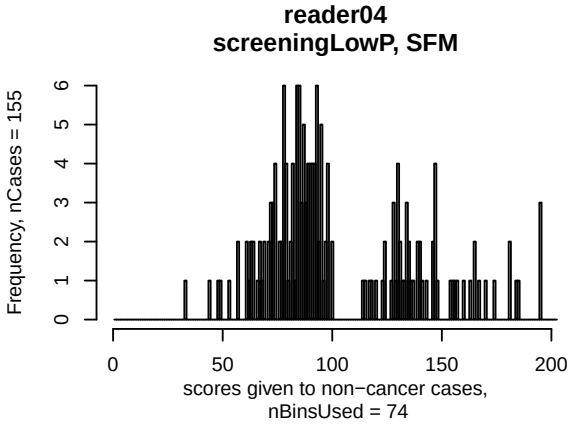

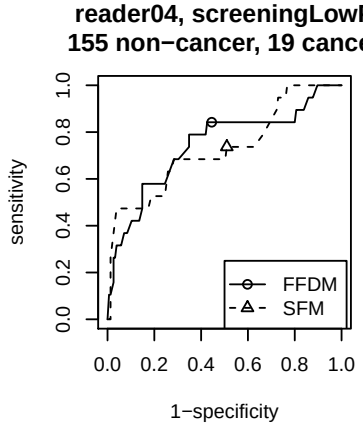

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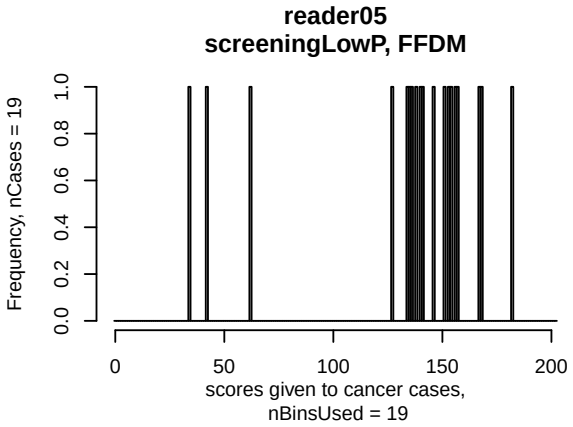

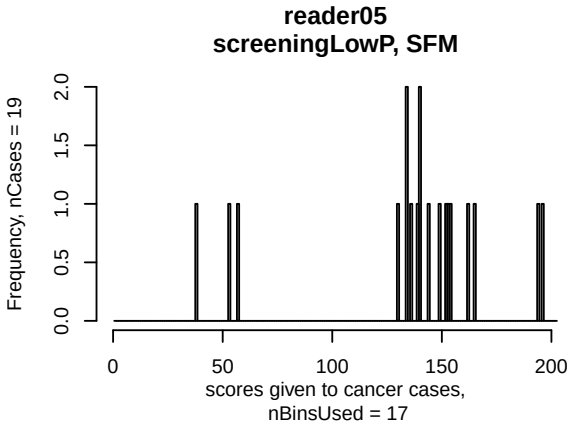

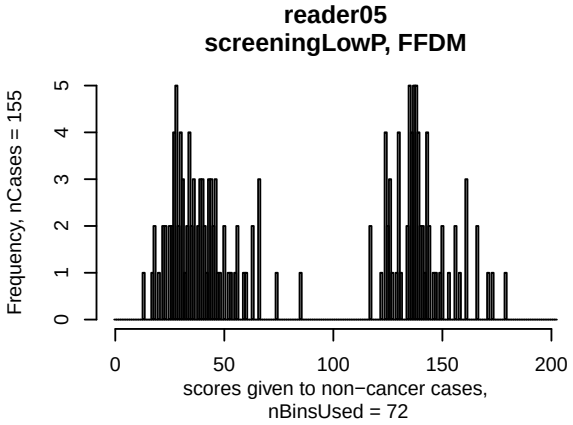

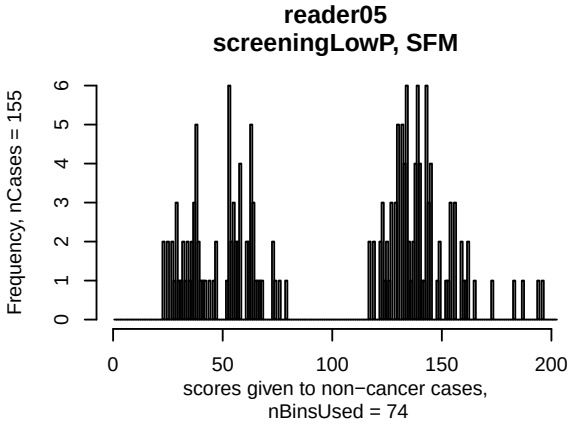

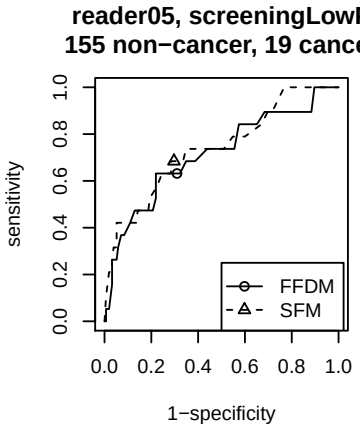

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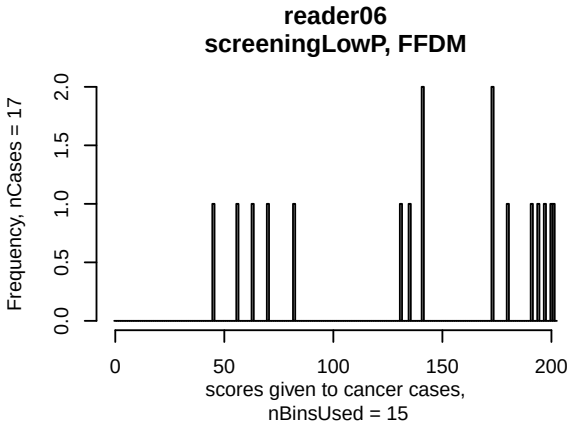
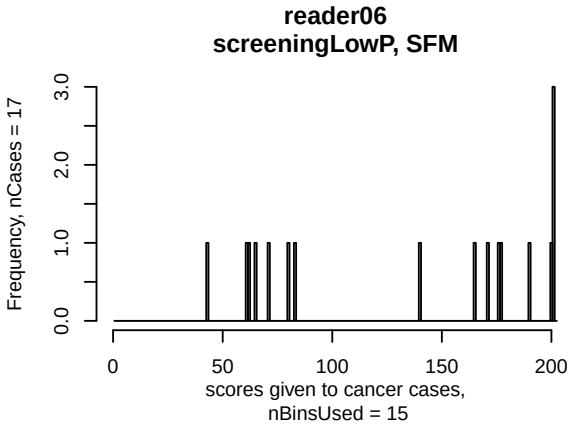
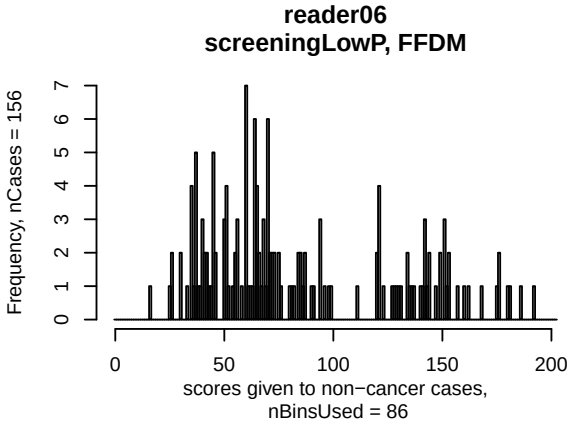
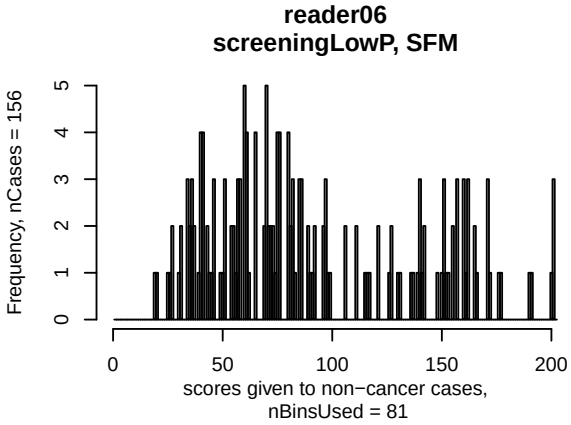
FFDM−SFM	0.017	0.061

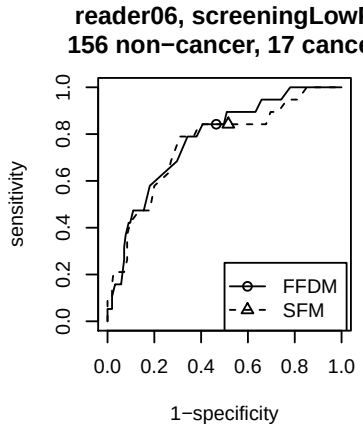
	Spec.	se
FFDM	0.774	0.054
SFM	0.757	0.061
FFDM−SFM	0.017	0.061







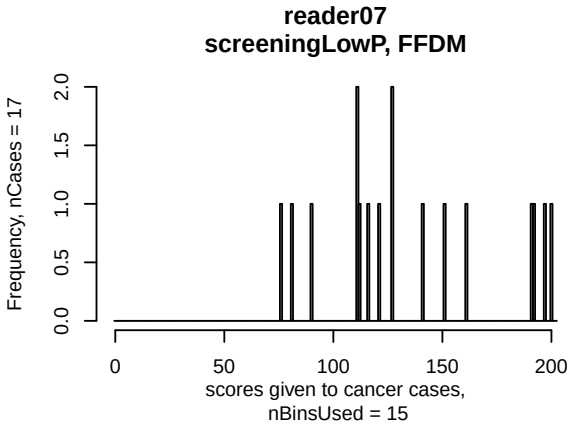


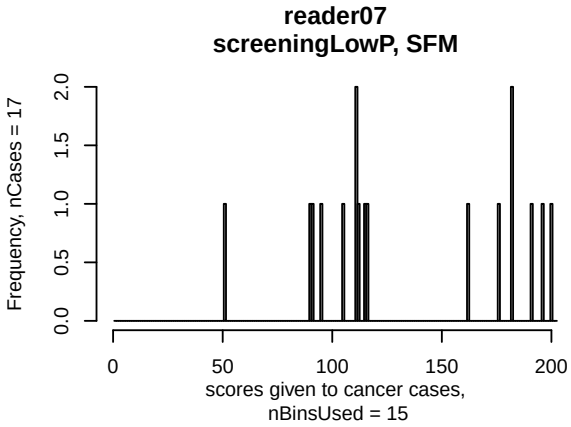


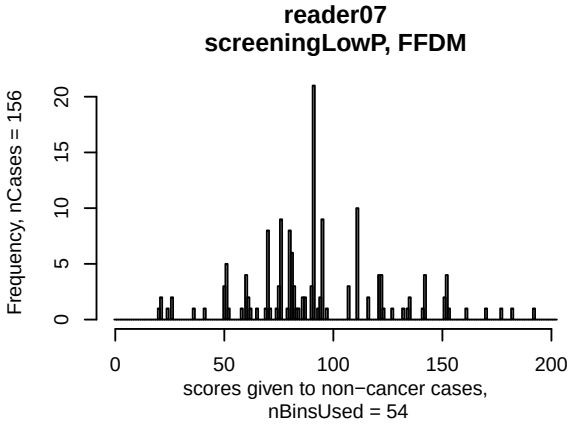
	AUC	se
FFDM	0.772	0.067
SFM	0.741	0.075
FFDM−SFM	0.032	0.08

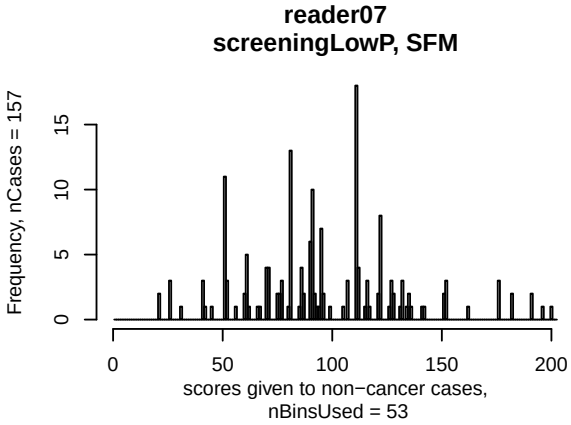
	Sens.	se
FFDM	0.772	0.067
SFM	0.741	0.075
FFDM−SFM	0.032	0.08

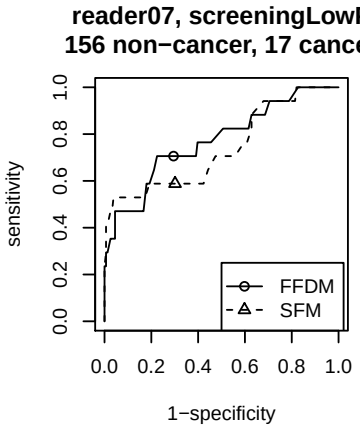
	Spec.	se
FFDM	0.772	0.067
SFM	0.741	0.075
FFDM−SFM	0.032	0.08







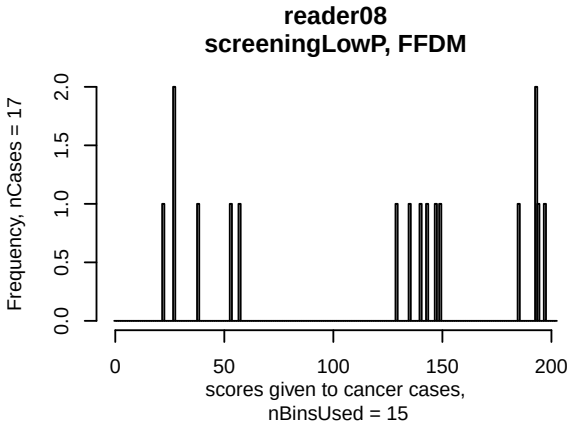


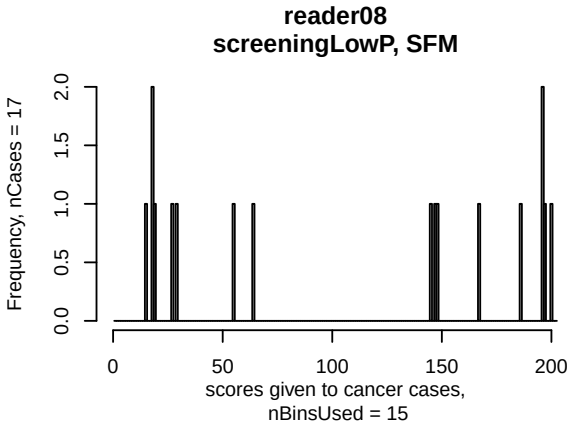


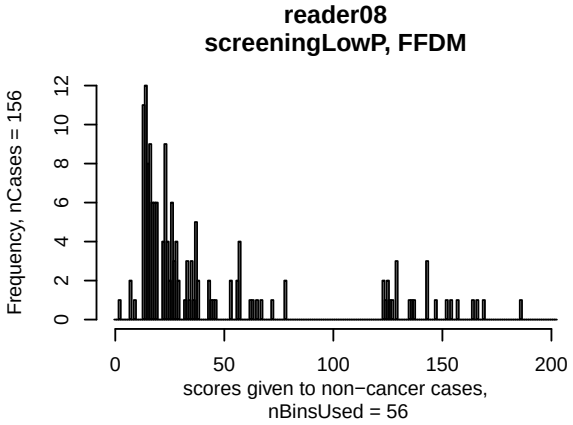
	AUC	se
FFDM	0.798	0.056
SFM	0.76	0.064
FFDM−SFM	0.038	0.075

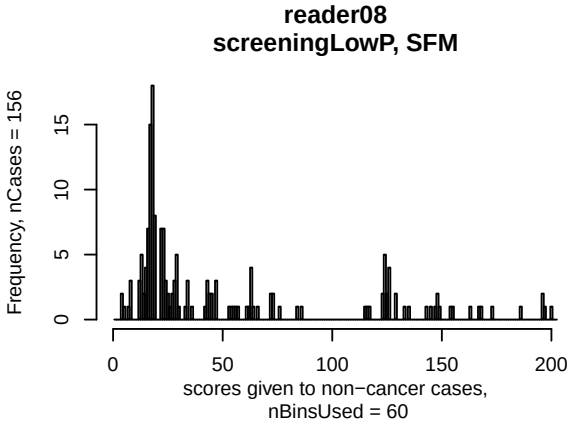
	Sens.	se
FFDM	0.798	0.056
SFM	0.76	0.064
FFDM−SFM	0.038	0.075

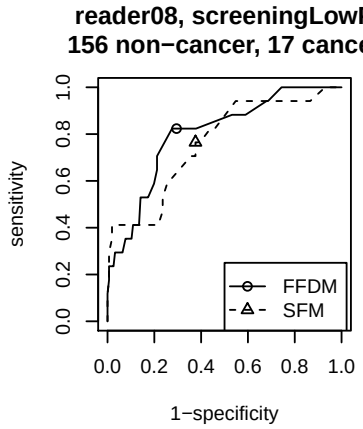
	Spec.	se
FFDM	0.798	0.056
SFM	0.76	0.064
FFDM−SFM	0.038	0.075







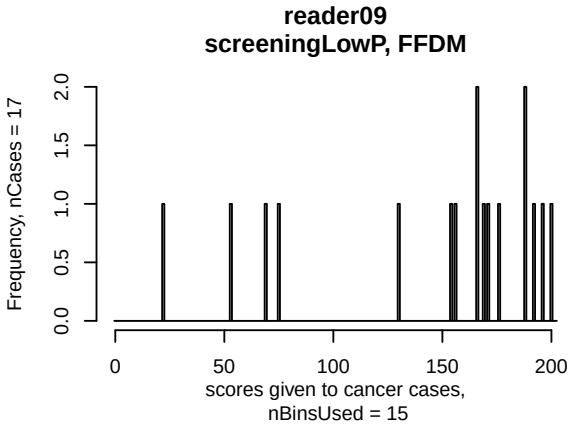


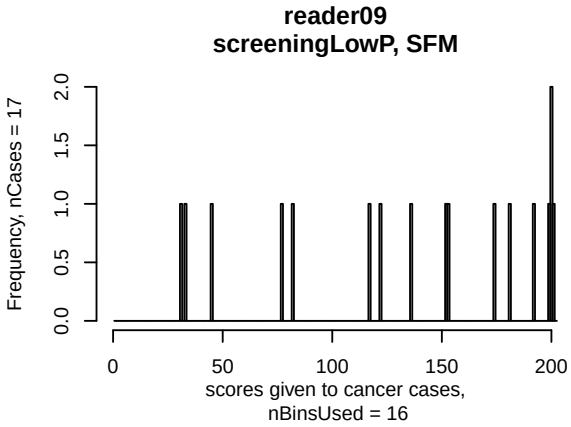


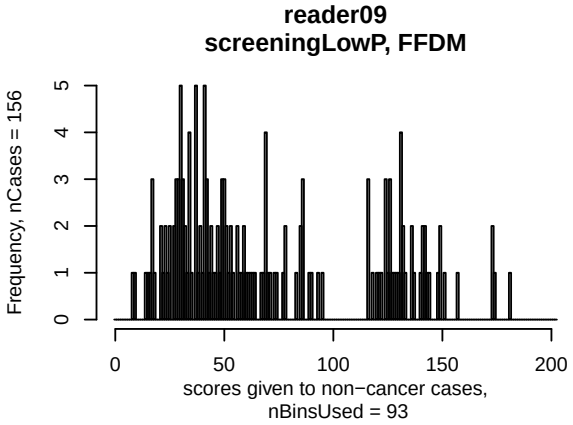
	AUC	se
FFDM	0.846	0.047
SFM	0.743	0.075
FFDM−SFM	0.103	0.057

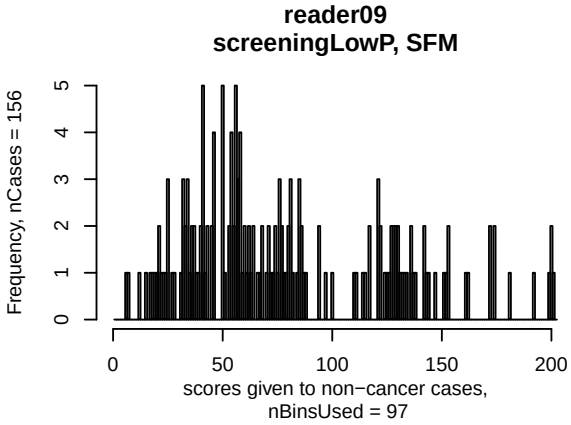
	Sens.	se
FFDM	0.846	0.047
SFM	0.743	0.075
FFDM−SFM	0.103	0.057

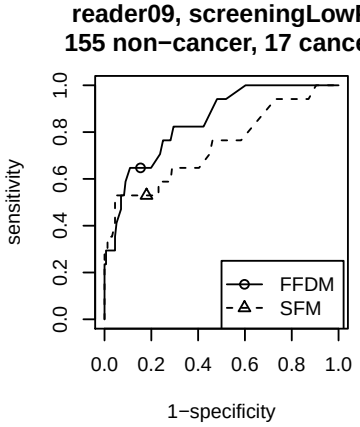
	Spec.	se
FFDM	0.846	0.047
SFM	0.743	0.075
FFDM−SFM	0.103	0.057







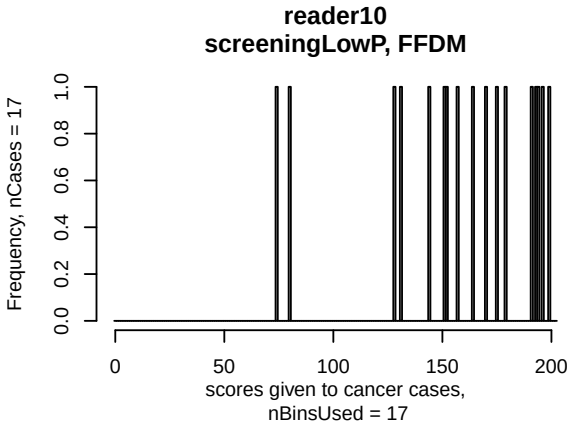


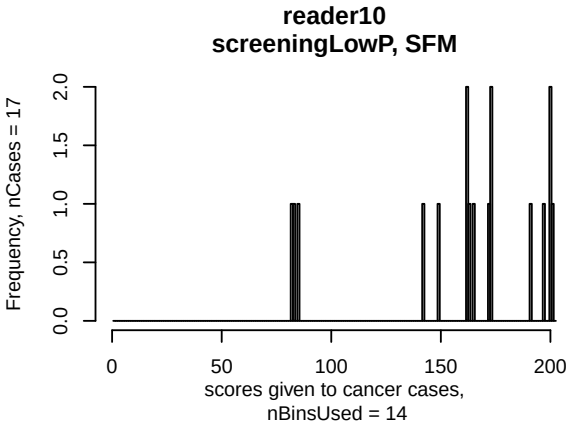


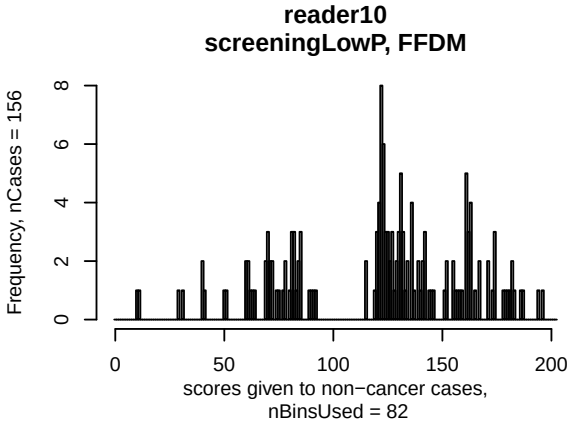
	AUC	se
FFDM	0.85	0.063
SFM	0.779	0.077
FFDM−SFM	0.071	0.074

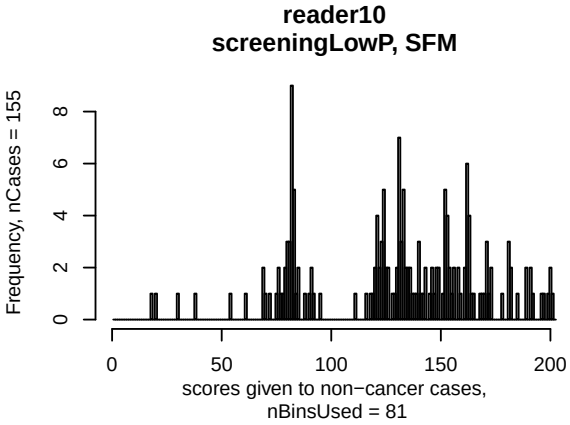
	Sens.	se
FFDM	0.85	0.063
SFM	0.779	0.077
FFDM−SFM	0.071	0.074

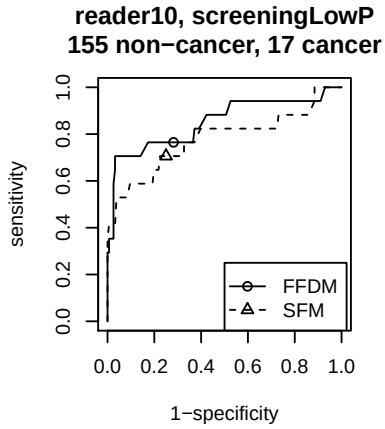
	Spec.	se
FFDM	0.85	0.063
SFM	0.779	0.077
FFDM−SFM	0.071	0.074







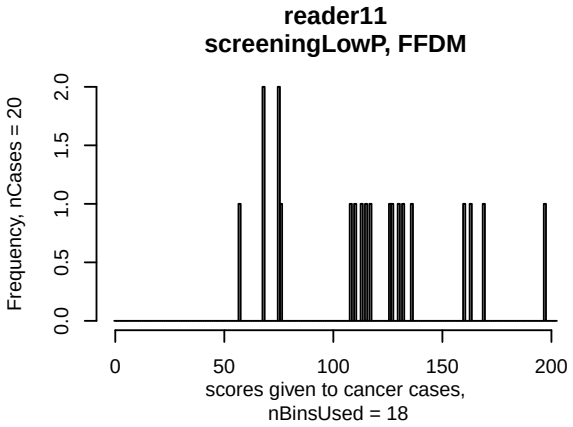


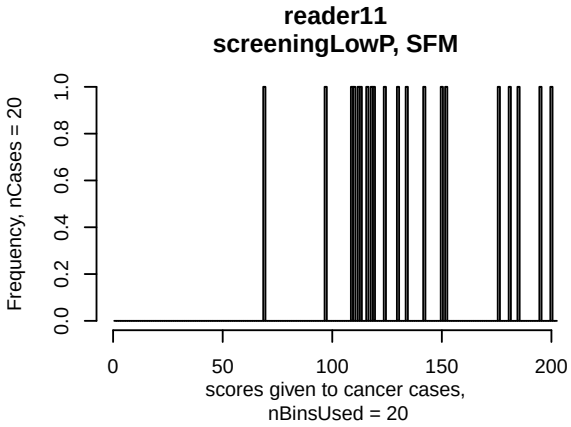


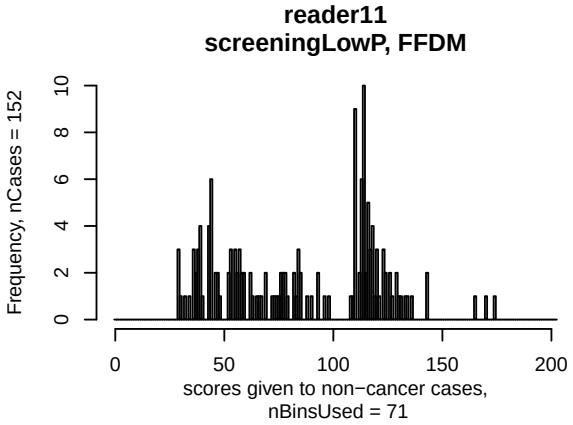
	AUC	se
FFDM	0.768	0.066
SFM	0.77	0.071
FFDM−SFM	−0.002	0.086

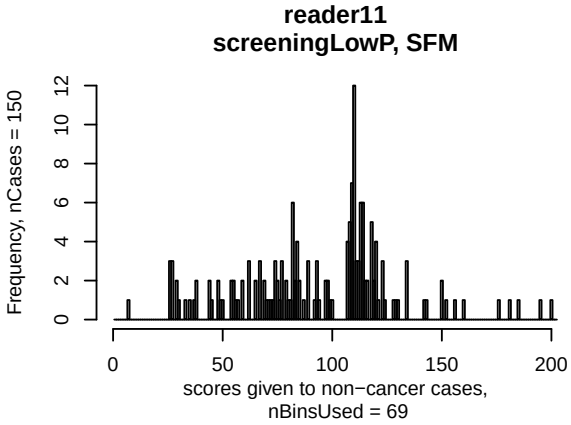
	Sens.	se
FFDM	0.768	0.066
SFM	0.77	0.071
FFDM−SFM	−0.002	0.086

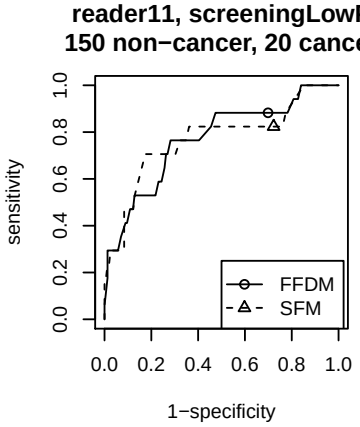
	Spec.	se
FFDM	0.768	0.066
SFM	0.77	0.071
FFDM−SFM	−0.002	0.086







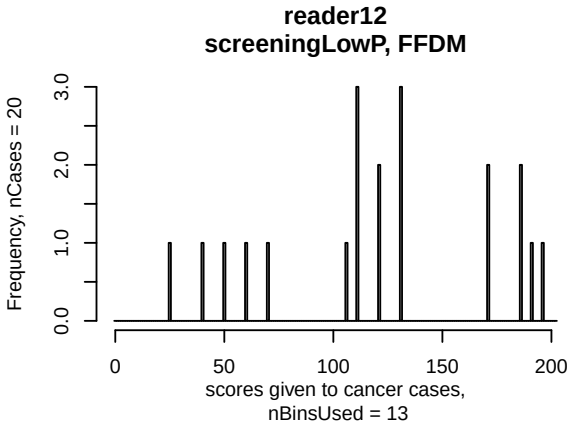


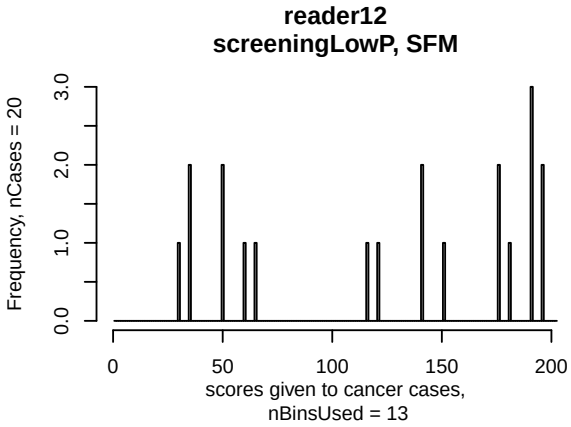


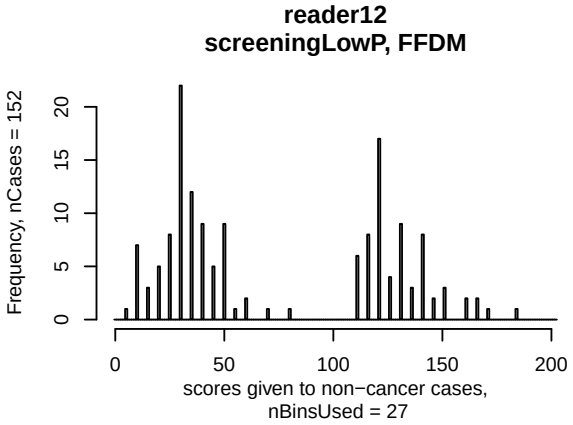
	AUC	se
FFDM	0.714	0.061
SFM	0.855	0.046
FFDM−SFM	−0.142	0.059

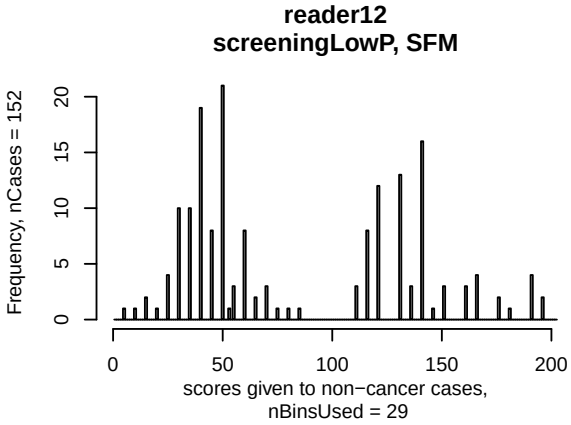
	Sens.	se
FFDM	0.714	0.061
SFM	0.855	0.046
FFDM−SFM	−0.142	0.059

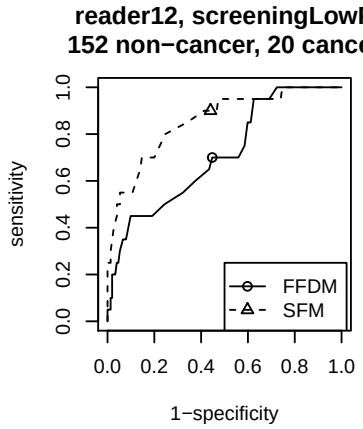
	Spec.	se
FFDM	0.714	0.061
SFM	0.855	0.046
FFDM−SFM	−0.142	0.059







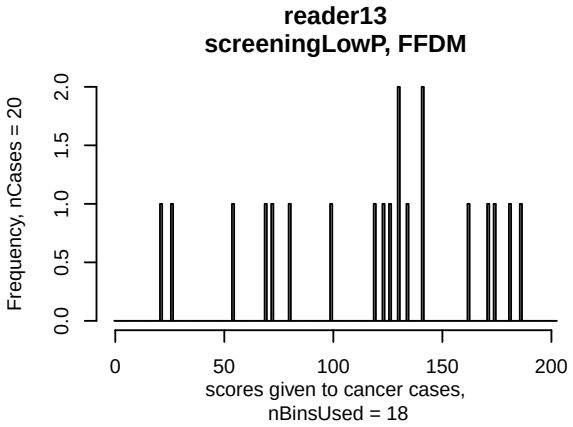


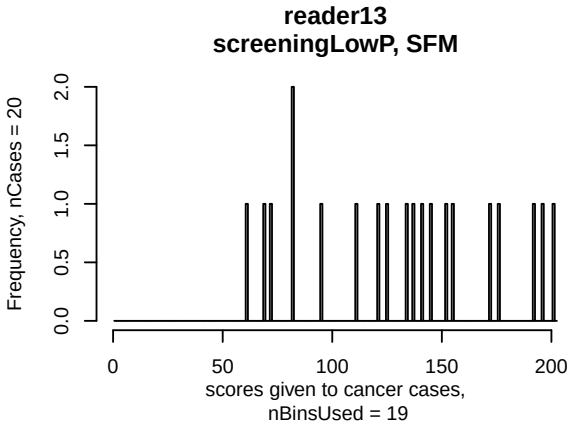


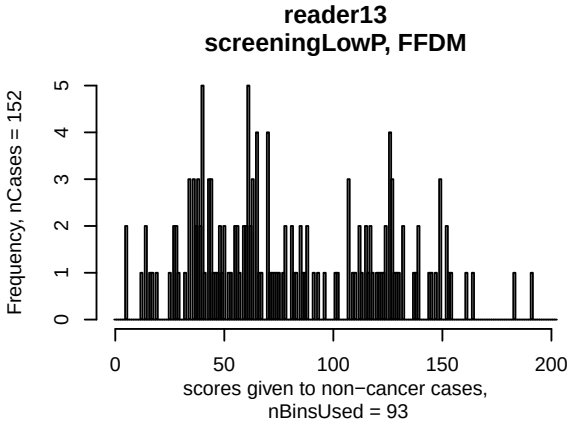
	AUC	se
FFDM	0.718	0.058
SFM	0.714	0.075
FFDM−SFM	0.004	0.069

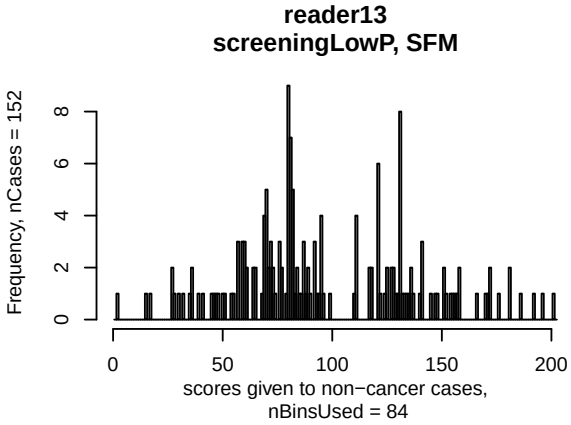
	Sens.	se
FFDM	0.718	0.058
SFM	0.714	0.075
FFDM−SFM	0.004	0.069

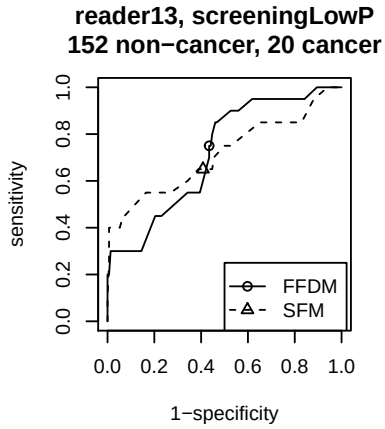
	Spec.	se
FFDM	0.718	0.058
SFM	0.714	0.075
FFDM−SFM	0.004	0.069







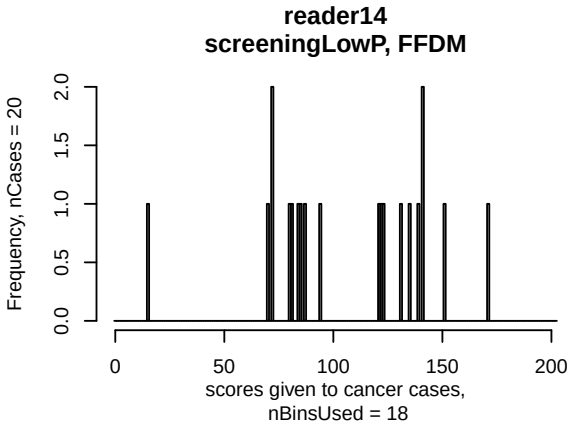


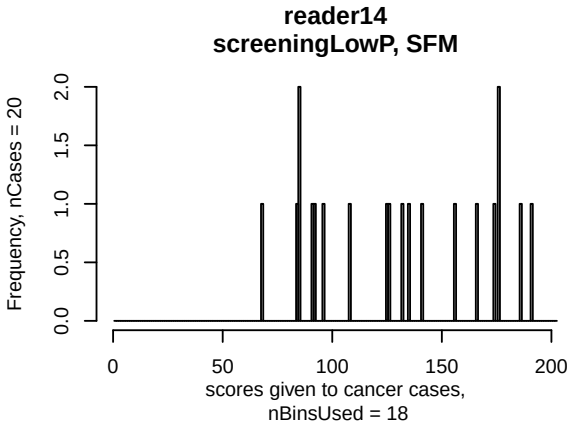


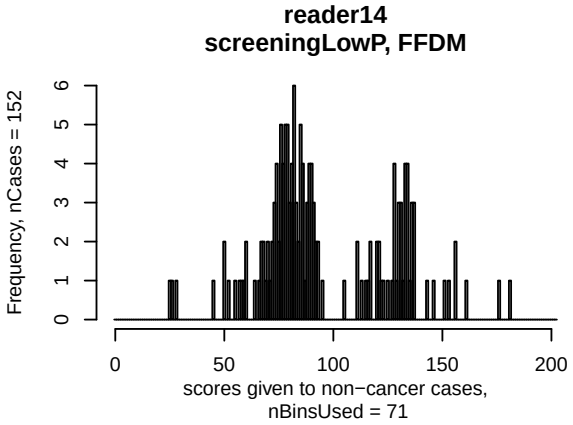
	AUC	se
FFDM	0.721	0.068
SFM	0.74	0.062
FFDM−SFM	−0.019	0.063

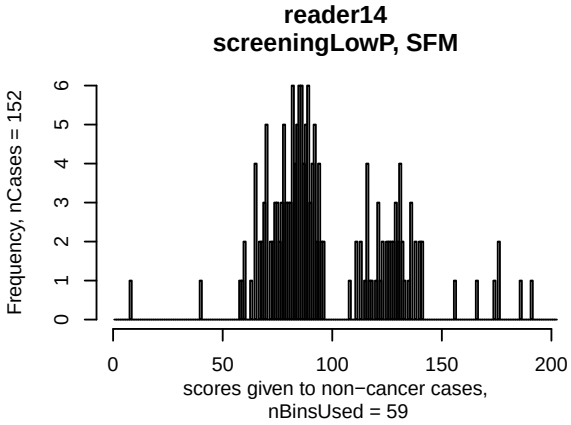
	Sens.	se
FFDM	0.721	0.068
SFM	0.74	0.062
FFDM−SFM	−0.019	0.063

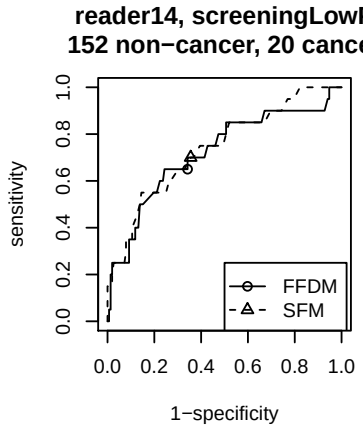
	Spec.	se
FFDM	0.721	0.068
SFM	0.74	0.062
FFDM−SFM	−0.019	0.063







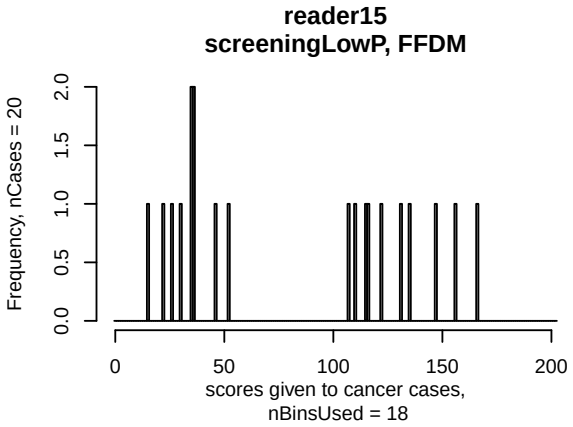


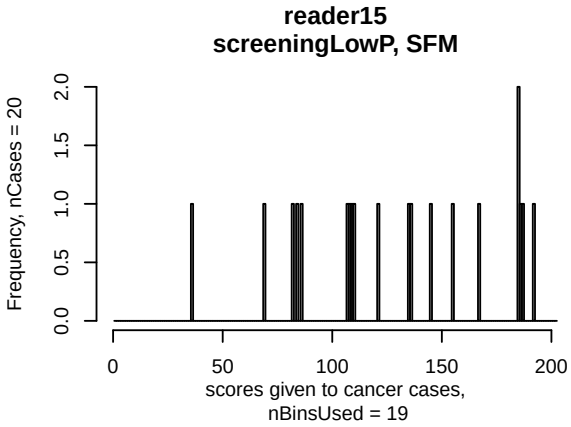


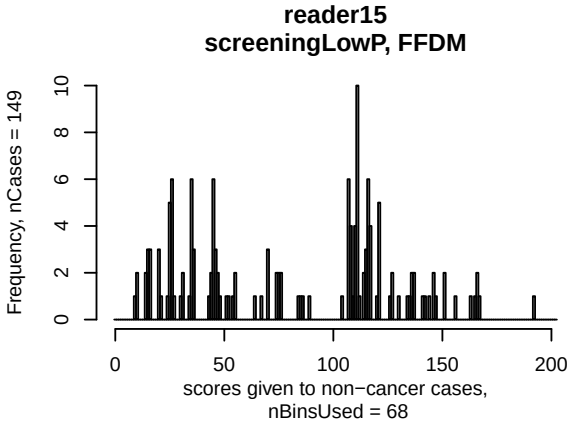
	AUC	se
FFDM	0.601	0.074
SFM	0.782	0.061
FFDM−SFM	−0.181	0.078

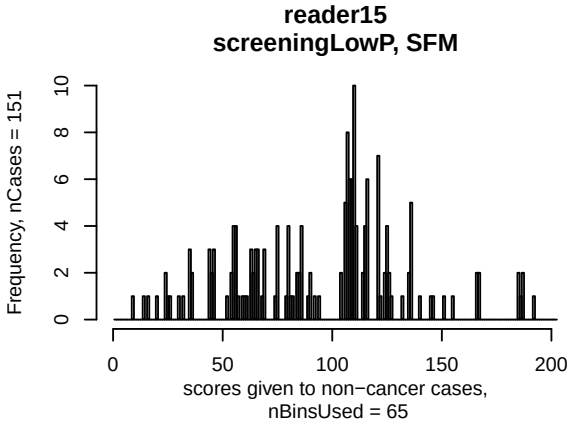
	Sens.	se
FFDM	0.601	0.074
SFM	0.782	0.061
FFDM−SFM	−0.181	0.078

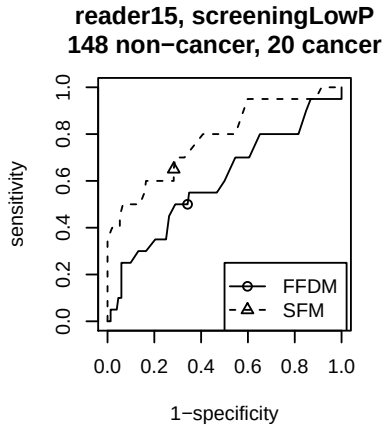
	Spec.	se
FFDM	0.601	0.074
SFM	0.782	0.061
FFDM−SFM	−0.181	0.078







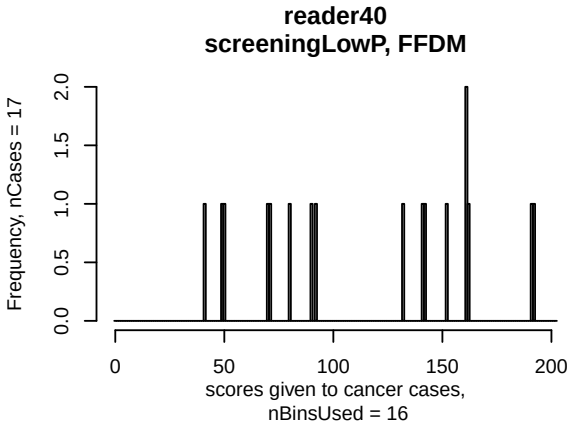


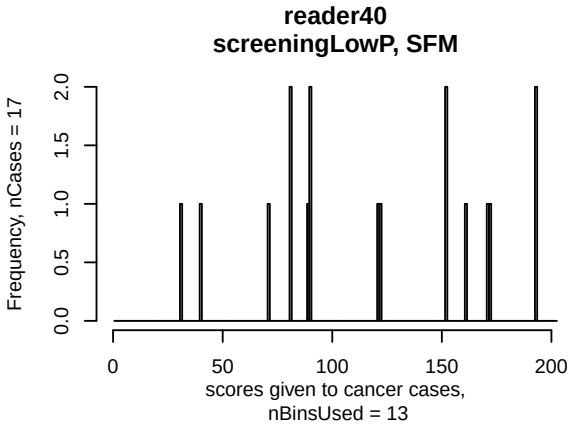


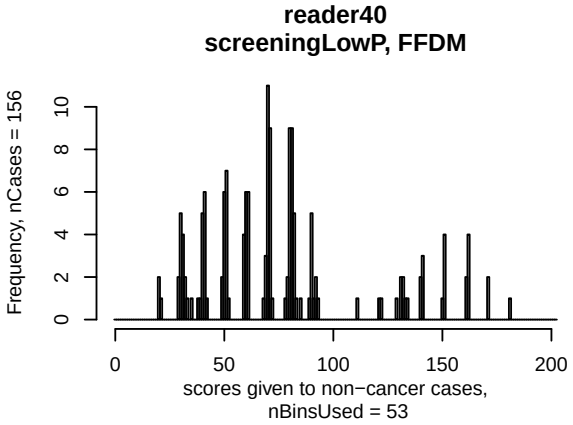
	AUC	se
FFDM	0.513	0.075
SFM	0.736	0.066
FFDM−SFM	−0.223	0.075

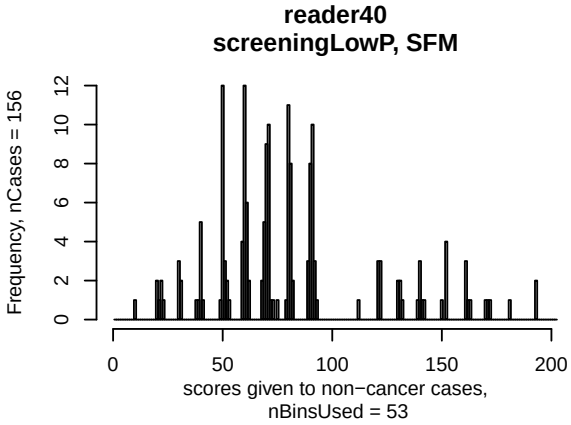
	Sens.	se
FFDM	0.513	0.075
SFM	0.736	0.066
FFDM−SFM	−0.223	0.075

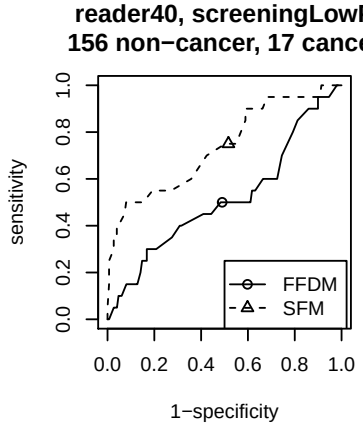
	Spec.	se
FFDM	0.513	0.075
SFM	0.736	0.066
FFDM−SFM	−0.223	0.075







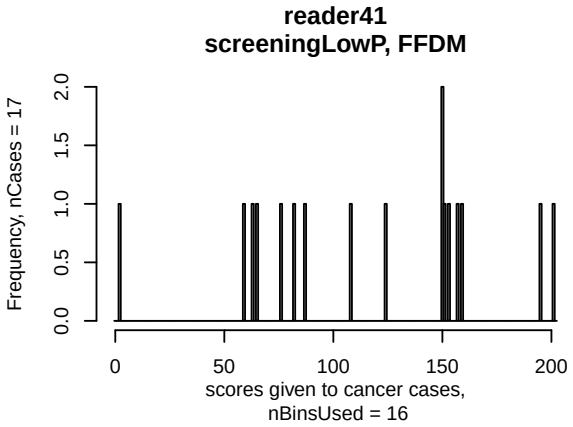


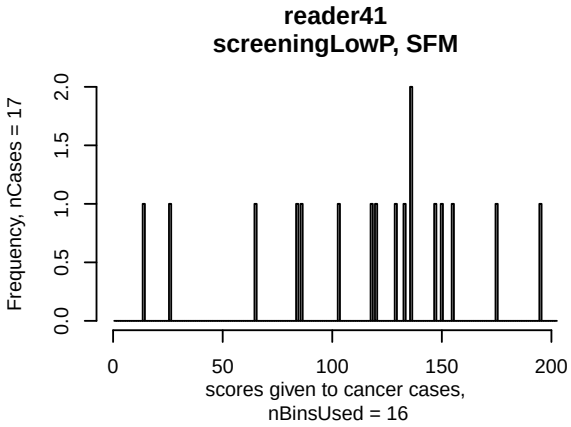


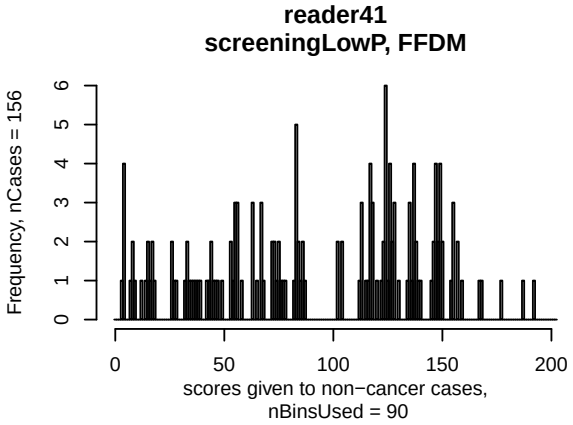
	AUC	se
FFDM	0.724	0.073
SFM	0.751	0.072
FFDM−SFM	−0.027	0.082

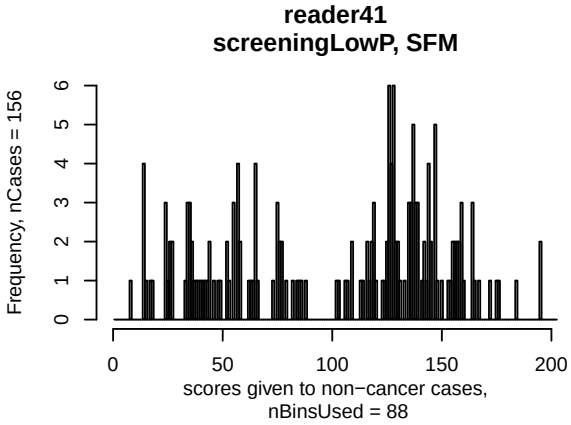
	Sens.	se
FFDM	0.724	0.073
SFM	0.751	0.072
FFDM−SFM	−0.027	0.082

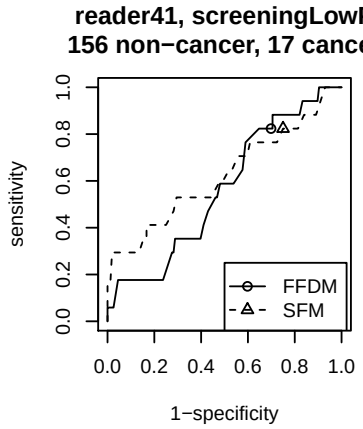
	Spec.	se
FFDM	0.724	0.073
SFM	0.751	0.072
FFDM−SFM	−0.027	0.082







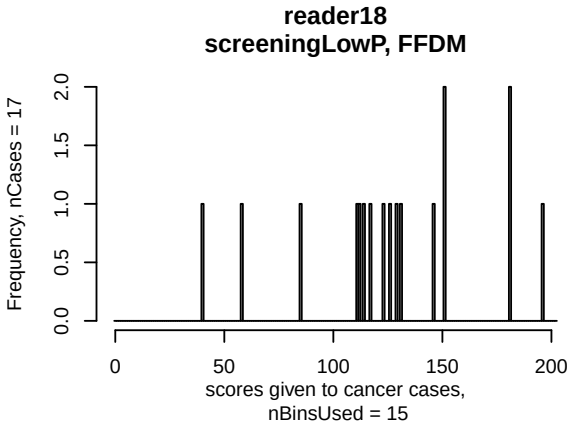


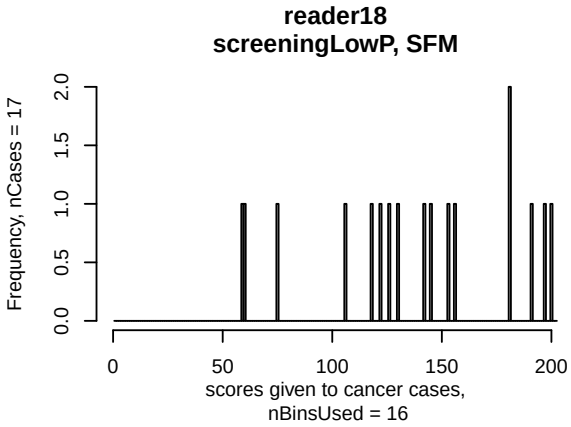


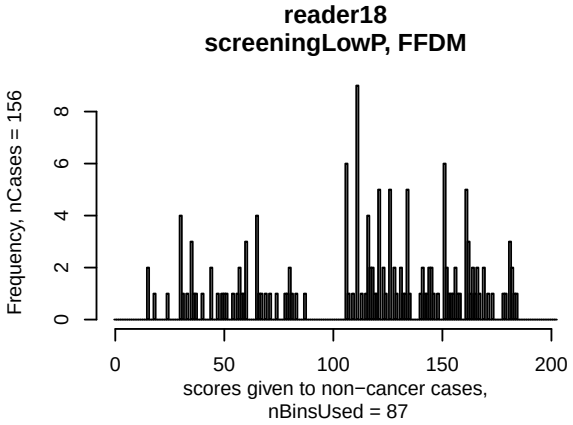
	AUC	se
FFDM	0.651	0.08
SFM	0.584	0.074
FFDM−SFM	0.067	0.08

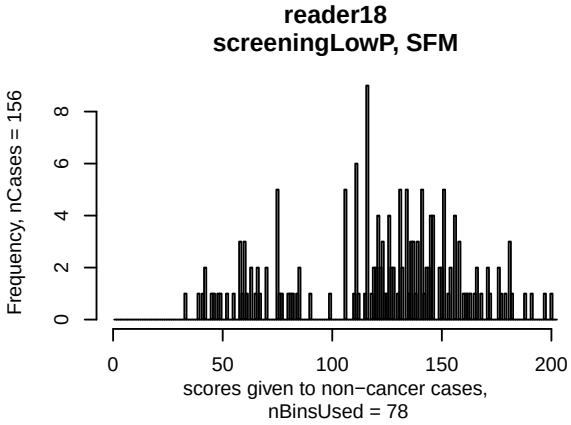
	Sens.	se
FFDM	0.651	0.08
SFM	0.584	0.074
FFDM−SFM	0.067	0.08

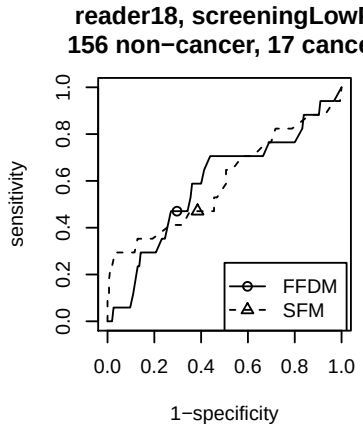
	Spec.	se
FFDM	0.651	0.08
SFM	0.584	0.074
FFDM−SFM	0.067	0.08







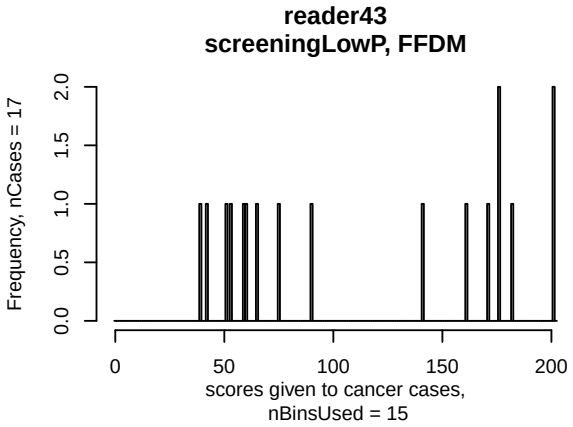


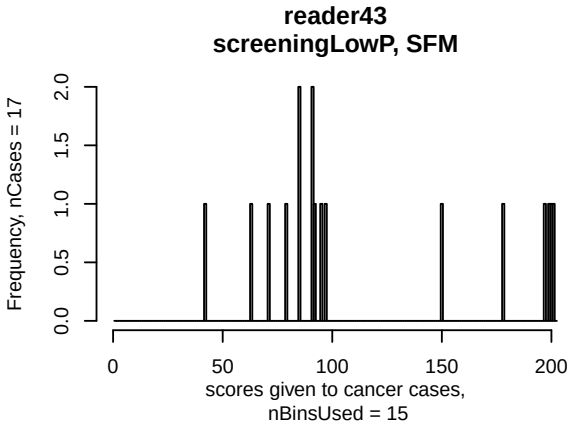


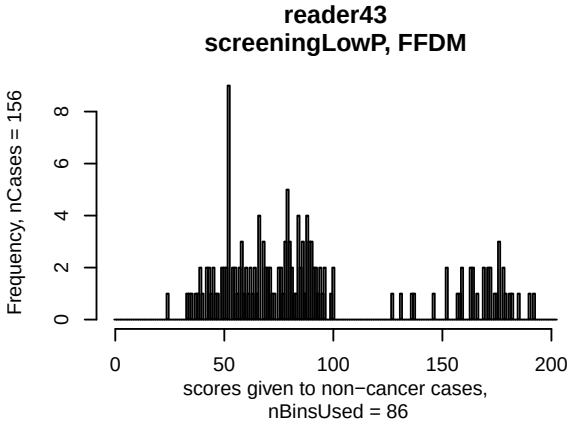
	AUC	se
FFDM	0.566	0.069
SFM	0.622	0.083
FFDM−SFM	−0.056	0.073

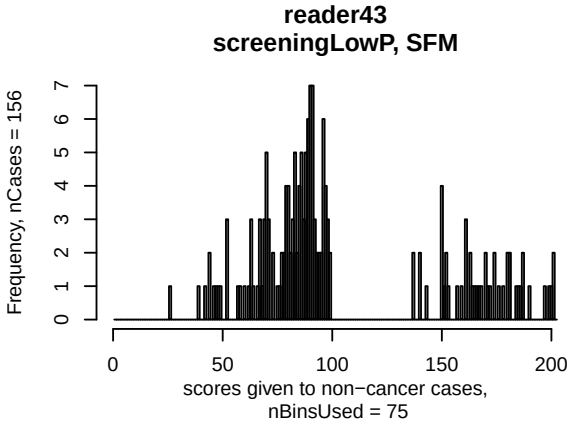
	Sens.	se
FFDM	0.566	0.069
SFM	0.622	0.083
FFDM−SFM	−0.056	0.073

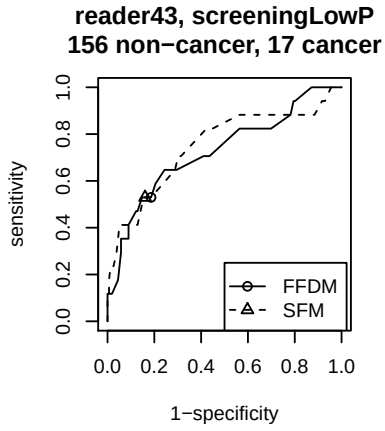
	Spec.	se
FFDM	0.566	0.069
SFM	0.622	0.083
FFDM−SFM	−0.056	0.073







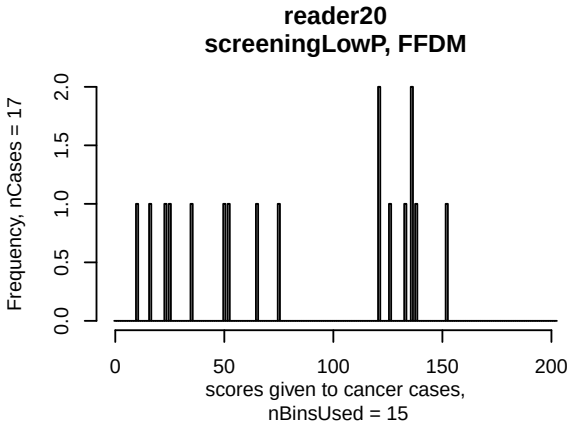


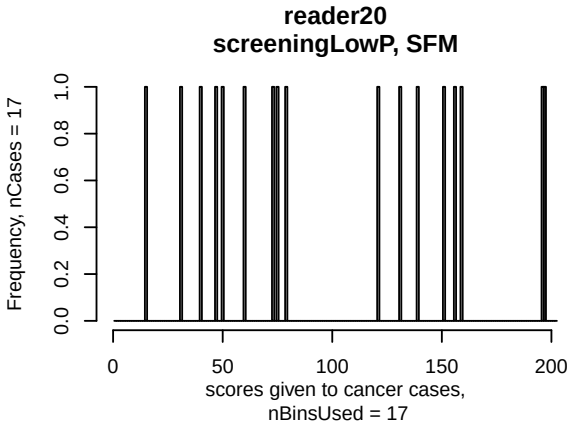


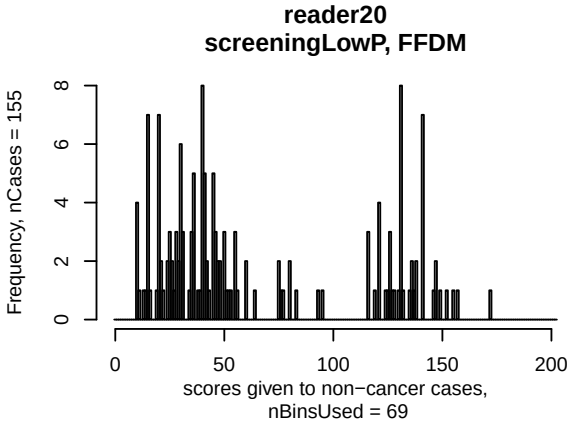
	AUC	se
FFDM	0.582	0.09
SFM	0.597	0.082
FFDM−SFM	−0.015	0.078

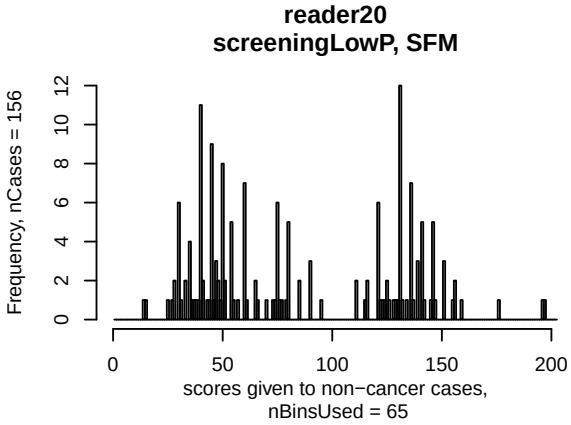
	Sens.	se
FFDM	0.582	0.09
SFM	0.597	0.082
FFDM−SFM	−0.015	0.078

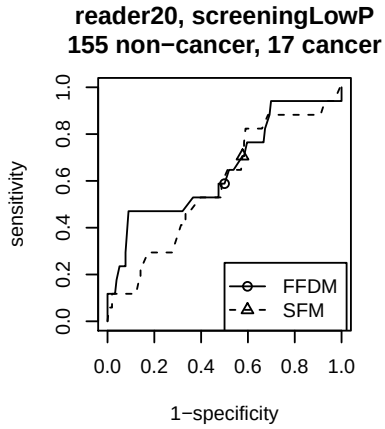
	Spec.	se
FFDM	0.582	0.09
SFM	0.597	0.082
FFDM−SFM	−0.015	0.078









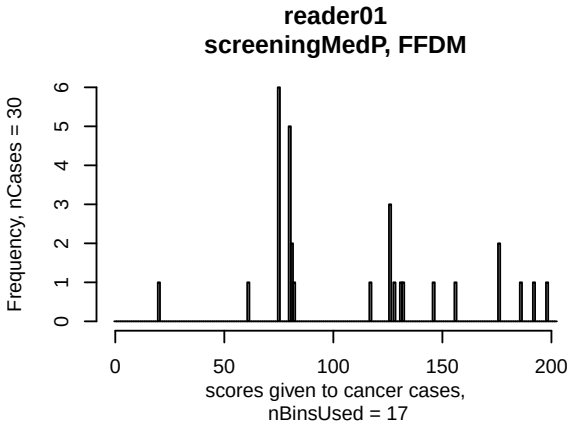


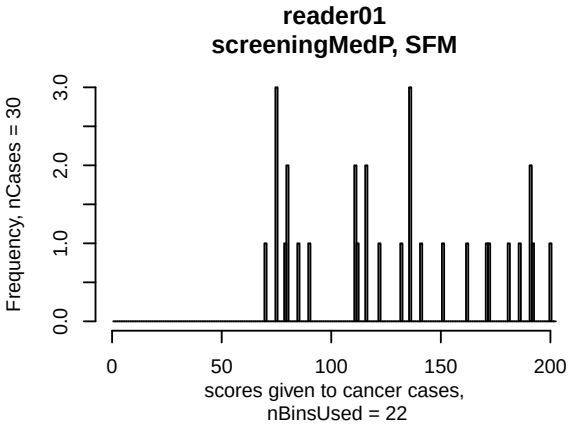
	AUC	se
FFDM	0.588	0.079
SFM	0.597	0.085
FFDM−SFM	−0.009	0.068

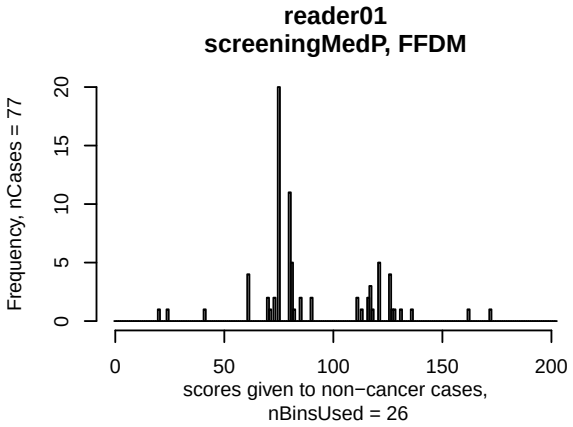
	Sens.	se
FFDM	0.588	0.079
SFM	0.597	0.085
FFDM−SFM	−0.009	0.068

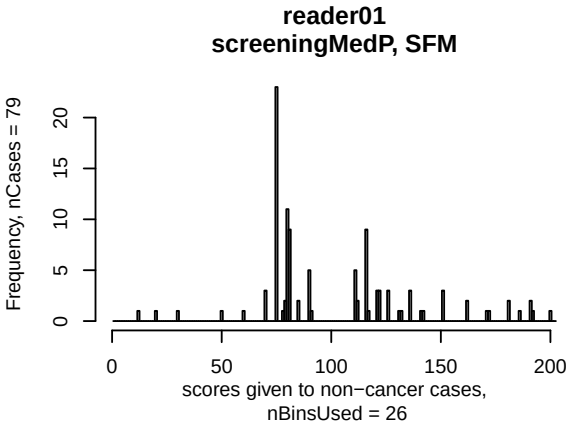
	Spec.	se
FFDM	0.588	0.079
SFM	0.597	0.085
FFDM−SFM	−0.009	0.068

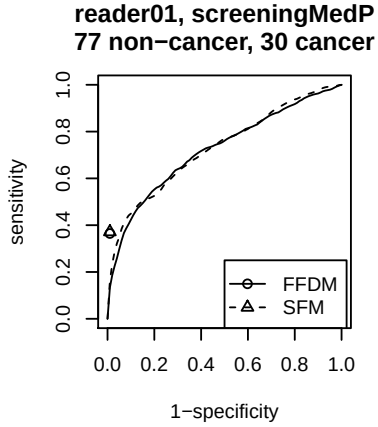
screeningMedP







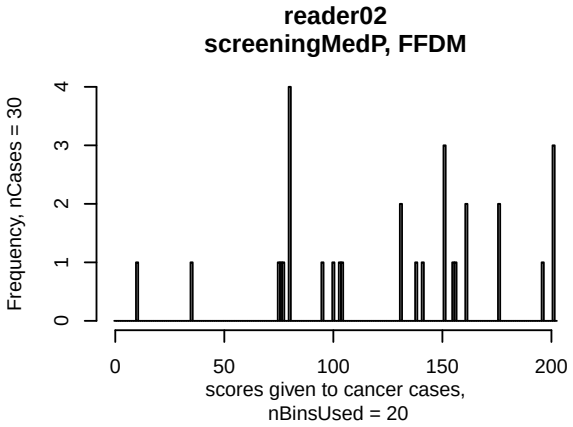


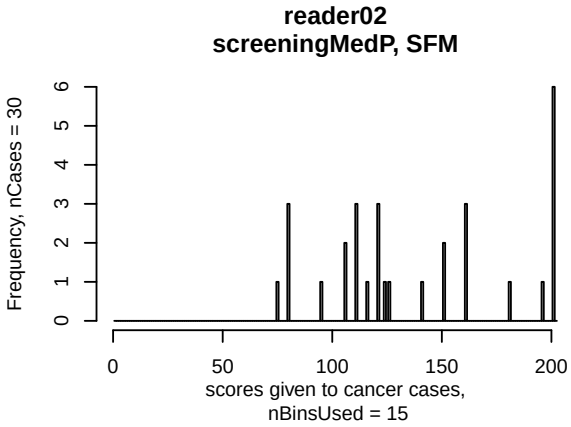


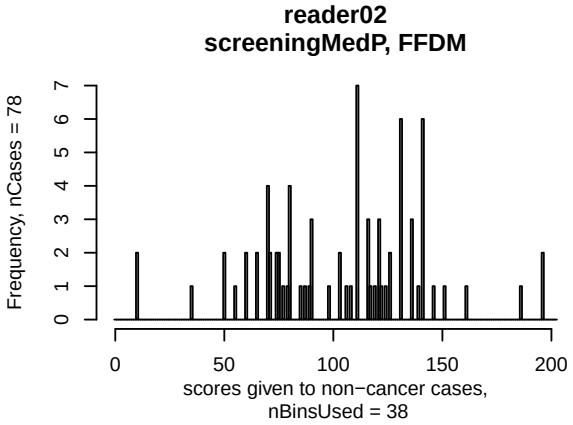
	AUC	se
FFDM	0.643	0.064
SFM	0.742	0.058
FFDM−SFM	−0.099	0.075

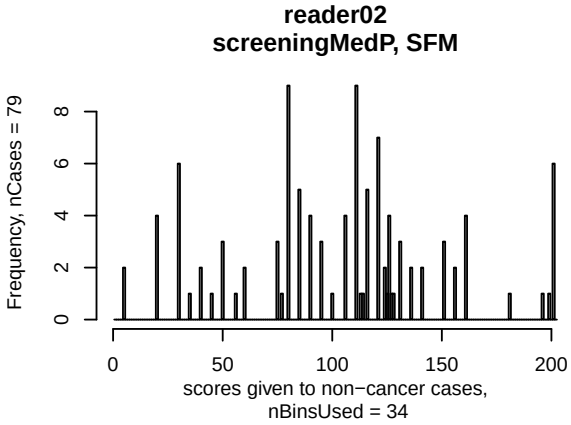
	Sens.	se
FFDM	0.643	0.064
SFM	0.742	0.058
FFDM−SFM	−0.099	0.075

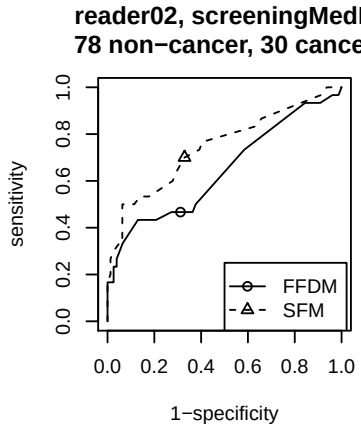
	Spec.	se
FFDM	0.643	0.064
SFM	0.742	0.058
FFDM−SFM	−0.099	0.075







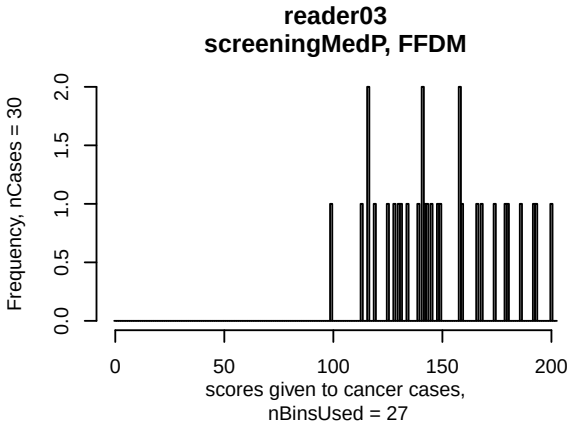


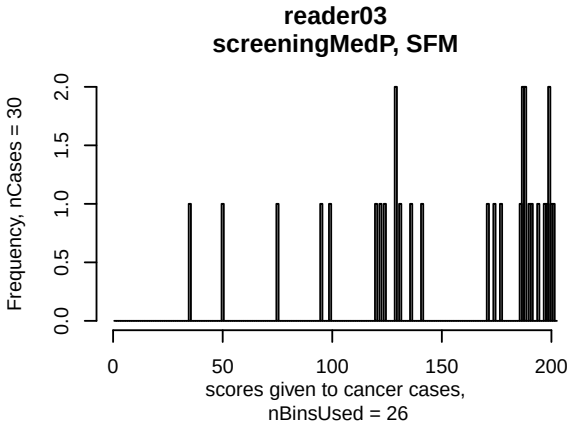


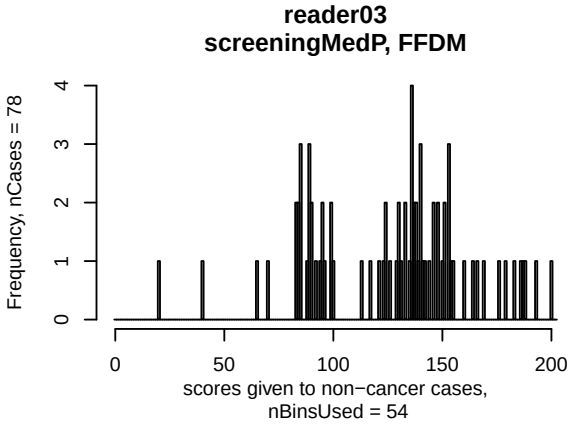
	AUC	se
FFDM	0.651	0.066
SFM	0.769	0.05
FFDM−SFM	−0.118	0.078

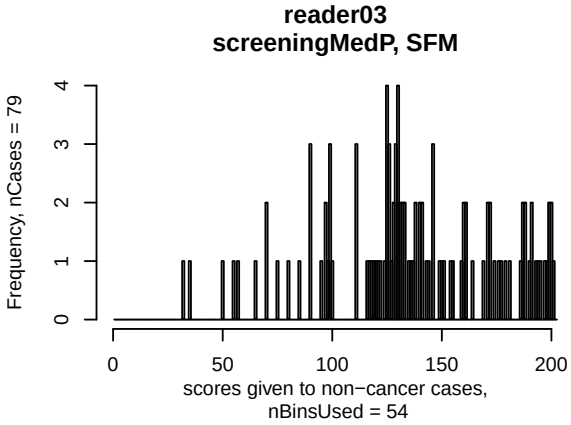
	Sens.	se
FFDM	0.651	0.066
SFM	0.769	0.05
FFDM−SFM	−0.118	0.078

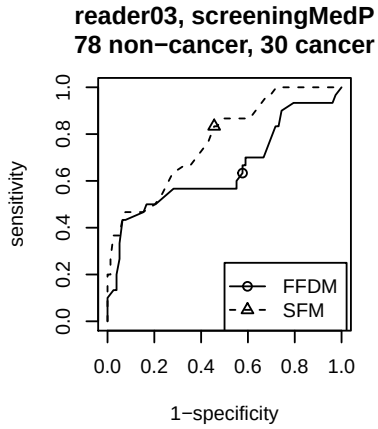
	Spec.	se
FFDM	0.651	0.066
SFM	0.769	0.05
FFDM−SFM	−0.118	0.078







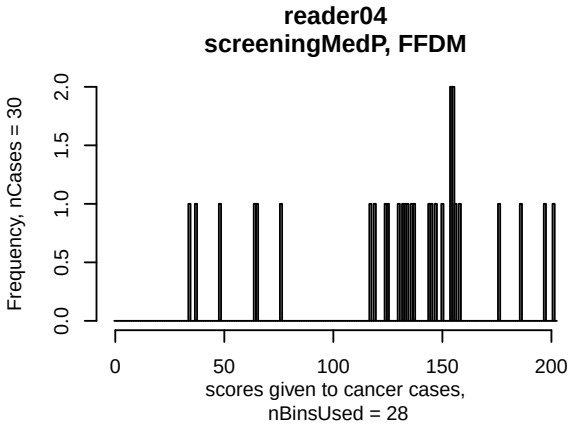


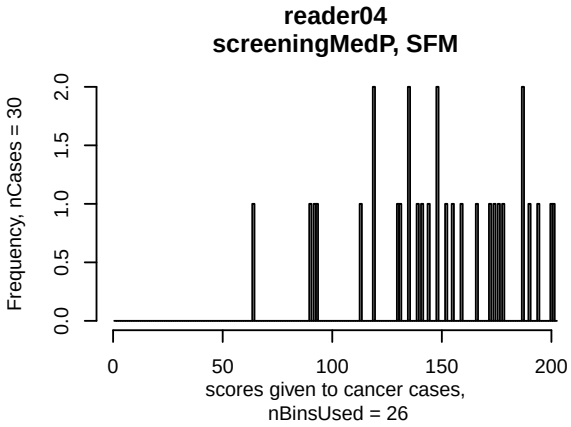


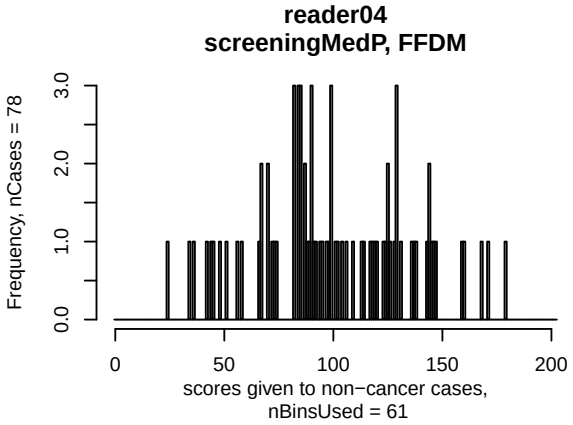
	AUC	se
FFDM	0.673	0.054
SFM	0.677	0.068
FFDM−SFM	−0.003	0.081

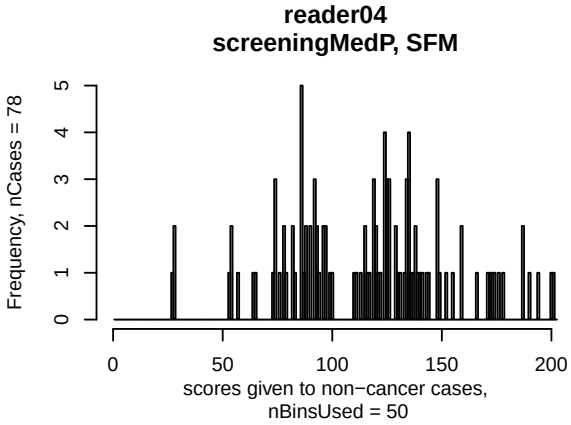
	Sens.	se
FFDM	0.673	0.054
SFM	0.677	0.068
FFDM−SFM	−0.003	0.081

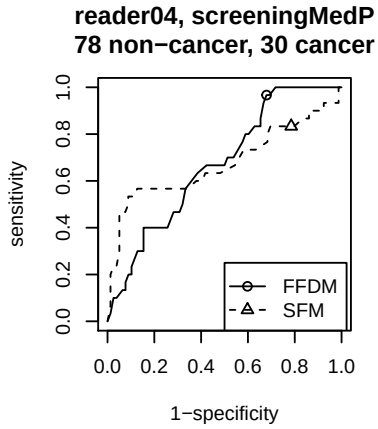
	Spec.	se
FFDM	0.673	0.054
SFM	0.677	0.068
FFDM−SFM	−0.003	0.081







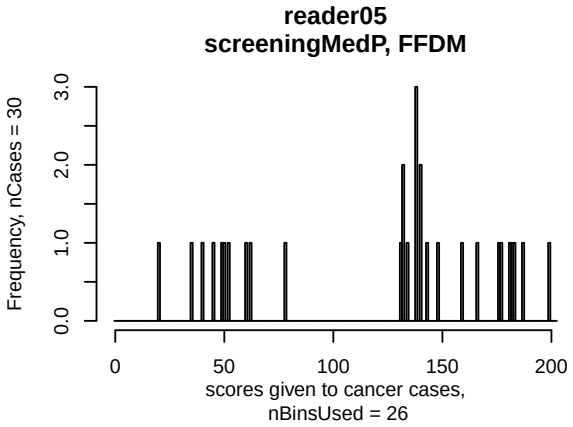


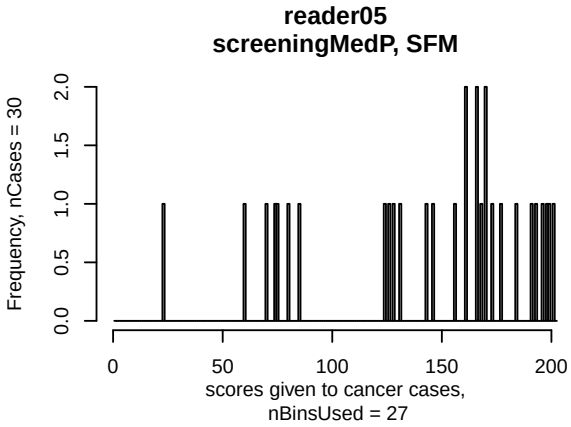


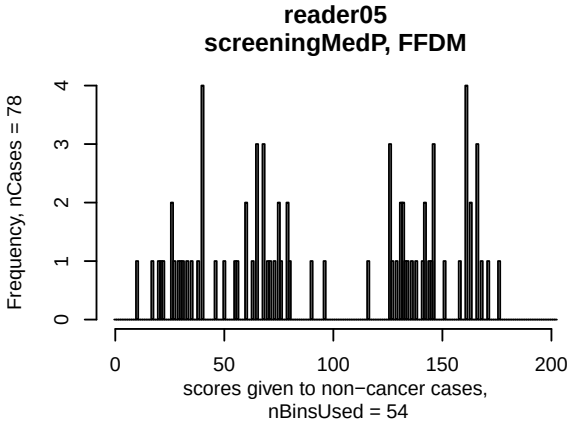
	AUC	se
FFDM	0.719	0.064
SFM	0.821	0.049
FFDM−SFM	−0.101	0.078

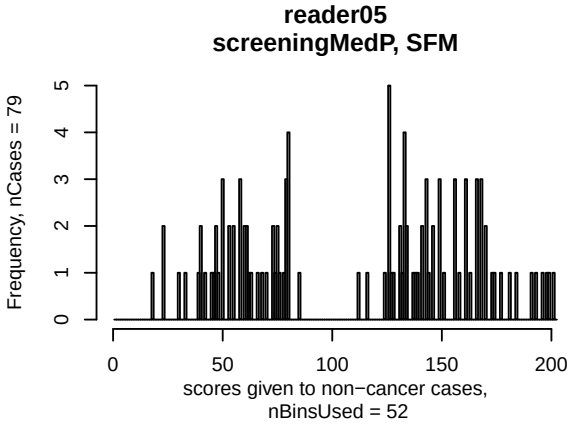
	Sens.	se
FFDM	0.719	0.064
SFM	0.821	0.049
FFDM−SFM	−0.101	0.078

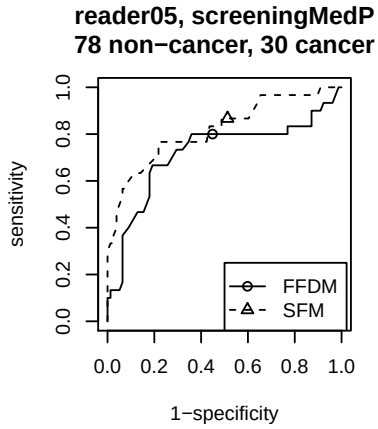
	Spec.	se
FFDM	0.719	0.064
SFM	0.821	0.049
FFDM−SFM	−0.101	0.078







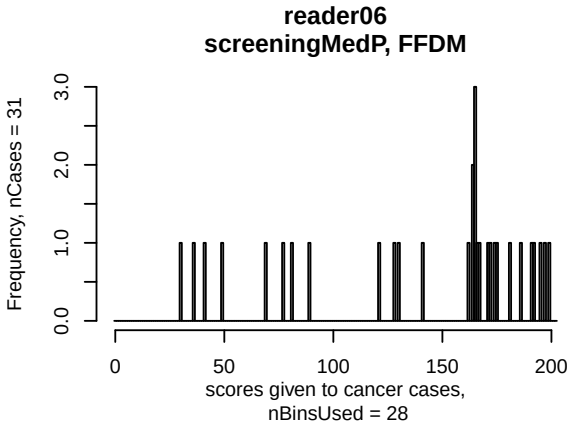


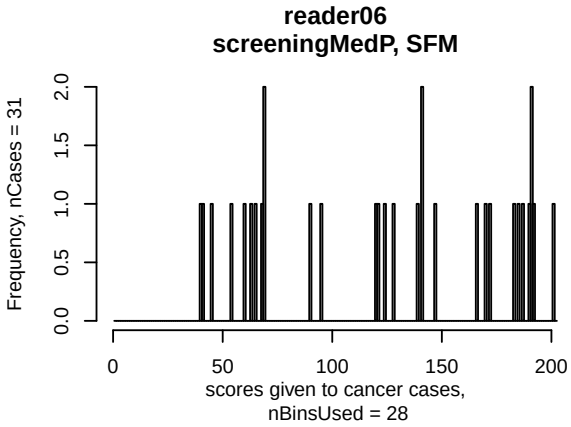


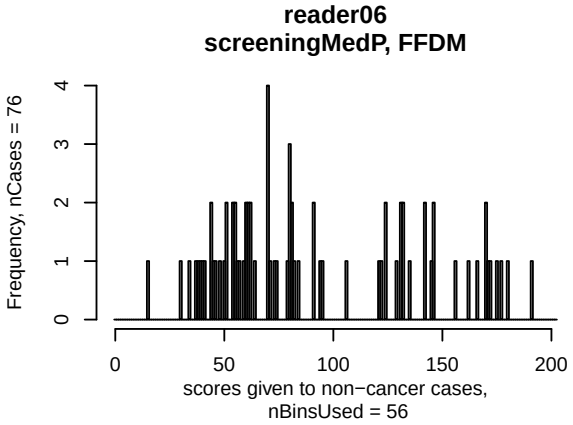
	AUC	se
FFDM	0.634	0.063
SFM	0.765	0.054
FFDM−SFM	−0.131	0.075

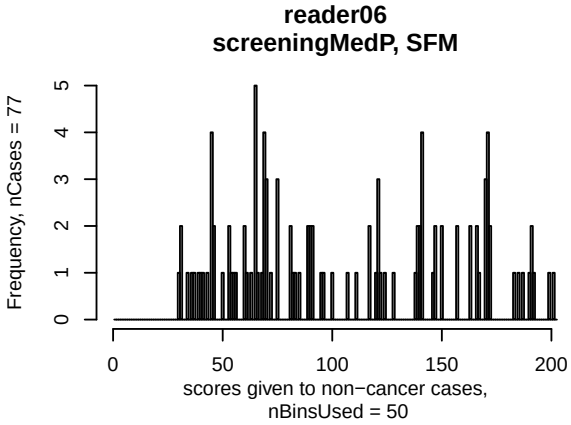
	Sens.	se
FFDM	0.634	0.063
SFM	0.765	0.054
FFDM−SFM	−0.131	0.075

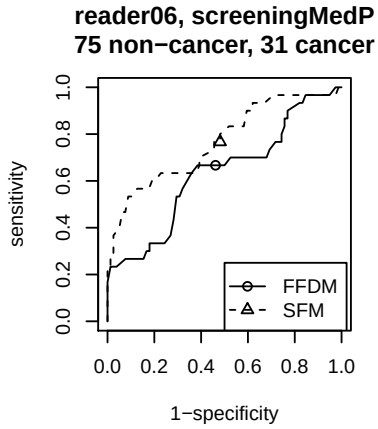
	Spec.	se
FFDM	0.634	0.063
SFM	0.765	0.054
FFDM−SFM	−0.131	0.075







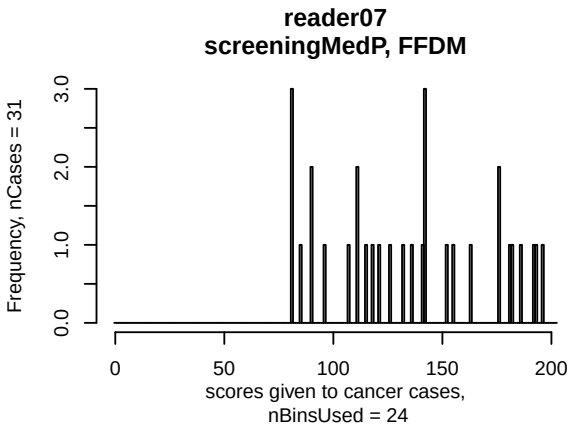


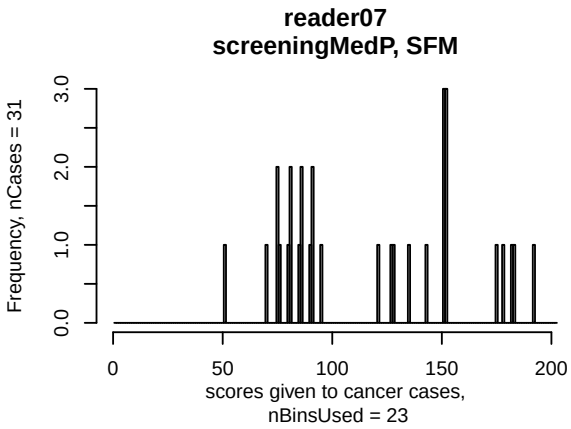


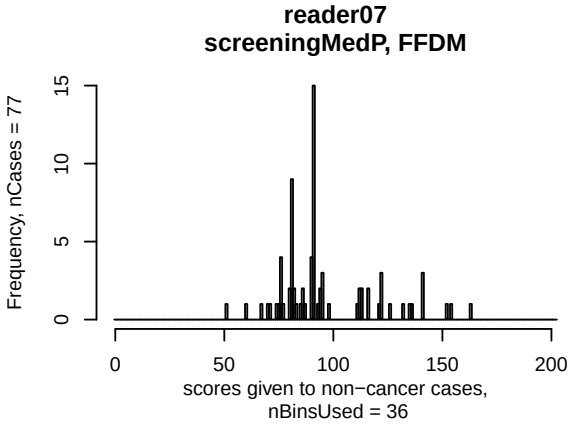
	AUC	se
FFDM	0.743	0.059
SFM	0.638	0.063
FFDM−SFM	0.106	0.077

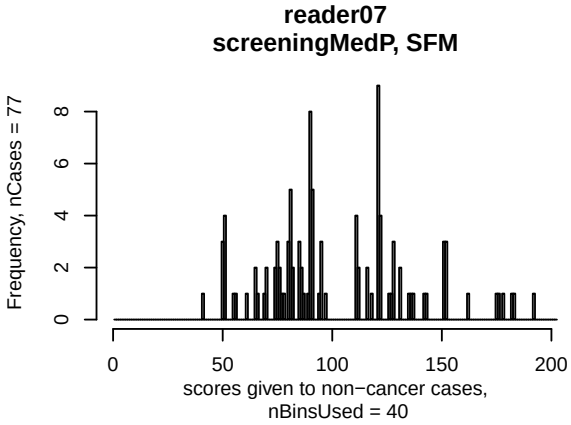
	Sens.	se
FFDM	0.743	0.059
SFM	0.638	0.063
FFDM−SFM	0.106	0.077

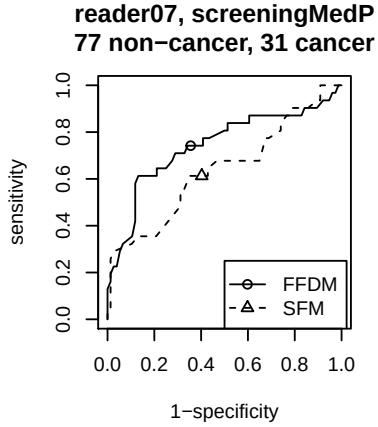
	Spec.	se
FFDM	0.743	0.059
SFM	0.638	0.063
FFDM−SFM	0.106	0.077







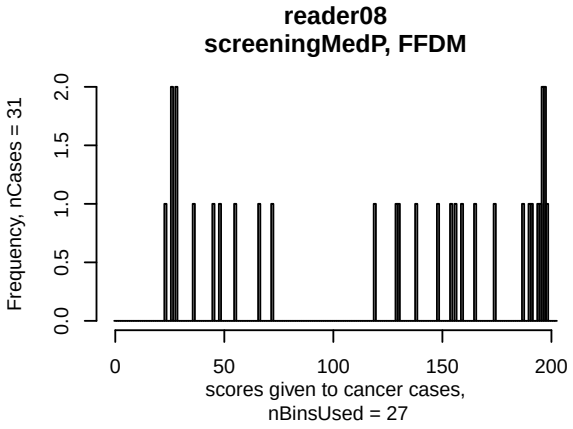


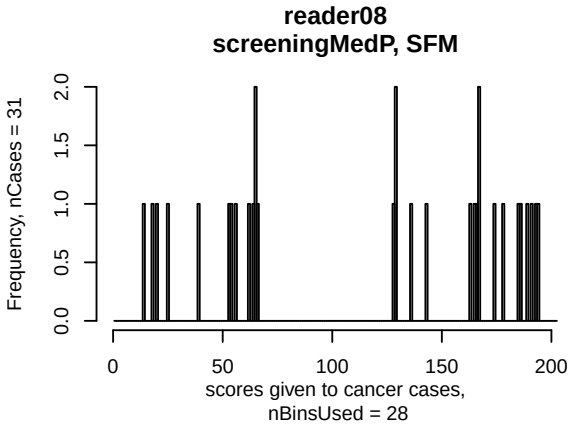


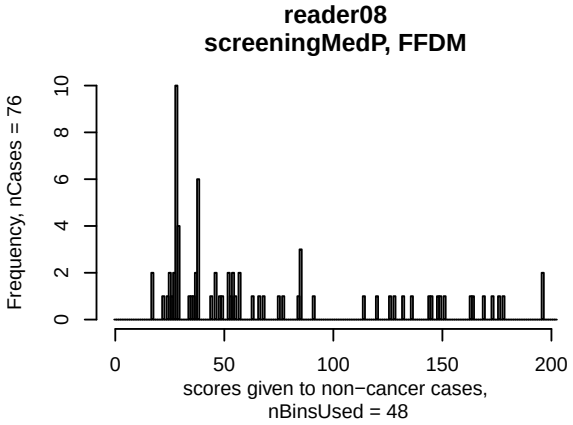
	AUC	se
FFDM	0.797	0.051
SFM	0.658	0.064
FFDM−SFM	0.138	0.061

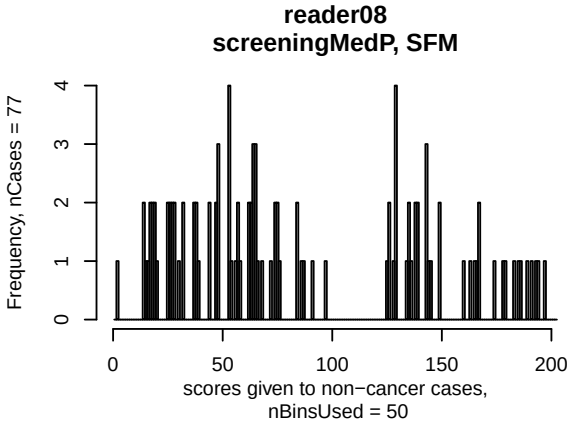
	Sens.	se
FFDM	0.797	0.051
SFM	0.658	0.064
FFDM−SFM	0.138	0.061

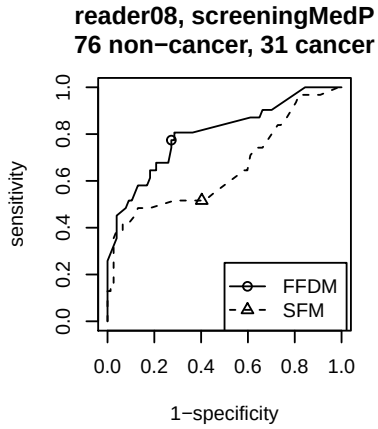
	Spec.	se
FFDM	0.797	0.051
SFM	0.658	0.064
FFDM−SFM	0.138	0.061







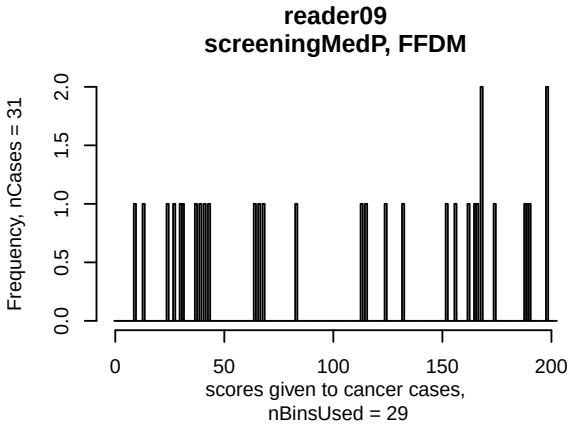


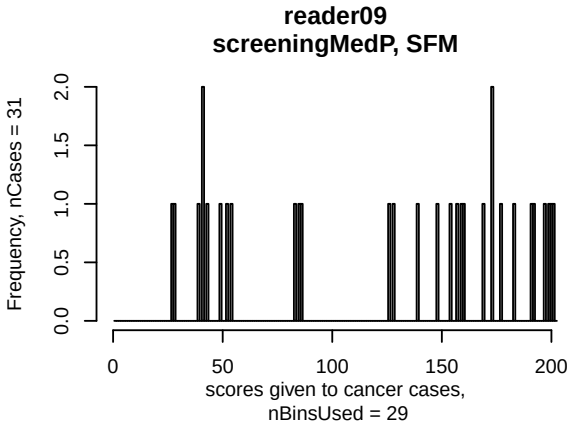


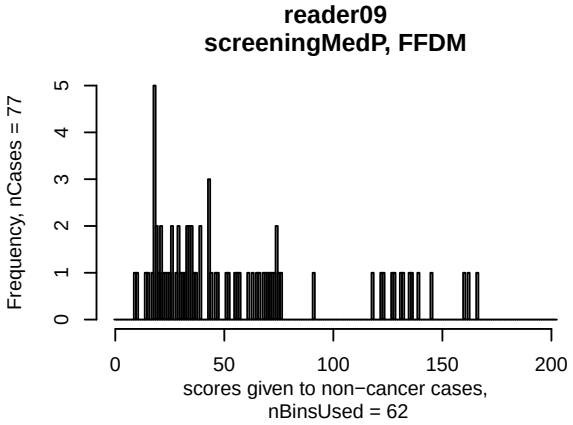
	AUC	se
FFDM	0.716	0.061
SFM	0.683	0.062
FFDM−SFM	0.034	0.054

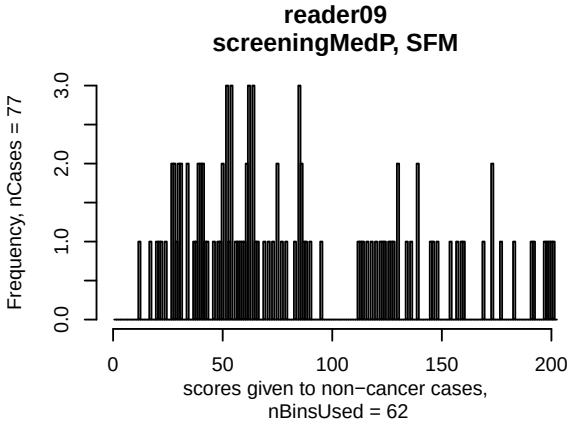
	Sens.	se
FFDM	0.716	0.061
SFM	0.683	0.062
FFDM−SFM	0.034	0.054

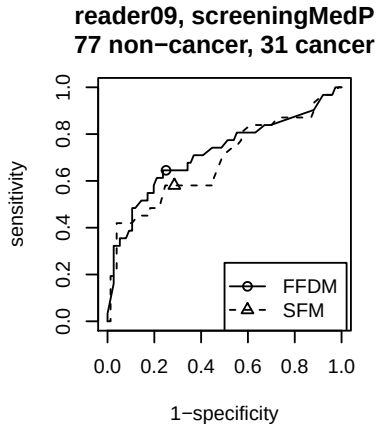
	Spec.	se
FFDM	0.716	0.061
SFM	0.683	0.062
FFDM−SFM	0.034	0.054







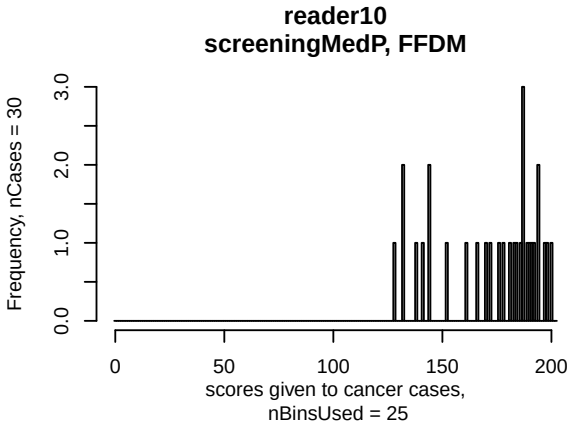


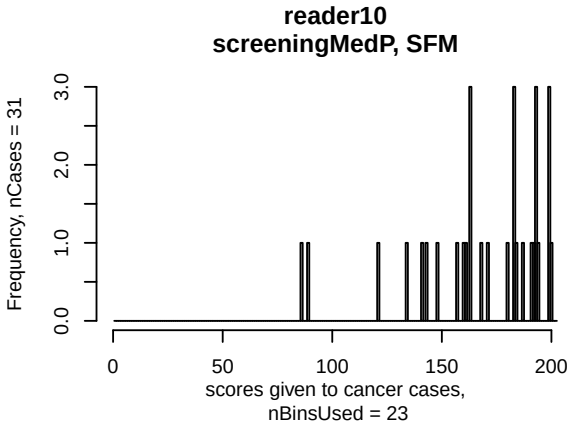


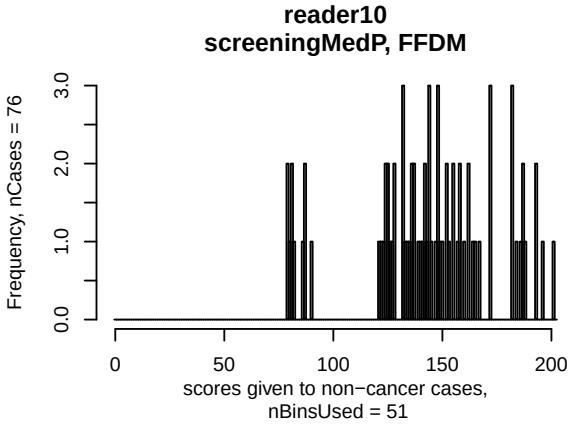
	AUC	se
FFDM	0.715	0.061
SFM	0.737	0.063
FFDM−SFM	−0.022	0.058

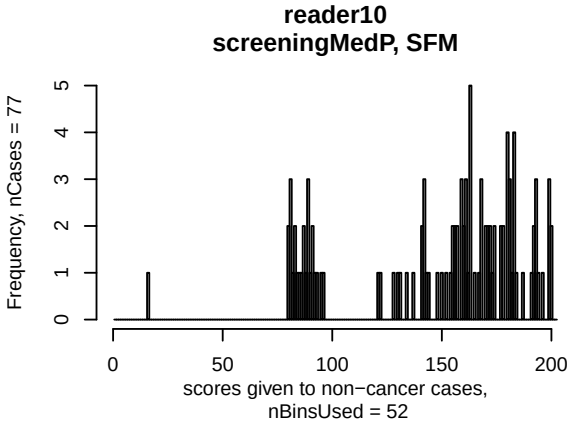
	Sens.	se
FFDM	0.715	0.061
SFM	0.737	0.063
FFDM−SFM	−0.022	0.058

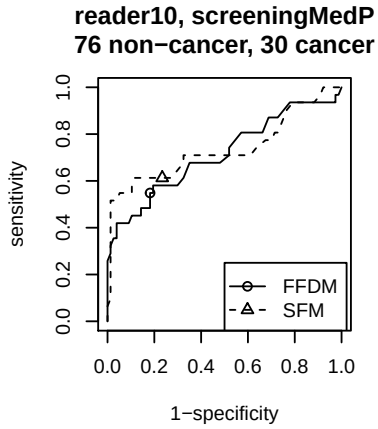
	Spec.	se
FFDM	0.715	0.061
SFM	0.737	0.063
FFDM−SFM	−0.022	0.058







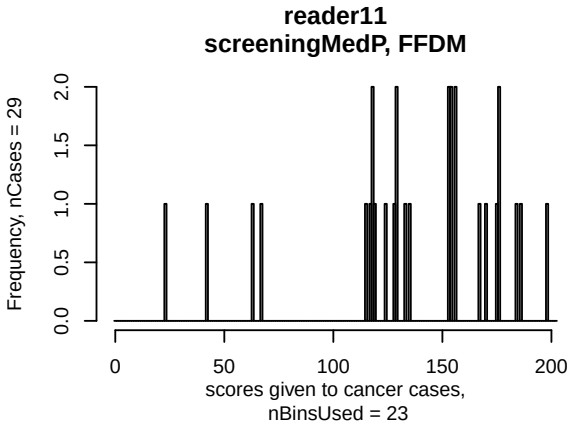


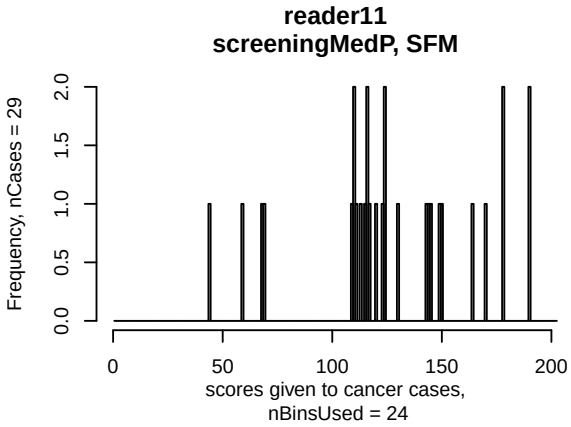


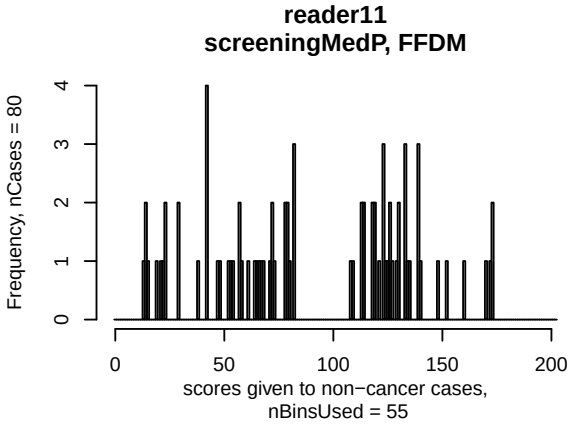
	AUC	se
FFDM	0.772	0.05
SFM	0.731	0.055
FFDM−SFM	0.04	0.065

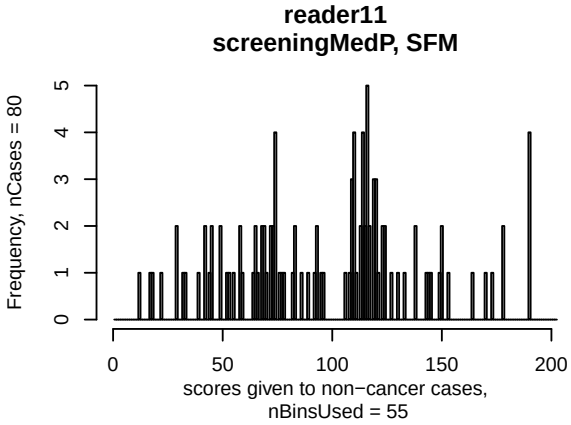
	Sens.	se
FFDM	0.772	0.05
SFM	0.731	0.055
FFDM−SFM	0.04	0.065

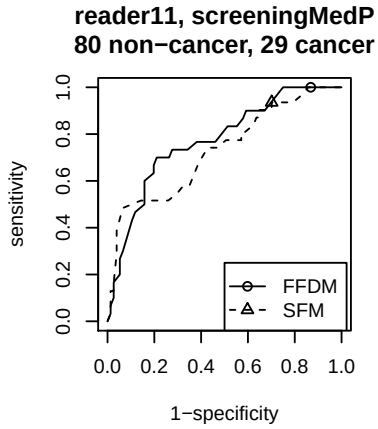
	Spec.	se
FFDM	0.772	0.05
SFM	0.731	0.055
FFDM−SFM	0.04	0.065







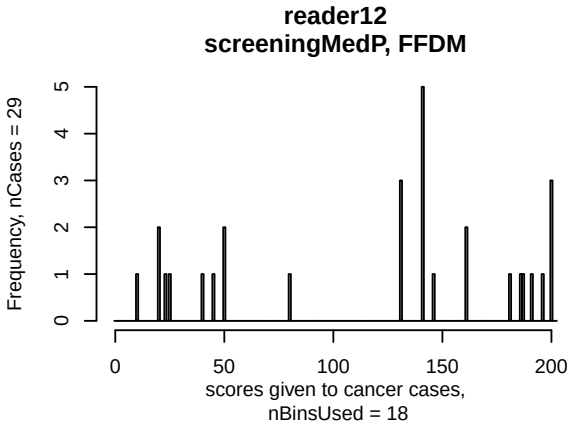


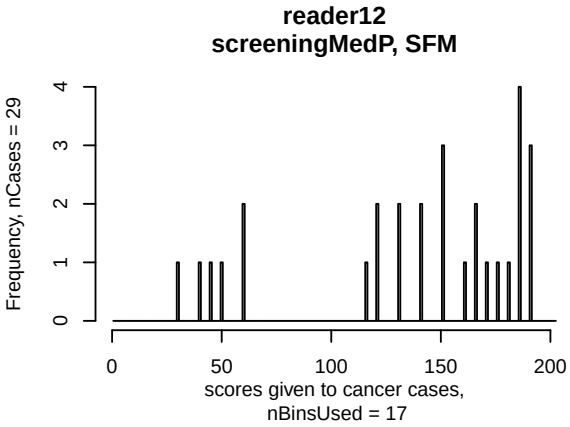


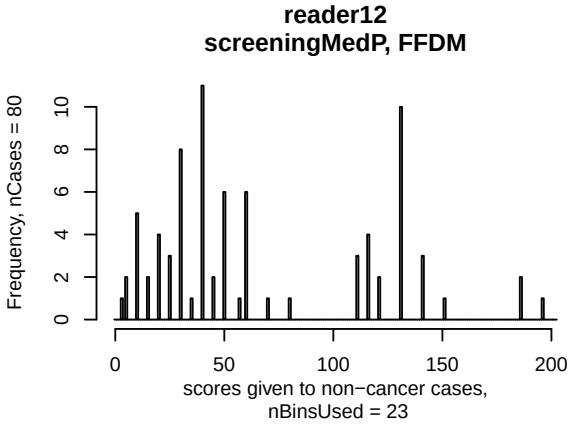
	AUC	se
FFDM	0.766	0.053
SFM	0.771	0.052
FFDM−SFM	−0.005	0.061

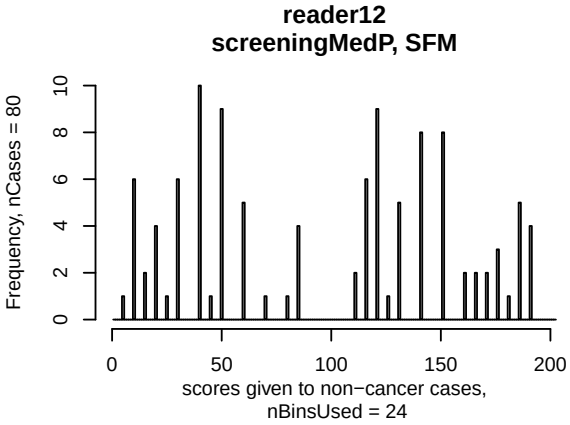
	Sens.	se
FFDM	0.766	0.053
SFM	0.771	0.052
FFDM−SFM	−0.005	0.061

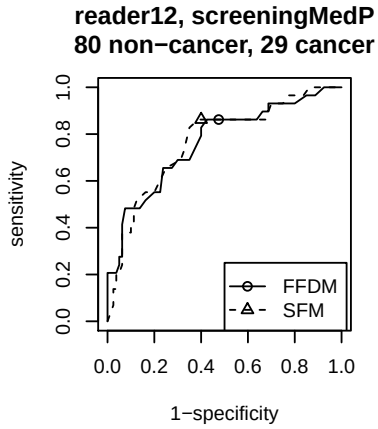
	Spec.	se
FFDM	0.766	0.053
SFM	0.771	0.052
FFDM−SFM	−0.005	0.061







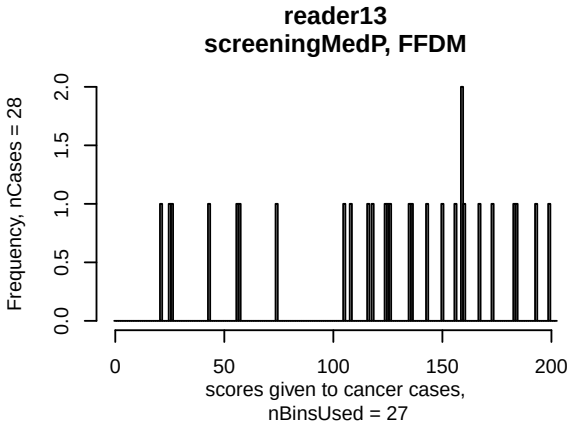


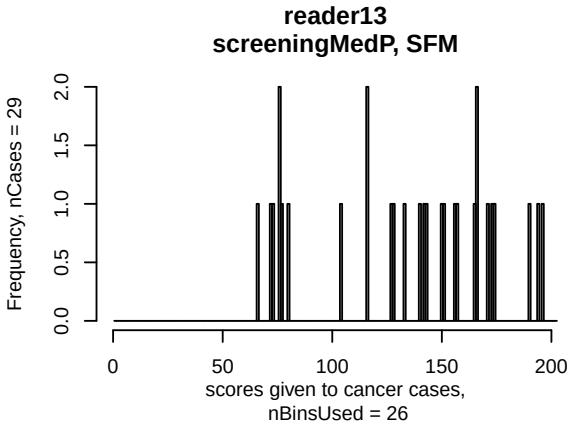


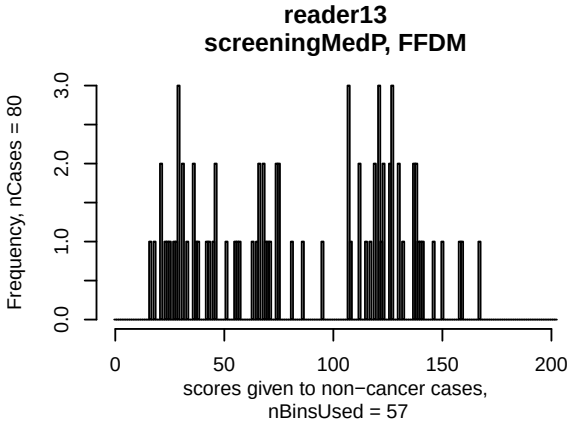
	AUC	se
FFDM	0.735	0.063
SFM	0.781	0.051
FFDM−SFM	−0.046	0.057

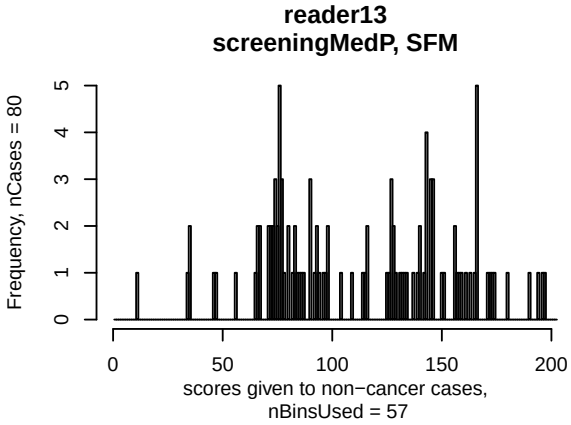
	Sens.	se
FFDM	0.735	0.063
SFM	0.781	0.051
FFDM−SFM	−0.046	0.057

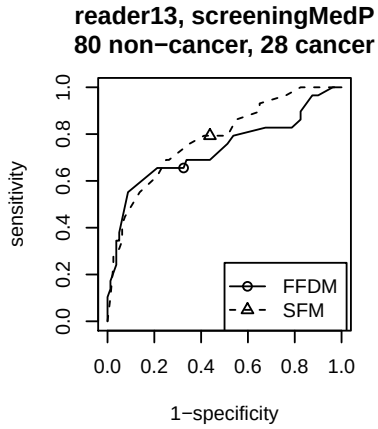
	Spec.	se
FFDM	0.735	0.063
SFM	0.781	0.051
FFDM−SFM	−0.046	0.057







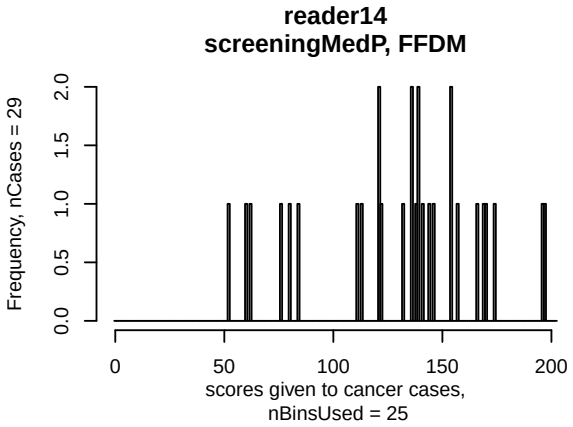


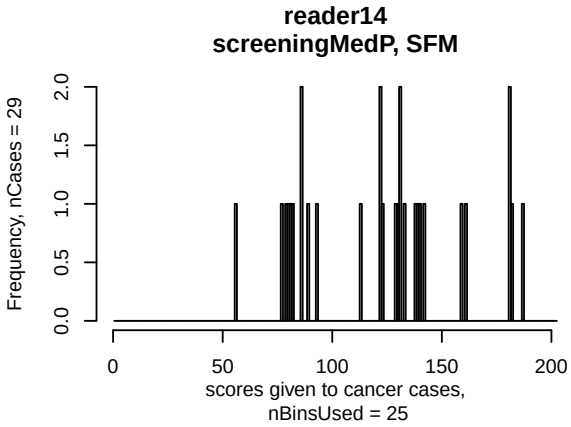


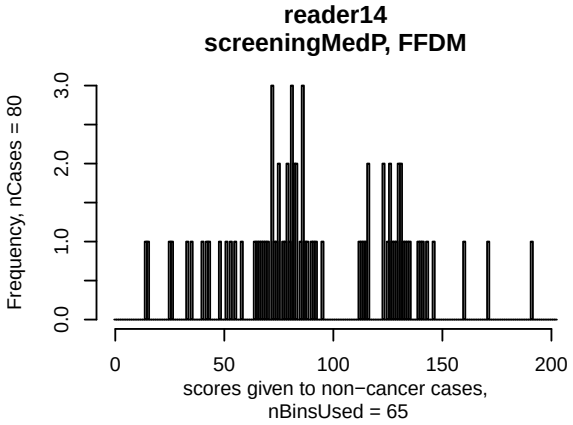
	AUC	se
FFDM	0.707	0.064
SFM	0.683	0.06
FFDM−SFM	0.025	0.066

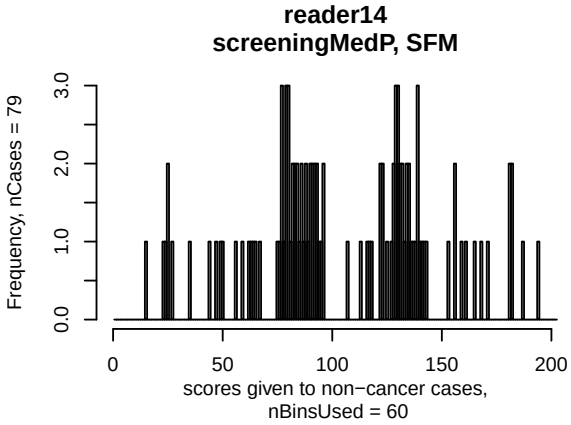
	Sens.	se
FFDM	0.707	0.064
SFM	0.683	0.06
FFDM−SFM	0.025	0.066

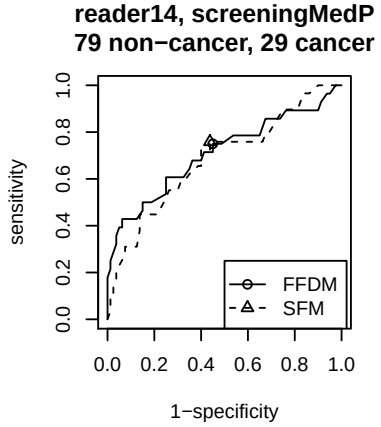
	Spec.	se
FFDM	0.707	0.064
SFM	0.683	0.06
FFDM−SFM	0.025	0.066







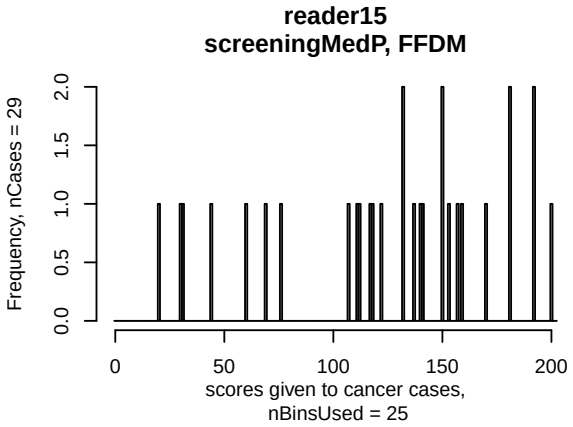


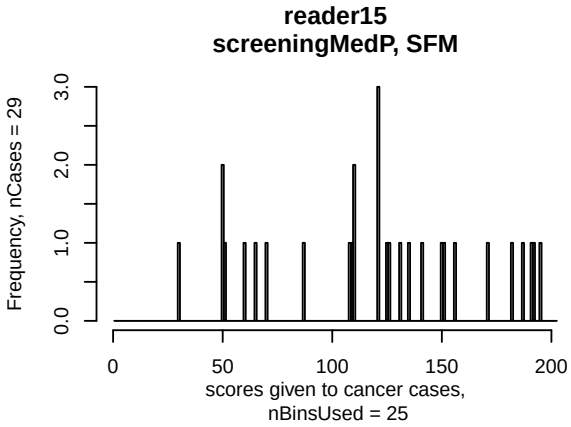


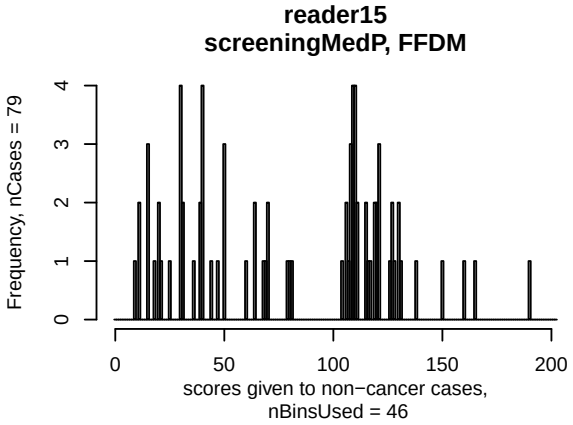
	AUC	se
FFDM	0.763	0.056
SFM	0.652	0.058
FFDM−SFM	0.111	0.076

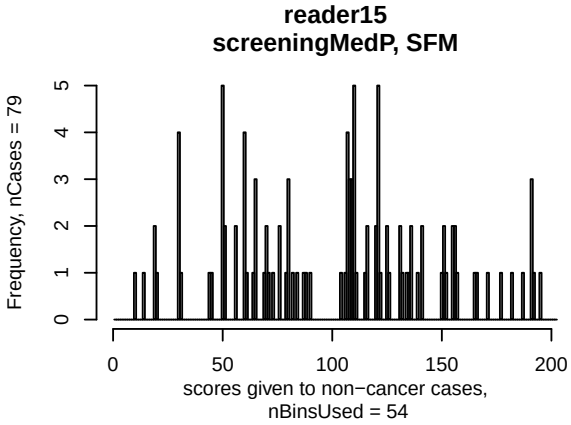
	Sens.	se
FFDM	0.763	0.056
SFM	0.652	0.058
FFDM−SFM	0.111	0.076

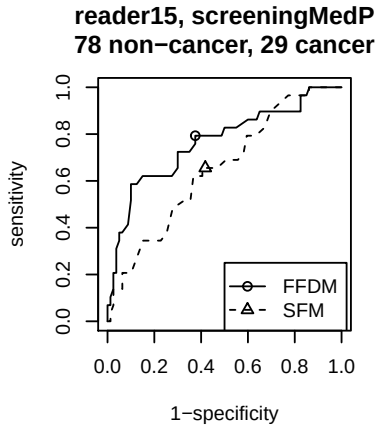
	Spec.	se
FFDM	0.763	0.056
SFM	0.652	0.058
FFDM−SFM	0.111	0.076







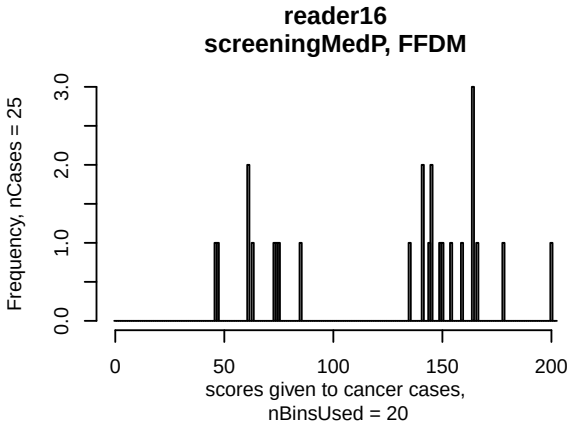


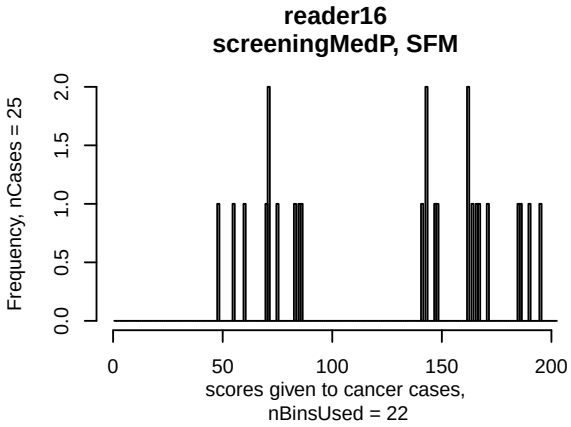


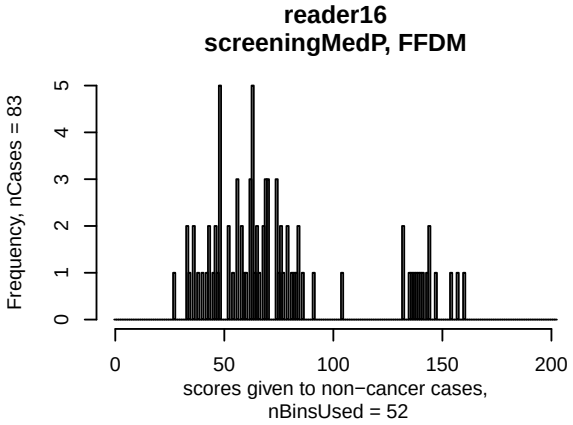
	AUC	se
FFDM	0.752	0.058
SFM	0.656	0.062
FFDM−SFM	0.096	0.077

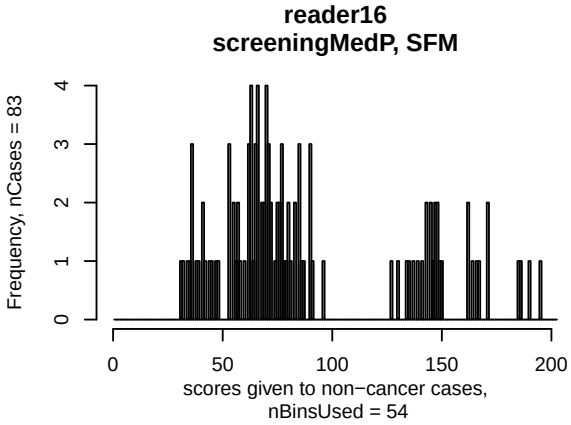
	Sens.	se
FFDM	0.752	0.058
SFM	0.656	0.062
FFDM−SFM	0.096	0.077

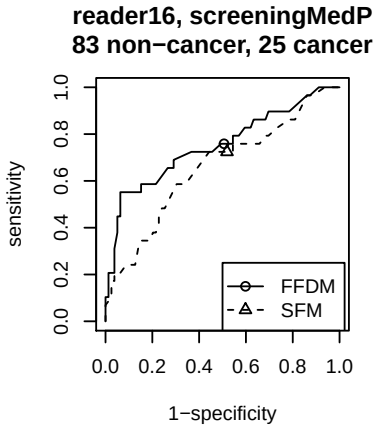
	Spec.	se
FFDM	0.752	0.058
SFM	0.656	0.062
FFDM−SFM	0.096	0.077







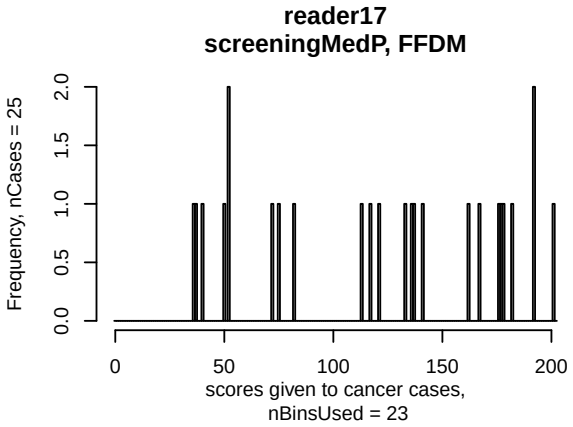


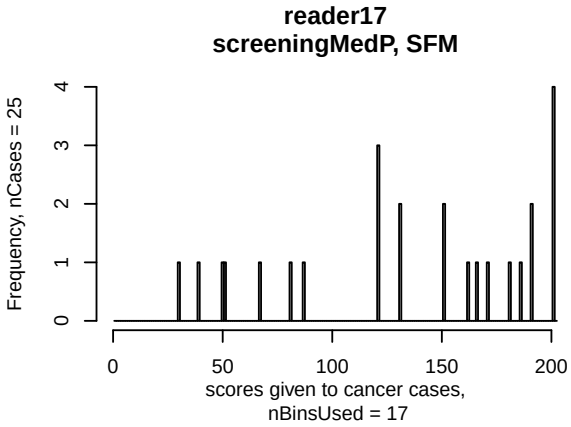


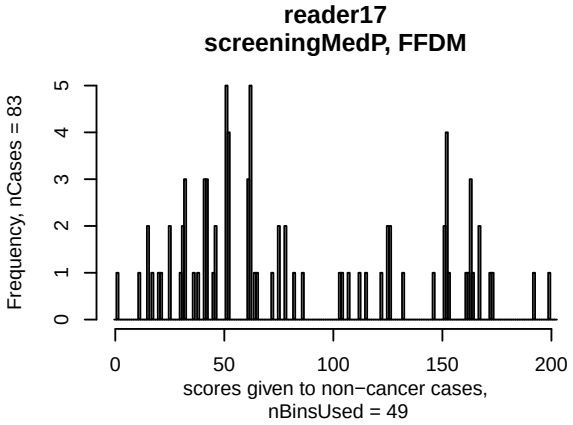
	AUC	se
FFDM	0.78	0.059
SFM	0.787	0.056
FFDM−SFM	−0.007	0.069

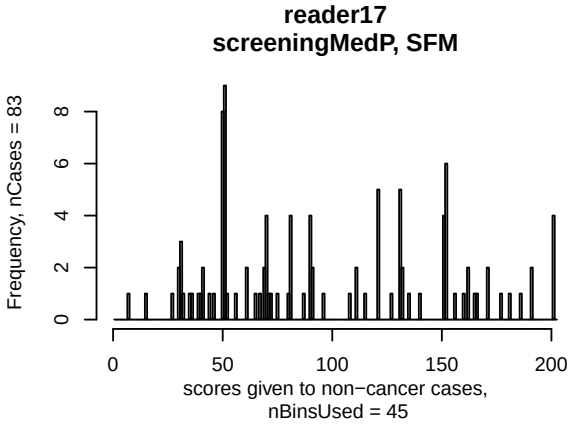
	Sens.	se
FFDM	0.78	0.059
SFM	0.787	0.056
FFDM−SFM	−0.007	0.069

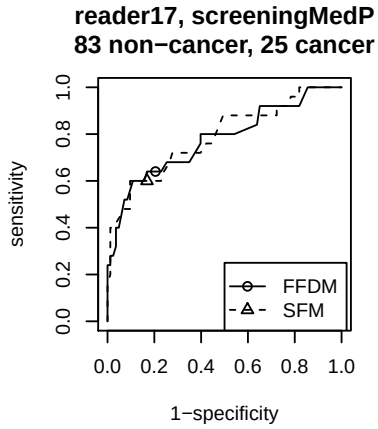
	Spec.	se
FFDM	0.78	0.059
SFM	0.787	0.056
FFDM−SFM	−0.007	0.069







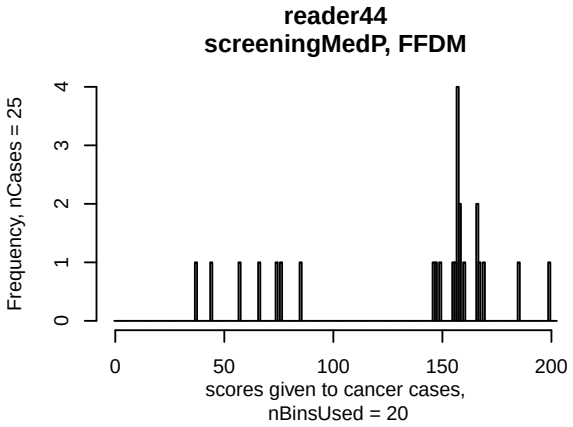


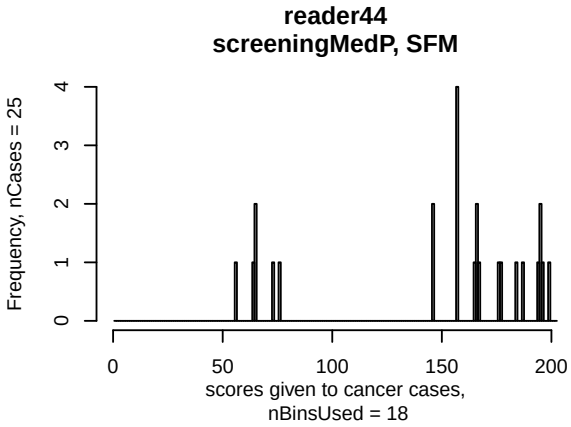


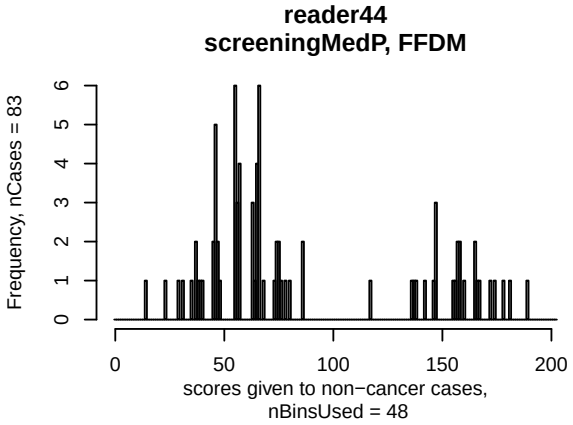
	AUC	se
FFDM	0.687	0.061
SFM	0.742	0.064
FFDM−SFM	−0.055	0.075

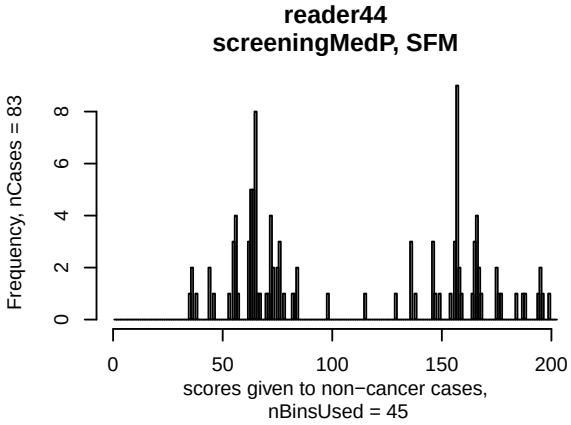
	Sens.	se
FFDM	0.687	0.061
SFM	0.742	0.064
FFDM−SFM	−0.055	0.075

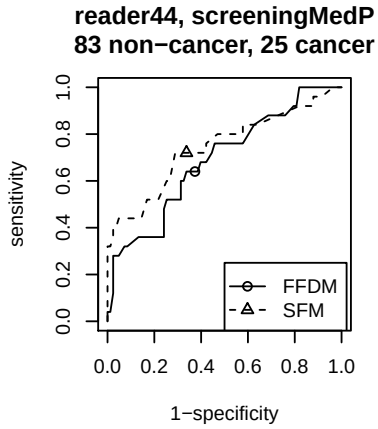
	Spec.	se
FFDM	0.687	0.061
SFM	0.742	0.064
FFDM−SFM	−0.055	0.075







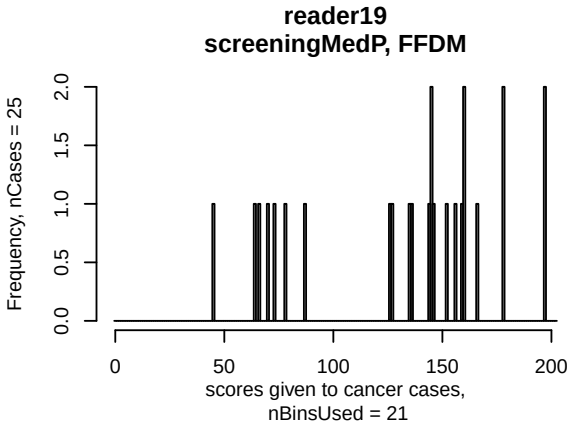


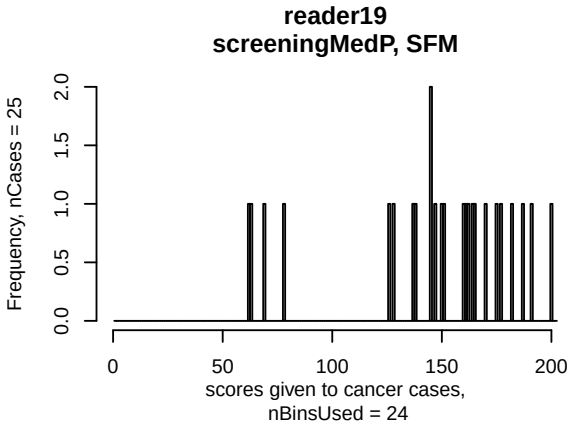


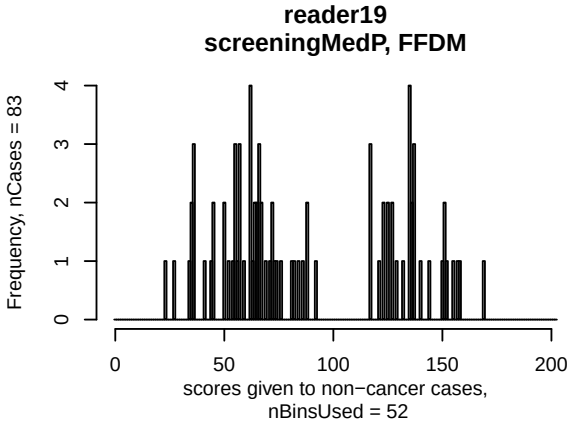
	AUC	se
FFDM	0.749	0.057
SFM	0.781	0.056
FFDM−SFM	−0.033	0.061

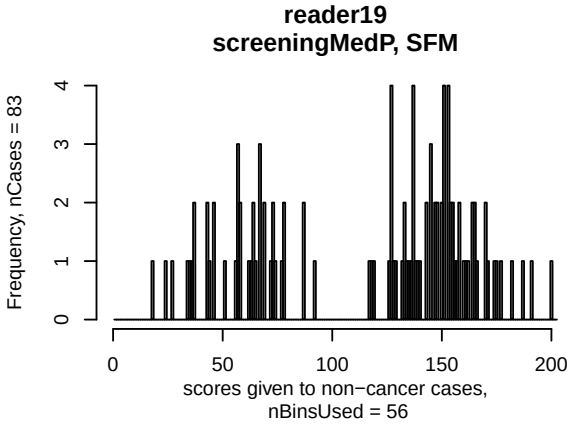
	Sens.	se
FFDM	0.749	0.057
SFM	0.781	0.056
FFDM−SFM	−0.033	0.061

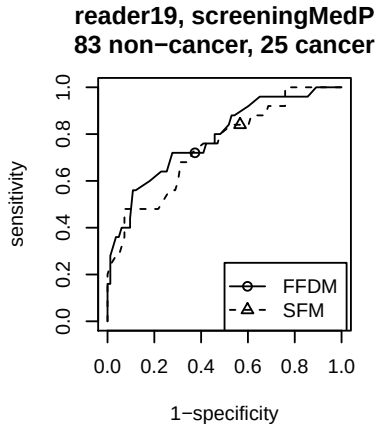
	Spec.	se
FFDM	0.749	0.057
SFM	0.781	0.056
FFDM−SFM	−0.033	0.061







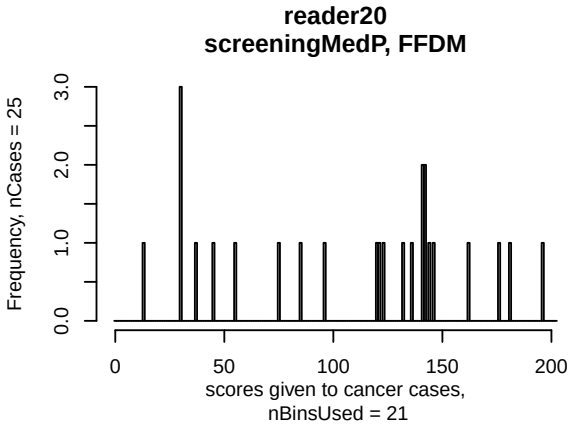


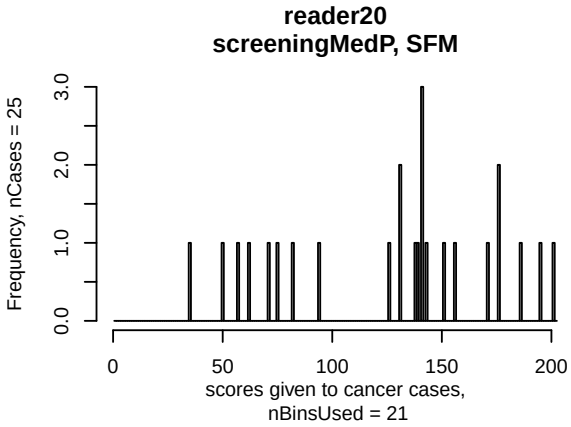


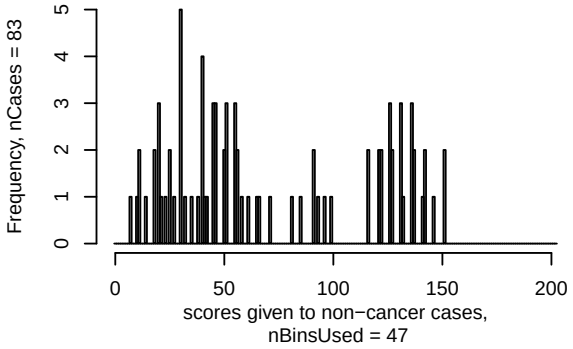
	AUC	se
FFDM	0.783	0.054
SFM	0.747	0.057
FFDM−SFM	0.036	0.054

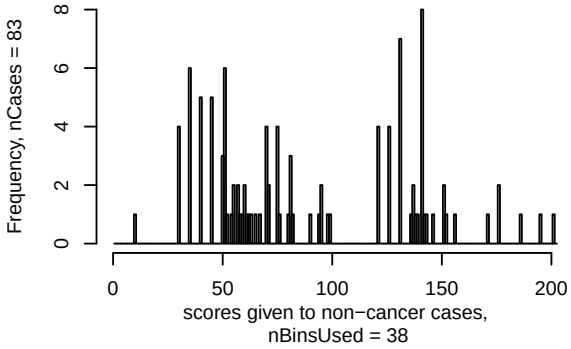
	Sens.	se
FFDM	0.783	0.054
SFM	0.747	0.057
FFDM−SFM	0.036	0.054

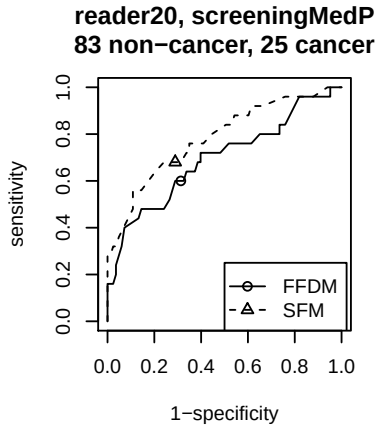
	Spec.	se
FFDM	0.783	0.054
SFM	0.747	0.057
FFDM−SFM	0.036	0.054









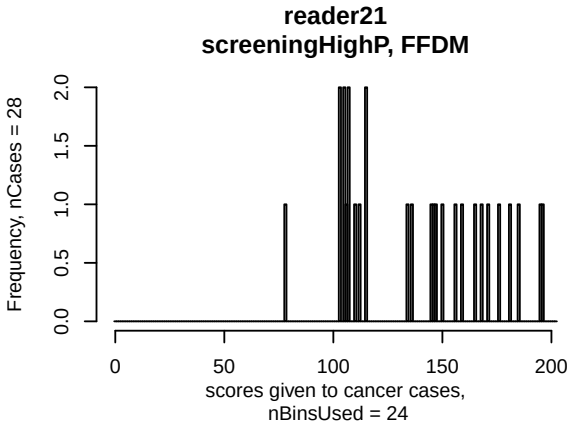


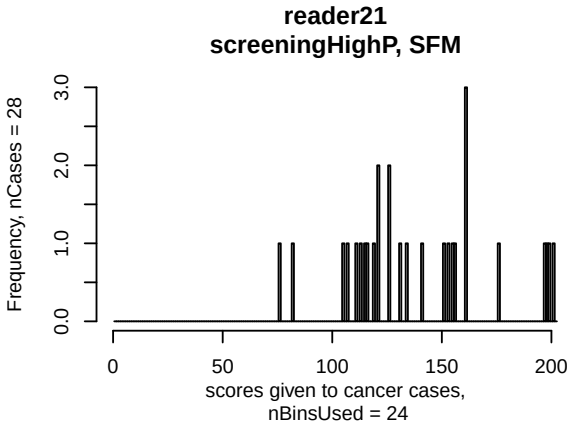
	AUC	se
FFDM	0.694	0.066
SFM	0.782	0.056
FFDM−SFM	−0.088	0.063

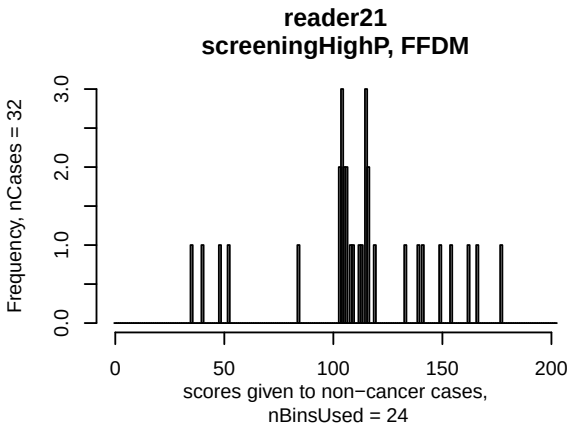
	Sens.	se
FFDM	0.694	0.066
SFM	0.782	0.056
FFDM−SFM	−0.088	0.063

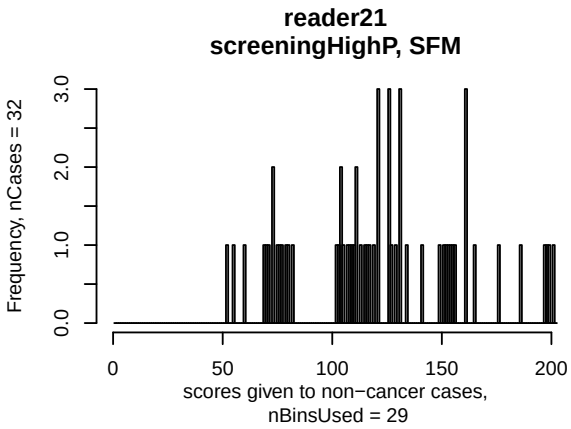
	Spec.	se
FFDM	0.694	0.066
SFM	0.782	0.056
FFDM−SFM	−0.088	0.063

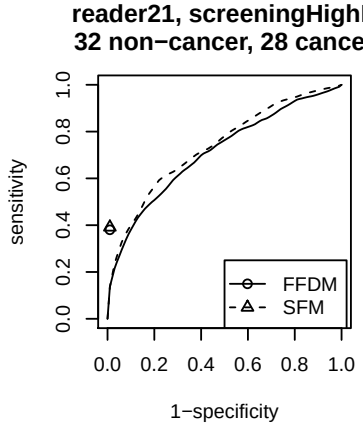
screeningHighP







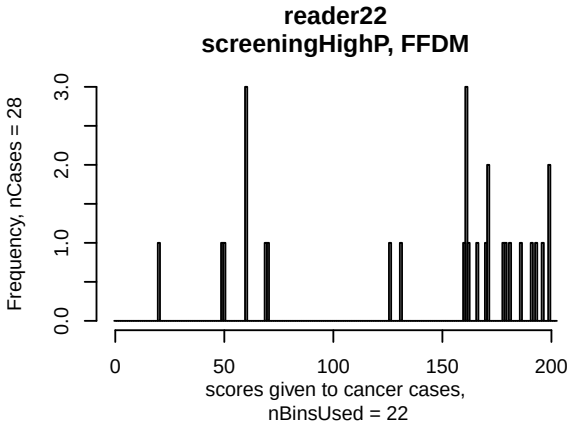


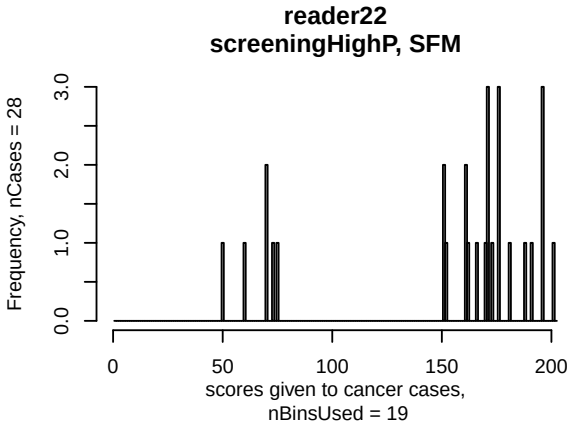


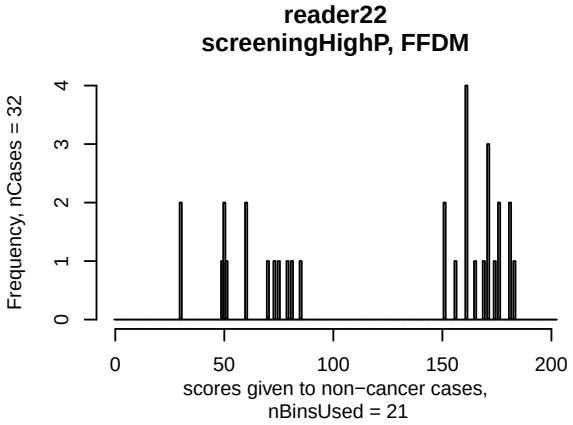
	AUC	se
FFDM	0.69	0.068
SFM	0.767	0.06
FFDM−SFM	−0.077	0.085

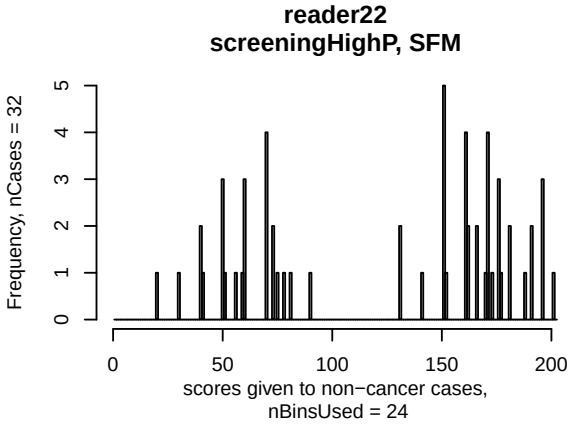
	Sens.	se
FFDM	0.69	0.068
SFM	0.767	0.06
FFDM−SFM	−0.077	0.085

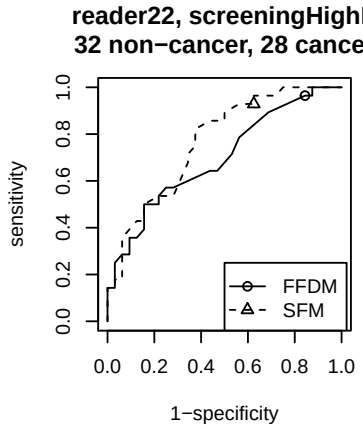
	Spec.	se
FFDM	0.69	0.068
SFM	0.767	0.06
FFDM−SFM	−0.077	0.085







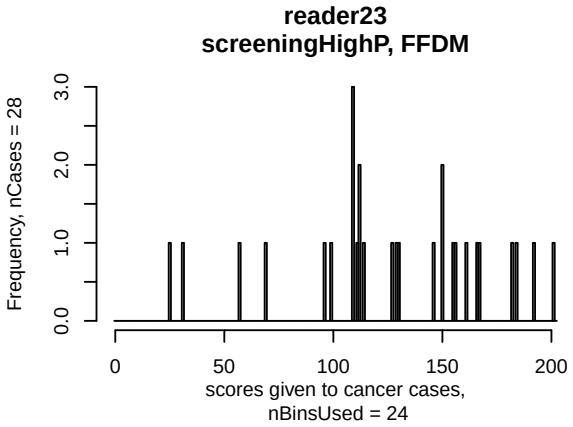


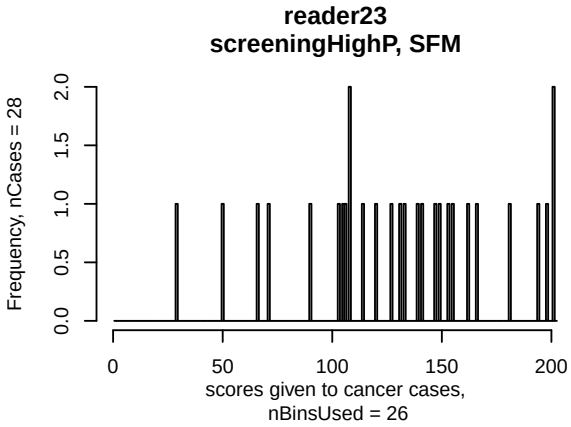


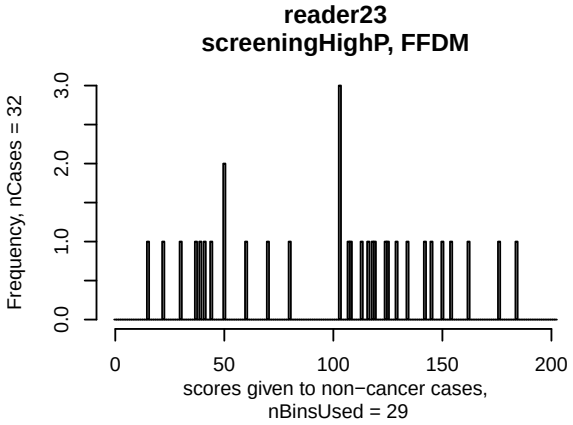
	AUC	se
FFDM	0.604	0.075
SFM	0.777	0.06
FFDM−SFM	−0.173	0.087

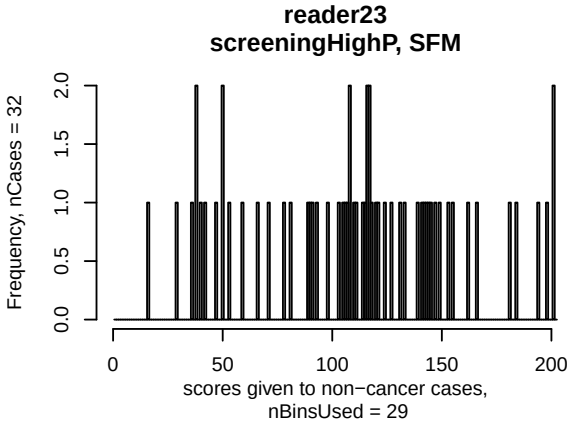
	Sens.	se
FFDM	0.604	0.075
SFM	0.777	0.06
FFDM−SFM	−0.173	0.087

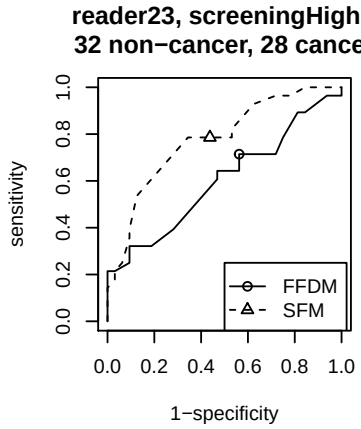
	Spec.	se
FFDM	0.604	0.075
SFM	0.777	0.06
FFDM−SFM	−0.173	0.087







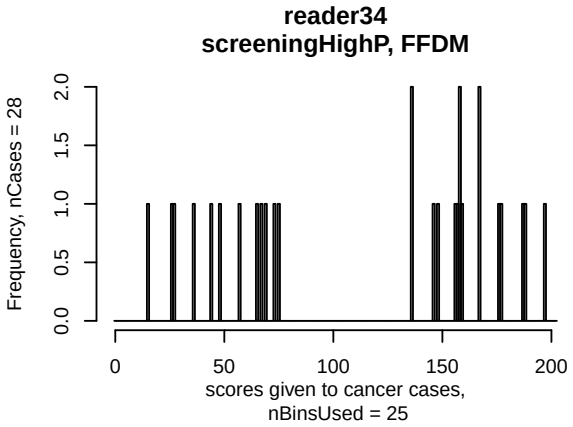


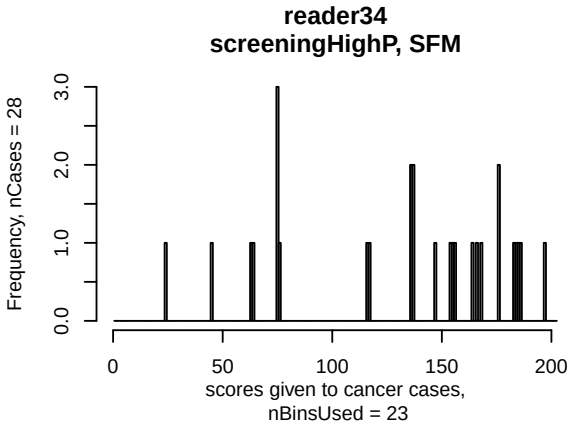


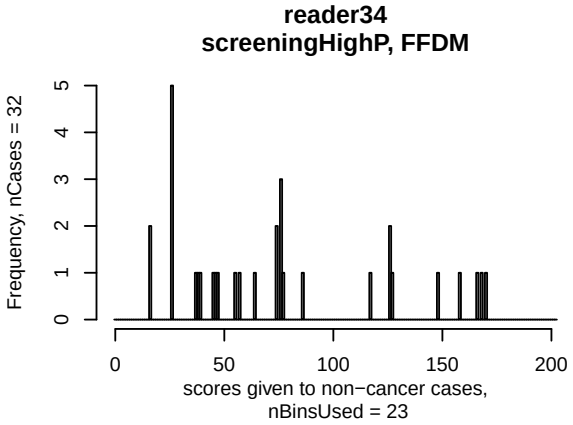
	AUC	se
FFDM	0.663	0.07
SFM	0.723	0.066
FFDM−SFM	−0.06	0.089

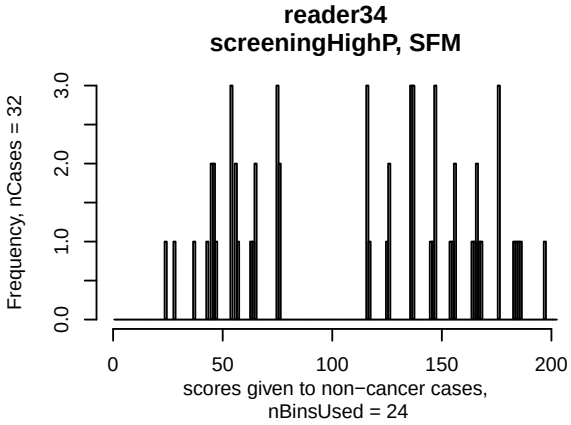
	Sens.	se
FFDM	0.663	0.07
SFM	0.723	0.066
FFDM−SFM	−0.06	0.089

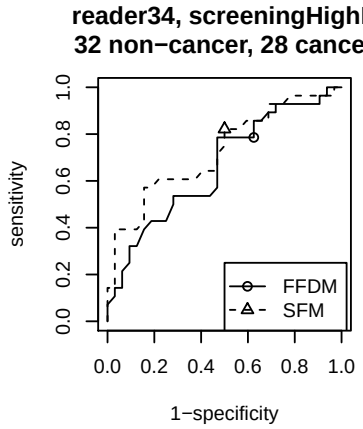
	Spec.	se
FFDM	0.663	0.07
SFM	0.723	0.066
FFDM−SFM	−0.06	0.089







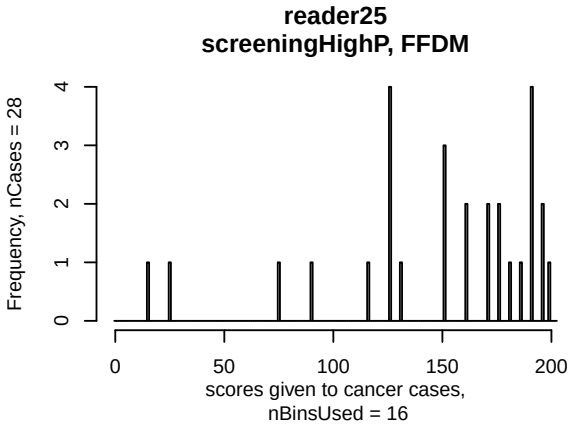


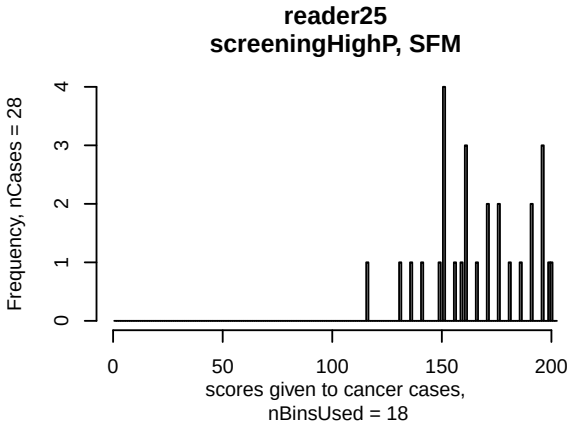


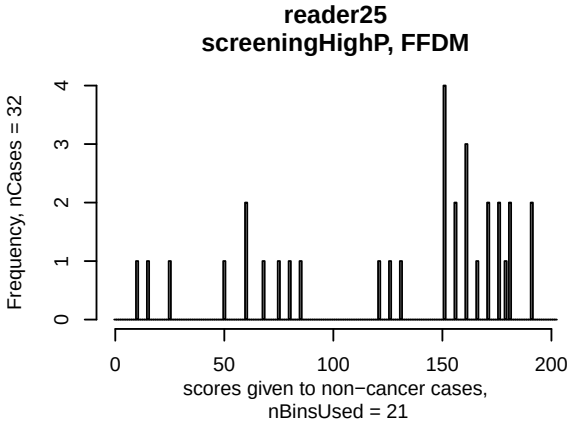
	AUC	se
FFDM	0.679	0.071
SFM	0.705	0.067
FFDM−SFM	−0.026	0.086

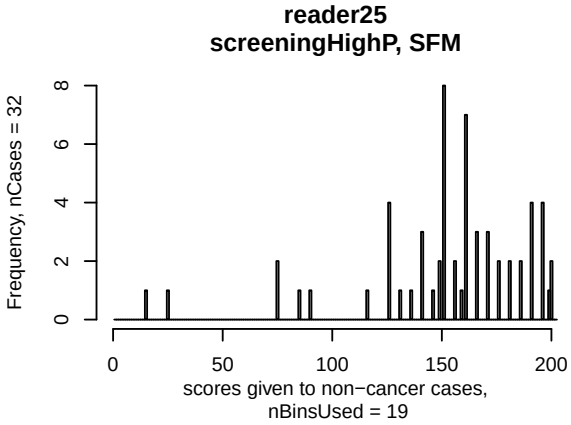
	Sens.	se
FFDM	0.679	0.071
SFM	0.705	0.067
FFDM−SFM	−0.026	0.086

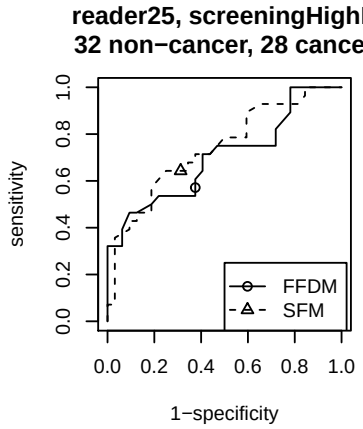
	Spec.	se
FFDM	0.679	0.071
SFM	0.705	0.067
FFDM−SFM	−0.026	0.086







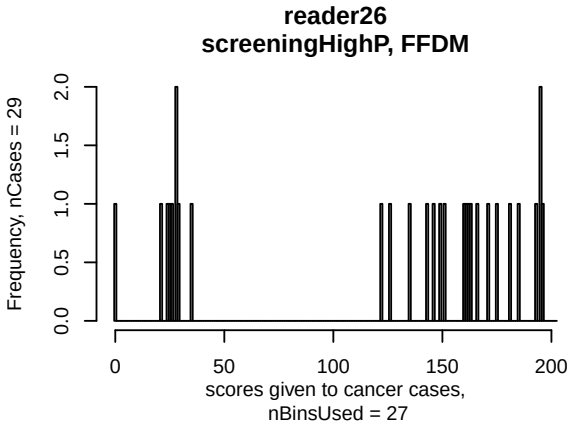


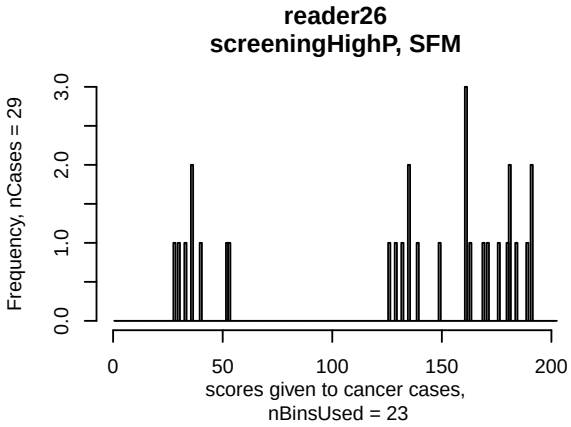


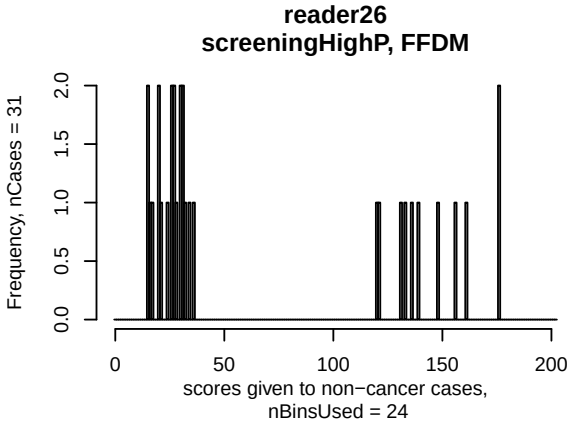
	AUC	se
FFDM	0.619	0.073
SFM	0.679	0.068
FFDM−SFM	−0.059	0.086

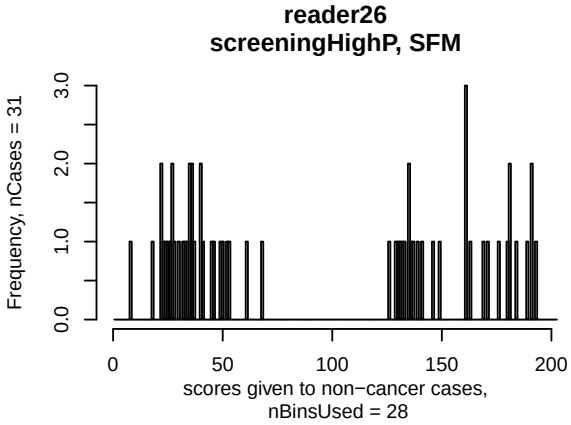
	Sens.	se
FFDM	0.619	0.073
SFM	0.679	0.068
FFDM−SFM	−0.059	0.086

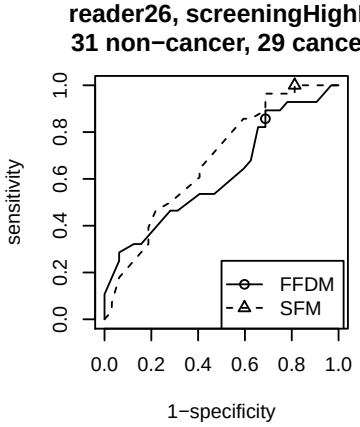
	Spec.	se
FFDM	0.619	0.073
SFM	0.679	0.068
FFDM−SFM	−0.059	0.086







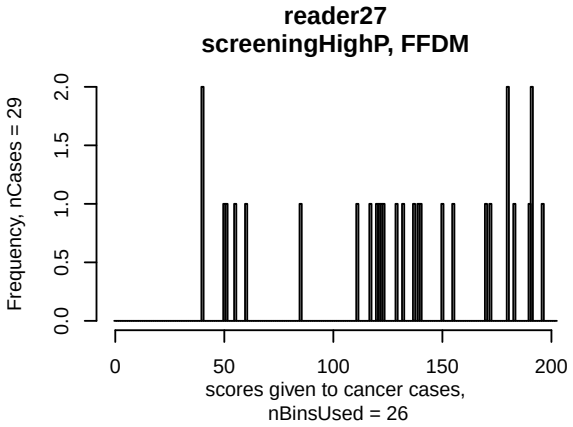


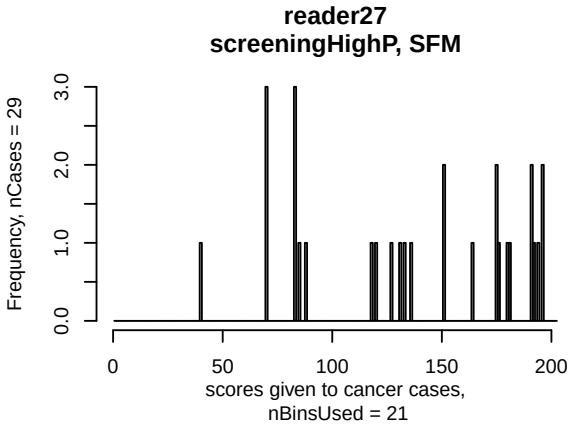


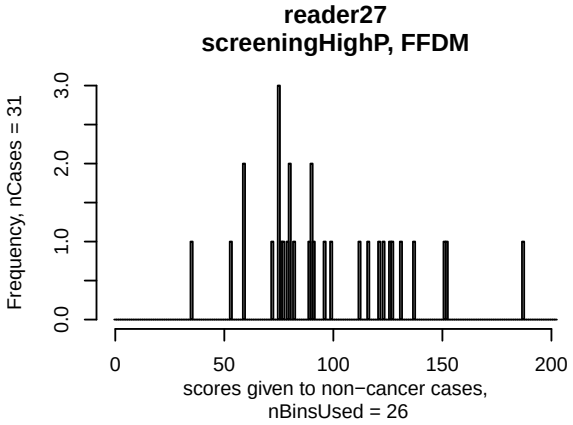
	AUC	se
FFDM	0.722	0.067
SFM	0.798	0.057
FFDM−SFM	−0.076	0.064

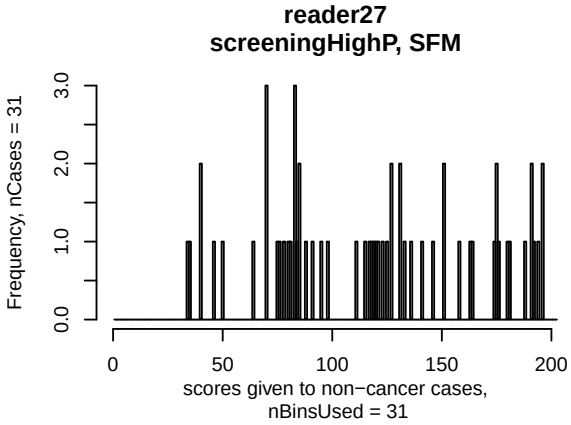
	Sens.	se
FFDM	0.722	0.067
SFM	0.798	0.057
FFDM−SFM	−0.076	0.064

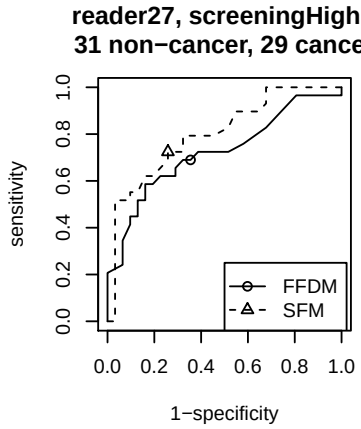
	Spec.	se
FFDM	0.722	0.067
SFM	0.798	0.057
FFDM−SFM	−0.076	0.064







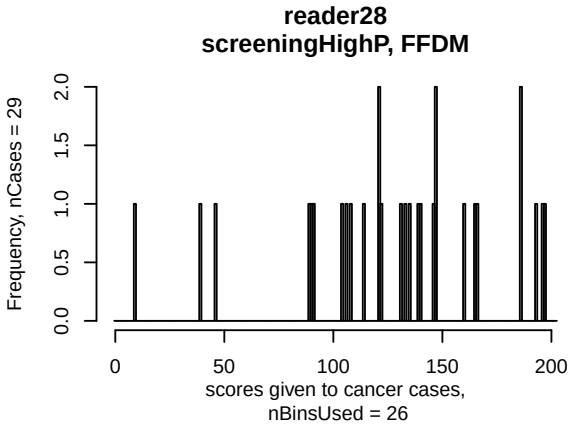


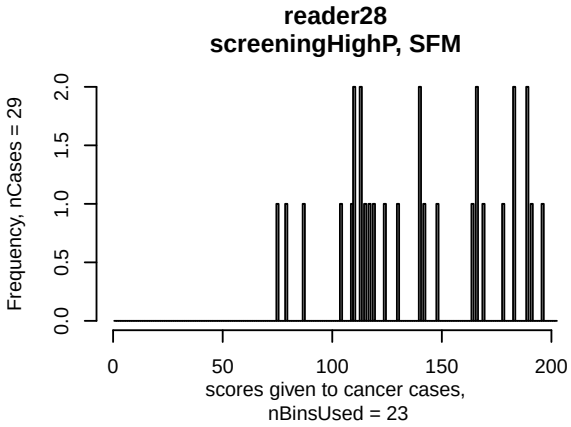


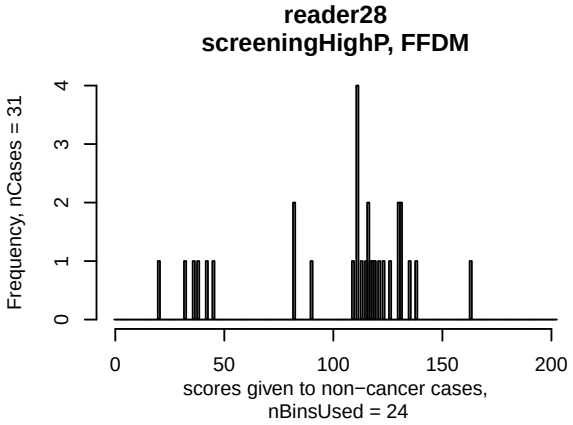
	AUC	se
FFDM	0.696	0.073
SFM	0.706	0.068
FFDM−SFM	−0.011	0.067

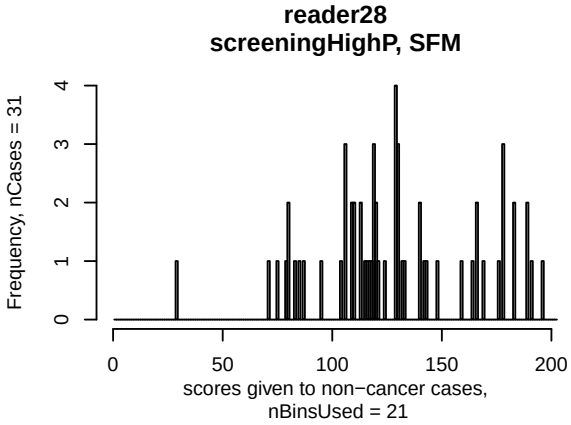
	Sens.	se
FFDM	0.696	0.073
SFM	0.706	0.068
FFDM−SFM	−0.011	0.067

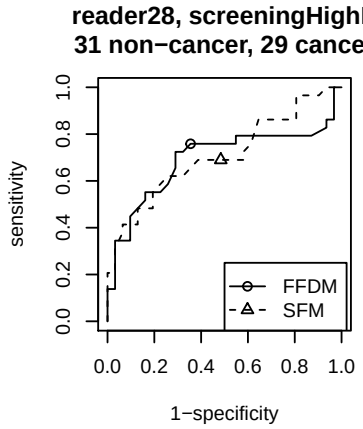
	Spec.	se
FFDM	0.696	0.073
SFM	0.706	0.068
FFDM−SFM	−0.011	0.067







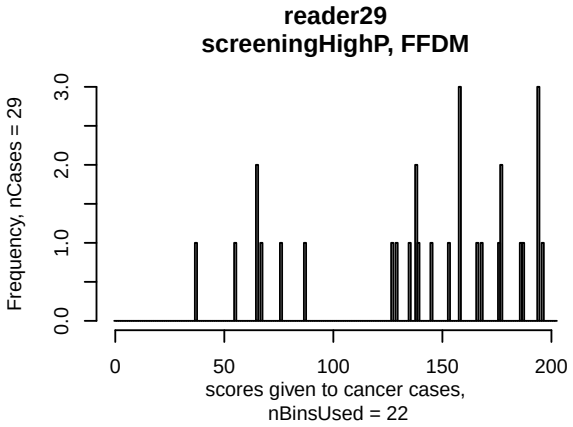


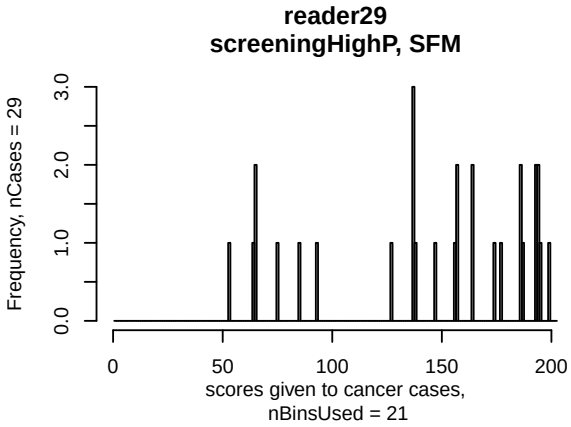


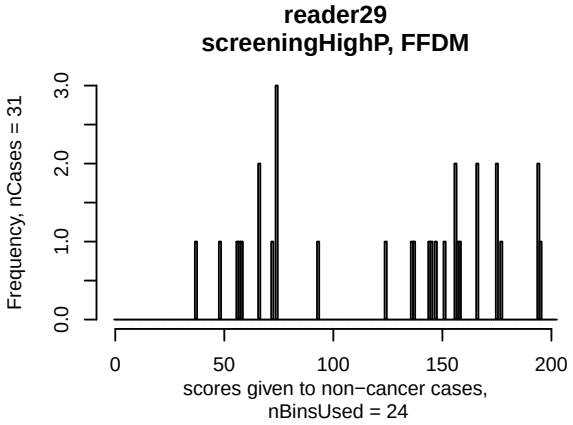
	AUC	se
FFDM	0.693	0.071
SFM	0.648	0.073
FFDM−SFM	0.045	0.066

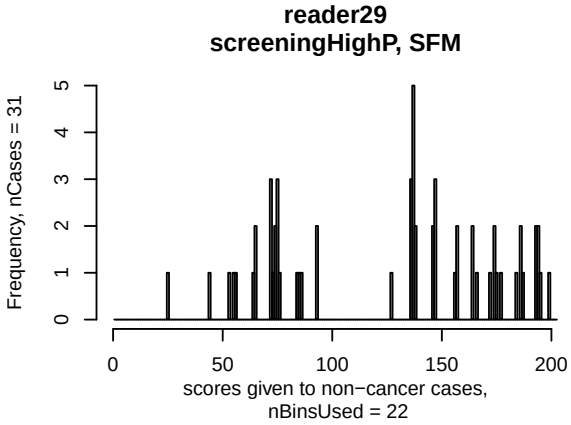
	Sens.	se
FFDM	0.693	0.071
SFM	0.648	0.073
FFDM−SFM	0.045	0.066

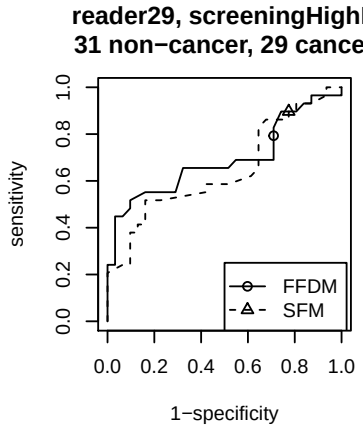
	Spec.	se
FFDM	0.693	0.071
SFM	0.648	0.073
FFDM−SFM	0.045	0.066







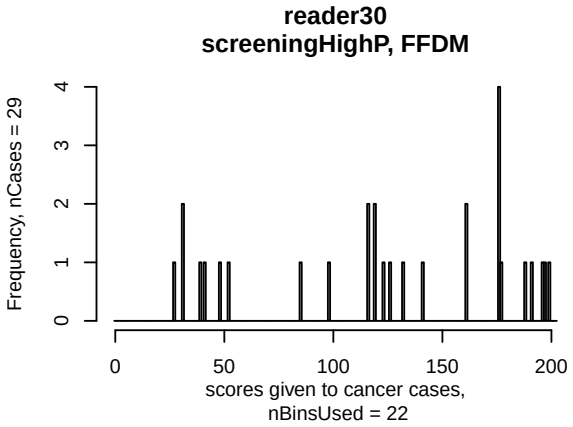


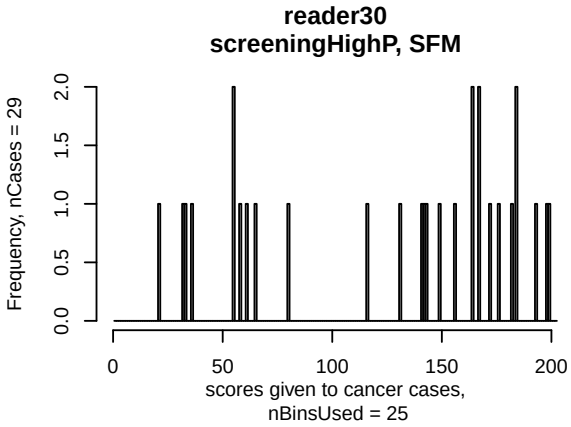


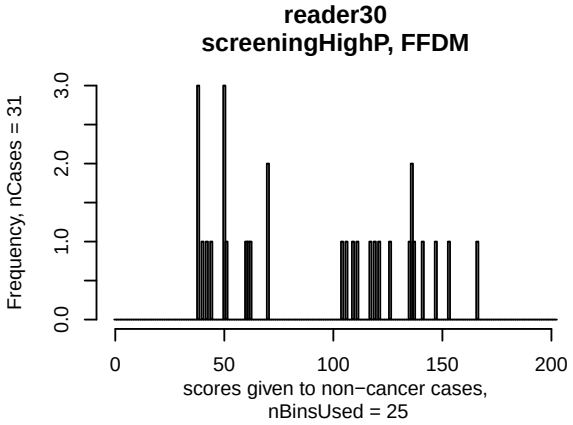
	AUC	se
FFDM	0.593	0.074
SFM	0.717	0.067
FFDM−SFM	−0.123	0.085

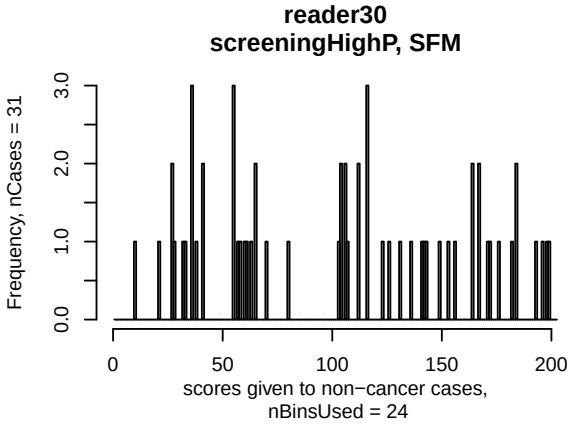
	Sens.	se
FFDM	0.593	0.074
SFM	0.717	0.067
FFDM−SFM	−0.123	0.085

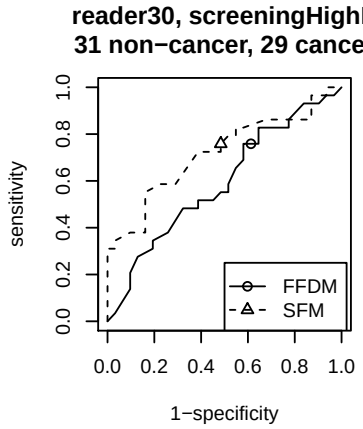
	Spec.	se
FFDM	0.593	0.074
SFM	0.717	0.067
FFDM−SFM	−0.123	0.085







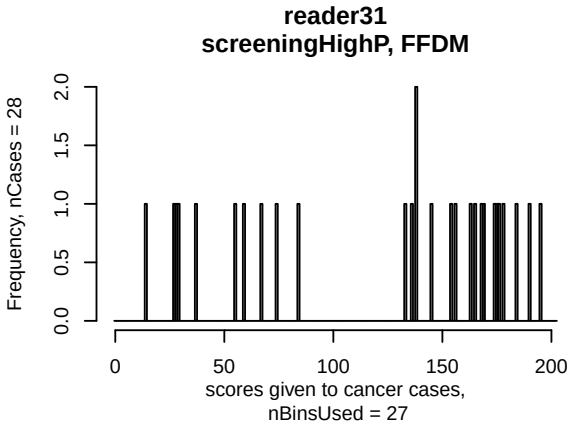


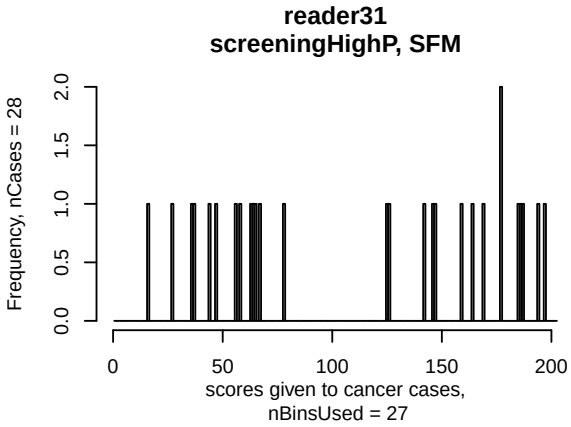


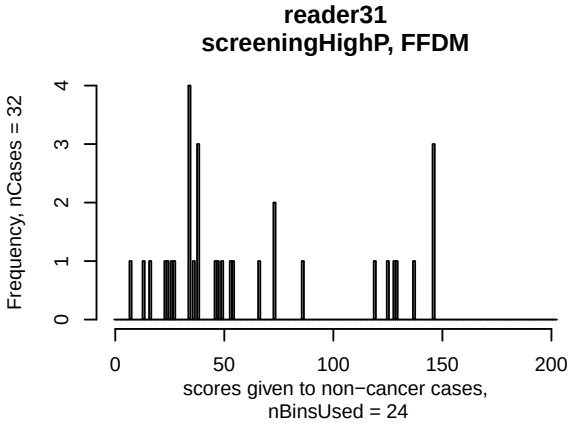
	AUC	se
FFDM	0.664	0.074
SFM	0.706	0.071
FFDM−SFM	−0.042	0.074

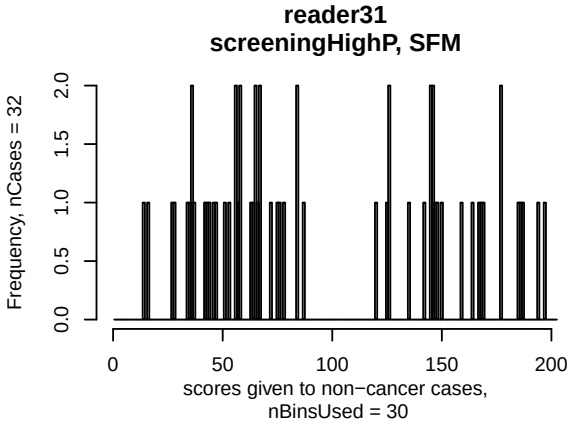
	Sens.	se
FFDM	0.664	0.074
SFM	0.706	0.071
FFDM−SFM	−0.042	0.074

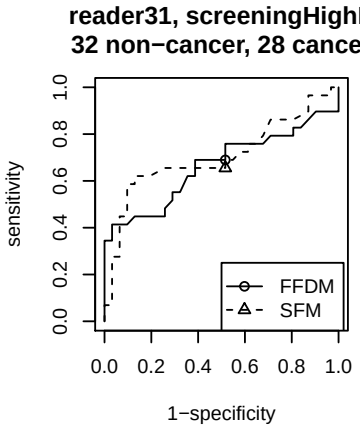
	Spec.	se
FFDM	0.664	0.074
SFM	0.706	0.071
FFDM−SFM	−0.042	0.074







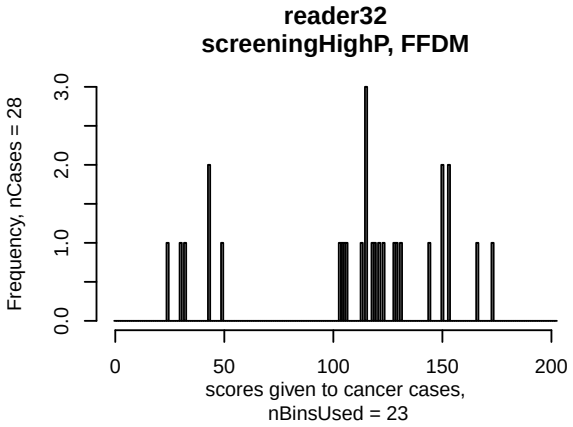


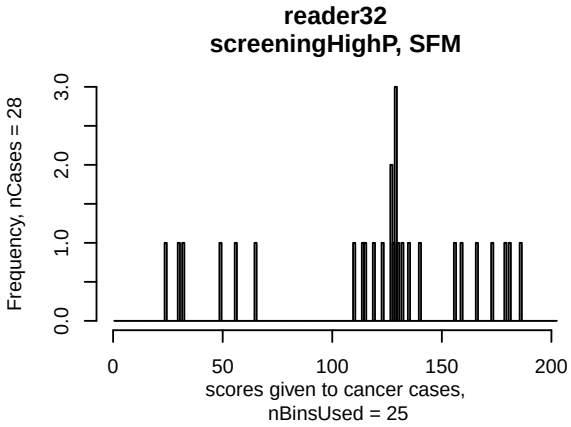


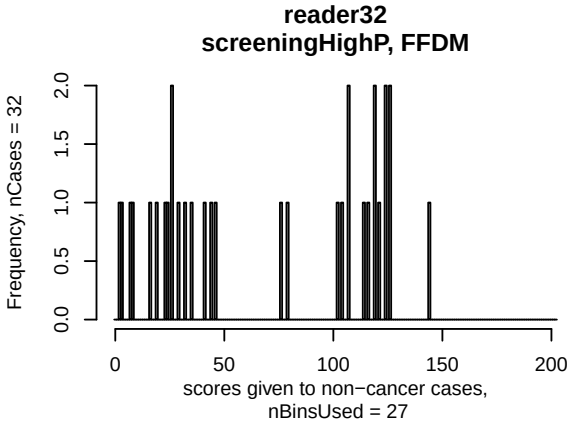
	AUC	se
FFDM	0.782	0.062
SFM	0.632	0.074
FFDM−SFM	0.15	0.086

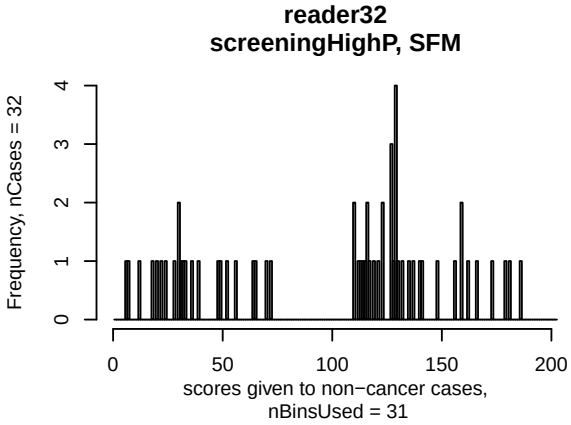
	Sens.	se
FFDM	0.782	0.062
SFM	0.632	0.074
FFDM−SFM	0.15	0.086

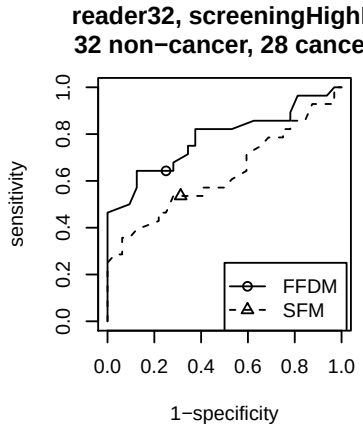
	Spec.	se
FFDM	0.782	0.062
SFM	0.632	0.074
FFDM−SFM	0.15	0.086







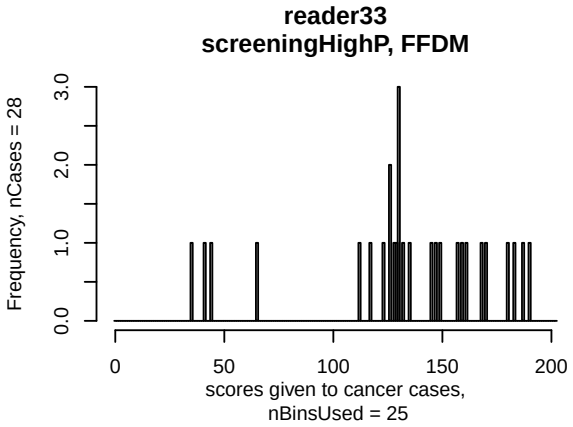


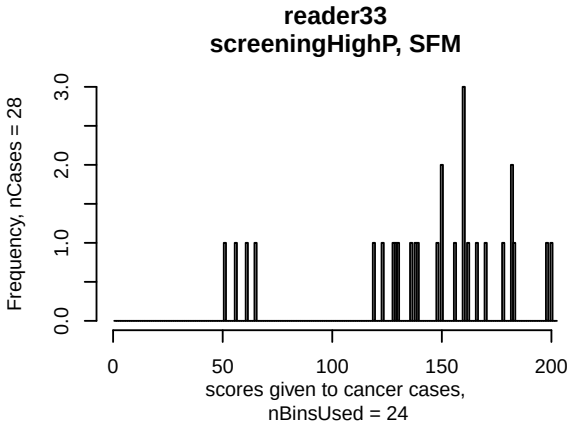


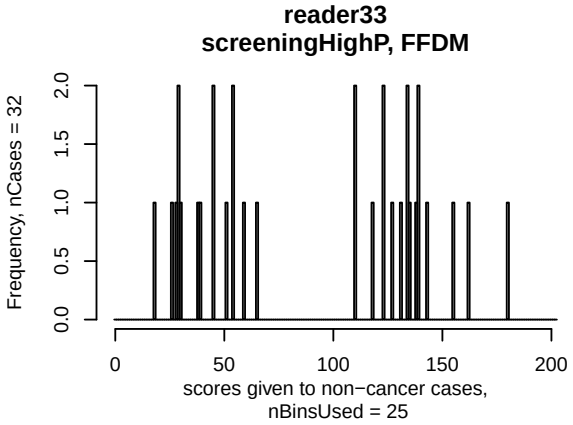
	AUC	se
FFDM	0.739	0.063
SFM	0.732	0.065
FFDM−SFM	0.008	0.068

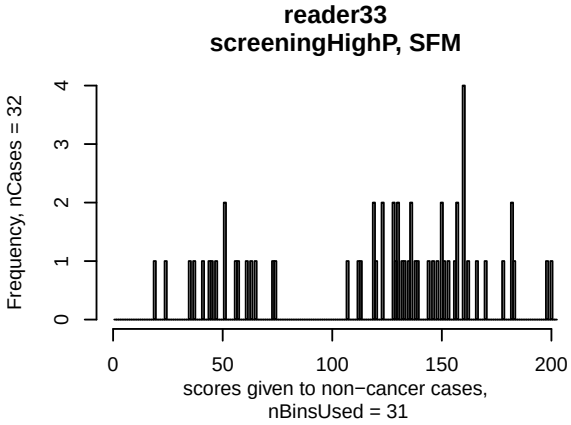
	Sens.	se
FFDM	0.739	0.063
SFM	0.732	0.065
FFDM−SFM	0.008	0.068

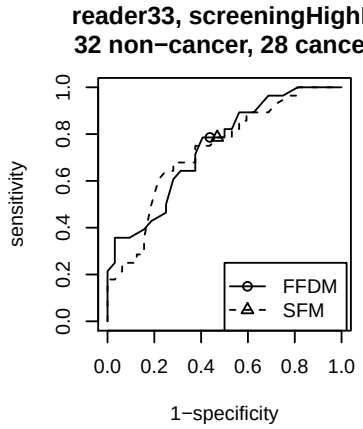
	Spec.	se
FFDM	0.739	0.063
SFM	0.732	0.065
FFDM−SFM	0.008	0.068







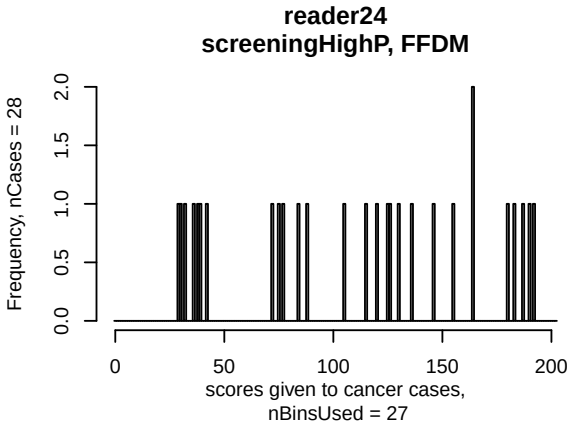


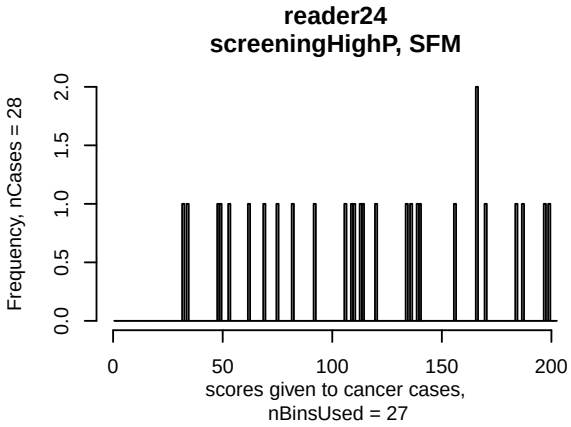


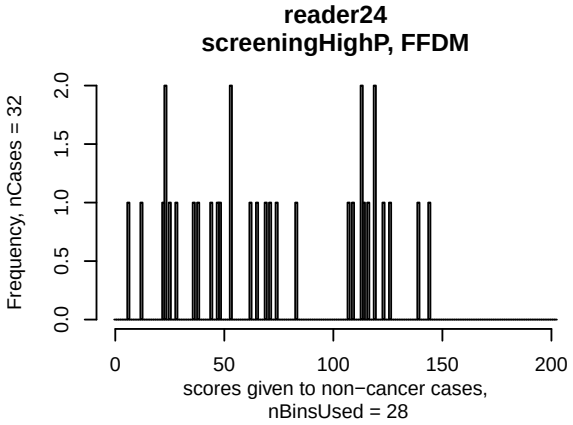
	AUC	se
FFDM	0.723	0.065
SFM	0.782	0.058
FFDM−SFM	−0.059	0.069

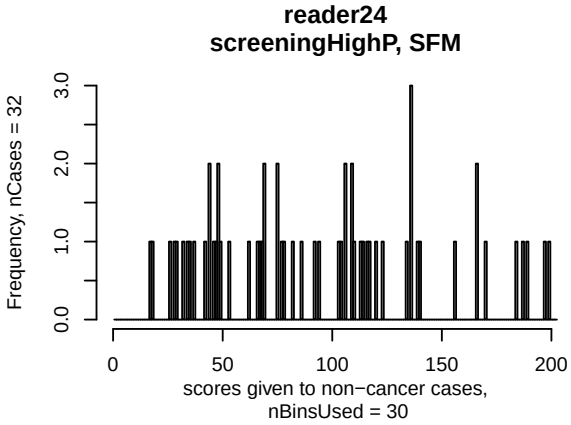
	Sens.	se
FFDM	0.723	0.065
SFM	0.782	0.058
FFDM−SFM	−0.059	0.069

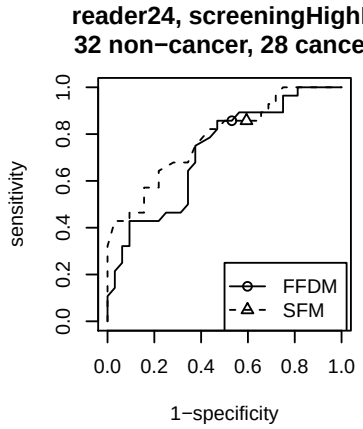
	Spec.	se
FFDM	0.723	0.065
SFM	0.782	0.058
FFDM−SFM	−0.059	0.069







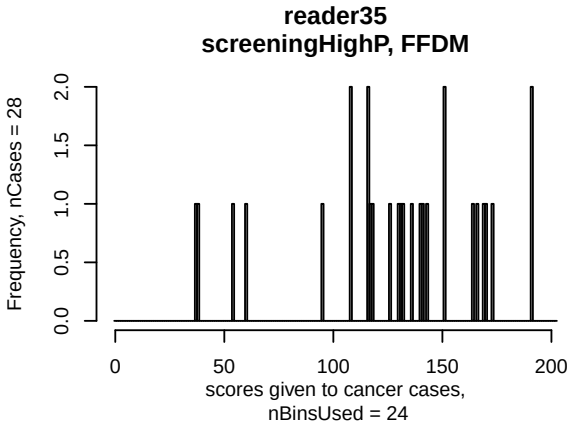


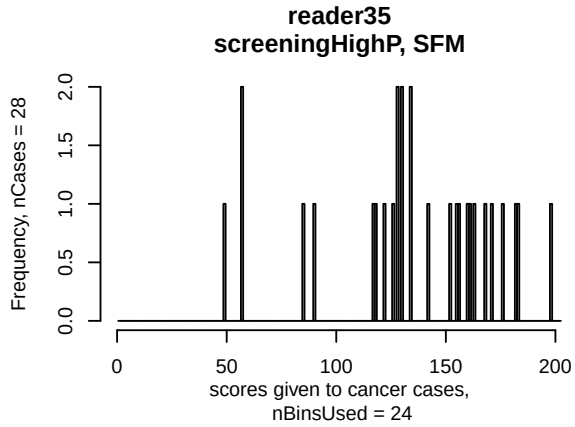


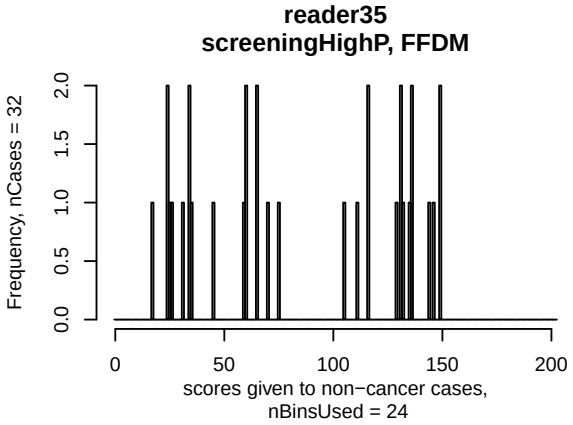
	AUC	se
FFDM	0.704	0.069
SFM	0.741	0.064
FFDM−SFM	−0.037	0.081

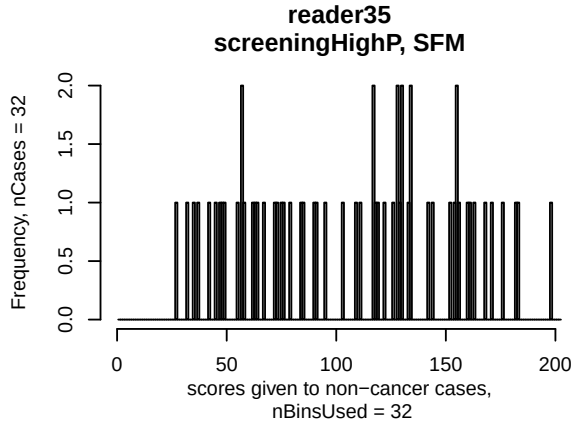
	Sens.	se
FFDM	0.704	0.069
SFM	0.741	0.064
FFDM−SFM	−0.037	0.081

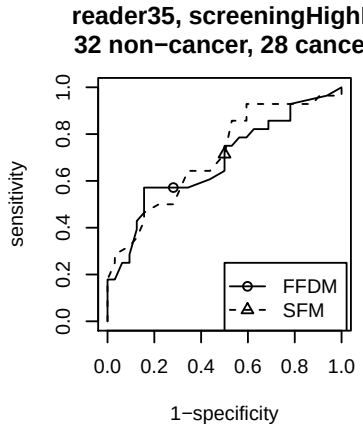
	Spec.	se
FFDM	0.704	0.069
SFM	0.741	0.064
FFDM−SFM	−0.037	0.081







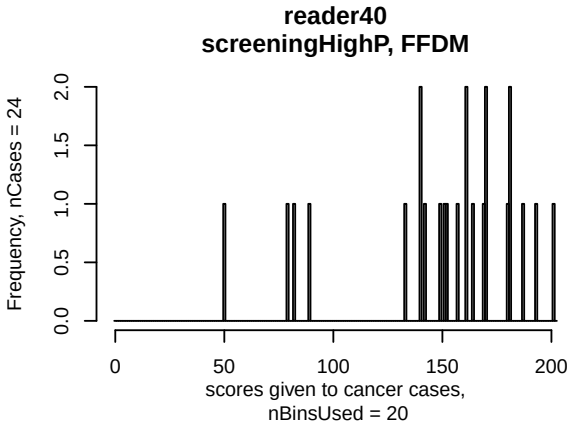


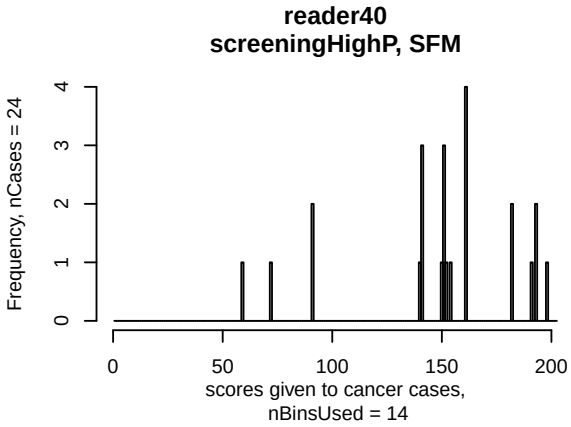


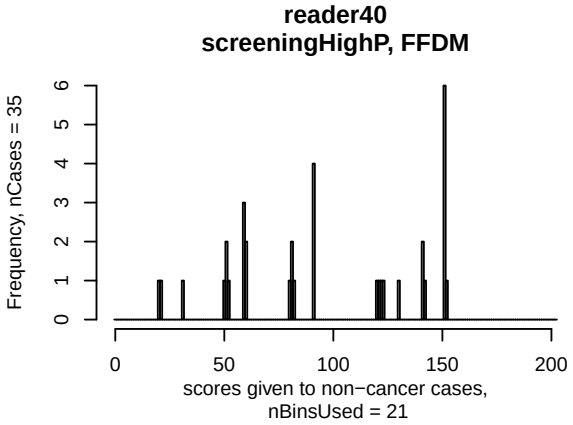
	AUC	se
FFDM	0.742	0.063
SFM	0.837	0.052
FFDM−SFM	−0.095	0.074

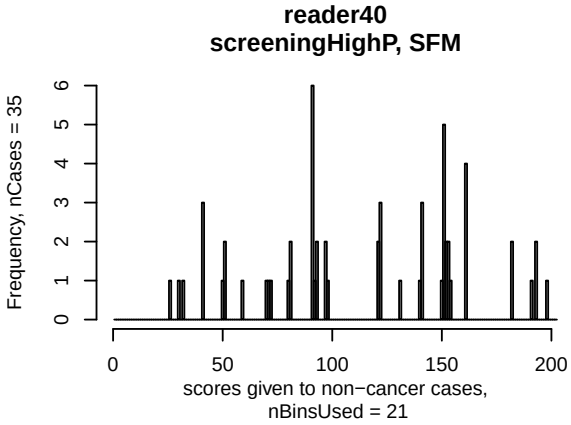
	Sens.	se
FFDM	0.742	0.063
SFM	0.837	0.052
FFDM−SFM	−0.095	0.074

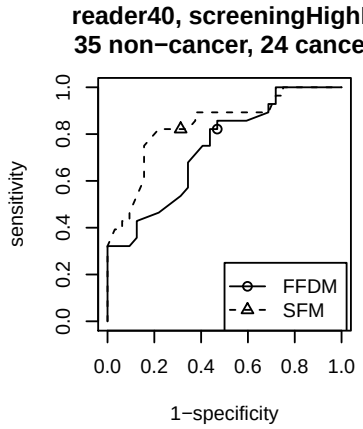
	Spec.	se
FFDM	0.742	0.063
SFM	0.837	0.052
FFDM−SFM	−0.095	0.074







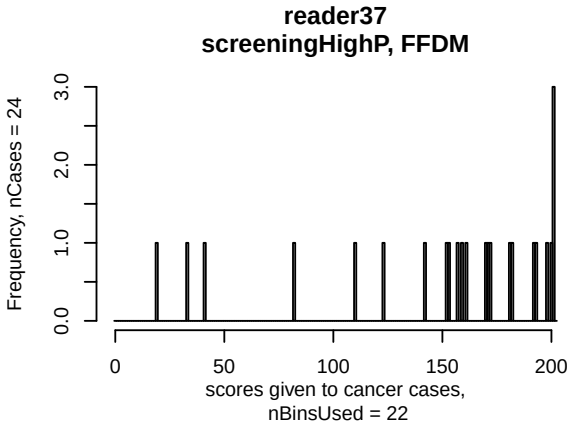


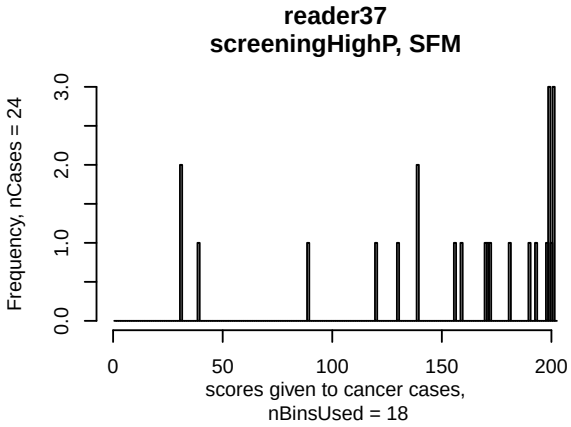


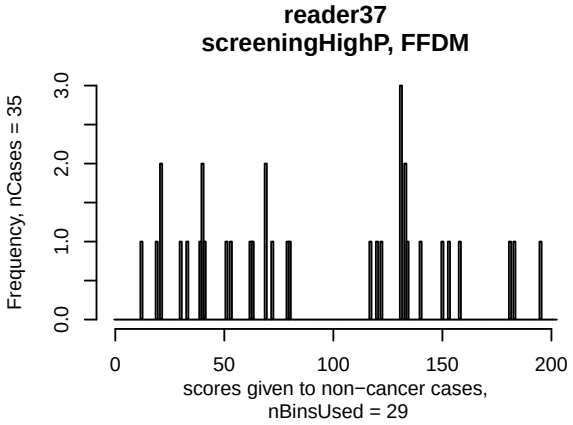
	AUC	se
FFDM	0.831	0.057
SFM	0.848	0.053
FFDM−SFM	−0.017	0.046

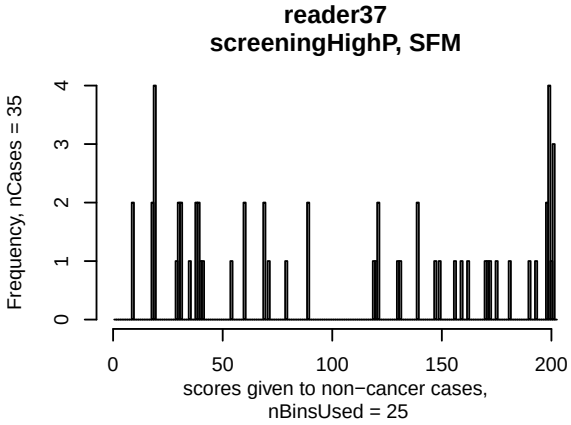
	Sens.	se
FFDM	0.831	0.057
SFM	0.848	0.053
FFDM−SFM	−0.017	0.046

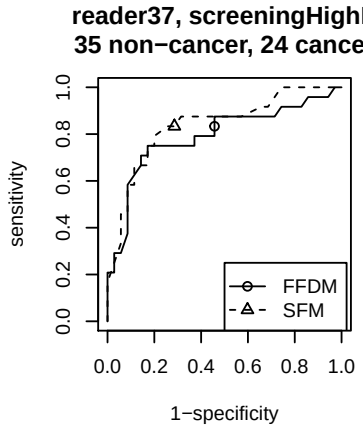
	Spec.	se
FFDM	0.831	0.057
SFM	0.848	0.053
FFDM−SFM	−0.017	0.046







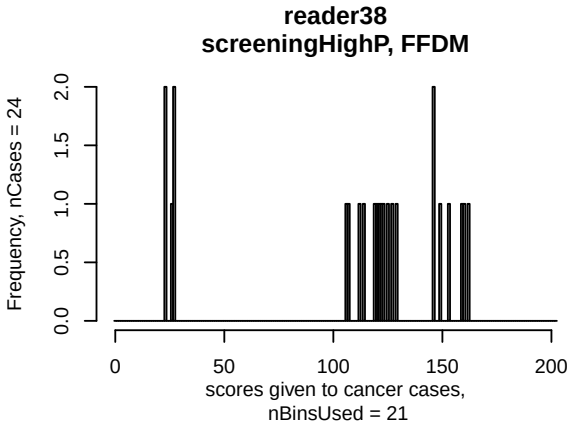


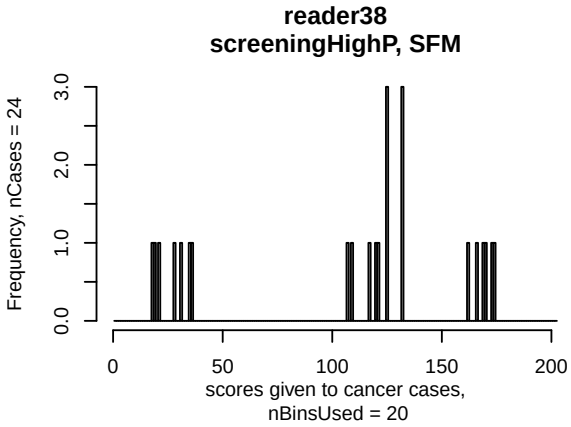


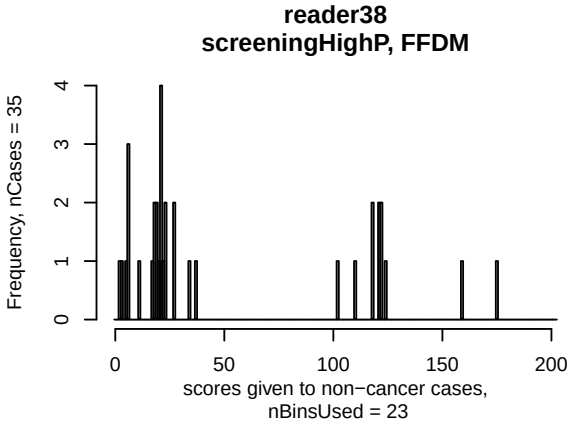
	AUC	se
FFDM	0.792	0.065
SFM	0.842	0.053
FFDM−SFM	−0.049	0.051

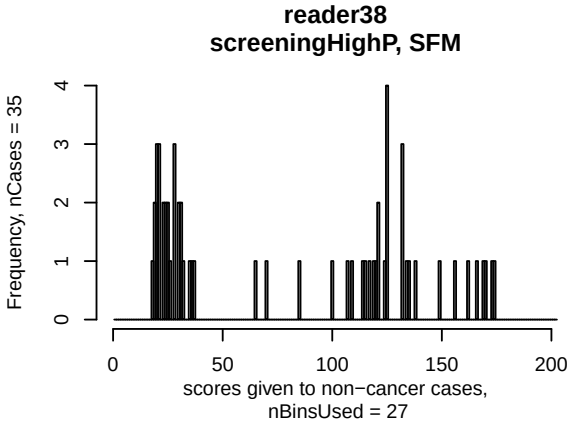
	Sens.	se
FFDM	0.792	0.065
SFM	0.842	0.053
FFDM−SFM	−0.049	0.051

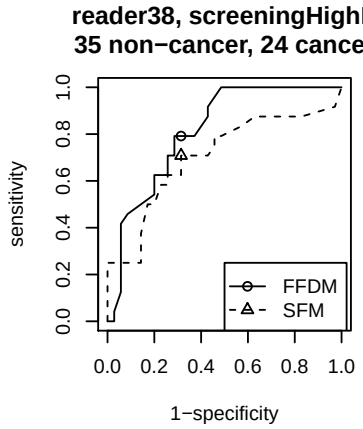
	Spec.	se
FFDM	0.792	0.065
SFM	0.842	0.053
FFDM−SFM	−0.049	0.051







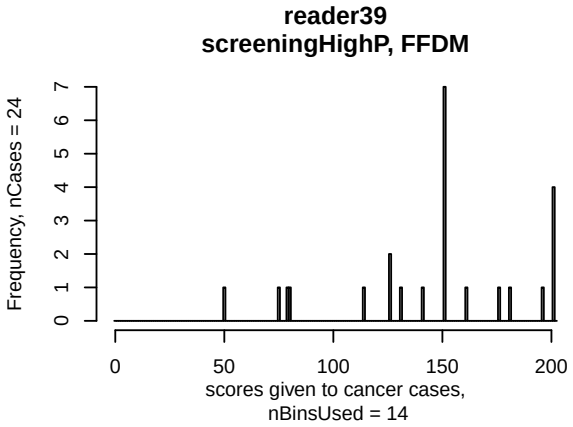


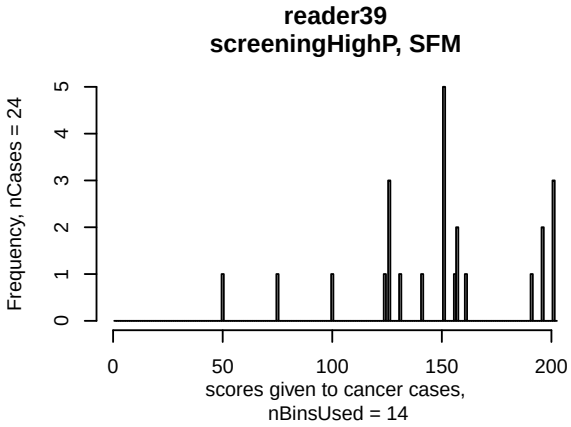


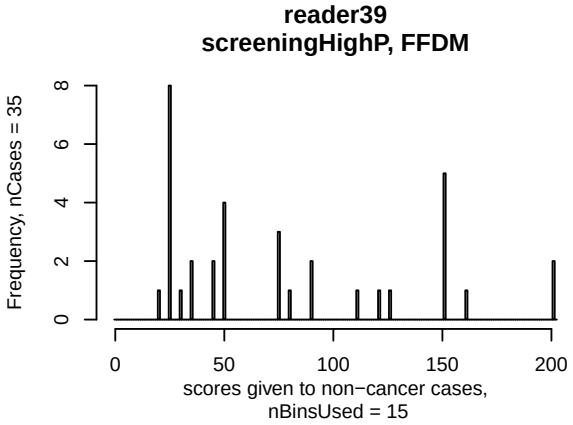
	AUC	se
FFDM	0.812	0.054
SFM	0.705	0.073
FFDM−SFM	0.108	0.073

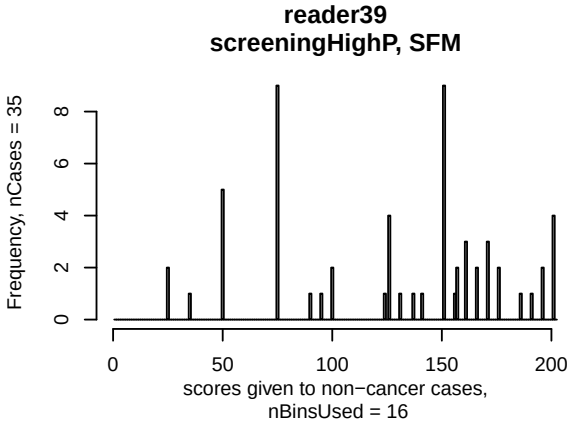
	Sens.	se
FFDM	0.812	0.054
SFM	0.705	0.073
FFDM−SFM	0.108	0.073

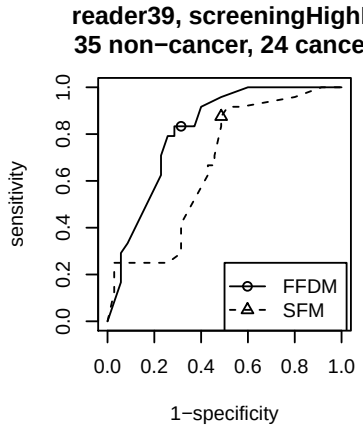
	Spec.	se
FFDM	0.812	0.054
SFM	0.705	0.073
FFDM−SFM	0.108	0.073







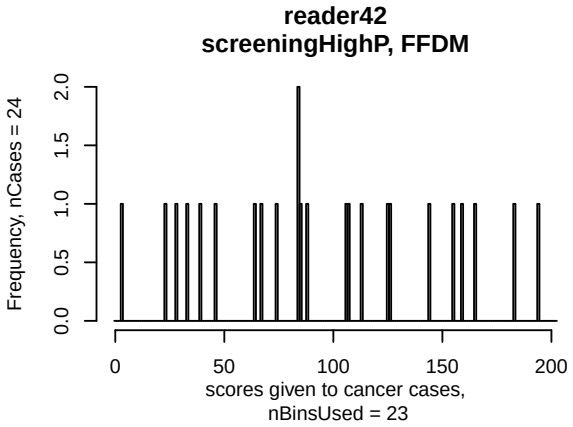


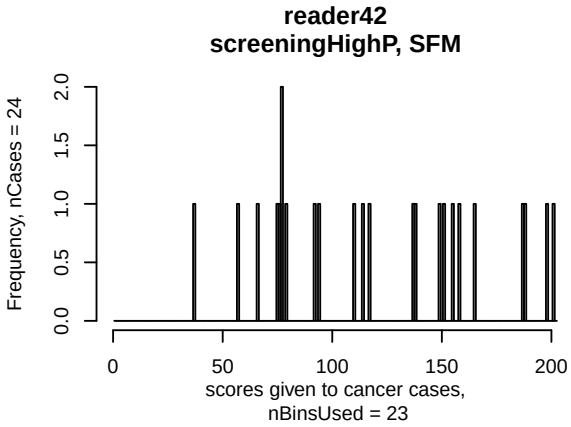


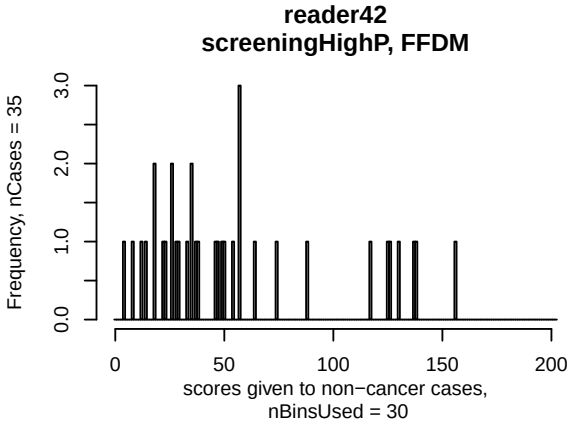
	AUC	se
FFDM	0.814	0.054
SFM	0.665	0.071
FFDM−SFM	0.149	0.066

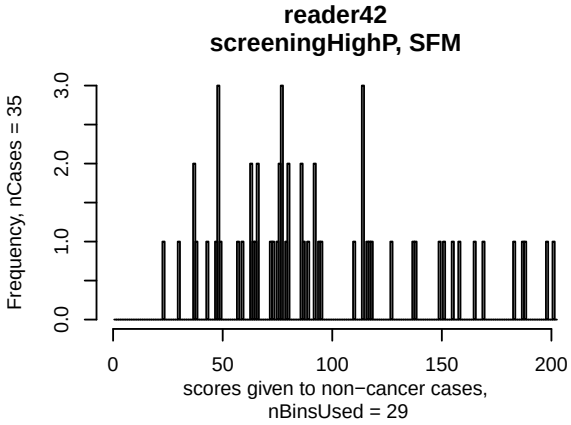
	Sens.	se
FFDM	0.814	0.054
SFM	0.665	0.071
FFDM−SFM	0.149	0.066

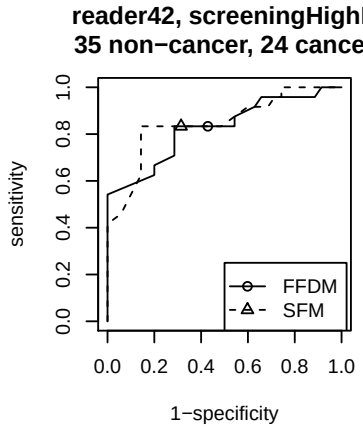
	Spec.	se
FFDM	0.814	0.054
SFM	0.665	0.071
FFDM−SFM	0.149	0.066









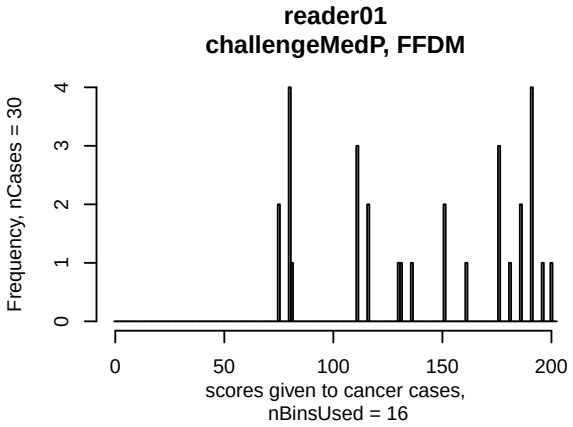


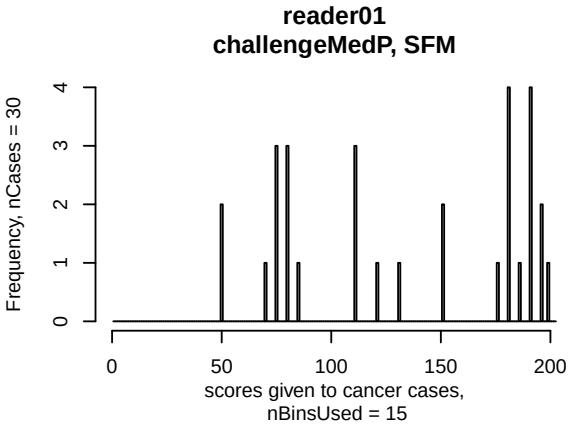
	AUC	se
FFDM	0.718	0.07
SFM	0.757	0.064
FFDM−SFM	−0.039	0.083

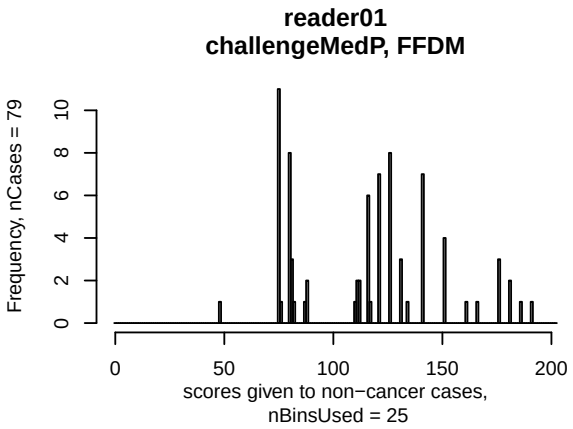
	Sens.	se
FFDM	0.718	0.07
SFM	0.757	0.064
FFDM−SFM	−0.039	0.083

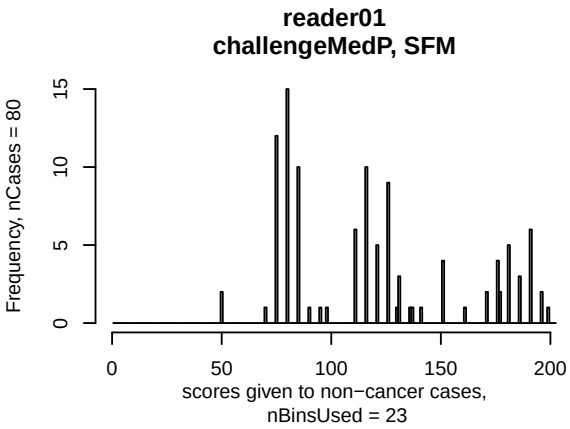
	Spec.	se
FFDM	0.718	0.07
SFM	0.757	0.064
FFDM−SFM	−0.039	0.083

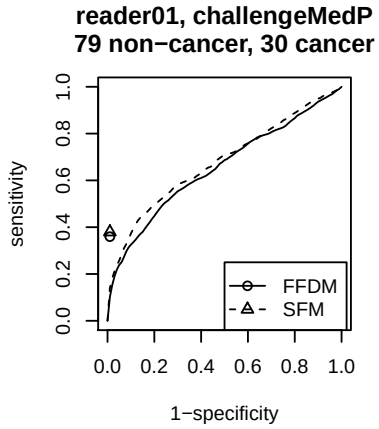
challengeMedP







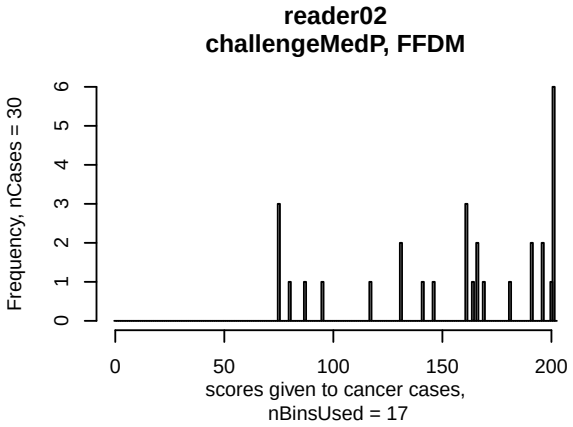


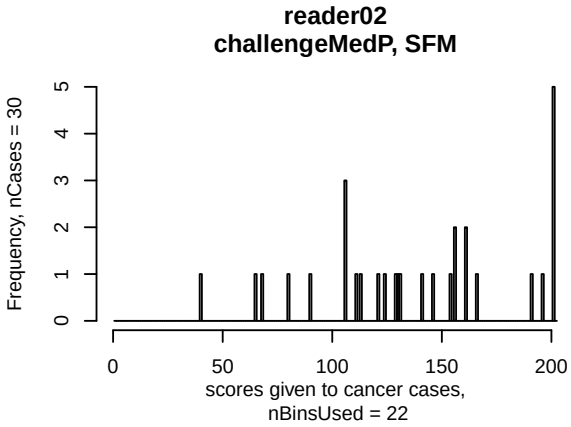


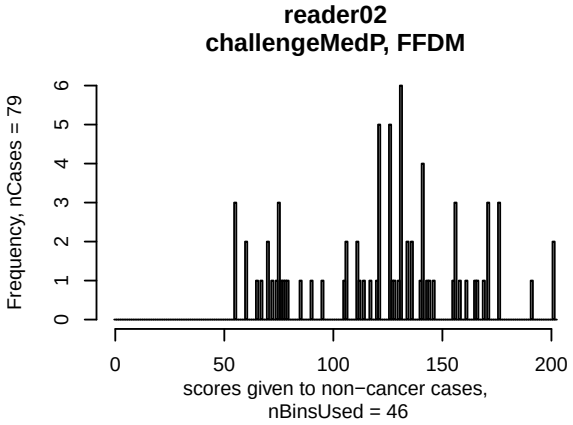
	AUC	se
FFDM	0.661	0.065
SFM	0.598	0.074
FFDM−SFM	0.063	0.083

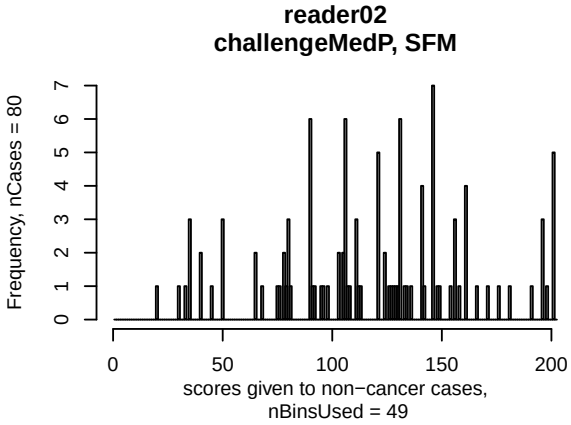
	Sens.	se
FFDM	0.661	0.065
SFM	0.598	0.074
FFDM−SFM	0.063	0.083

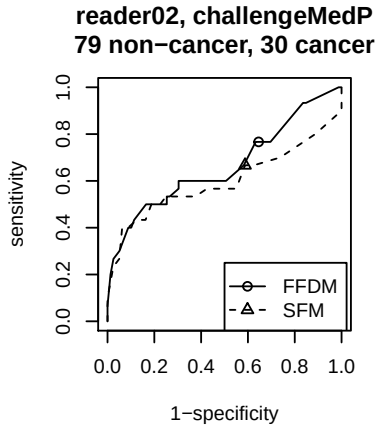
	Spec.	se
FFDM	0.661	0.065
SFM	0.598	0.074
FFDM−SFM	0.063	0.083







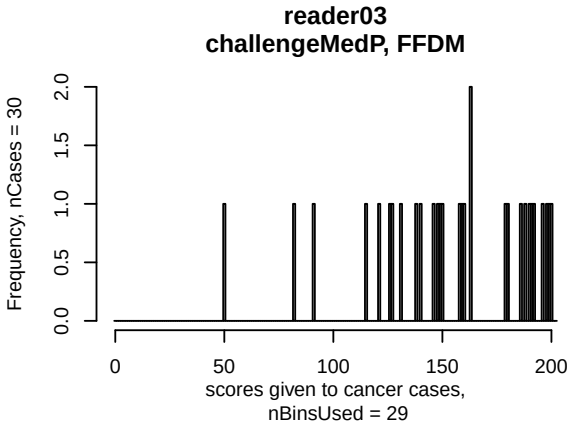


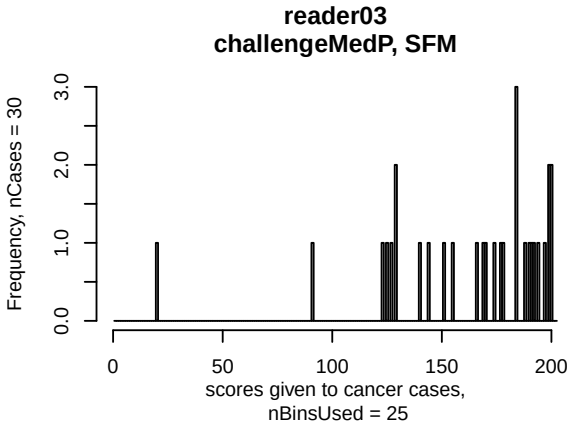


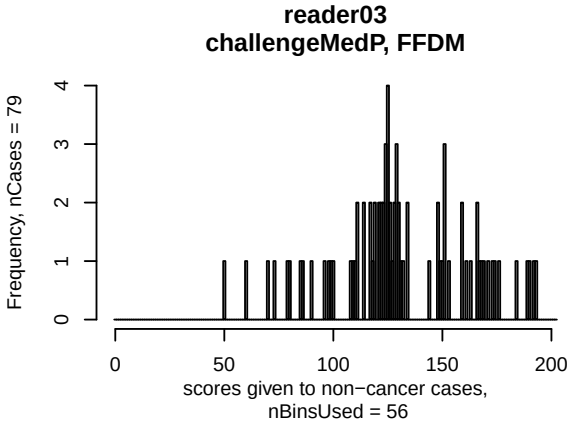
	AUC	se
FFDM	0.731	0.06
SFM	0.672	0.06
FFDM−SFM	0.059	0.059

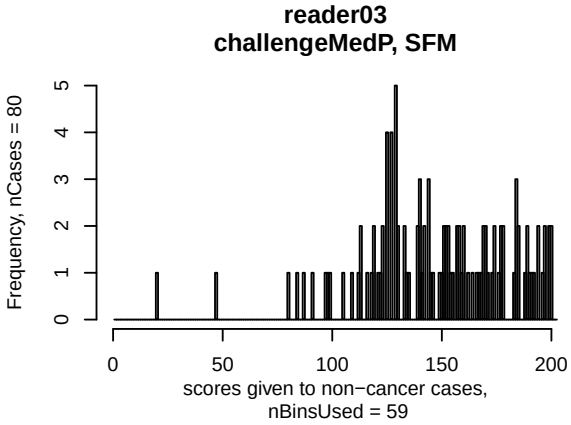
	Sens.	se
FFDM	0.731	0.06
SFM	0.672	0.06
FFDM−SFM	0.059	0.059

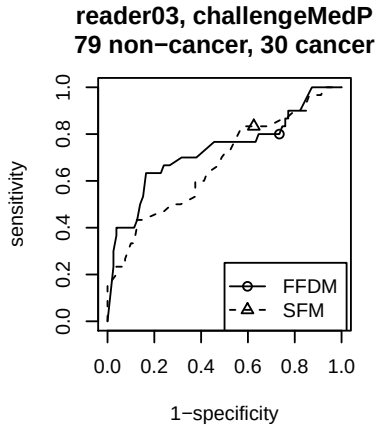
	Spec.	se
FFDM	0.731	0.06
SFM	0.672	0.06
FFDM−SFM	0.059	0.059







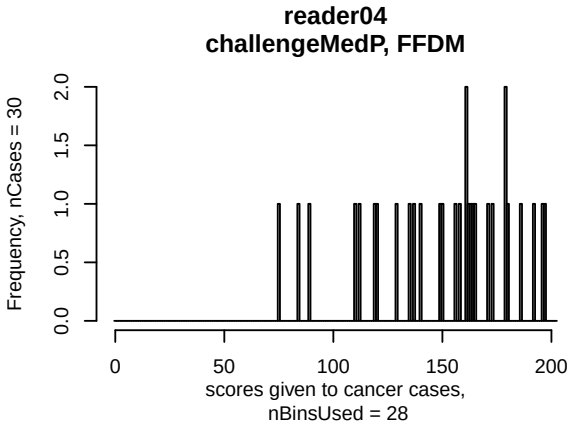


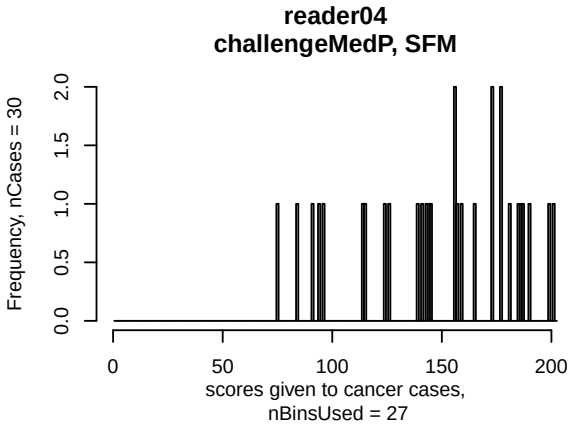


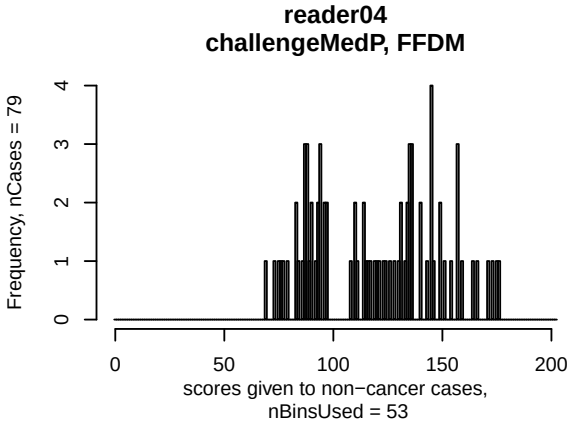
	AUC	se
FFDM	0.706	0.059
SFM	0.71	0.062
FFDM−SFM	−0.004	0.066

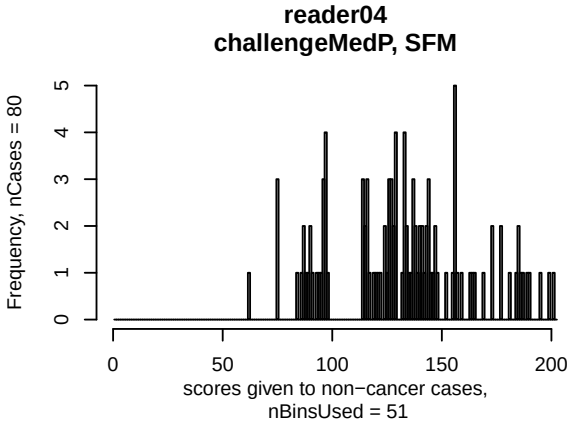
	Sens.	se
FFDM	0.706	0.059
SFM	0.71	0.062
FFDM−SFM	−0.004	0.066

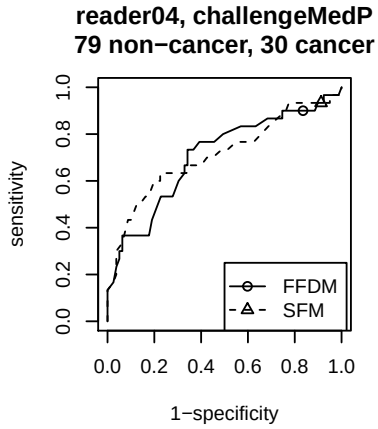
	Spec.	se
FFDM	0.706	0.059
SFM	0.71	0.062
FFDM−SFM	−0.004	0.066







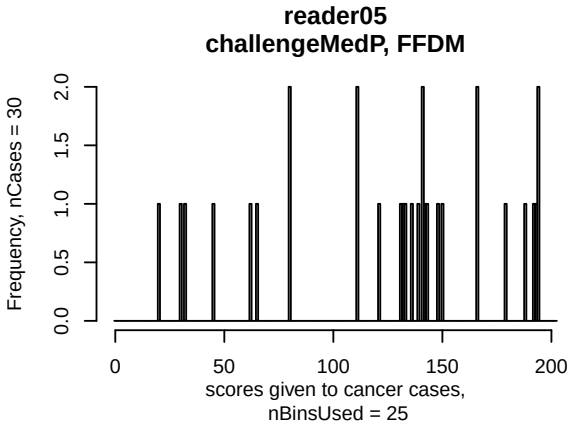


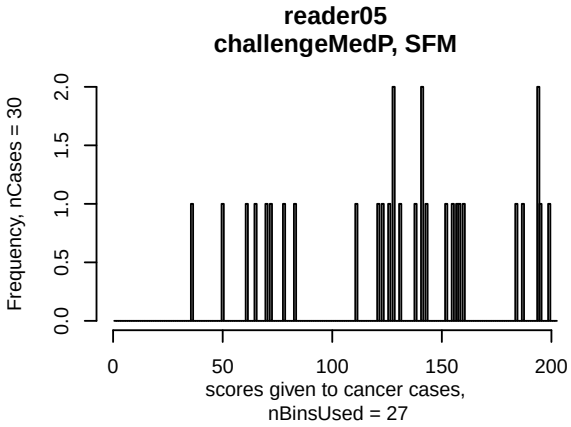


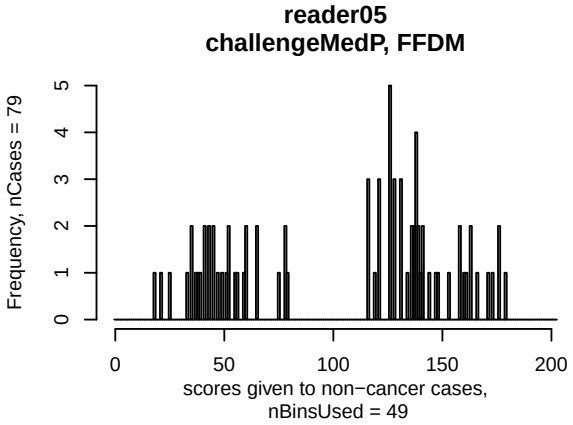
	AUC	se
FFDM	0.76	0.057
SFM	0.694	0.066
FFDM−SFM	0.066	0.066

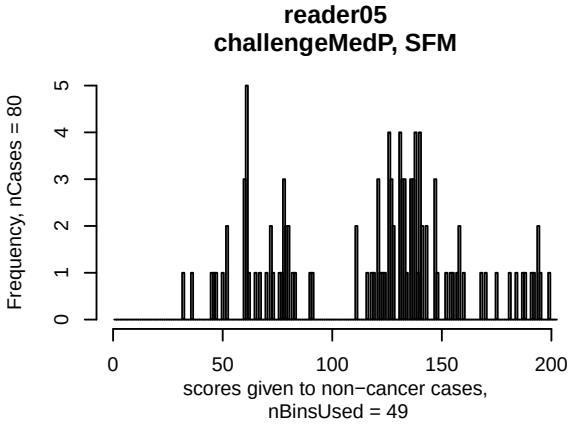
	Sens.	se
FFDM	0.76	0.057
SFM	0.694	0.066
FFDM−SFM	0.066	0.066

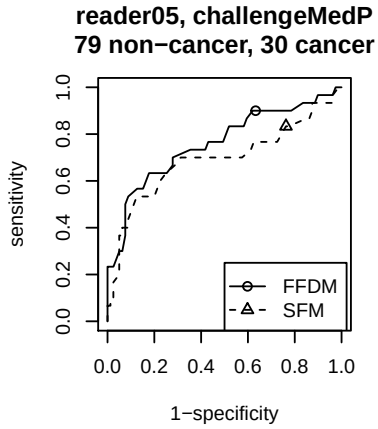
	Spec.	se
FFDM	0.76	0.057
SFM	0.694	0.066
FFDM−SFM	0.066	0.066







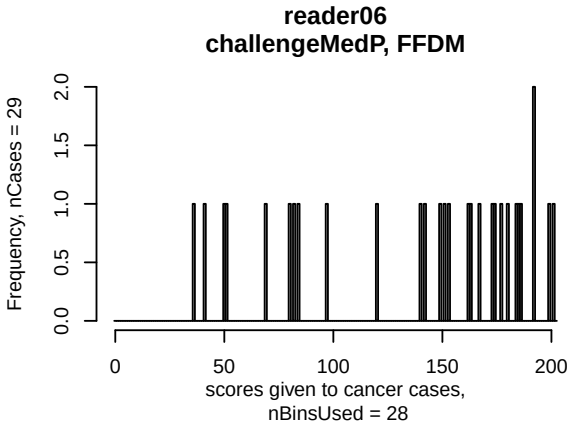


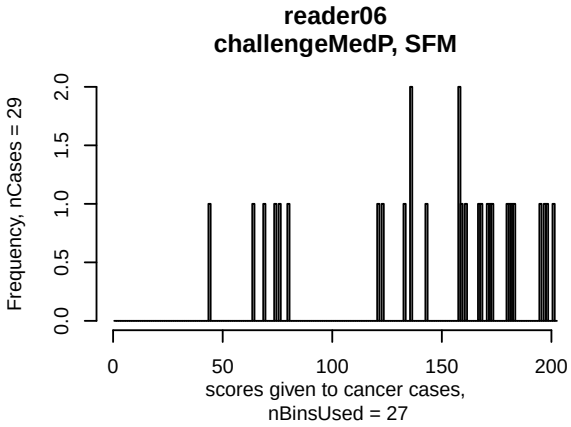


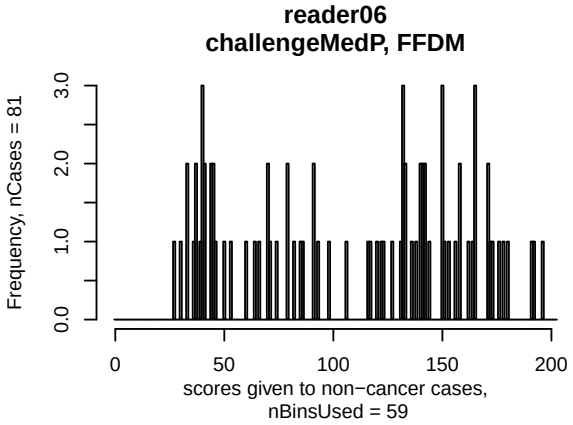
	AUC	se
FFDM	0.629	0.064
SFM	0.609	0.066
FFDM−SFM	0.02	0.069

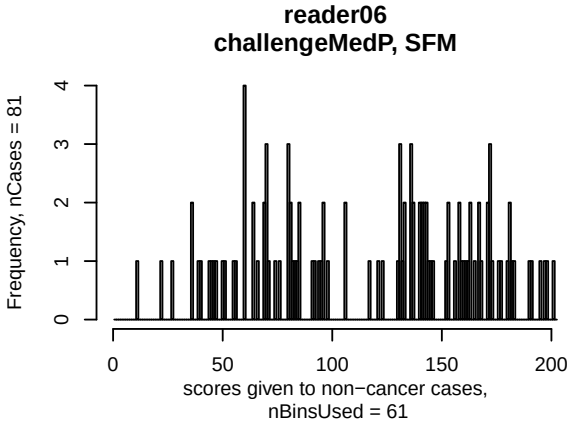
	Sens.	se
FFDM	0.629	0.064
SFM	0.609	0.066
FFDM−SFM	0.02	0.069

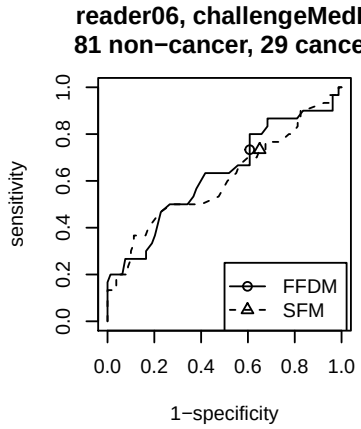
	Spec.	se
FFDM	0.629	0.064
SFM	0.609	0.066
FFDM−SFM	0.02	0.069







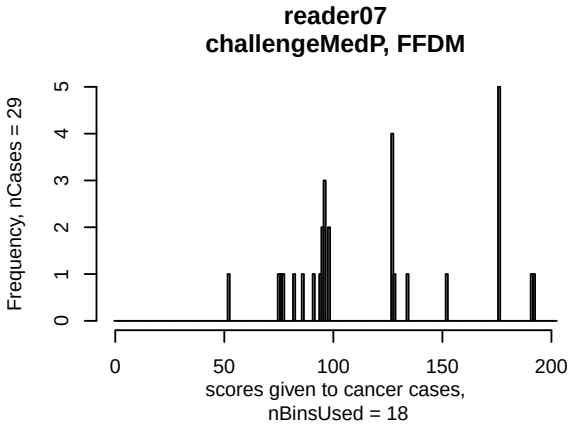


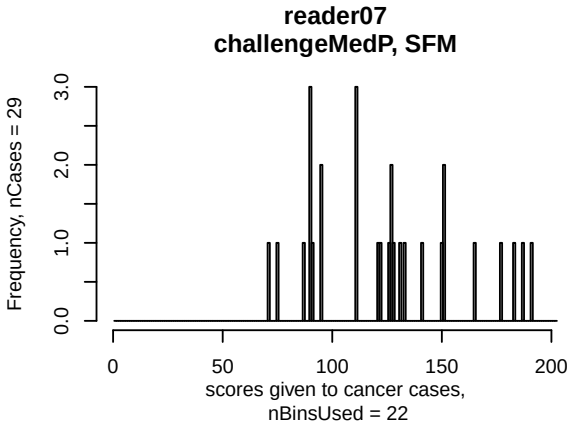


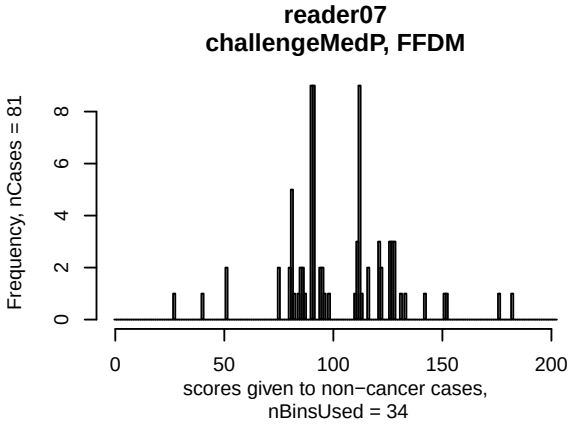
	AUC	se
FFDM	0.678	0.062
SFM	0.723	0.058
FFDM−SFM	−0.045	0.068

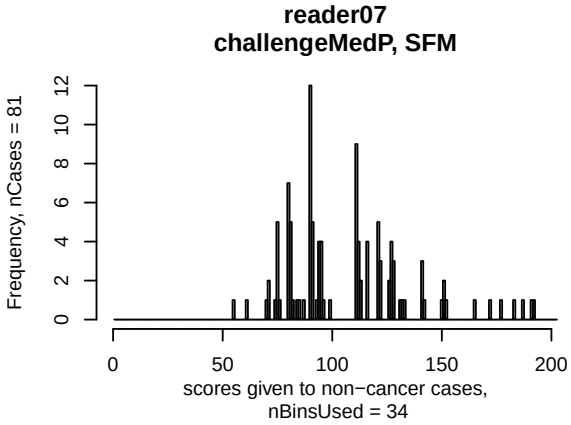
	Sens.	se
FFDM	0.678	0.062
SFM	0.723	0.058
FFDM−SFM	−0.045	0.068

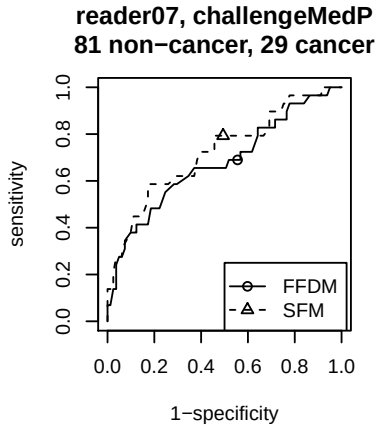
	Spec.	se
FFDM	0.678	0.062
SFM	0.723	0.058
FFDM−SFM	−0.045	0.068







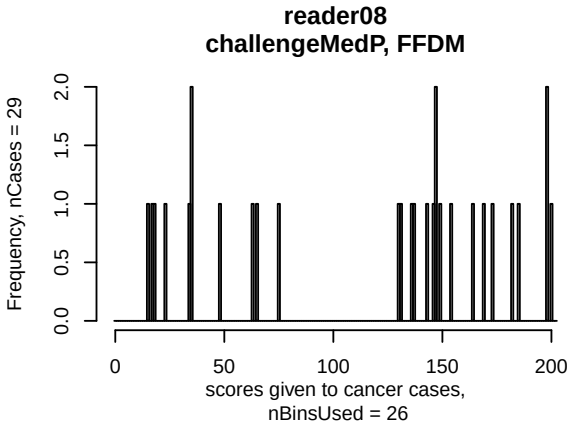


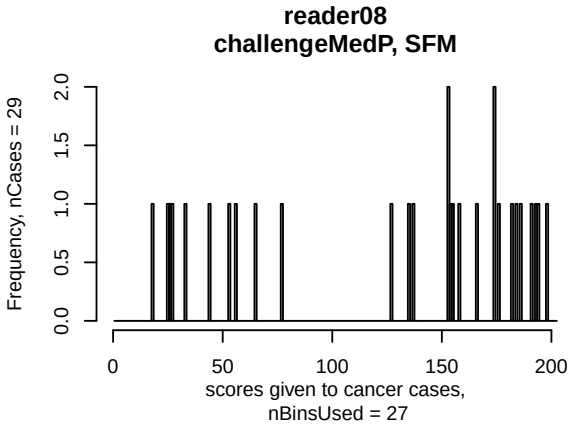


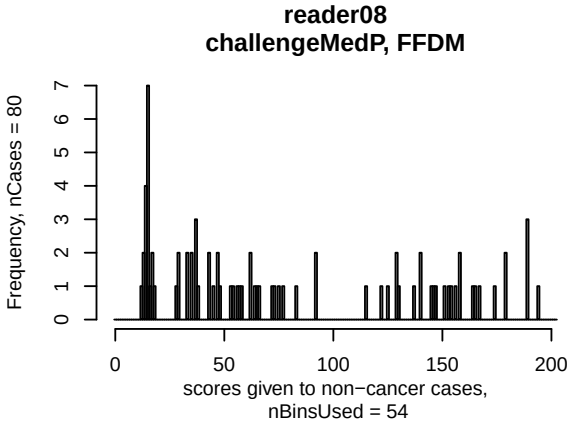
	AUC	se
FFDM	0.633	0.067
SFM	0.712	0.059
FFDM−SFM	−0.08	0.069

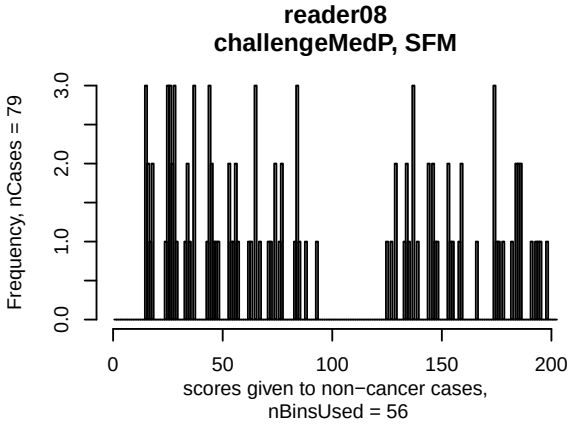
	Sens.	se
FFDM	0.633	0.067
SFM	0.712	0.059
FFDM−SFM	−0.08	0.069

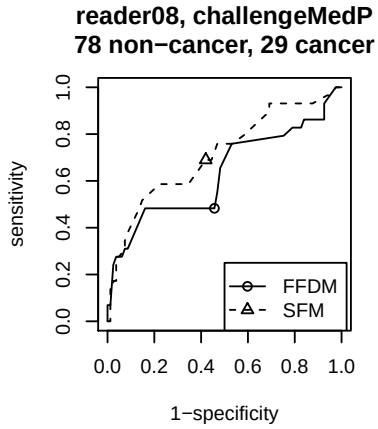
	Spec.	se
FFDM	0.633	0.067
SFM	0.712	0.059
FFDM−SFM	−0.08	0.069







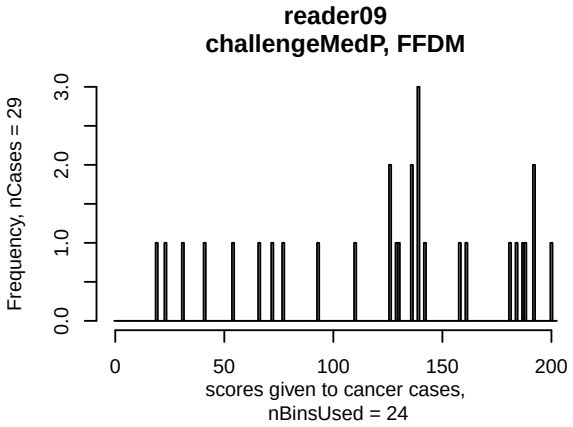


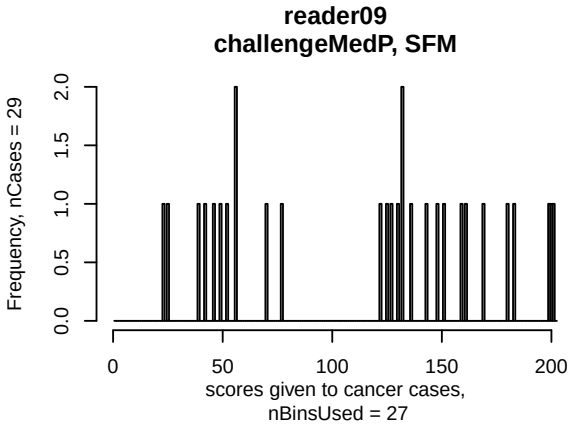


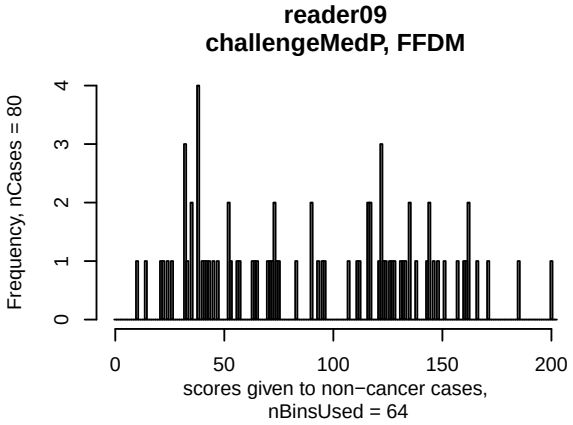
	AUC	se
FFDM	0.656	0.06
SFM	0.689	0.063
FFDM−SFM	−0.033	0.071

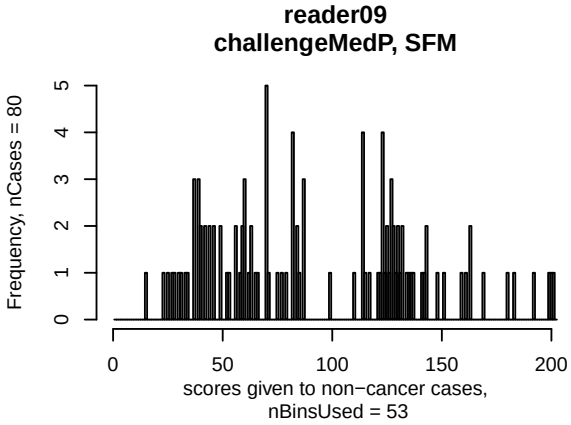
	Sens.	se
FFDM	0.656	0.06
SFM	0.689	0.063
FFDM−SFM	−0.033	0.071

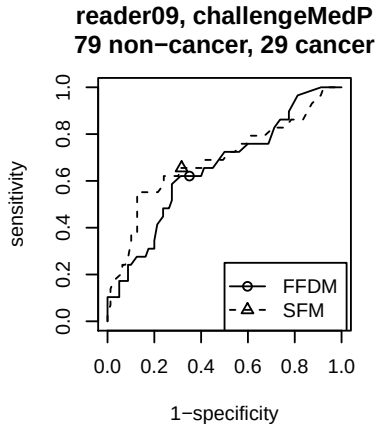
	Spec.	se
FFDM	0.656	0.06
SFM	0.689	0.063
FFDM−SFM	−0.033	0.071







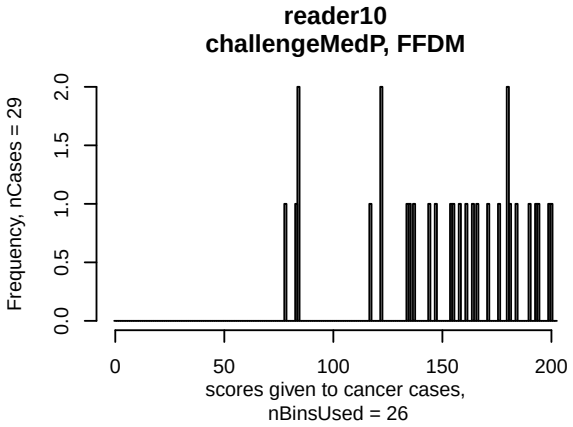


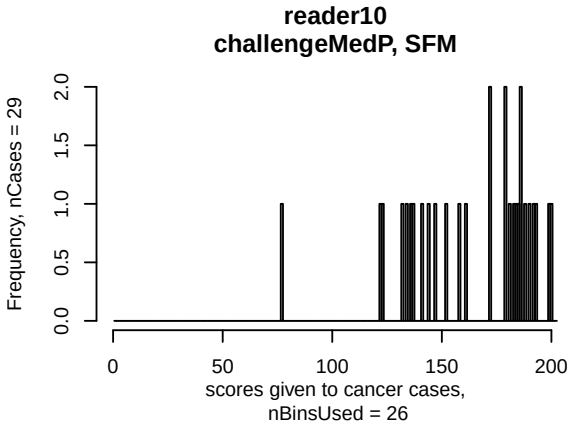


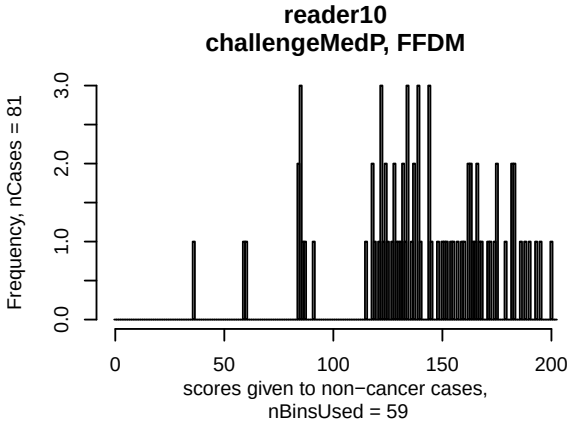
	AUC	se
FFDM	0.67	0.063
SFM	0.656	0.07
FFDM−SFM	0.014	0.082

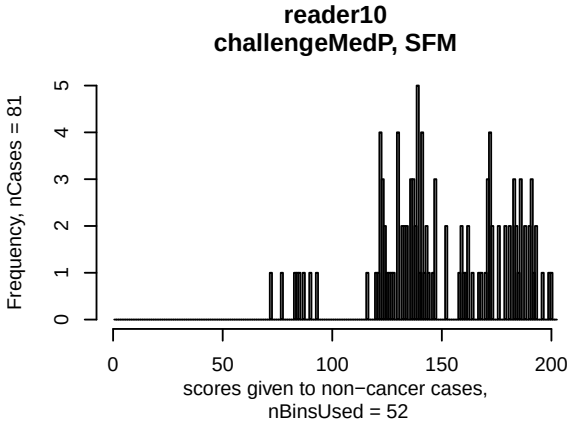
	Sens.	se
FFDM	0.67	0.063
SFM	0.656	0.07
FFDM−SFM	0.014	0.082

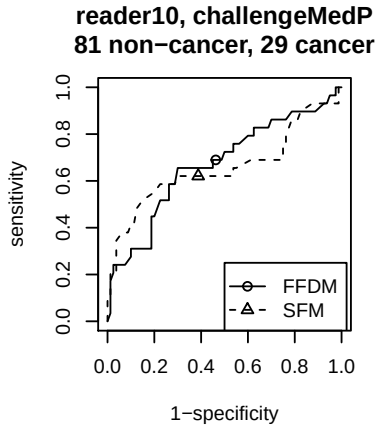
	Spec.	se
FFDM	0.67	0.063
SFM	0.656	0.07
FFDM−SFM	0.014	0.082







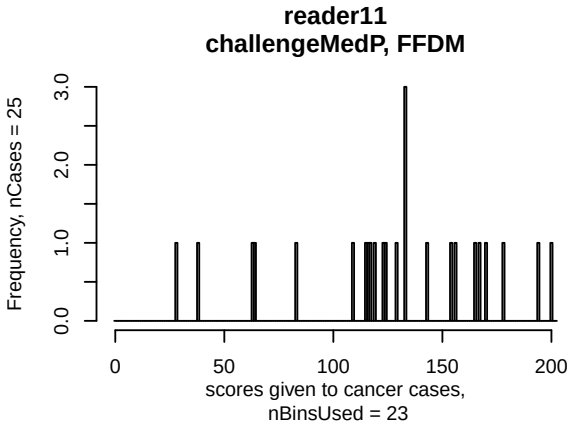


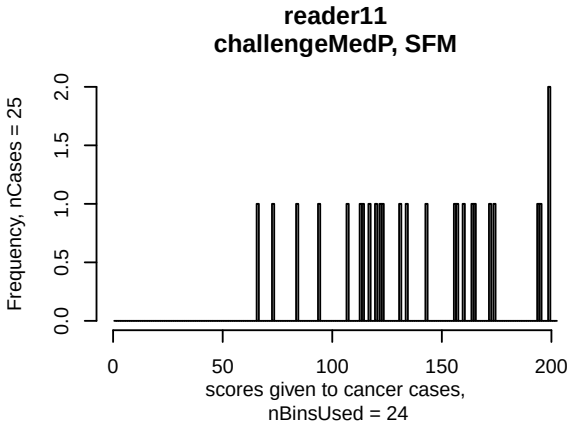


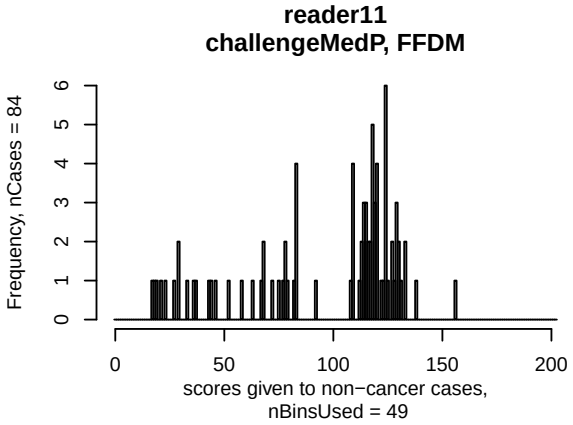
	AUC	se
FFDM	0.599	0.067
SFM	0.684	0.06
FFDM−SFM	−0.085	0.078

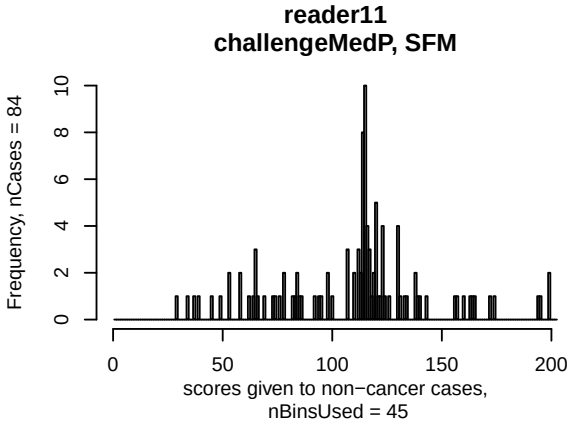
	Sens.	se
FFDM	0.599	0.067
SFM	0.684	0.06
FFDM−SFM	−0.085	0.078

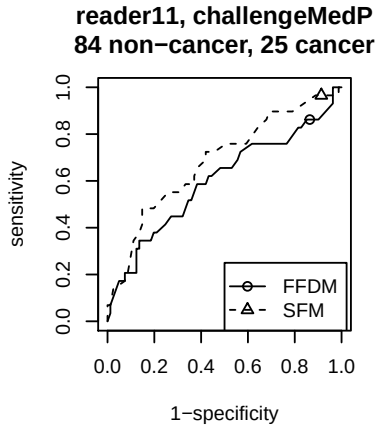
	Spec.	se
FFDM	0.599	0.067
SFM	0.684	0.06
FFDM−SFM	−0.085	0.078







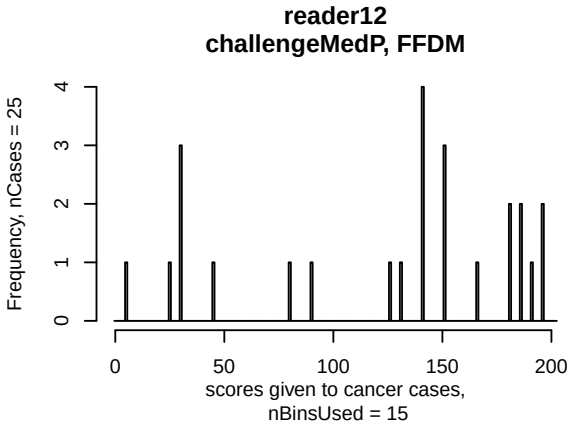


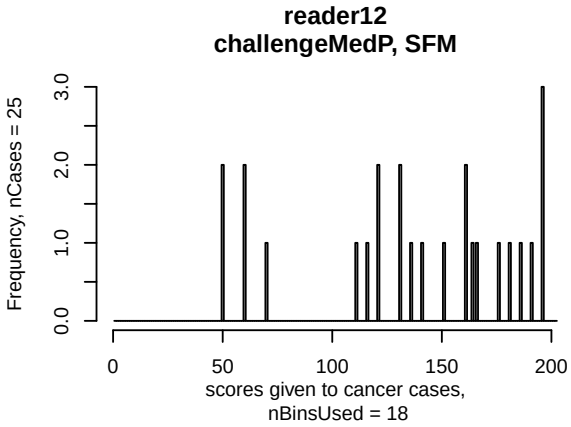


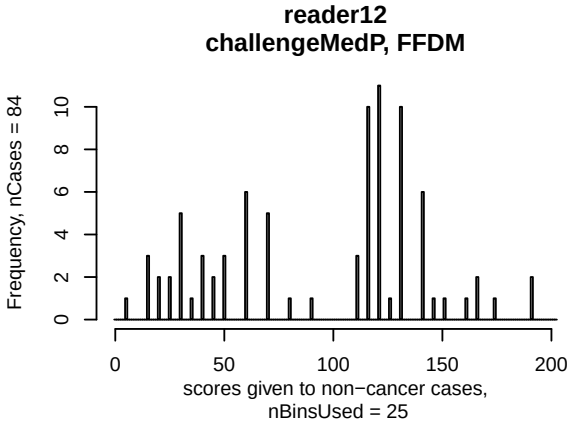
	AUC	se
FFDM	0.721	0.068
SFM	0.77	0.062
FFDM−SFM	−0.049	0.067

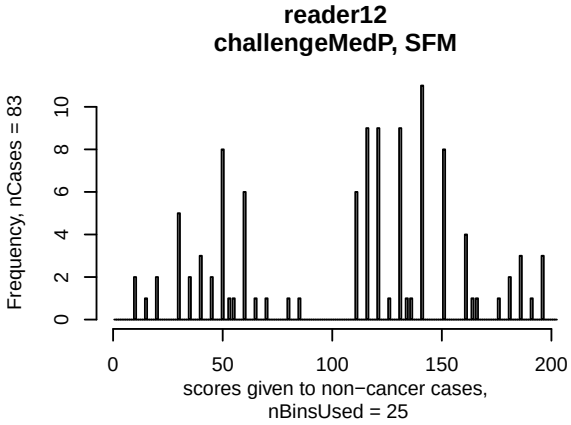
	Sens.	se
FFDM	0.721	0.068
SFM	0.77	0.062
FFDM−SFM	−0.049	0.067

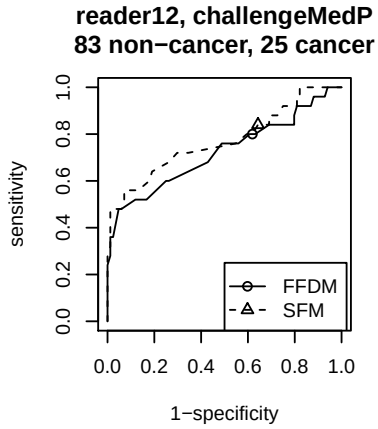
	Spec.	se
FFDM	0.721	0.068
SFM	0.77	0.062
FFDM−SFM	−0.049	0.067







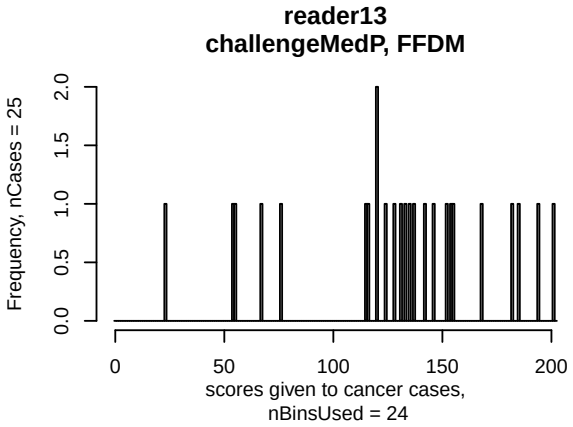


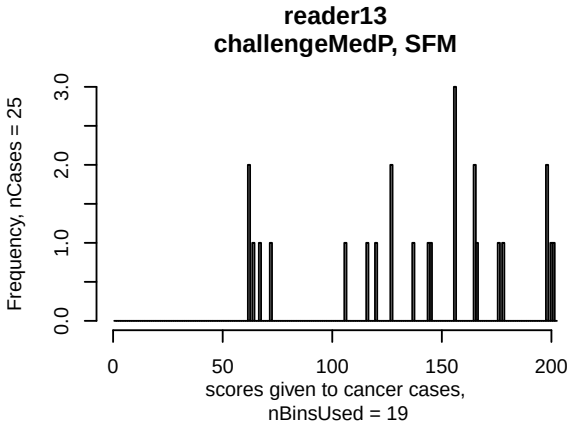


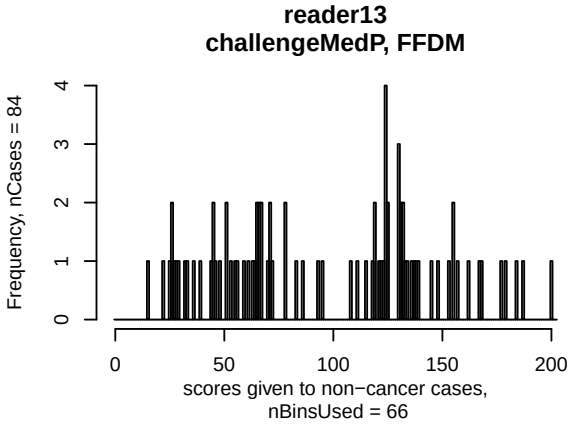
	AUC	se
FFDM	0.682	0.075
SFM	0.725	0.06
FFDM−SFM	−0.042	0.072

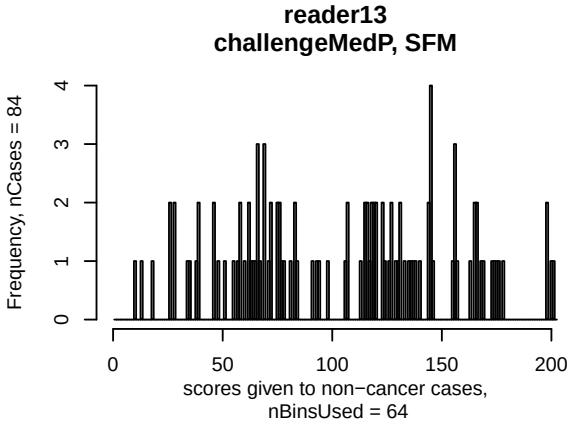
	Sens.	se
FFDM	0.682	0.075
SFM	0.725	0.06
FFDM−SFM	−0.042	0.072

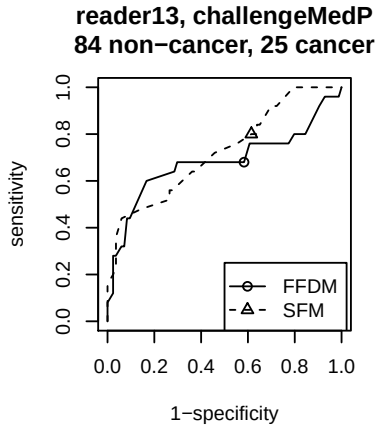
	Spec.	se
FFDM	0.682	0.075
SFM	0.725	0.06
FFDM−SFM	−0.042	0.072







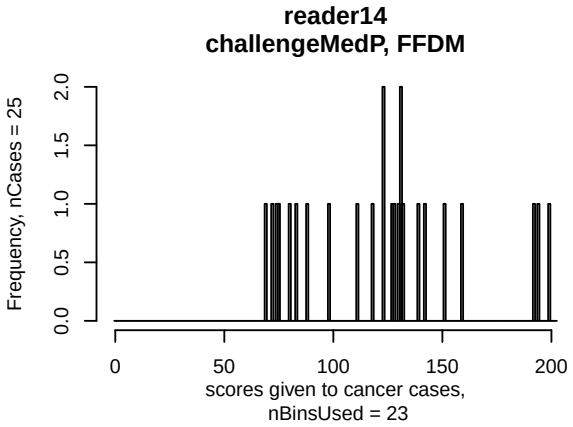


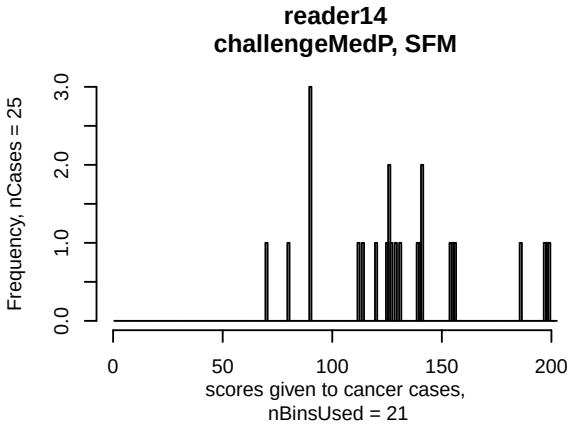


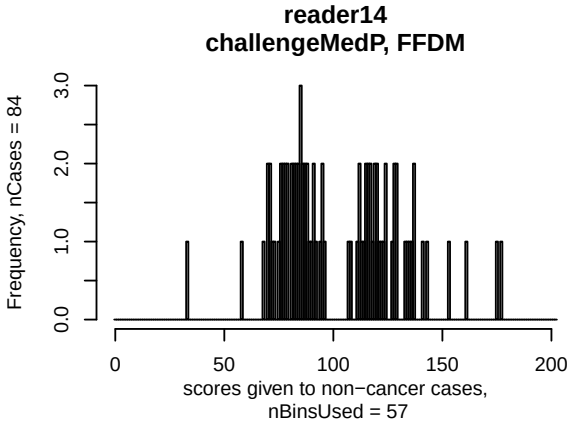
	AUC	se
FFDM	0.682	0.06
SFM	0.749	0.058
FFDM−SFM	−0.066	0.064

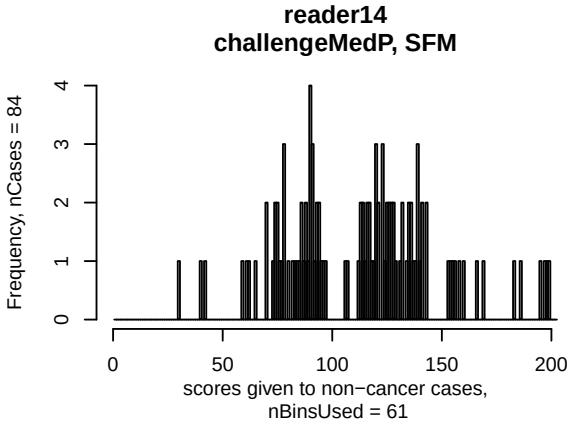
	Sens.	se
FFDM	0.682	0.06
SFM	0.749	0.058
FFDM−SFM	−0.066	0.064

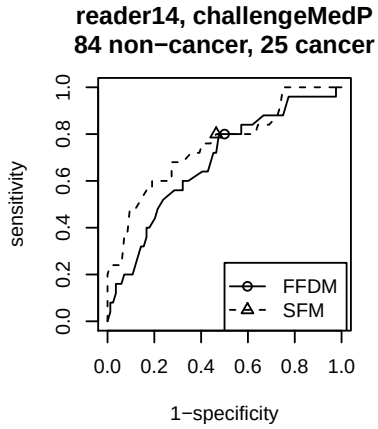
	Spec.	se
FFDM	0.682	0.06
SFM	0.749	0.058
FFDM−SFM	−0.066	0.064







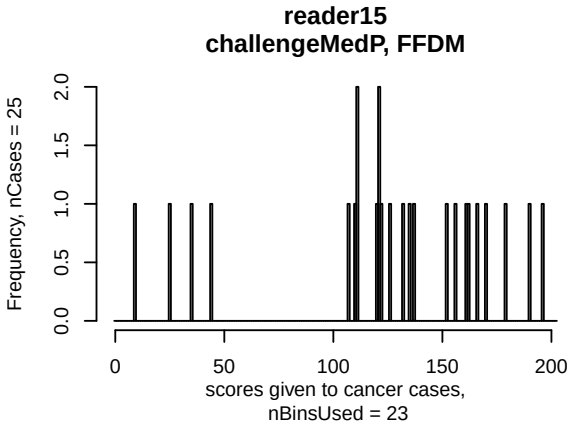


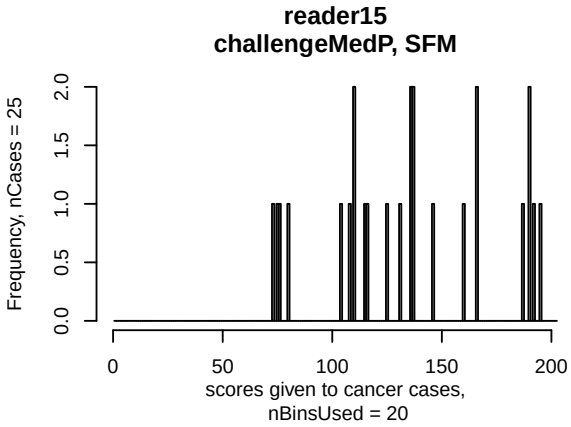


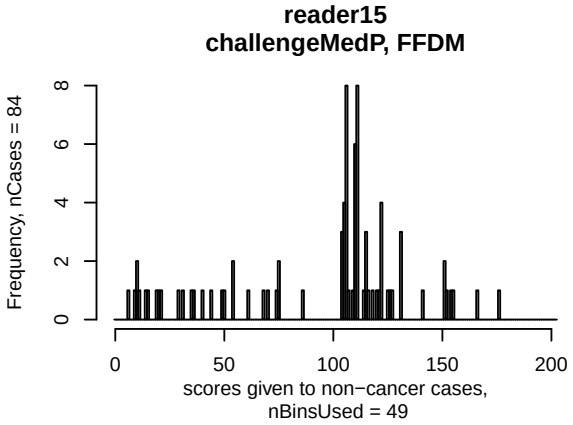
	AUC	se
FFDM	0.655	0.071
SFM	0.71	0.06
FFDM−SFM	−0.055	0.077

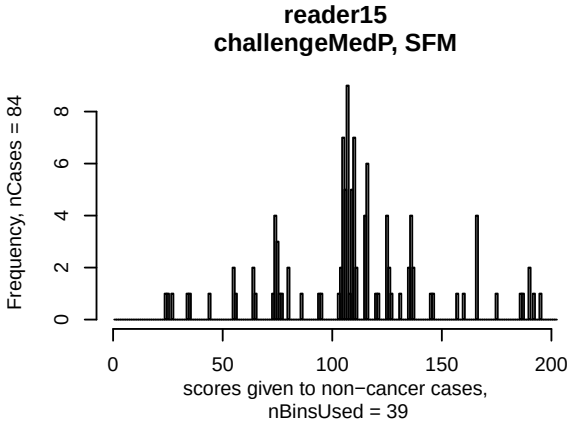
	Sens.	se
FFDM	0.655	0.071
SFM	0.71	0.06
FFDM−SFM	−0.055	0.077

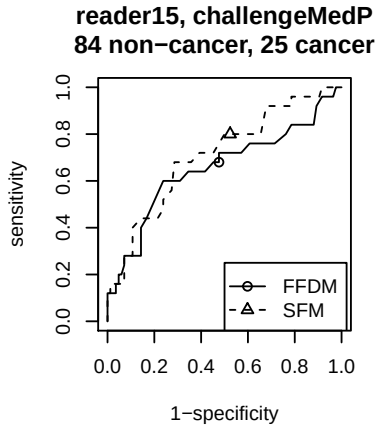
	Spec.	se
FFDM	0.655	0.071
SFM	0.71	0.06
FFDM−SFM	−0.055	0.077







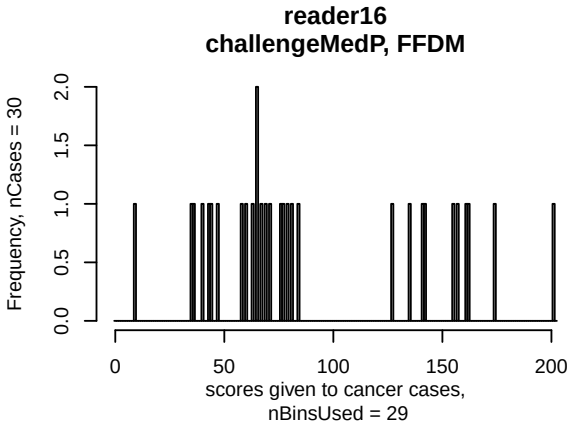


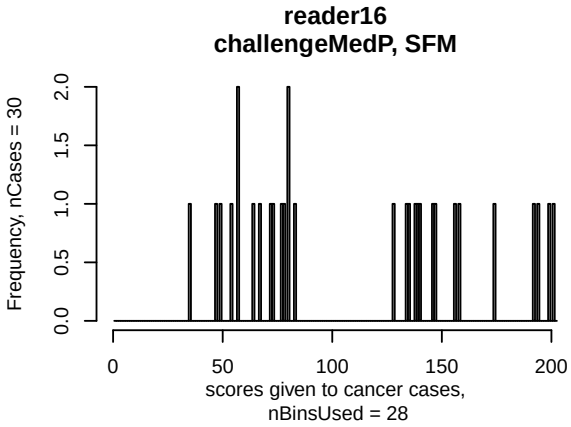


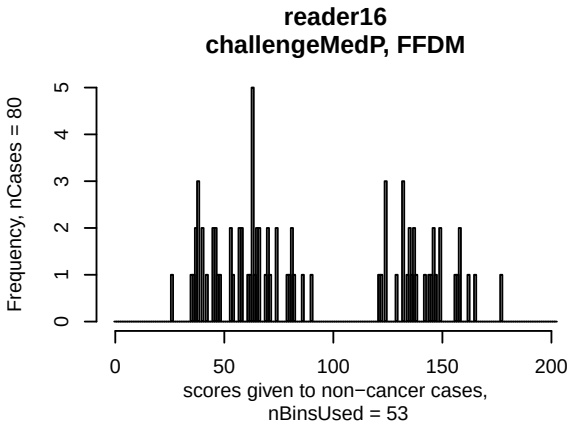
	AUC	se
FFDM	0.735	0.065
SFM	0.744	0.063
FFDM−SFM	−0.009	0.07

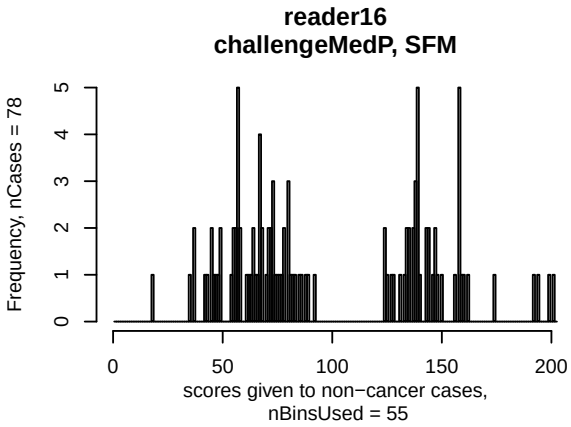
	Sens.	se
FFDM	0.735	0.065
SFM	0.744	0.063
FFDM−SFM	−0.009	0.07

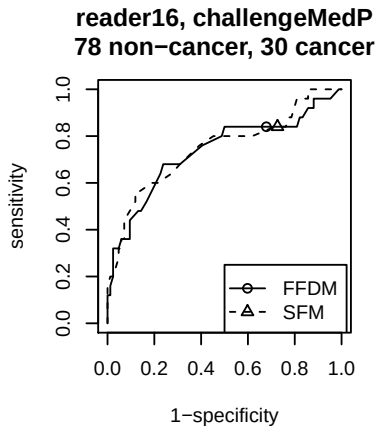
	Spec.	se
FFDM	0.735	0.065
SFM	0.744	0.063
FFDM−SFM	−0.009	0.07







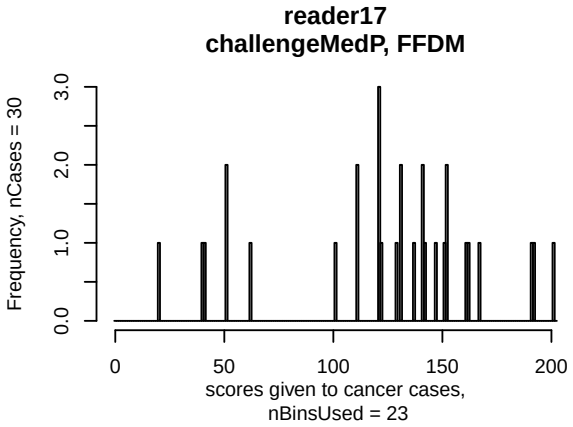


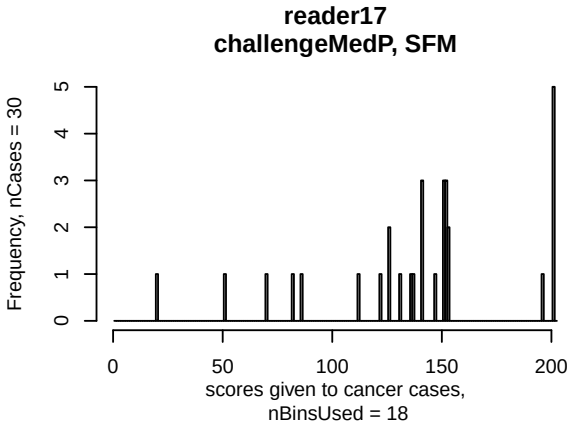


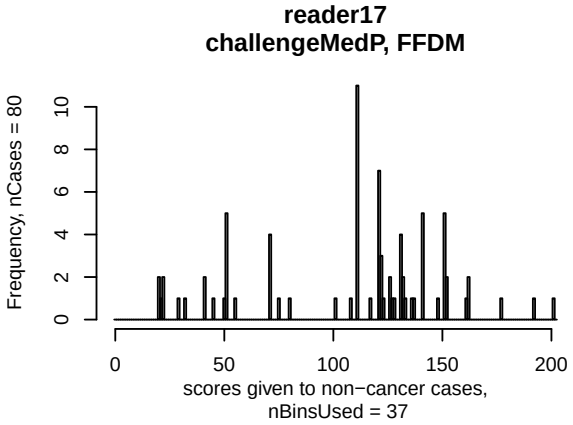
	AUC	se
FFDM	0.512	0.065
SFM	0.597	0.064
FFDM−SFM	−0.085	0.098

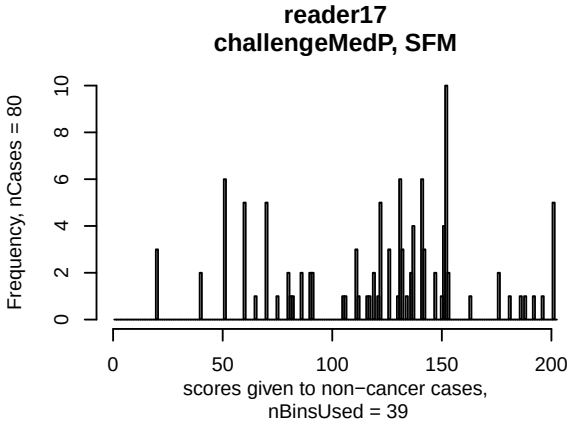
	Sens.	se
FFDM	0.512	0.065
SFM	0.597	0.064
FFDM−SFM	−0.085	0.098

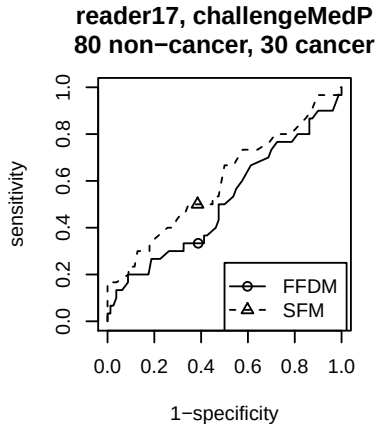
	Spec.	se
FFDM	0.512	0.065
SFM	0.597	0.064
FFDM−SFM	−0.085	0.098







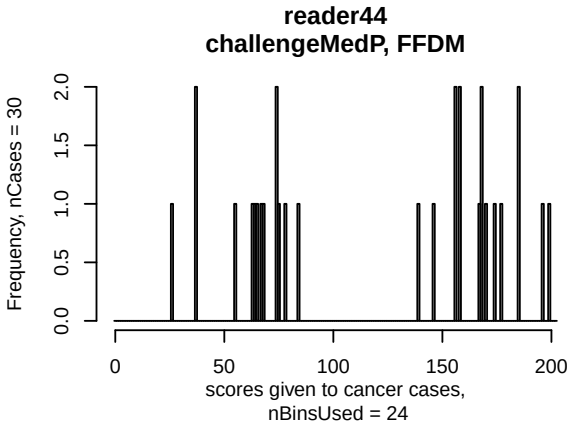


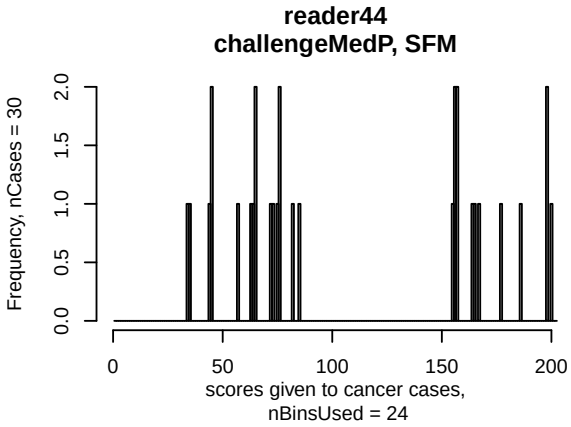


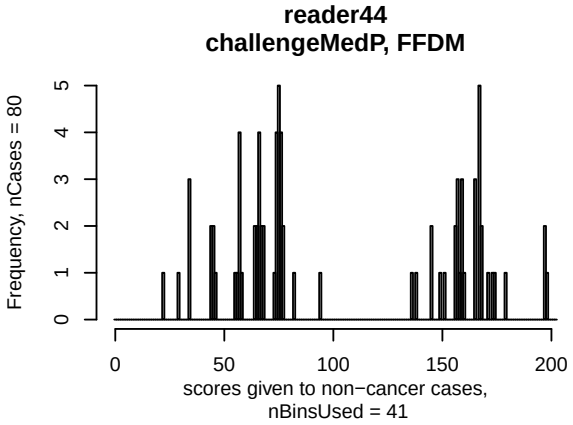
	AUC	se
FFDM	0.612	0.064
SFM	0.689	0.059
FFDM−SFM	−0.077	0.08

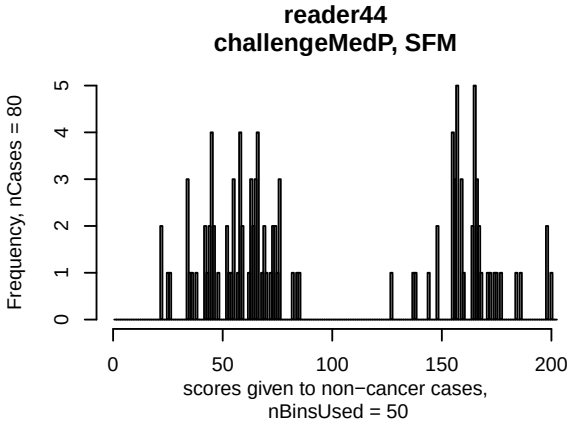
	Sens.	se
FFDM	0.612	0.064
SFM	0.689	0.059
FFDM−SFM	−0.077	0.08

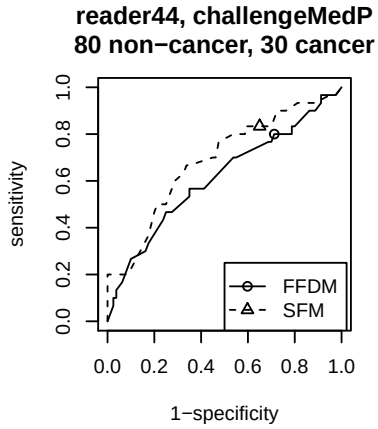
	Spec.	se
FFDM	0.612	0.064
SFM	0.689	0.059
FFDM−SFM	−0.077	0.08







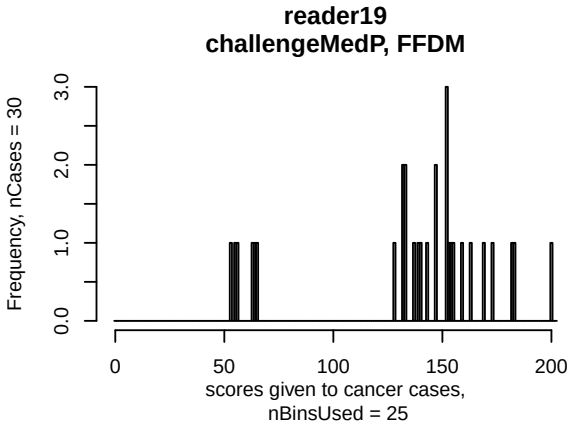


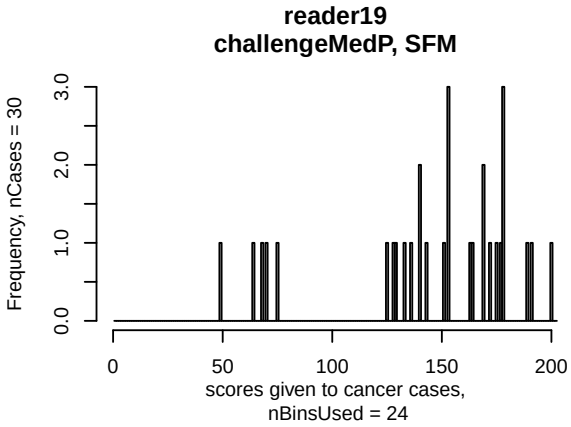


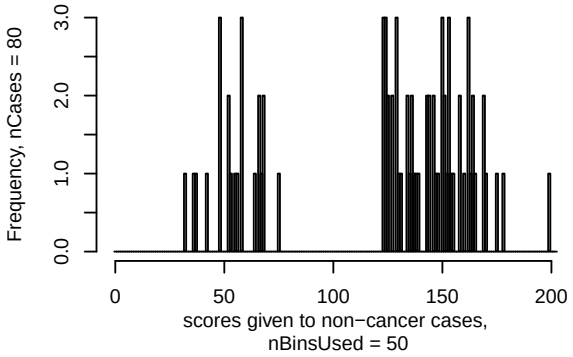
	AUC	se
FFDM	0.581	0.065
SFM	0.593	0.062
FFDM−SFM	−0.012	0.074

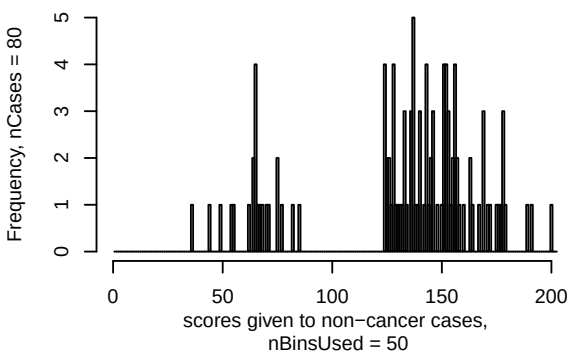
	Sens.	se
FFDM	0.581	0.065
SFM	0.593	0.062
FFDM−SFM	−0.012	0.074

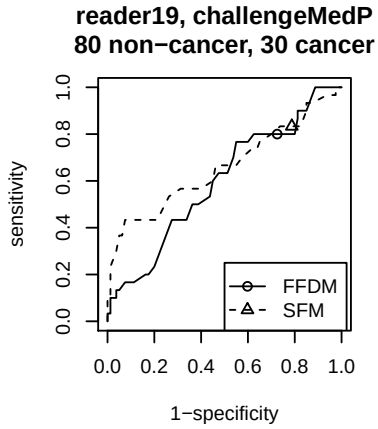
	Spec.	se
FFDM	0.581	0.065
SFM	0.593	0.062
FFDM−SFM	−0.012	0.074







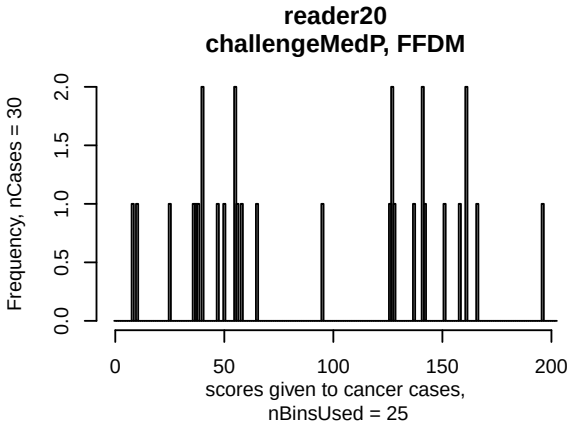


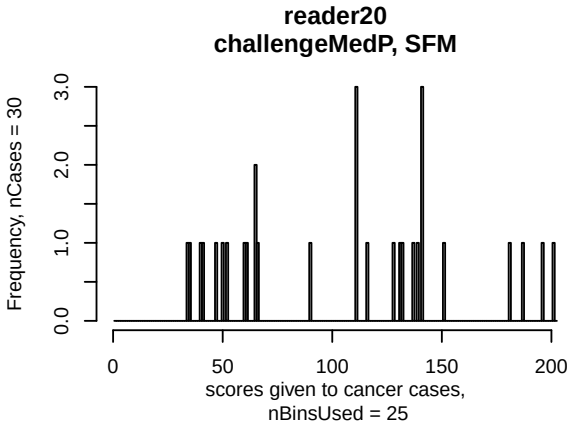


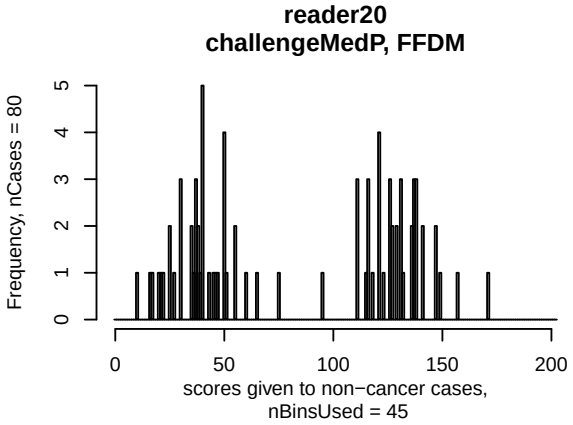
	AUC	se
FFDM	0.595	0.06
SFM	0.659	0.066
FFDM−SFM	−0.065	0.078

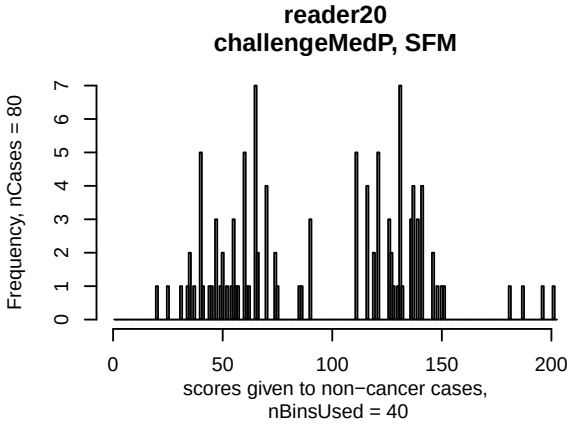
	Sens.	se
FFDM	0.595	0.06
SFM	0.659	0.066
FFDM−SFM	−0.065	0.078

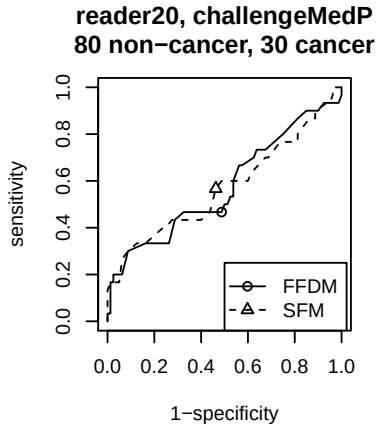
	Spec.	se
FFDM	0.595	0.06
SFM	0.659	0.066
FFDM−SFM	−0.065	0.078









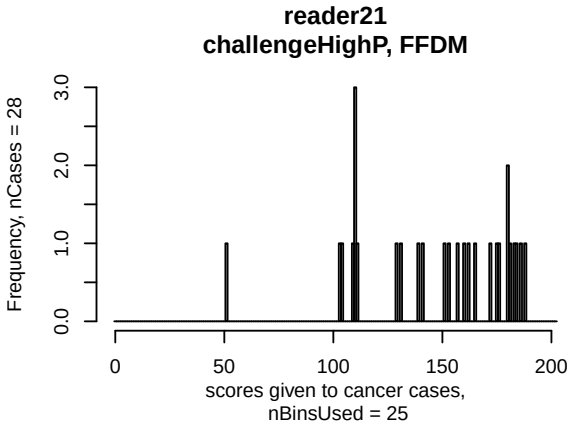


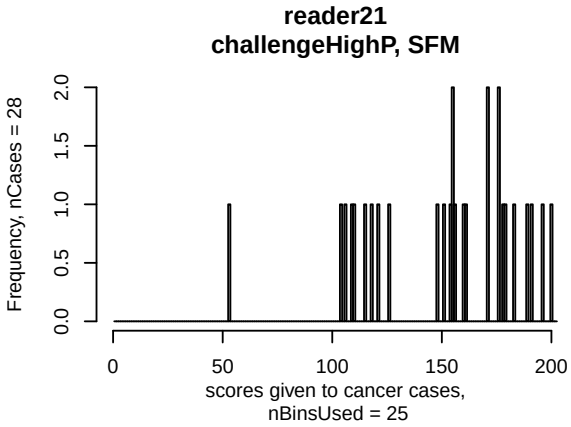
	AUC	se
FFDM	0.578	0.066
SFM	0.577	0.068
FFDM−SFM	0.001	0.087

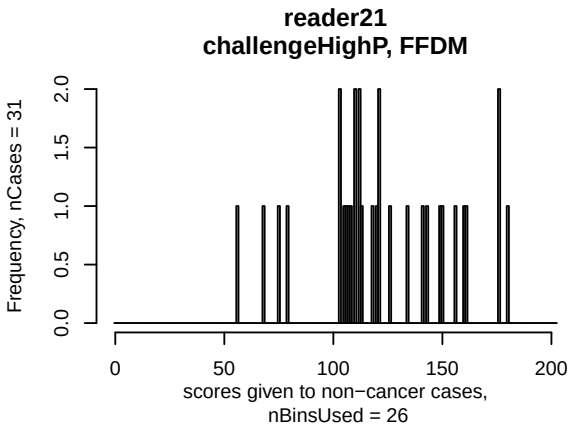
	Sens.	se
FFDM	0.578	0.066
SFM	0.577	0.068
FFDM−SFM	0.001	0.087

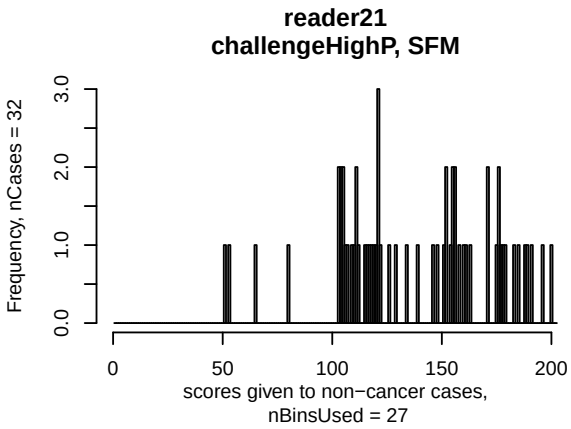
	Spec.	se
FFDM	0.578	0.066
SFM	0.577	0.068
FFDM−SFM	0.001	0.087

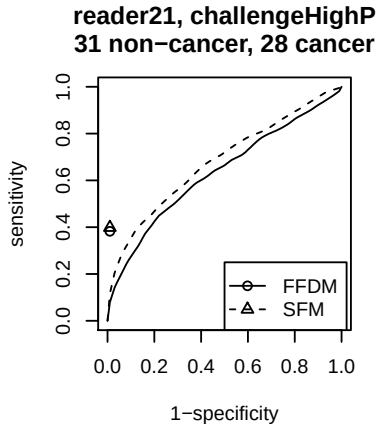
challengeHighP







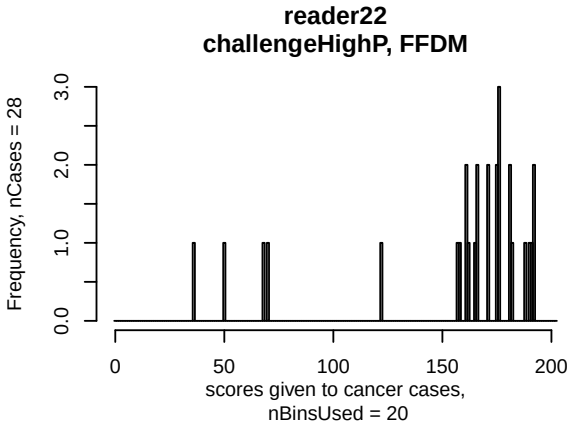


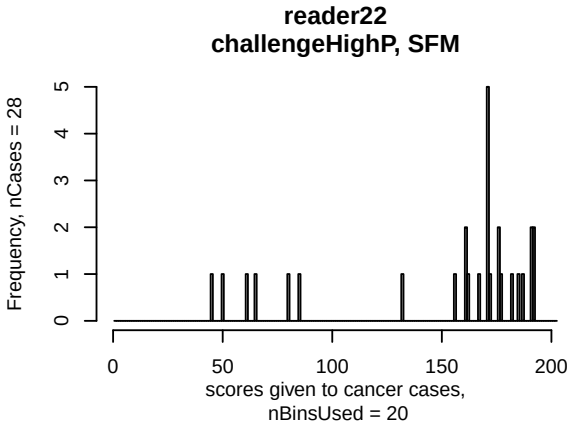


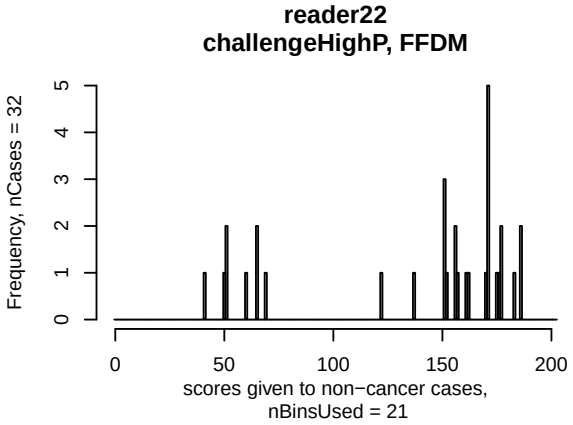
	AUC	se
FFDM	0.7	0.069
SFM	0.7	0.069
FFDM−SFM	0.001	0.063

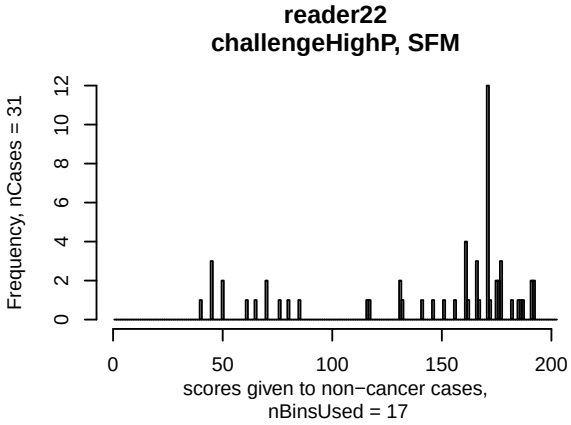
	Sens.	se
FFDM	0.7	0.069
SFM	0.7	0.069
FFDM−SFM	0.001	0.063

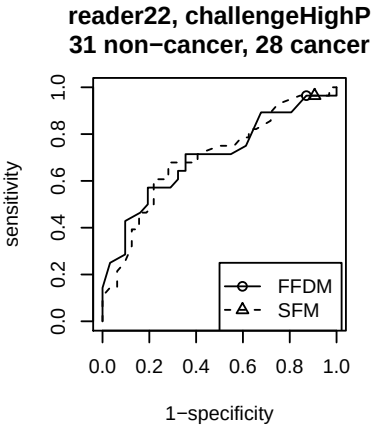
	Spec.	se
FFDM	0.7	0.069
SFM	0.7	0.069
FFDM−SFM	0.001	0.063







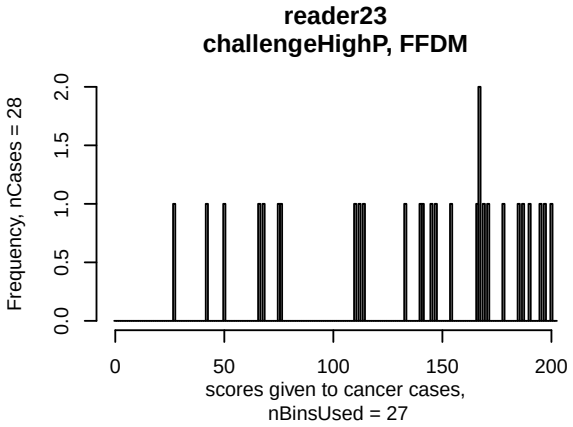


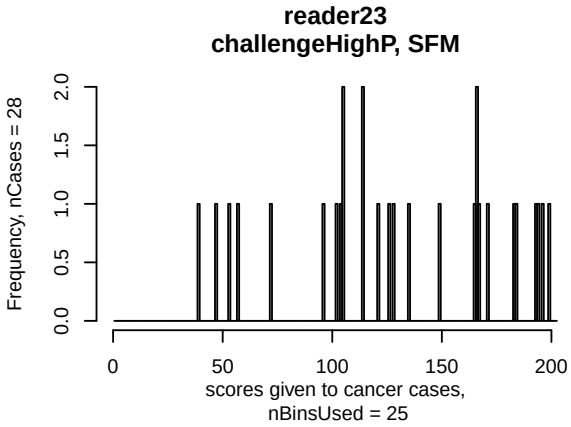


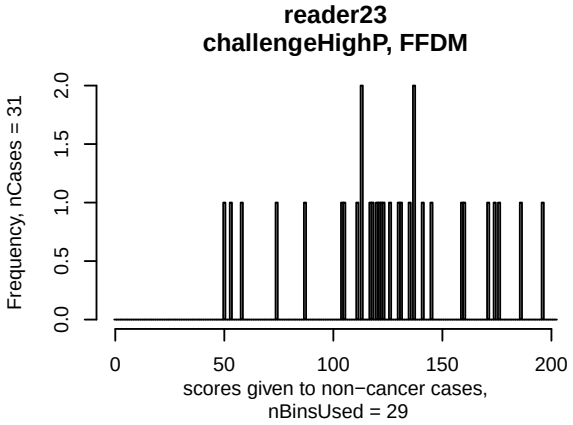
	AUC	se
FFDM	0.66	0.071
SFM	0.641	0.073
FFDM−SFM	0.02	0.087

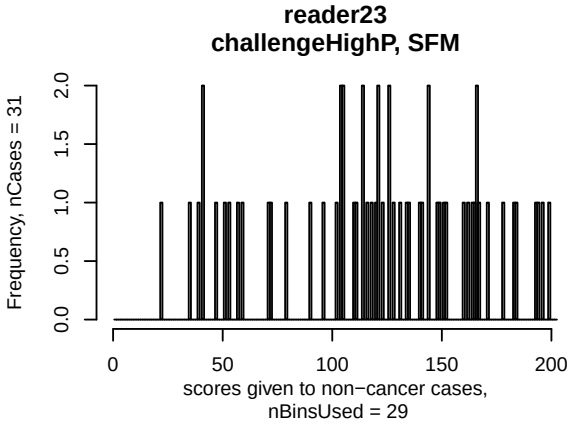
	Sens.	se
FFDM	0.66	0.071
SFM	0.641	0.073
FFDM−SFM	0.02	0.087

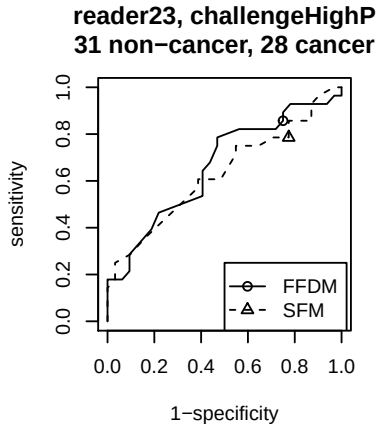
	Spec.	se
FFDM	0.66	0.071
SFM	0.641	0.073
FFDM−SFM	0.02	0.087







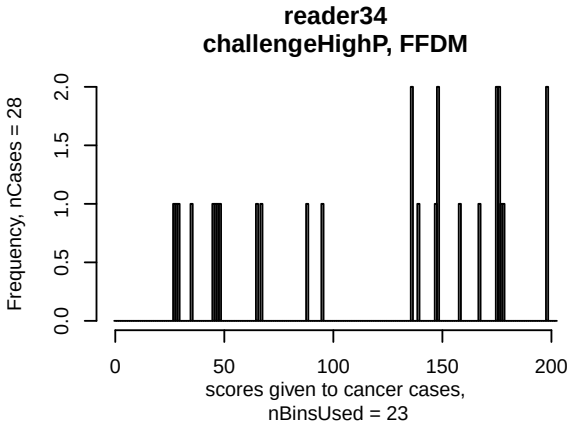


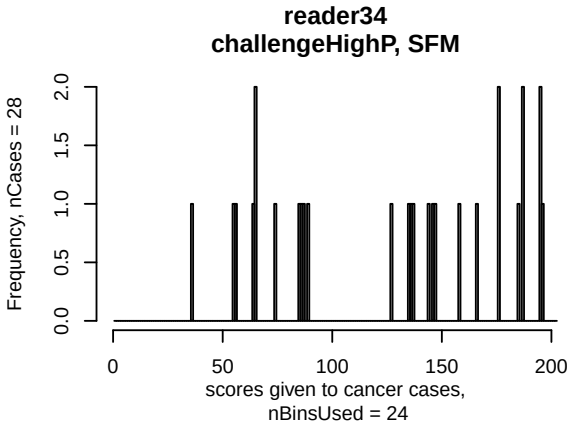


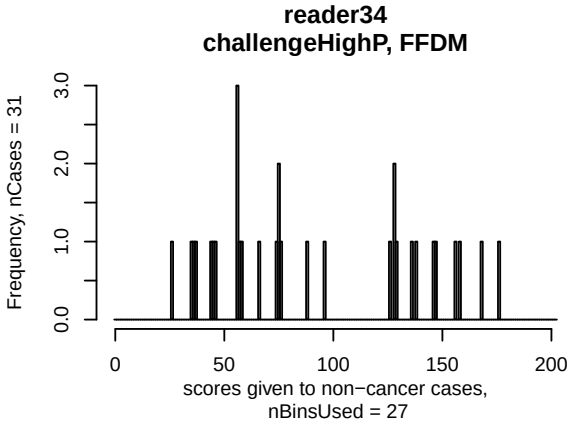
	AUC	se
FFDM	0.593	0.079
SFM	0.607	0.076
FFDM−SFM	−0.013	0.081

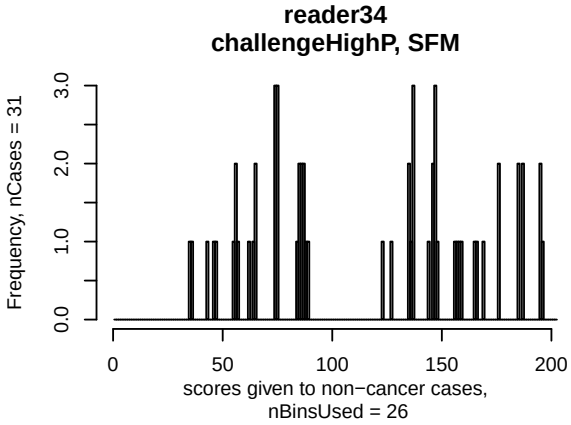
	Sens.	se
FFDM	0.593	0.079
SFM	0.607	0.076
FFDM−SFM	−0.013	0.081

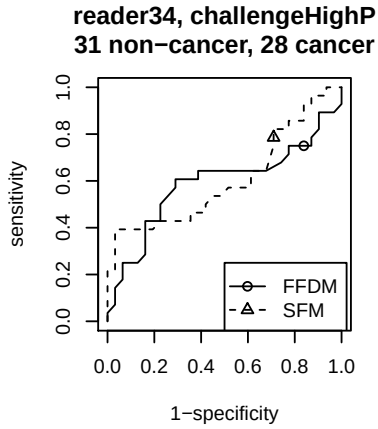
	Spec.	se
FFDM	0.593	0.079
SFM	0.607	0.076
FFDM−SFM	−0.013	0.081







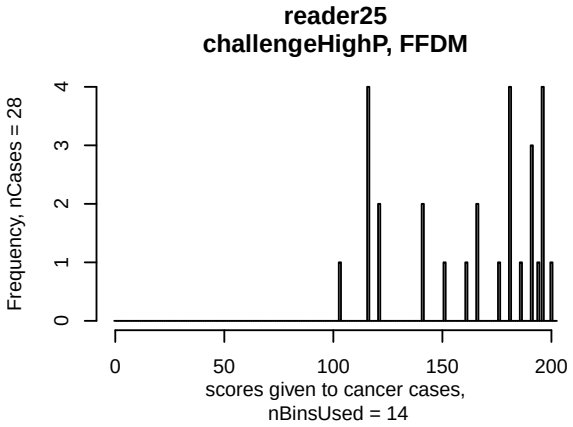


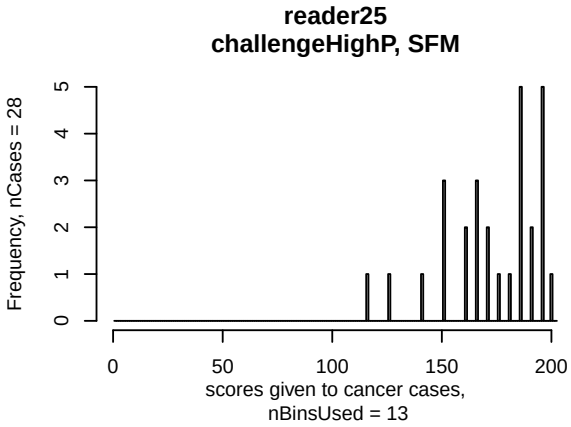


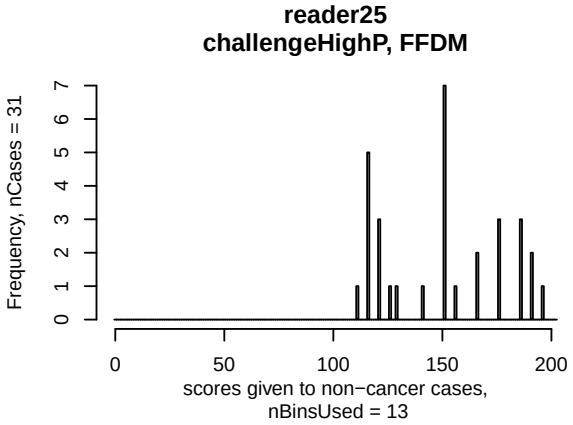
	AUC	se
FFDM	0.629	0.077
SFM	0.624	0.074
FFDM−SFM	0.005	0.078

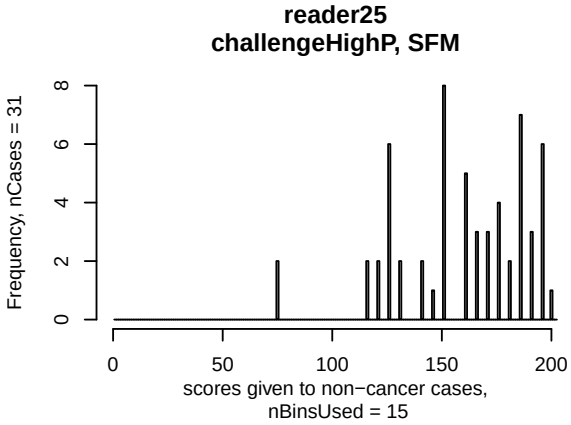
	Sens.	se
FFDM	0.629	0.077
SFM	0.624	0.074
FFDM−SFM	0.005	0.078

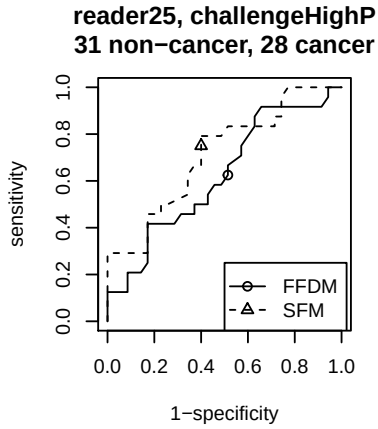
	Spec.	se
FFDM	0.629	0.077
SFM	0.624	0.074
FFDM−SFM	0.005	0.078







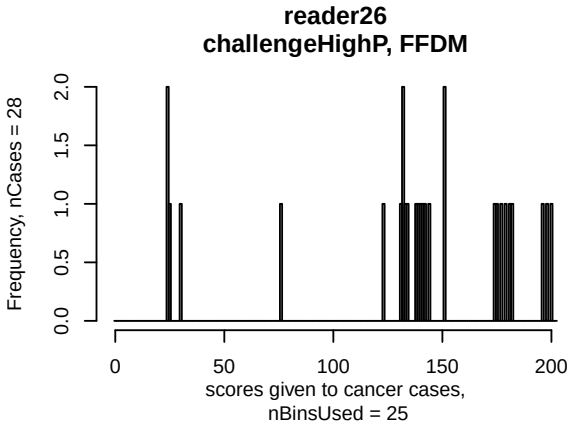


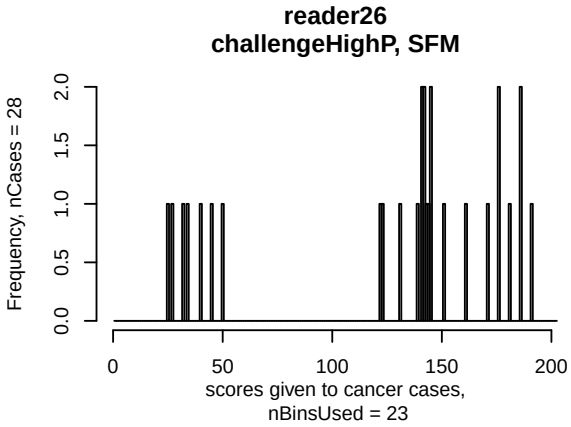


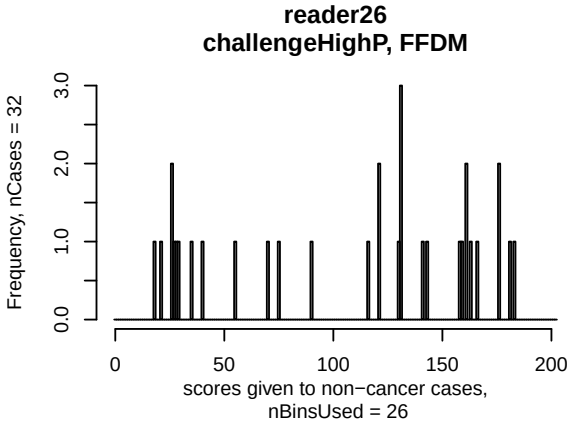
	AUC	se
FFDM	0.633	0.075
SFM	0.757	0.062
FFDM−SFM	−0.124	0.077

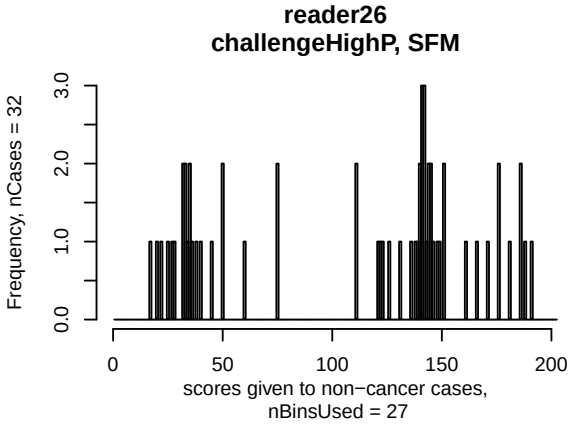
	Sens.	se
FFDM	0.633	0.075
SFM	0.757	0.062
FFDM−SFM	−0.124	0.077

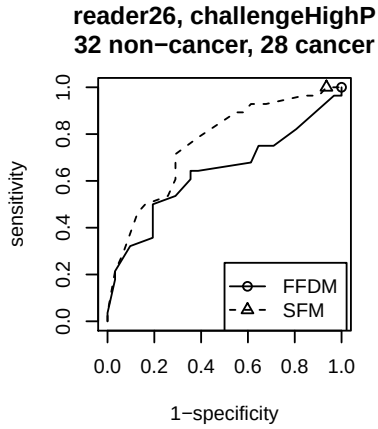
	Spec.	se
FFDM	0.633	0.075
SFM	0.757	0.062
FFDM−SFM	−0.124	0.077







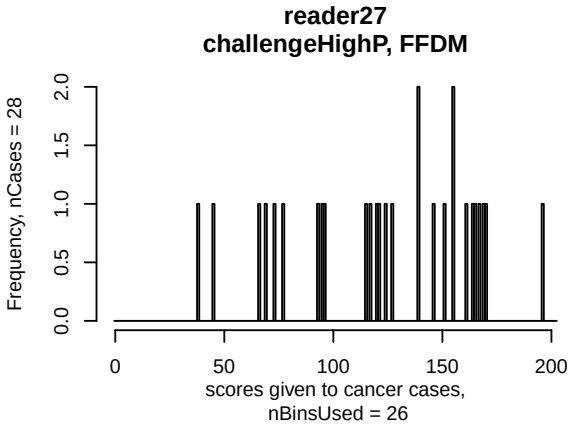


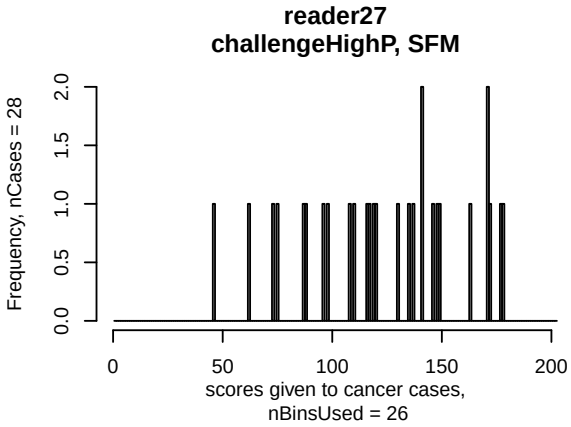


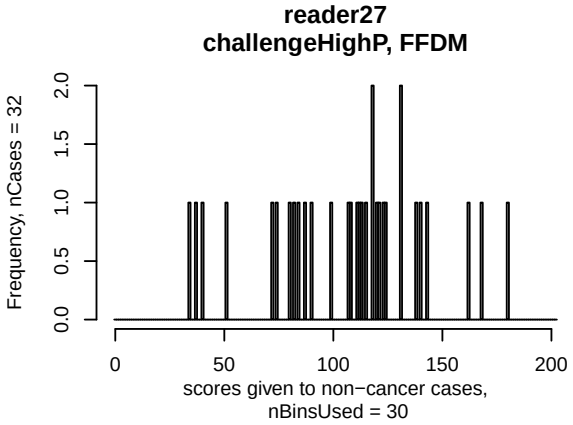
	AUC	se
FFDM	0.648	0.073
SFM	0.673	0.071
FFDM−SFM	−0.025	0.073

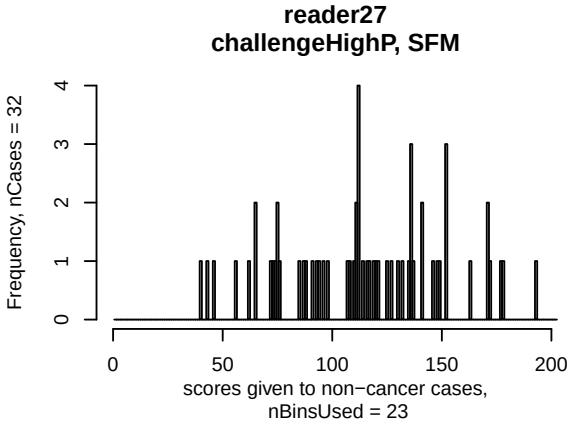
	Sens.	se
FFDM	0.648	0.073
SFM	0.673	0.071
FFDM−SFM	−0.025	0.073

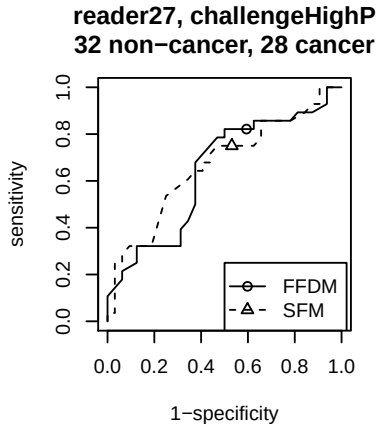
	Spec.	se
FFDM	0.648	0.073
SFM	0.673	0.071
FFDM−SFM	−0.025	0.073







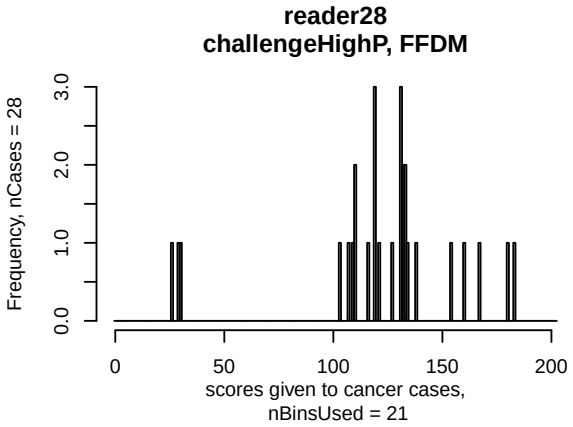


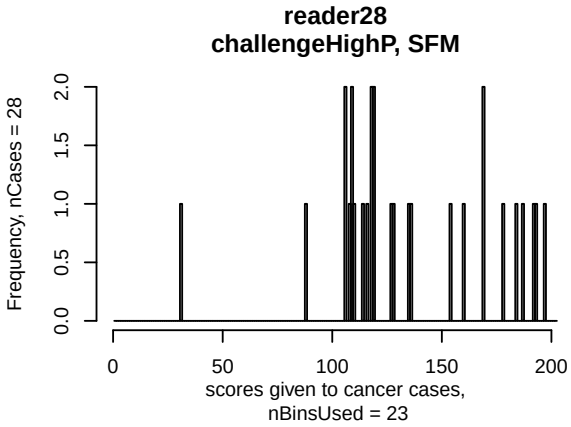


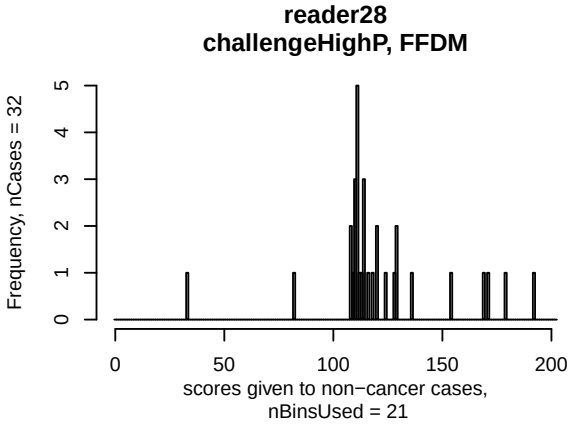
	AUC	se
FFDM	0.631	0.074
SFM	0.647	0.072
FFDM−SFM	−0.016	0.08

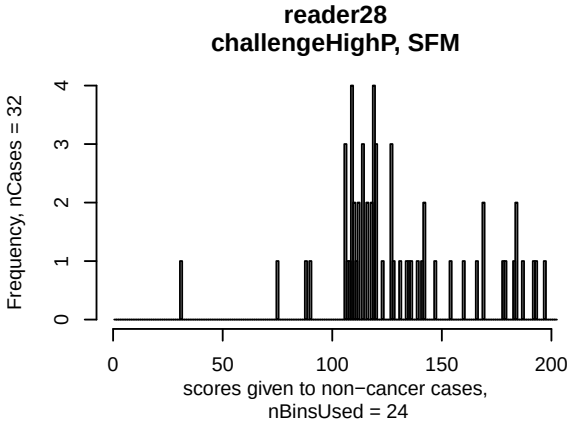
	Sens.	se
FFDM	0.631	0.074
SFM	0.647	0.072
FFDM−SFM	−0.016	0.08

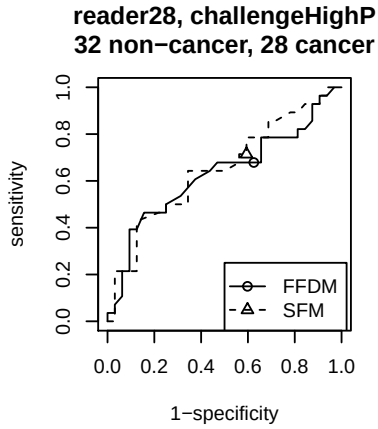
	Spec.	se
FFDM	0.631	0.074
SFM	0.647	0.072
FFDM−SFM	−0.016	0.08







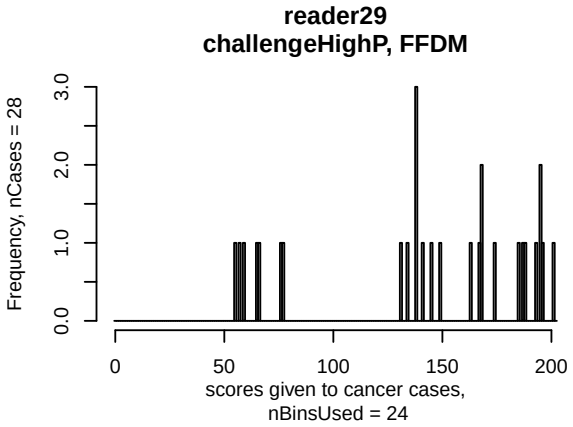


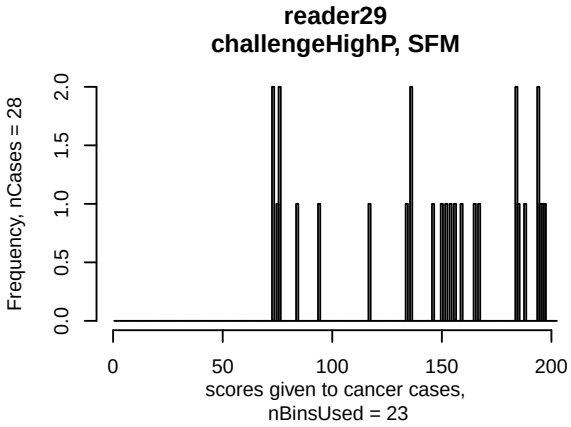


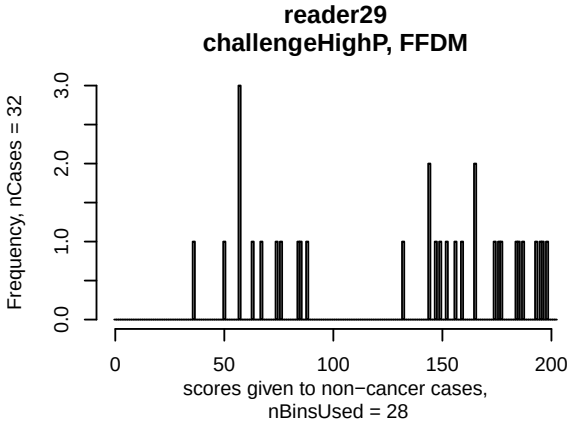
	AUC	se
FFDM	0.586	0.078
SFM	0.551	0.077
FFDM−SFM	0.036	0.103

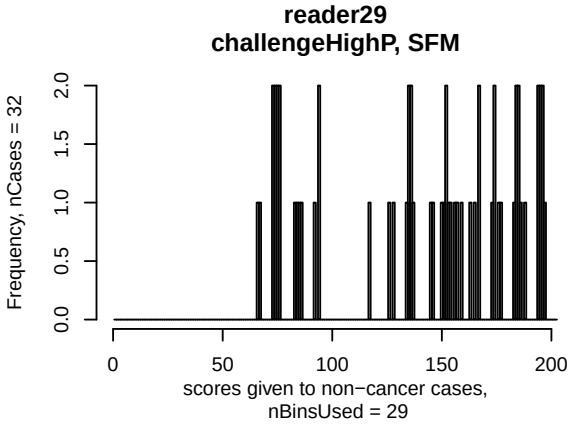
	Sens.	se
FFDM	0.586	0.078
SFM	0.551	0.077
FFDM−SFM	0.036	0.103

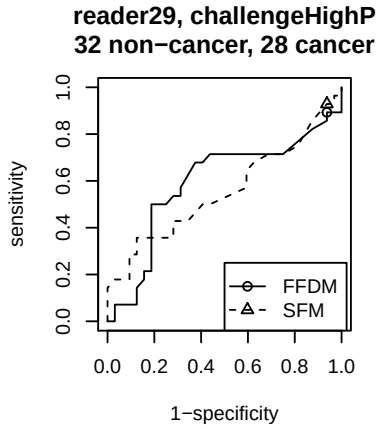
	Spec.	se
FFDM	0.586	0.078
SFM	0.551	0.077
FFDM−SFM	0.036	0.103







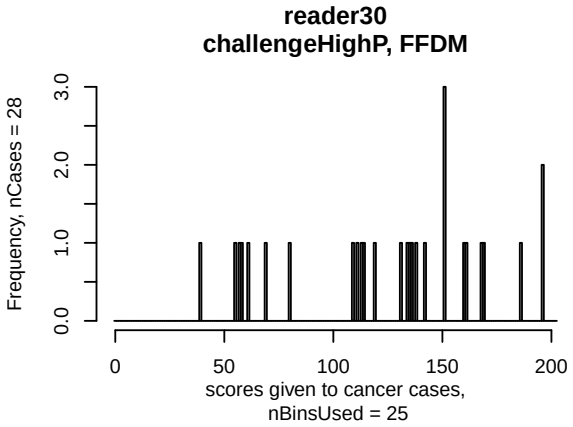


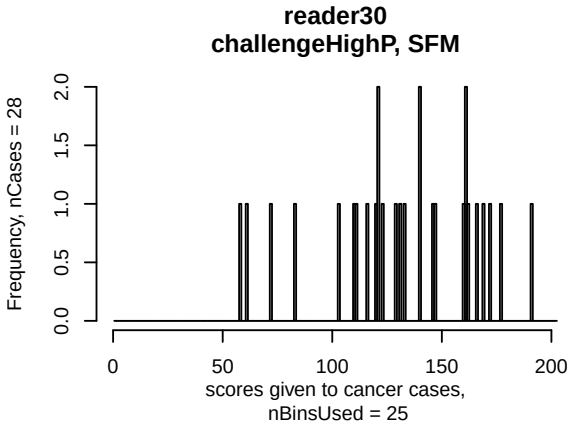


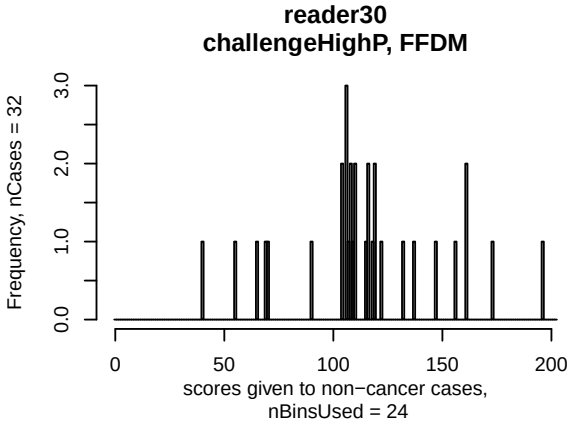
	AUC	se
FFDM	0.546	0.075
SFM	0.561	0.075
FFDM−SFM	−0.015	0.089

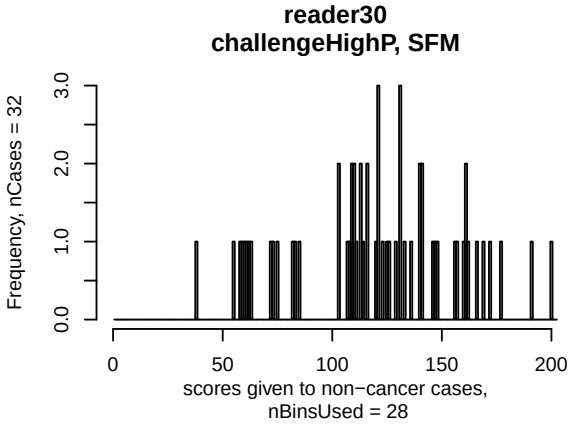
	Sens.	se
FFDM	0.546	0.075
SFM	0.561	0.075
FFDM−SFM	−0.015	0.089

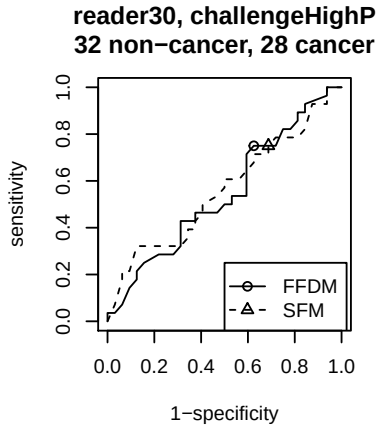
	Spec.	se
FFDM	0.546	0.075
SFM	0.561	0.075
FFDM−SFM	−0.015	0.089







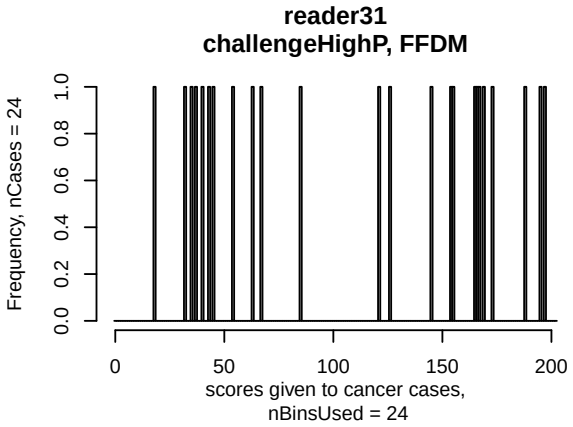


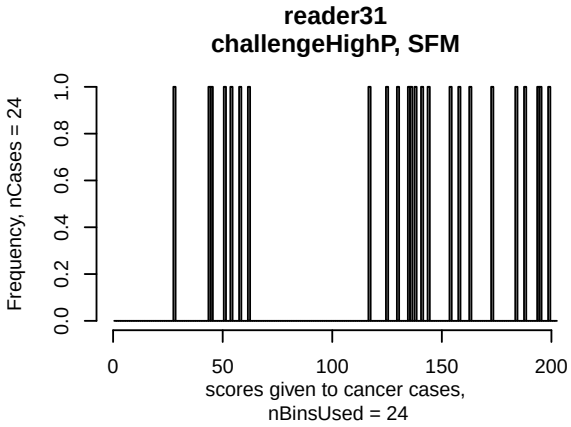


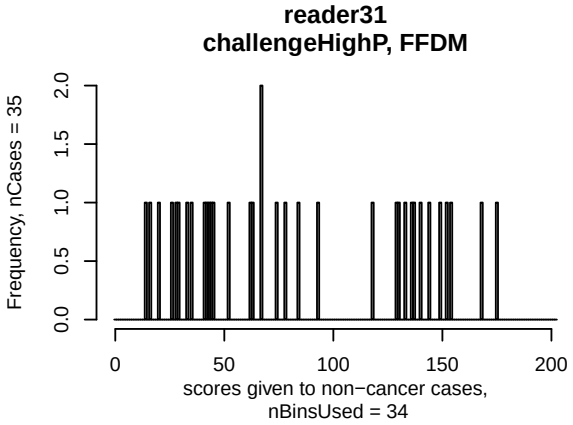
	AUC	se
FFDM	0.61	0.077
SFM	0.696	0.069
FFDM−SFM	−0.086	0.081

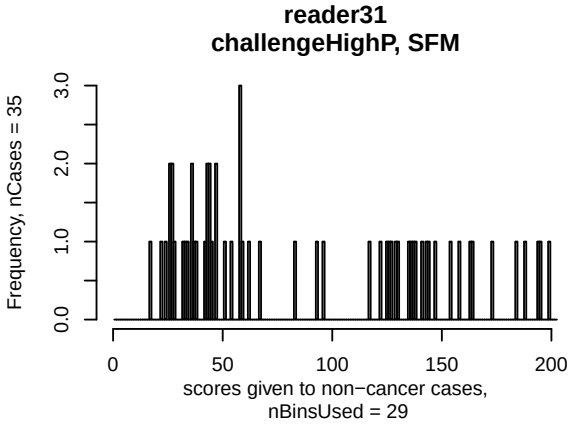
	Sens.	se
FFDM	0.61	0.077
SFM	0.696	0.069
FFDM−SFM	−0.086	0.081

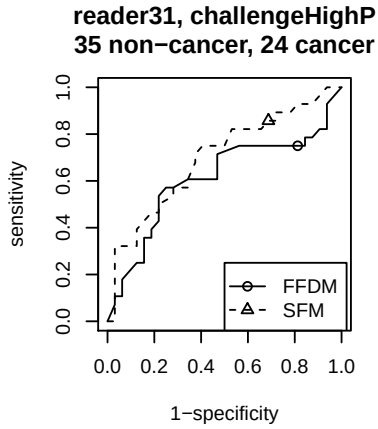
	Spec.	se
FFDM	0.61	0.077
SFM	0.696	0.069
FFDM−SFM	−0.086	0.081







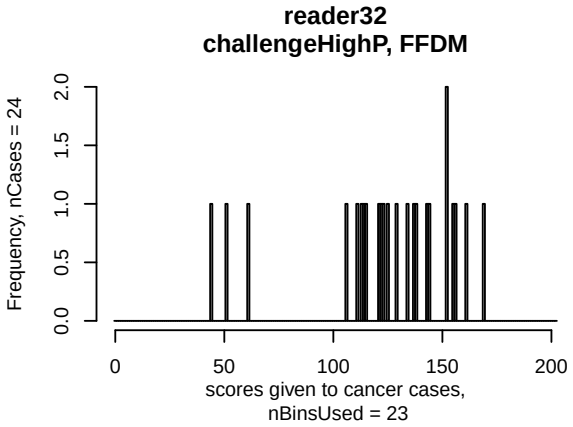


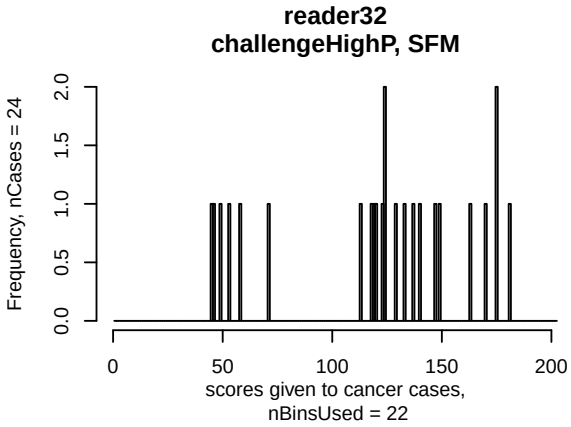


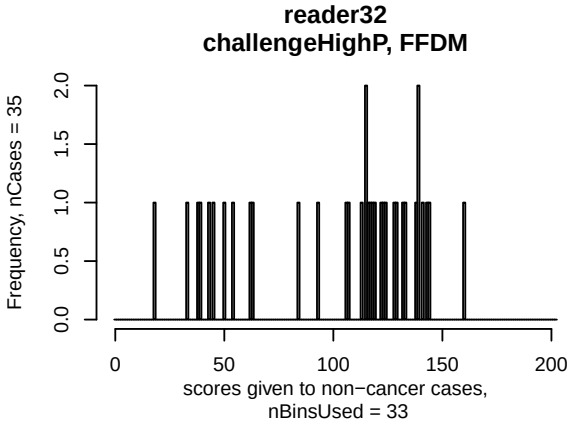
	AUC	se
FFDM	0.638	0.077
SFM	0.814	0.056
FFDM−SFM	−0.176	0.086

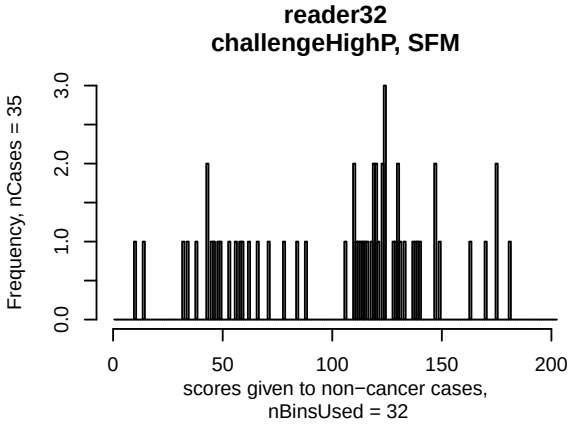
	Sens.	se
FFDM	0.638	0.077
SFM	0.814	0.056
FFDM−SFM	−0.176	0.086

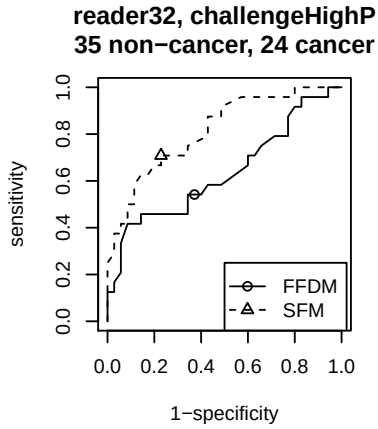
	Spec.	se
FFDM	0.638	0.077
SFM	0.814	0.056
FFDM−SFM	−0.176	0.086







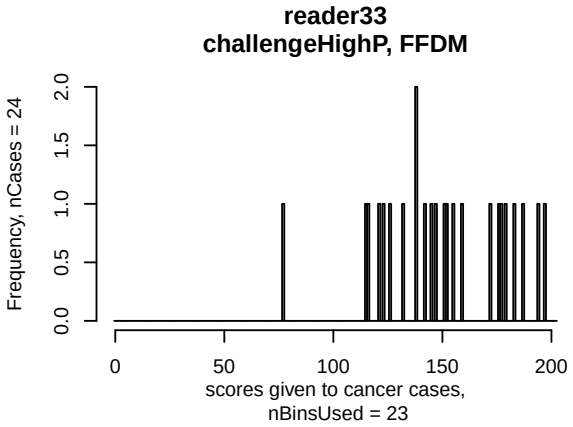


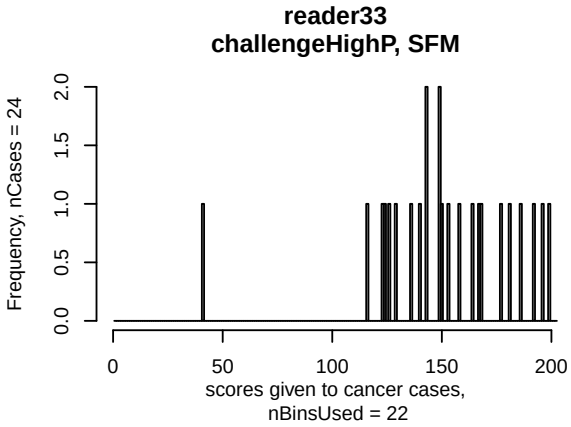


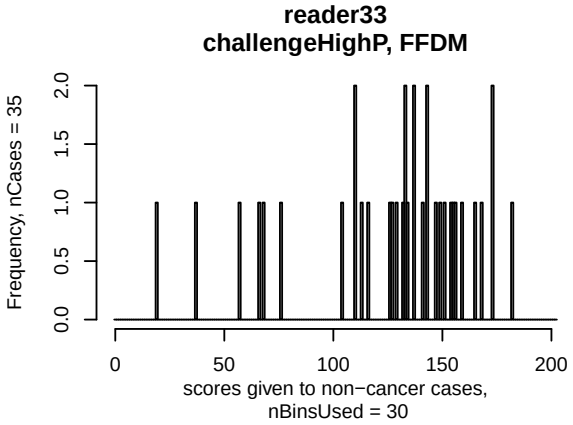
	AUC	se
FFDM	0.67	0.072
SFM	0.708	0.071
FFDM−SFM	−0.038	0.084

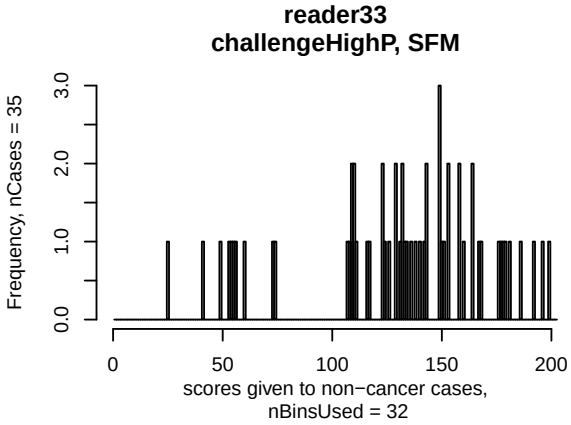
	Sens.	se
FFDM	0.67	0.072
SFM	0.708	0.071
FFDM−SFM	−0.038	0.084

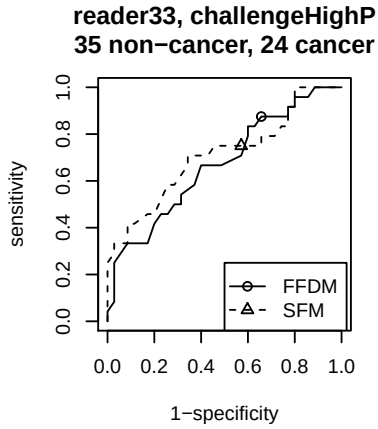
	Spec.	se
FFDM	0.67	0.072
SFM	0.708	0.071
FFDM−SFM	−0.038	0.084







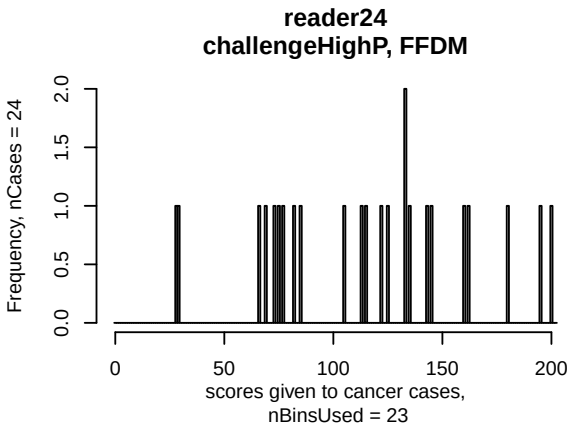


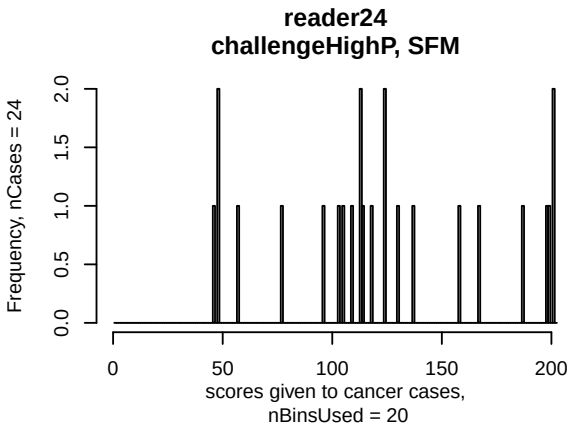


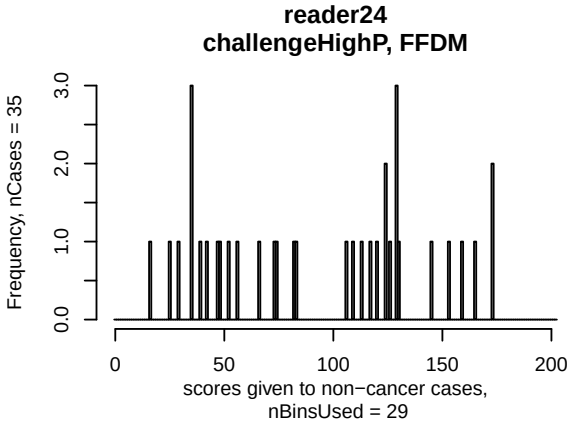
	AUC	se
FFDM	0.672	0.071
SFM	0.752	0.064
FFDM−SFM	−0.08	0.081

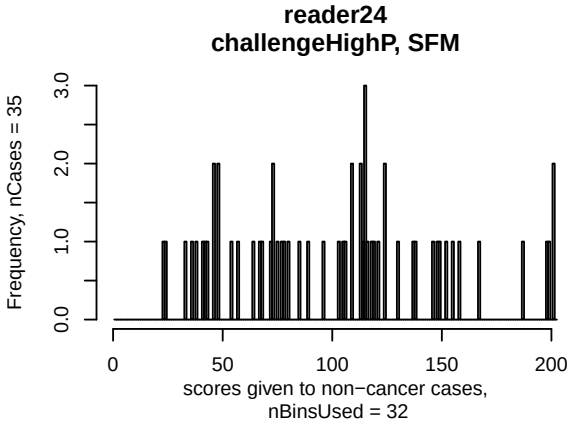
	Sens.	se
FFDM	0.672	0.071
SFM	0.752	0.064
FFDM−SFM	−0.08	0.081

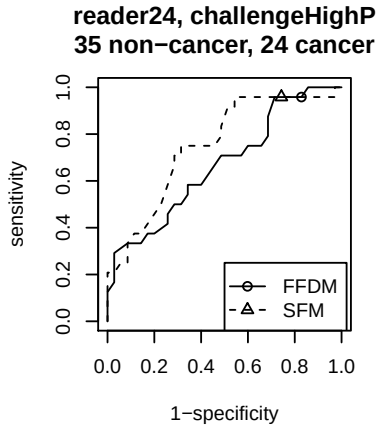
	Spec.	se
FFDM	0.672	0.071
SFM	0.752	0.064
FFDM−SFM	−0.08	0.081







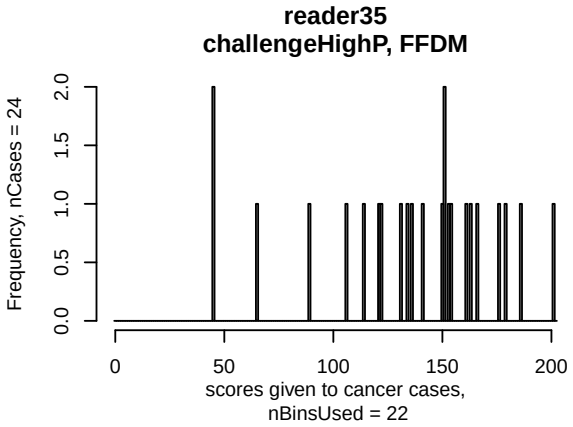


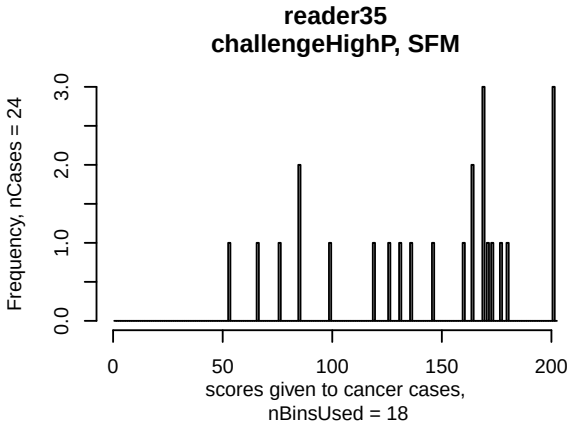


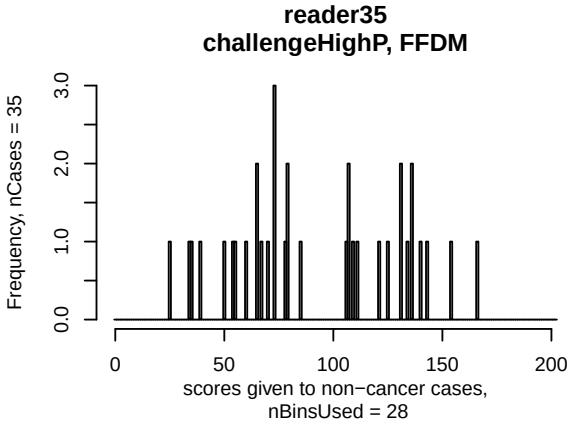
	AUC	se
FFDM	0.623	0.074
SFM	0.71	0.068
FFDM−SFM	−0.087	0.085

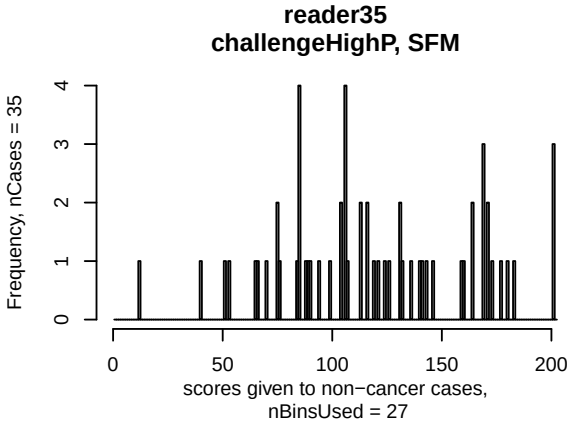
	Sens.	se
FFDM	0.623	0.074
SFM	0.71	0.068
FFDM−SFM	−0.087	0.085

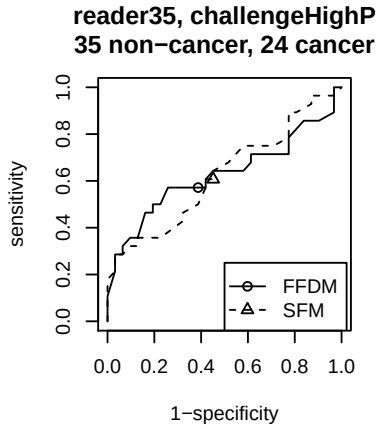
	Spec.	se
FFDM	0.623	0.074
SFM	0.71	0.068
FFDM−SFM	−0.087	0.085







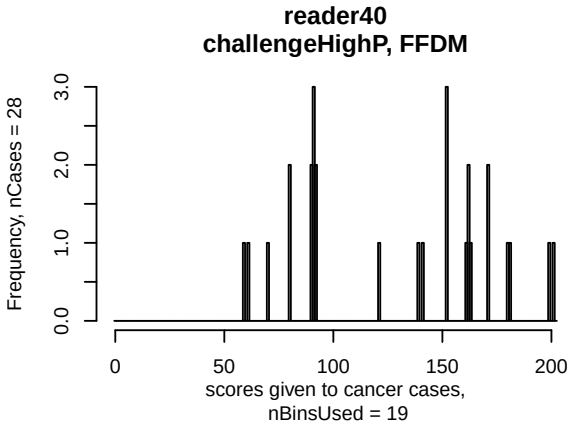


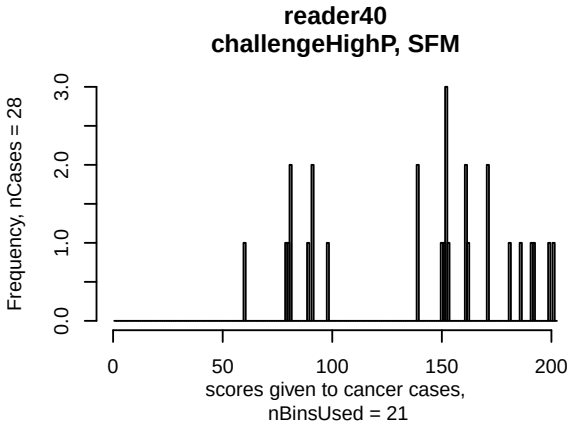


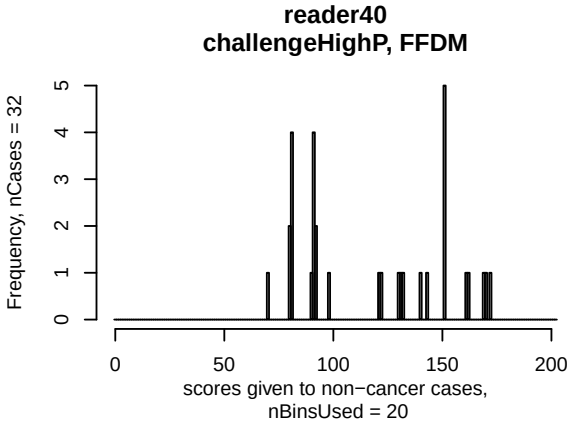
	AUC	se
FFDM	0.779	0.065
SFM	0.744	0.072
FFDM−SFM	0.035	0.076

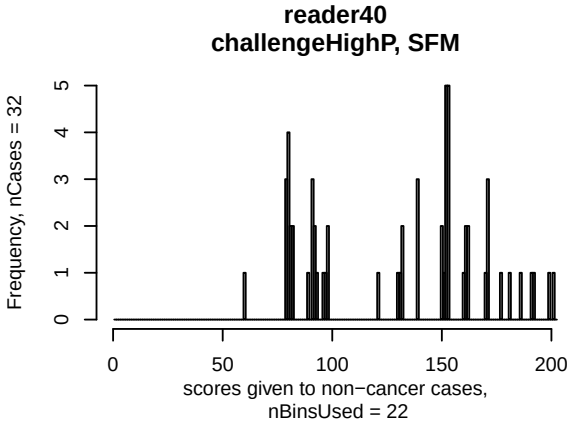
	Sens.	se
FFDM	0.779	0.065
SFM	0.744	0.072
FFDM−SFM	0.035	0.076

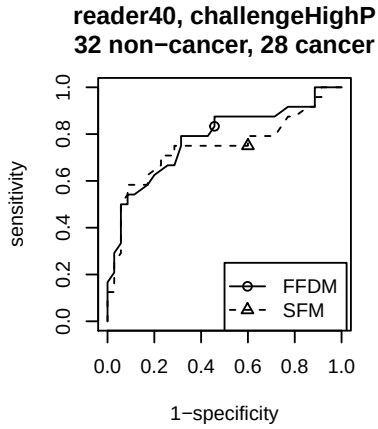
	Spec.	se
FFDM	0.779	0.065
SFM	0.744	0.072
FFDM−SFM	0.035	0.076







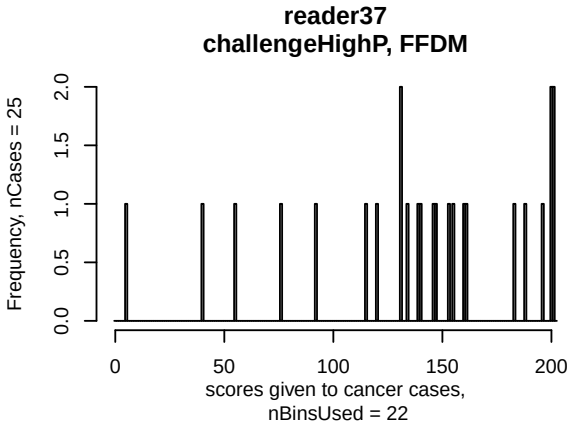


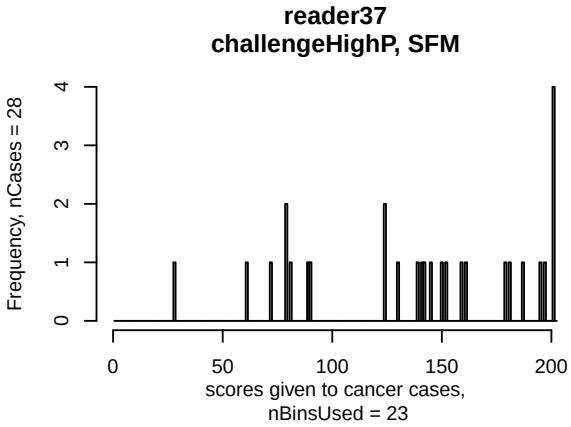


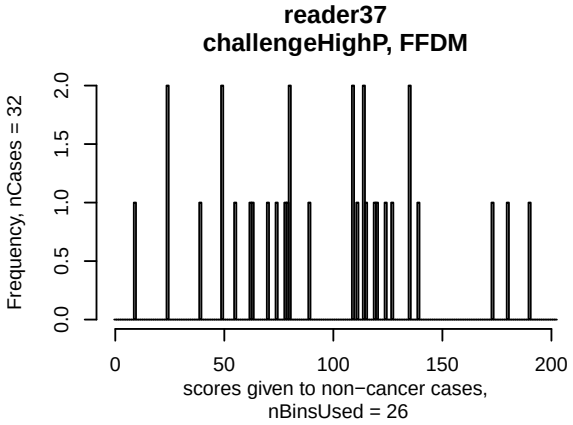
	AUC	se
FFDM	0.576	0.078
SFM	0.624	0.075
FFDM−SFM	−0.047	0.092

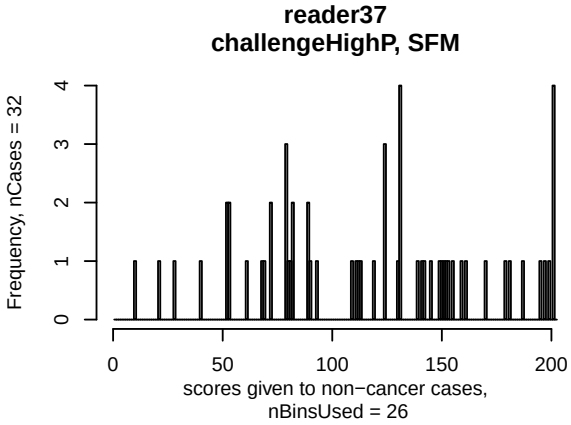
	Sens.	se
FFDM	0.576	0.078
SFM	0.624	0.075
FFDM−SFM	−0.047	0.092

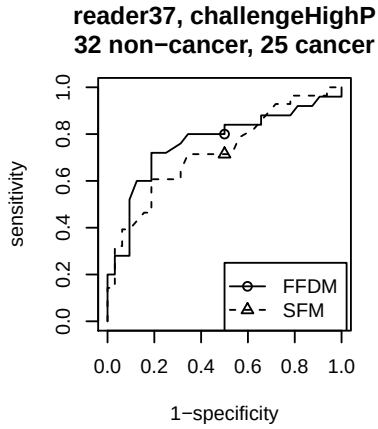
	Spec.	se
FFDM	0.576	0.078
SFM	0.624	0.075
FFDM−SFM	−0.047	0.092







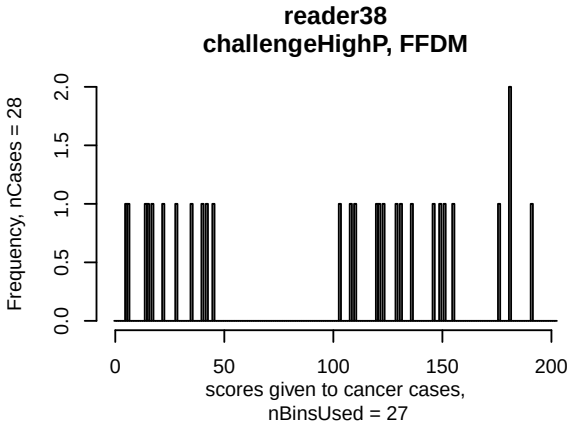


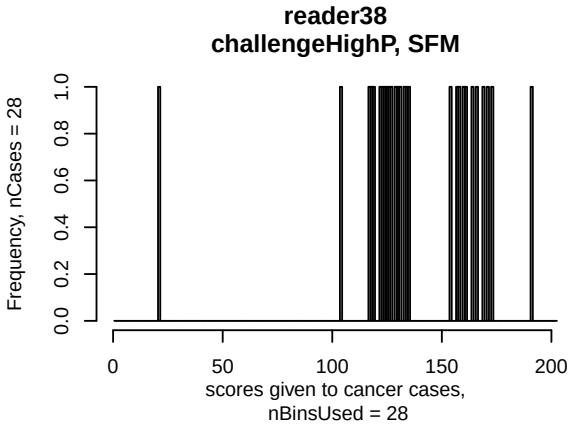


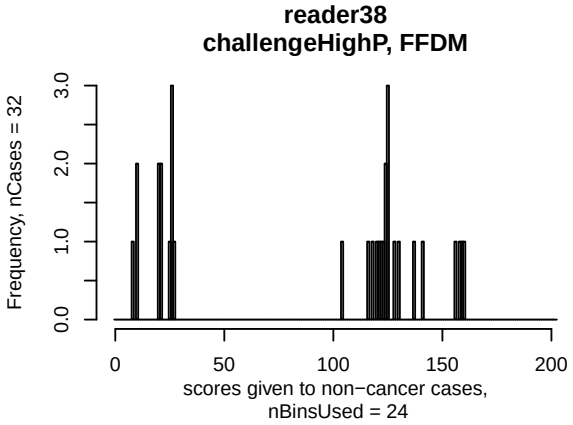
	AUC	se
FFDM	0.768	0.068
SFM	0.723	0.066
FFDM−SFM	0.044	0.083

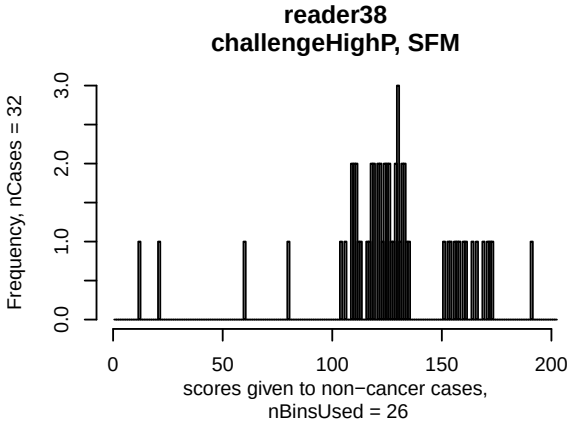
	Sens.	se
FFDM	0.768	0.068
SFM	0.723	0.066
FFDM−SFM	0.044	0.083

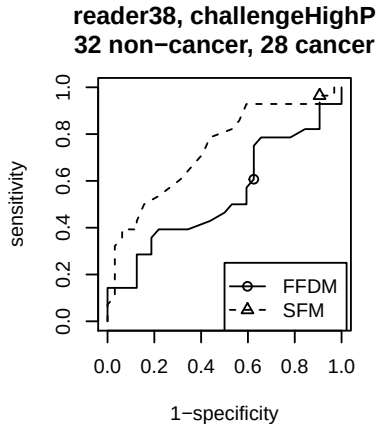
	Spec.	se
FFDM	0.768	0.068
SFM	0.723	0.066
FFDM−SFM	0.044	0.083







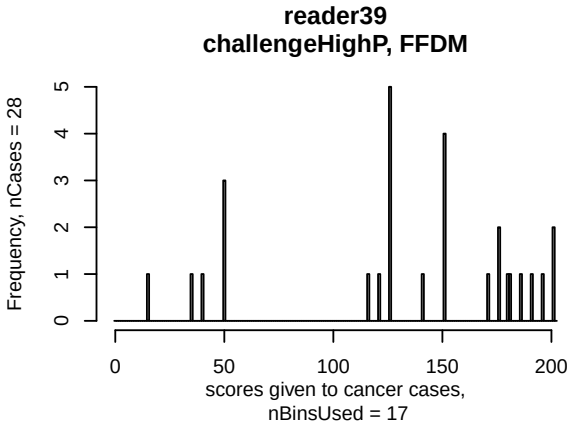


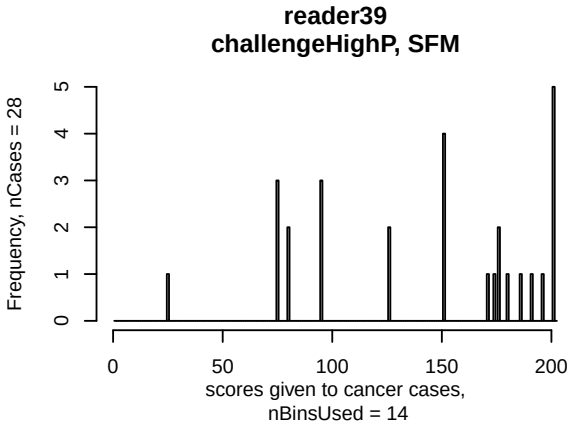


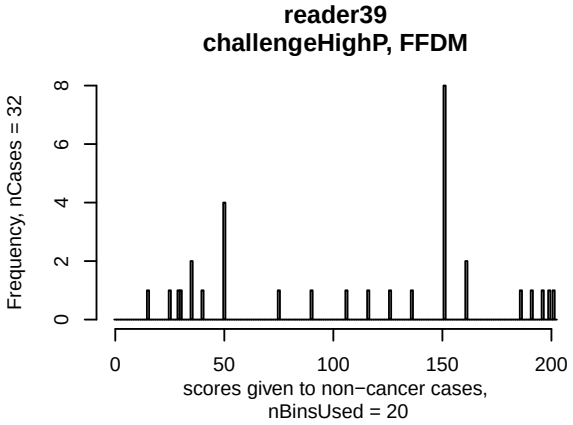
	AUC	se
FFDM	0.537	0.077
SFM	0.733	0.065
FFDM−SFM	−0.196	0.078

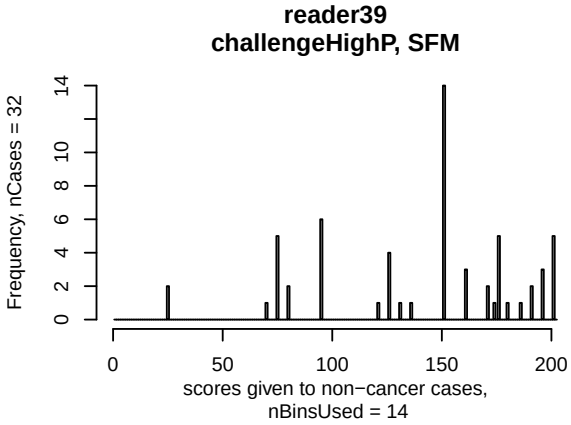
	Sens.	se
FFDM	0.537	0.077
SFM	0.733	0.065
FFDM−SFM	−0.196	0.078

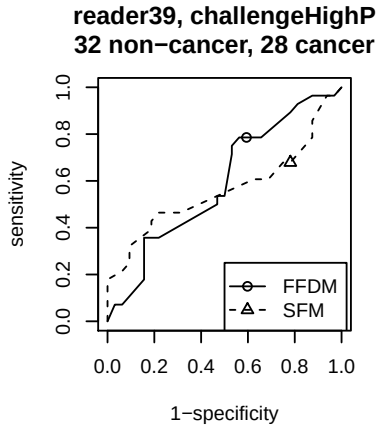
	Spec.	se
FFDM	0.537	0.077
SFM	0.733	0.065
FFDM−SFM	−0.196	0.078







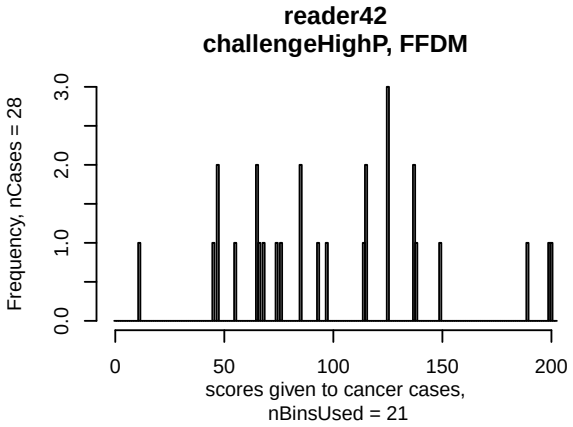


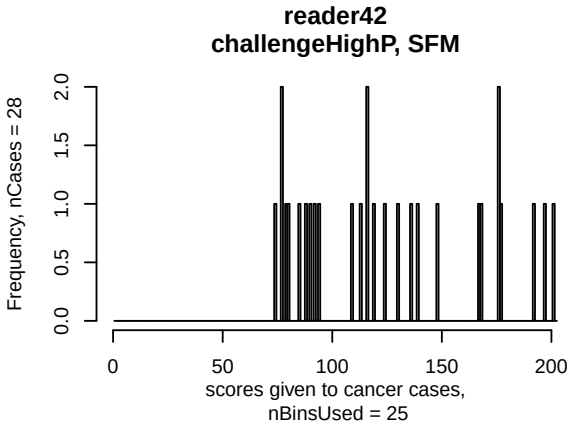


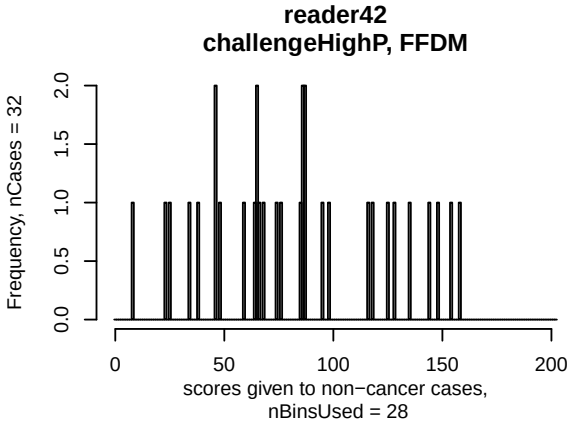
	AUC	se
FFDM	0.592	0.074
SFM	0.564	0.078
FFDM−SFM	0.028	0.091

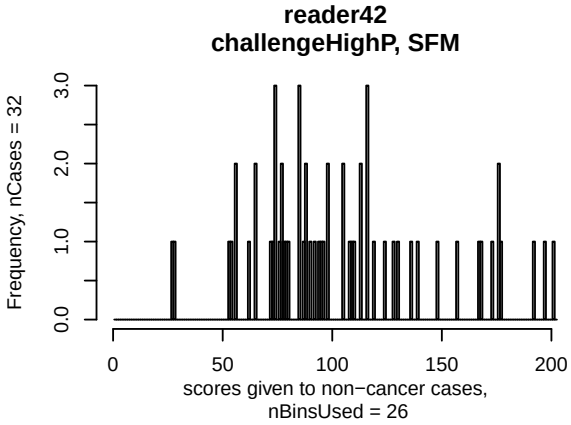
	Sens.	se
FFDM	0.592	0.074
SFM	0.564	0.078
FFDM−SFM	0.028	0.091

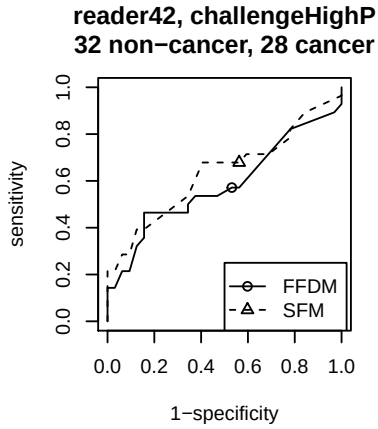
	Spec.	se
FFDM	0.592	0.074
SFM	0.564	0.078
FFDM−SFM	0.028	0.091











	AUC	se
FFDM	0.6	0.073
SFM	0.786	0.058
FFDM−SFM	−0.186	0.087

	Sens.	se
FFDM	0.6	0.073
SFM	0.786	0.058
FFDM−SFM	−0.186	0.087

	Spec.	se
FFDM	0.6	0.073
SFM	0.786	0.058
FFDM−SFM	−0.186	0.087

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