A

Exact best cut-off distribution

Continuous distribution

Experimental best cut-off

$\infty \leftarrow$ n_{mutant}
n_{BRCA1} (except the standard method)
$n_{neutral}$ (if $n_{mutant} > 1$)
$n_{pathogenic}$ (if $n_{mutant} > 1$) $\rightarrow 1$

$\updownarrow$

$n_{best\ exact}$

B

Approximate best cut-off distribution

Exact best cut-off distribution ($n_{best\ exact}$)

1 best cut-off $\neq$ Experimental best cut-off

$\infty \leftarrow$ $n_{bootstrap}$ $\rightarrow 1$

C

Best cut-off distribution

Probability system

Null accuracy (probability = 0.5 (class 3))

Same accuracy (same variant classification)

Perfect accuracy (class 1 or class 5)

Quantile system

D

Legend: a = 0, a = 0.1, a = 0.5, a = 1, a = 2, a = 5, a = 10, a = 50

y-axis: f_{cor} (0.0 to 1.0)
x-axis: $n_{neutral} + n_{pathogenic}$ (0 to 50)

S22 Fig. Additional information about the classification model
(**A**) Schematic of the exact best cut-off distribution influenced by different parameters, assuming no ties. The number of neutral ($n_{neutral}$) and pathogenic ($n_{pathogenic}$) variants influence the exact best cut-off distribution only if the number of values per mutant (n_{mutant}) is above 1. The number of values in the WT reference (n_{BRCA1}) does not influence the exact best cut-off distribution in the standard method, only in the standard with reference and MWW methods.
(**B**) Schematic of the approximate best cut-off distribution influenced by the number of bootstraps performed. Importantly, a single bootstrap ($n_{bootstrap} = 1$) does not lead to the experimental best cut-off, except if $n_{best\ exact} = 1$.
(**C**) Accuracy of the probability and quantile systems of classification. The schematic illustration is valid, using either the exact or approximate best cut-off distribution.
(**D**) Correcting factor fcor used in the probability system of classification, depending on the parameter a (see the S1 Text). $f_{cor} = (n_{neutral} + n_{pathogenic}) / (n_{neutral} + n_{pathogenic} + a)$. The framed value (a = 2) was the value used in S13-S15 Tables.