

Figure S1: Comparison of HER2 IHC four- and three-category score ONEST plots. (A,B) are the OPA results from 100 curves and (C,D) the mean and 95% confidence interval of 1000 curves randomly generated from all possible combinations of pathologists.

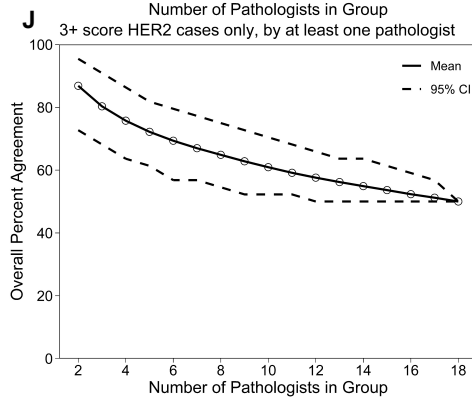
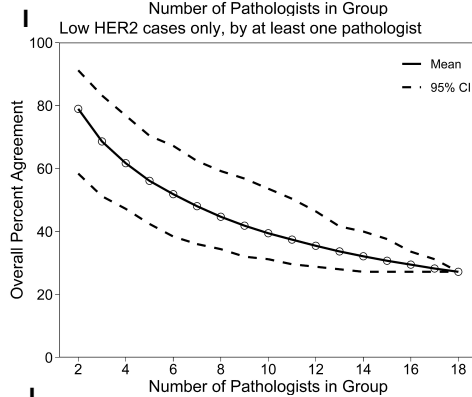
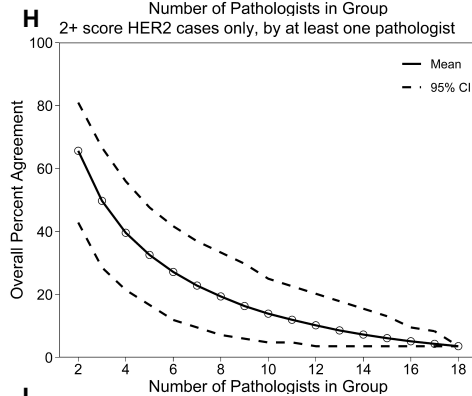
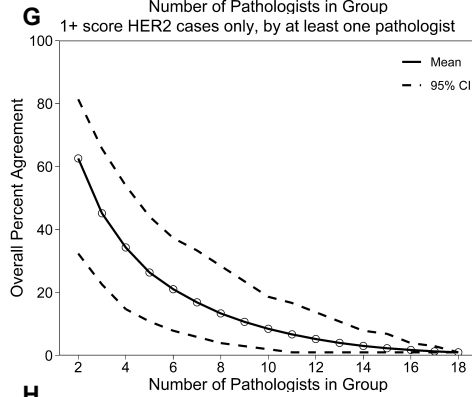
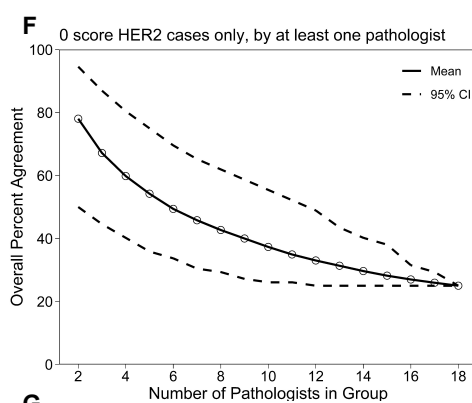
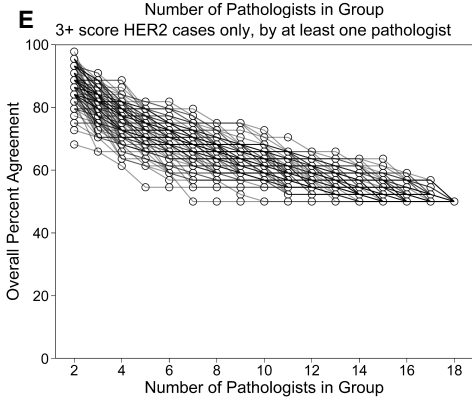
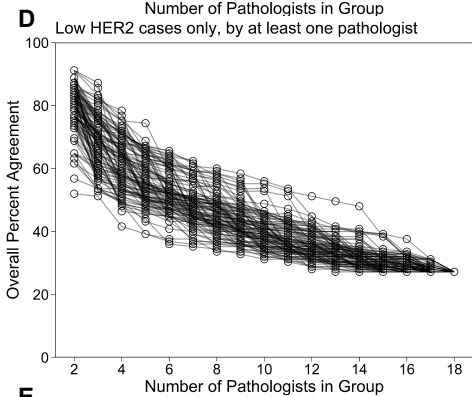
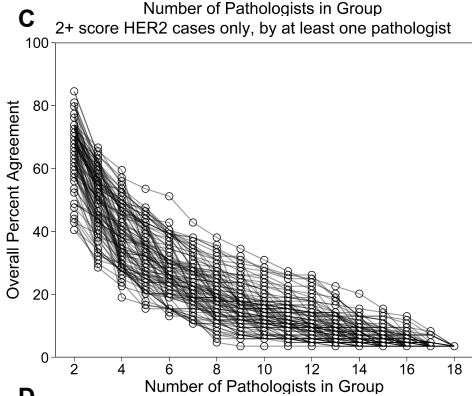
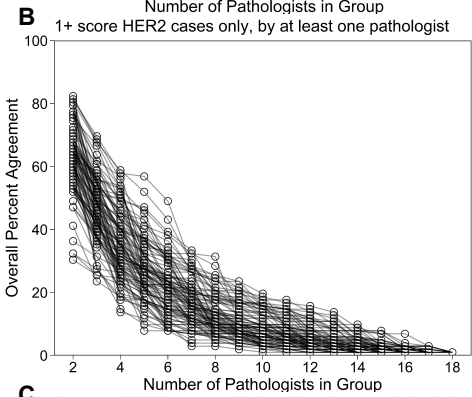
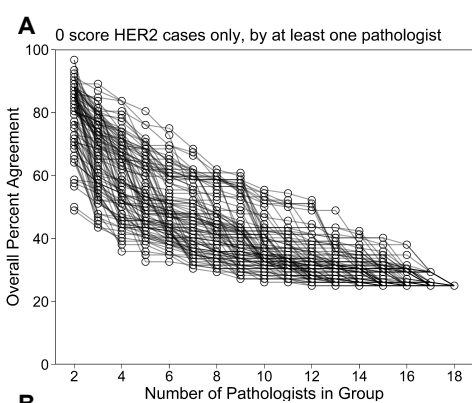


Figure S2: HER2 IHC ONEST plots for each subset of cases (0, 1+, 2+, Low, or 3+ cases only). Cases with at least one score for the category were included in the analysis. “Low” is the result of combining 1+ and 2+ cases into the same category. (A-E) are the OPA results from 100 curves and (F-J) the mean and 95% confidence interval of 1000 curves randomly generated from all possible combinations of pathologists.

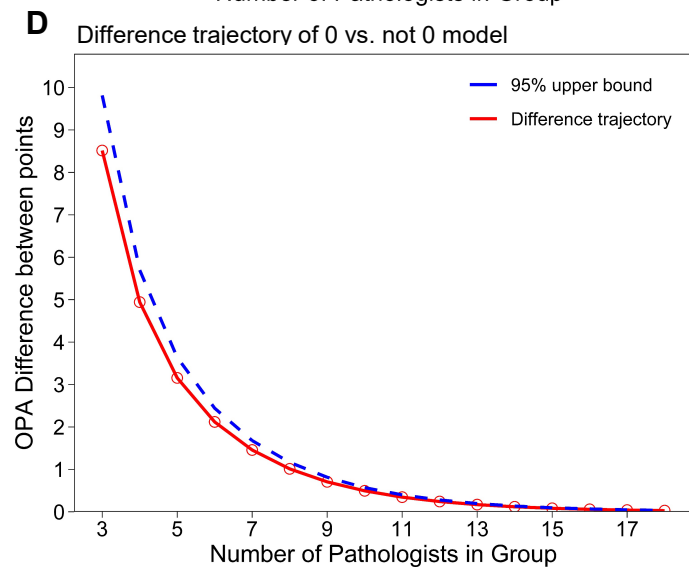
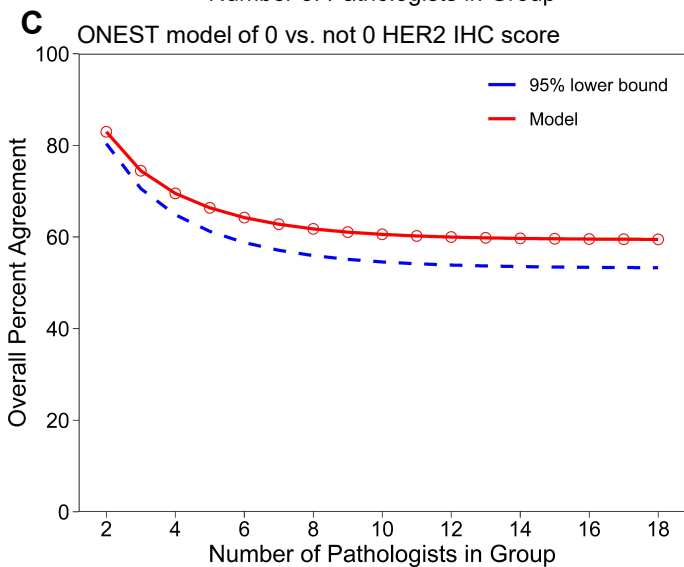
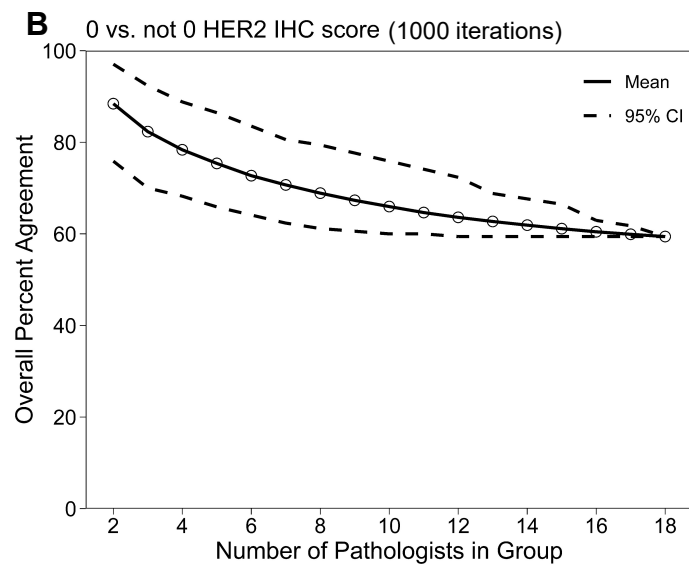
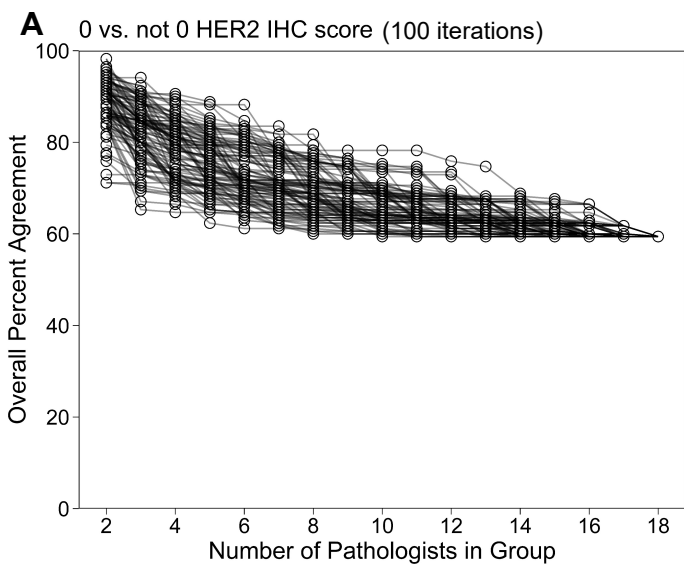


Figure S3: HER2 IHC 0 vs. not 0 with ONEST model and difference trajectory.

(A) is the OPA result from 100 curves and (B) the mean and 95% confidence interval of 1000 curves randomly generated from all possible combinations of pathologists. (C) is a plot of the statistical ONEST model used to predict the presence of a nonzero plateau of OPA. (D) is the OPA difference between successive groups of pathologists. The lower bound of OPA plateaus at 54.5% with 10 pathologists inside the group (0.399% difference less than 0.5%).

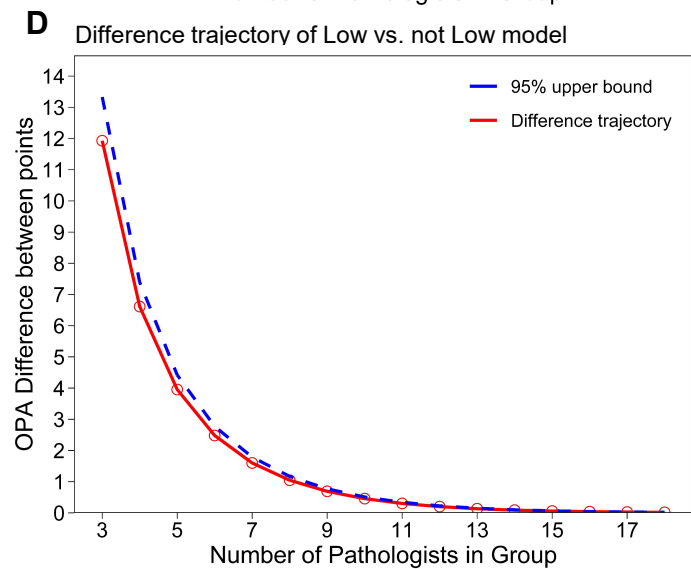
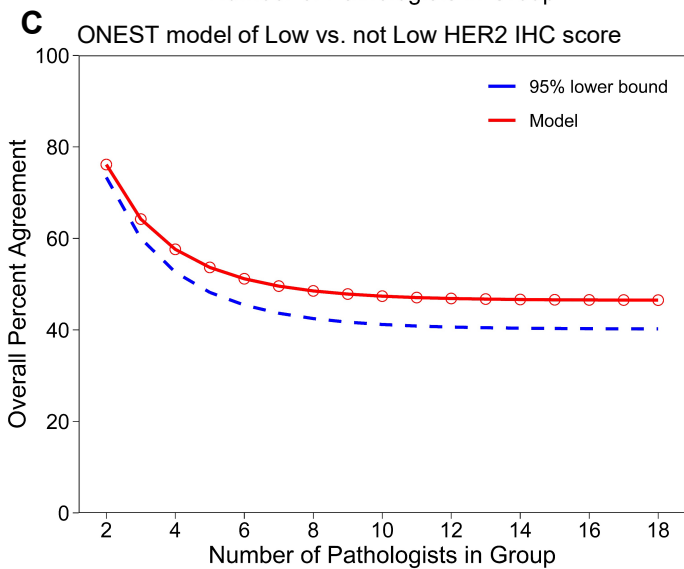
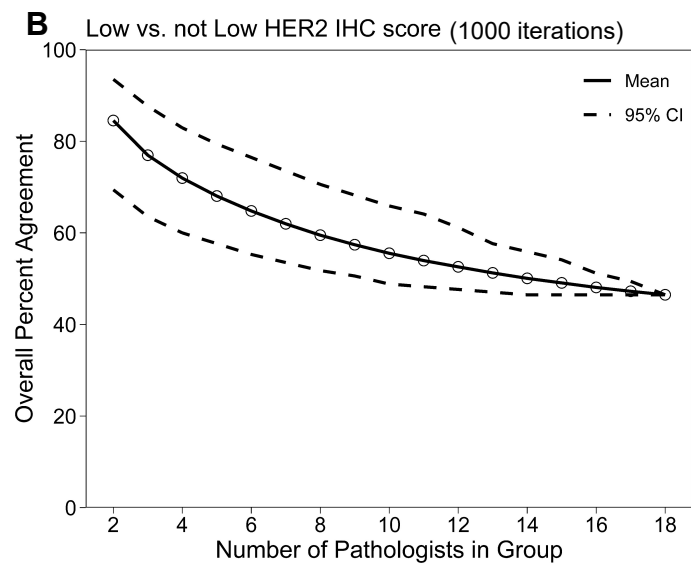
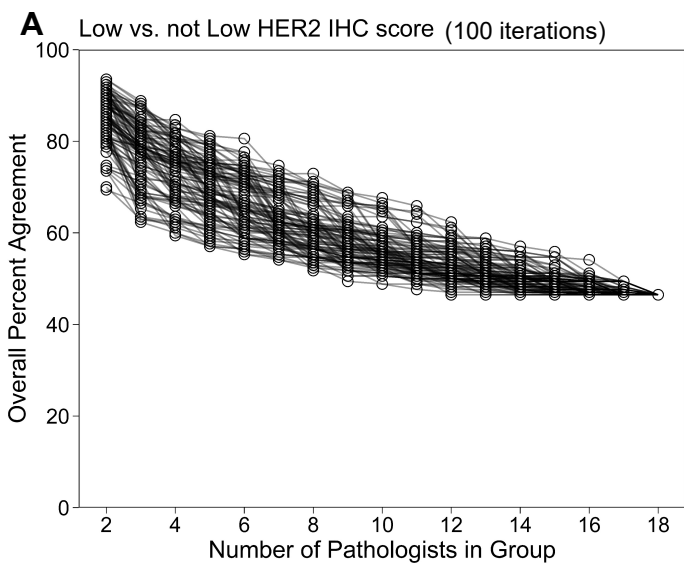


Figure S4: HER2 IHC Low vs. not Low with ONEST model and difference trajectory. (A) is the OPA result from 100 curves and (B) the mean and 95% confidence interval of 1000 curves randomly generated from all possible combinations of pathologists. (C) is a plot of the statistical ONEST model used to predict the presence of a nonzero plateau of OPA. (D) is the OPA difference between successive groups of pathologists. The lower bound of OPA plateaus at 41.2% with 10 pathologists inside the group (0.339% difference less than 0.5%).

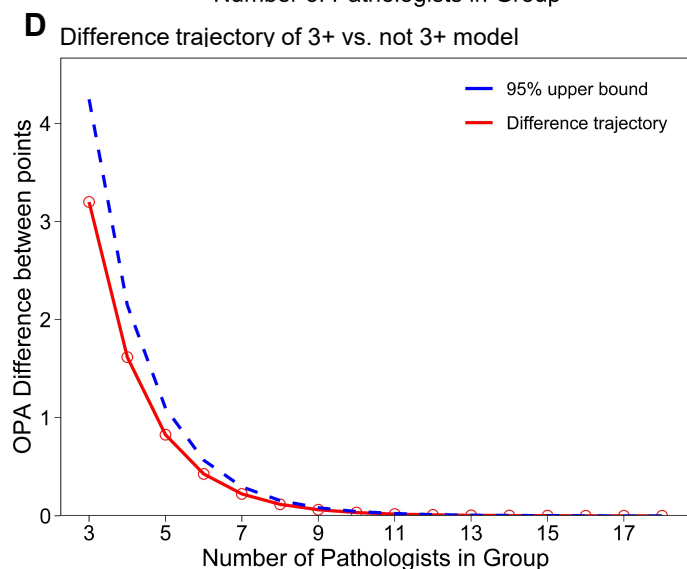
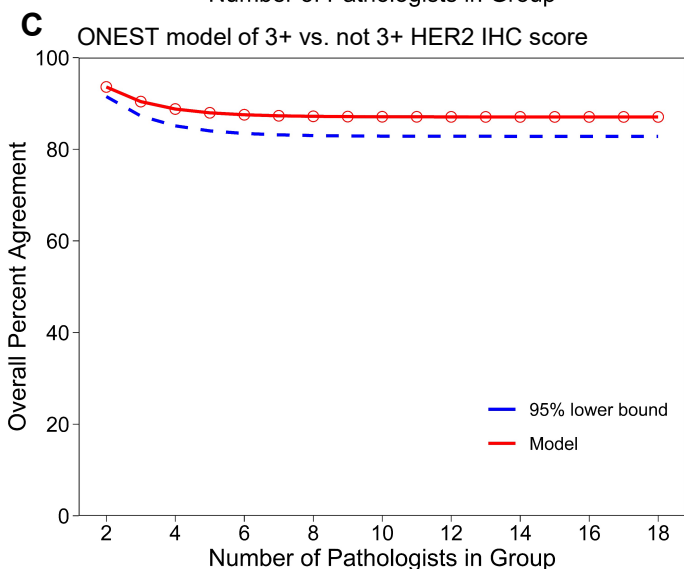
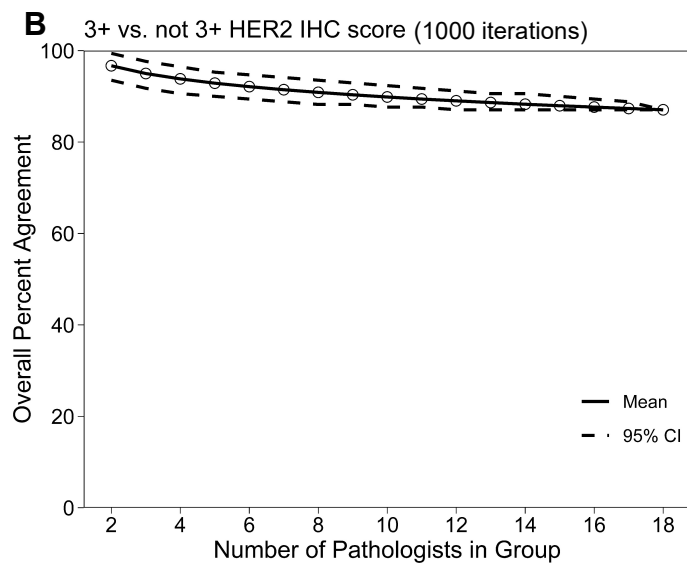
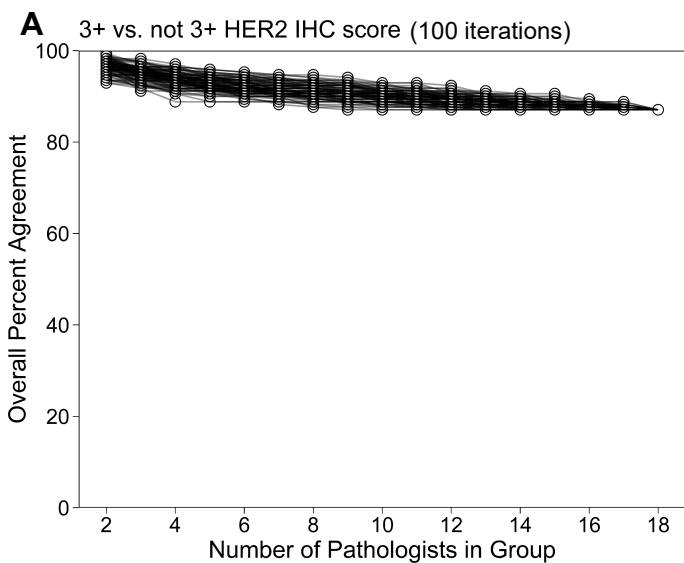


Figure S5: HER2 IHC 3+ vs not 3+ with ONEST model and difference trajectory. (A) is the OPA result from 100 curves and (B) the mean and 95% confidence interval of 1000 curves randomly generated from all possible combinations of pathologists. (C) is a plot of the statistical ONEST model used to predict the presence of a nonzero plateau of OPA. (D) is the OPA difference between successive groups of pathologists. The lower bound of OPA plateaus at 83.5% with 6 pathologists inside the group (0.295% difference less than 0.5%).

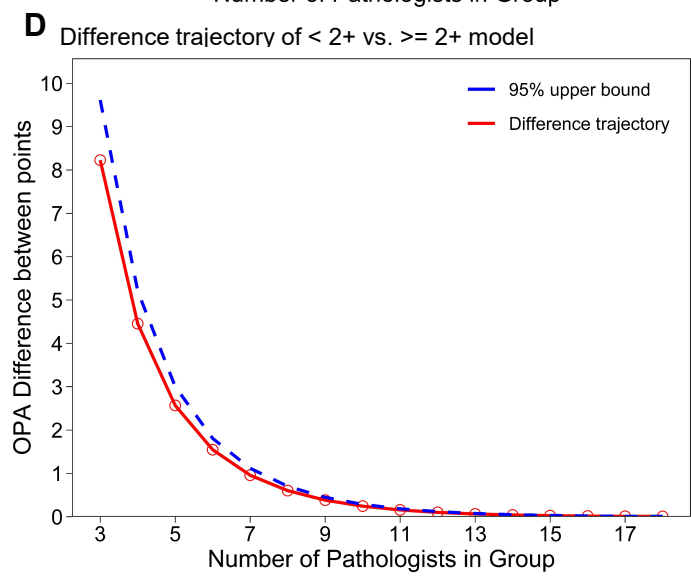
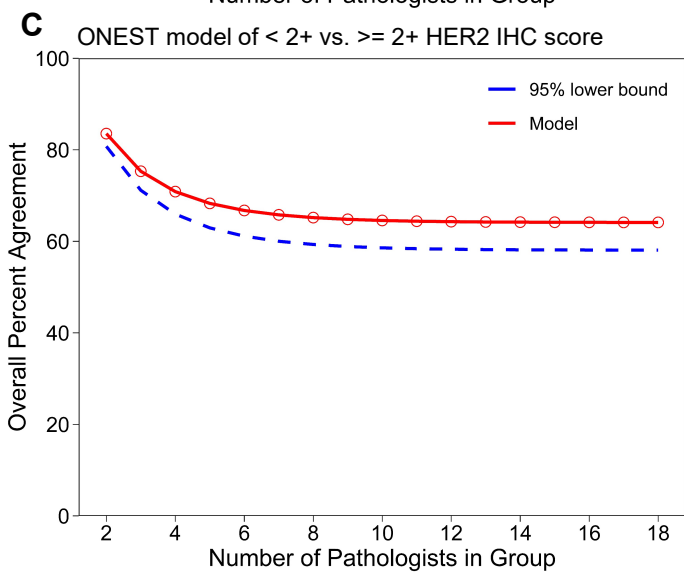
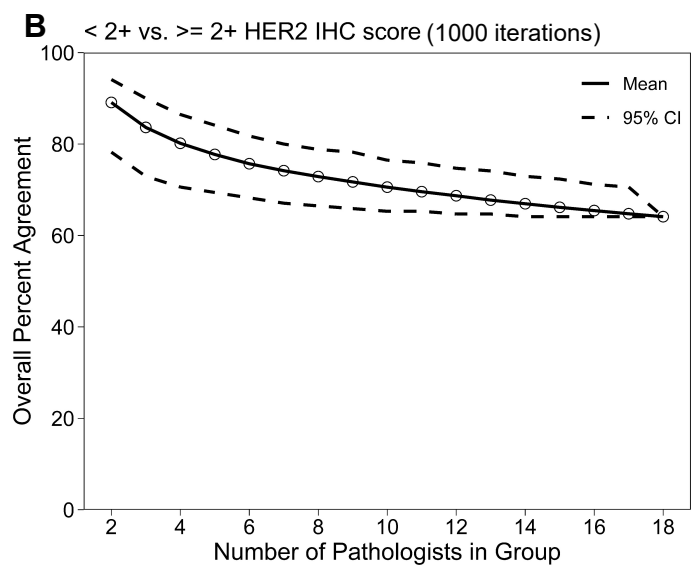
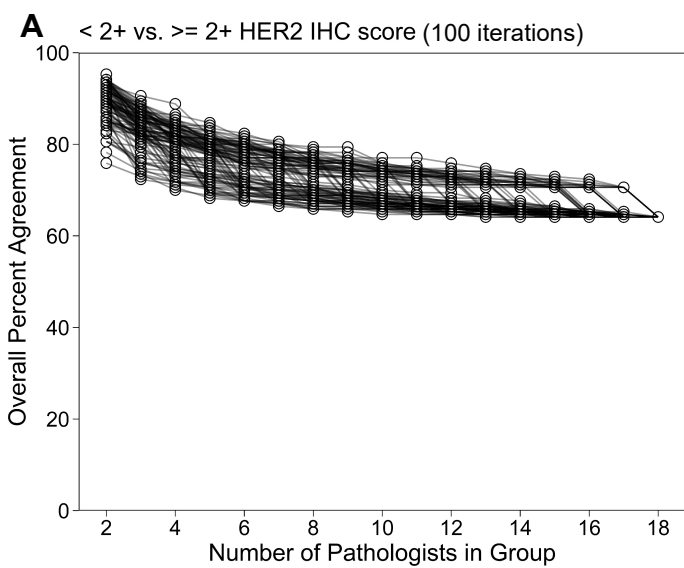


Figure S6: HER2 IHC < 2+ vs \geq 2+ with ONEST model and difference trajectory. (A) is the OPA result from 100 curves and (B) the mean and 95% confidence interval of 1000 curves randomly generated from all possible combinations of pathologists. (C) is a plot of the statistical ONEST model used to predict the presence of a nonzero plateau of OPA. (D) is the OPA difference between successive groups of pathologists. The lower bound of OPA plateaus at 59.3% with 8 pathologists inside the group (0.448% difference less than 0.5%).

Table S1: Amount of HER2 IHC ratings for each subset of cases amongst 18 pathologists and 170 cases of breast cancer.

HER2 IHC group	0 counts	1+ counts	2+ counts	3+ counts	Total Ratings
0 only	786	785	85	0	1656
1+ only	372	1073	388	3	1836
2+ only	74	633	628	177	1512
3+ only	0	18	201	573	792

Each subset is defined by only including cases with the score from at least one pathologist

Table S2: Number of HER2 IHC cases scored by at least one pathologist for each subset of cases amongst 18 pathologists and 170 cases of breast cancer.

HER2 IHC group	0 counts	1+ counts	2+ counts	3+ counts	Total Cases
0 only	92	69	29	0	92
1+ only	69	102	61	2	102
2+ only	29	61	84	22	84
3+ only	0	2	22	44	44

Each subset is defined by only including cases with the score from at least one pathologist