

**Supplementary Table S1: Impact of strength of the spiked-in gene expression changes on signature performance.**

The impact of multiple mechanisms of resistance on the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and area under curve (AUC) of receiver operating characteristic (ROC) curves of the predictive gene signatures tested, where the spiked-in gene expression changes were either optimal (2-fold), weak (1.4-fold) or strong (2.8-fold).

Optimal gene expression changes (2-fold)							
Proportion of resistant cases	Number of resistance mechanisms	Sensitivity	Specificity	PPV	NPV	Accuracy	AUC
0.5	1	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.000 (1.000-1.000)
0.5	2	0.99 (0.97-1.00)	1.00 (0.99-1.00)	1.00 (0.99-1.00)	0.99 (0.97-1.00)	0.99 (0.98-1.00)	1.000 (0.999-1.000)
0.5	3	0.95 (0.93-0.97)	0.98 (0.96-0.99)	0.98 (0.96-0.99)	0.96 (0.93-0.97)	0.96 (0.95-0.98)	0.992 (0.987-0.997)
0.5	4	0.91 (0.87-0.94)	0.93 (0.90-0.96)	0.93 (0.90-0.96)	0.91 (0.87-0.94)	0.92 (0.89-0.95)	0.971 (0.955-0.983)
0.5	5	0.85 (0.80-0.90)	0.88 (0.82-0.91)	0.87 (0.82-0.91)	0.86 (0.80-0.90)	0.87 (0.81-0.90)	0.931 (0.886-0.955)
0.6	1	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.000 (1.000-1.000)
0.6	2	0.99 (0.97-1.00)	1.00 (0.99-1.00)	1.00 (0.99-1.00)	0.98 (0.96-1.00)	0.99 (0.98-1.00)	0.999 (0.997-1.000)
0.6	3	0.96 (0.94-0.98)	0.97 (0.94-0.99)	0.98 (0.96-0.99)	0.94 (0.91-0.96)	0.96 (0.94-0.98)	0.992 (0.985-0.996)
0.6	4	0.91 (0.87-0.94)	0.91 (0.86-0.95)	0.94 (0.91-0.96)	0.87 (0.82-0.92)	0.91 (0.88-0.94)	0.966 (0.943-0.980)
0.6	5	0.87 (0.83-0.91)	0.85 (0.79-0.89)	0.90 (0.85-0.93)	0.81 (0.75-0.86)	0.86 (0.81-0.90)	0.930 (0.882-0.954)
0.7	1	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.000 (1.000-1.000)
0.7	2	0.99 (0.98-1.00)	1.00 (0.99-1.00)	1.00 (0.99-1.00)	0.98 (0.95-0.99)	0.99 (0.98-1.00)	1.000 (0.998-1.000)
0.7	3	0.96 (0.92-0.98)	0.96 (0.93-0.98)	0.98 (0.97-0.99)	0.91 (0.83-0.95)	0.96 (0.93-0.98)	0.991 (0.977-0.996)
0.7	4	0.93 (0.88-0.95)	0.90 (0.84-0.94)	0.95 (0.93-0.97)	0.84 (0.74-0.89)	0.92 (0.87-0.95)	0.967 (0.933-0.980)
0.7	5	0.89 (0.85-0.92)	0.82 (0.76-0.88)	0.92 (0.89-0.94)	0.75 (0.68-0.82)	0.87 (0.82-0.90)	0.927 (0.888-0.953)
0.8	1	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.000 (1.000-1.000)
0.8	2	0.99 (0.98-1.00)	1.00 (0.98-1.00)	1.00 (1.00-1.00)	0.97 (0.94-0.99)	0.99 (0.98-1.00)	1.000 (0.998-1.000)
0.8	3	0.96 (0.93-0.98)	0.95 (0.90-0.97)	0.99 (0.97-0.99)	0.87 (0.77-0.93)	0.96 (0.93-0.98)	0.990 (0.974-0.996)
0.8	4	0.93 (0.90-0.96)	0.86 (0.81-0.90)	0.96 (0.95-0.98)	0.77 (0.67-0.85)	0.92 (0.89-0.95)	0.963 (0.933-0.980)
0.8	5	0.90 (0.86-0.93)	0.76 (0.71-0.81)	0.94 (0.92-0.95)	0.66 (0.55-0.75)	0.87 (0.83-0.91)	0.920 (0.870-0.947)
0.9	1	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.000 (1.000-1.000)
0.9	2	0.99 (0.98-1.00)	0.99 (0.96-1.00)	1.00 (1.00-1.00)	0.94 (0.86-0.98)	0.99 (0.98-1.00)	0.999 (0.998-1.000)
0.9	3	0.97 (0.95-0.98)	0.90 (0.85-0.95)	0.99 (0.98-0.99)	0.78 (0.62-0.87)	0.96 (0.93-0.98)	0.987 (0.967-0.995)
0.9	4	0.94 (0.91-0.97)	0.73 (0.66-0.79)	0.97 (0.96-0.98)	0.59 (0.46-0.72)	0.92 (0.89-0.95)	0.943 (0.898-0.967)
0.9	5	0.91 (0.85-0.95)	0.56 (0.49-0.63)	0.95 (0.94-0.96)	0.43 (0.28-0.55)	0.88 (0.82-0.91)	0.866 (0.786-0.919)
0.95	1	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.000 (1.000-1.000)
0.95	2	0.99 (0.98-1.00)	0.98 (0.92-1.00)	1.00 (1.00-1.00)	0.89 (0.70-0.96)	0.99 (0.98-1.00)	0.999 (0.994-1.000)
0.95	3	0.97 (0.92-0.99)	0.66 (0.48-0.80)	0.98 (0.97-0.99)	0.53 (0.26-0.73)	0.95 (0.90-0.98)	0.951 (0.864-0.987)
0.95	4	0.93 (0.88-0.96)	0.36 (0.24-0.46)	0.96 (0.96-0.97)	0.22 (0.13-0.34)	0.90 (0.85-0.93)	0.803 (0.728-0.881)
0.95	5	0.89 (0.84-0.94)	0.26 (0.19-0.35)	0.96 (0.95-0.96)	0.12 (0.08-0.18)	0.86 (0.81-0.90)	0.687 (0.619-0.754)

Weak gene expression changes (1.4-fold)							
Proportion of resistant cases	Number of resistance mechanisms	Sensitivity	Specificity	PPV	NPV	Accuracy	AUC
0.5	1	0.98 (0.96-1.00)	0.99 (0.96-1.00)	0.99 (0.97-1.00)	0.985 (0.962-0.998)	0.99 (0.97-1.00)	0.999 (0.996-1.000)
0.5	2	0.91 (0.87-0.94)	0.92 (0.87-0.95)	0.92 (0.87-0.95)	0.909 (0.872-0.938)	0.91 (0.87-0.94)	0.968 (0.935-0.982)
0.5	3	0.83 (0.77-0.87)	0.83 (0.77-0.88)	0.83 (0.77-0.88)	0.827 (0.775-0.869)	0.83 (0.77-0.87)	0.900 (0.844-0.936)
0.5	4	0.75 (0.70-0.79)	0.74 (0.69-0.79)	0.75 (0.70-0.79)	0.748 (0.697-0.787)	0.75 (0.70-0.79)	0.818 (0.762-0.855)
0.5	5	0.68 (0.63-0.72)	0.67 (0.63-0.71)	0.68 (0.64-0.71)	0.679 (0.642-0.717)	0.68 (0.64-0.72)	0.736 (0.689-0.784)
0.6	1	0.99 (0.97-1.00)	0.99 (0.97-1.00)	0.99 (0.98-1.00)	0.978 (0.955-0.995)	0.99 (0.97-1.00)	0.999 (0.996-1.000)
0.6	2	0.92 (0.89-0.95)	0.91 (0.87-0.95)	0.94 (0.91-0.96)	0.882 (0.844-0.921)	0.92 (0.89-0.94)	0.970 (0.949-0.984)
0.6	3	0.84 (0.80-0.88)	0.79 (0.74-0.84)	0.86 (0.82-0.89)	0.767 (0.706-0.816)	0.82 (0.77-0.86)	0.892 (0.843-0.925)
0.6	4	0.78 (0.73-0.82)	0.70 (0.63-0.74)	0.79 (0.75-0.82)	0.679 (0.609-0.731)	0.75 (0.69-0.79)	0.812 (0.747-0.855)
0.6	5	0.72 (0.69-0.76)	0.61 (0.57-0.66)	0.74 (0.71-0.77)	0.597 (0.558-0.642)	0.68 (0.65-0.71)	0.729 (0.682-0.771)
0.7	1	0.99 (0.97-1.00)	0.99 (0.96-1.00)	0.99 (0.99-1.00)	0.969 (0.932-0.994)	0.99 (0.97-1.00)	0.999 (0.996-1.000)
0.7	2	0.92 (0.89-0.95)	0.89 (0.84-0.93)	0.95 (0.93-0.97)	0.834 (0.771-0.886)	0.91 (0.88-0.94)	0.967 (0.944-0.982)
0.7	3	0.87 (0.81-0.90)	0.76 (0.70-0.79)	0.89 (0.86-0.91)	0.708 (0.617-0.764)	0.83 (0.78-0.86)	0.895 (0.845-0.921)
0.7	4	0.81 (0.74-0.84)	0.63 (0.57-0.67)	0.84 (0.81-0.86)	0.581 (0.502-0.643)	0.75 (0.70-0.79)	0.797 (0.738-0.839)
0.7	5	0.75 (0.69-0.79)	0.54 (0.49-0.58)	0.79 (0.77-0.81)	0.485 (0.432-0.541)	0.69 (0.65-0.73)	0.708 (0.659-0.754)
0.8	1	0.99 (0.97-1.00)	0.99 (0.97-1.00)	1.00 (0.99-1.00)	0.955 (0.905-0.990)	0.99 (0.97-1.00)	0.999 (0.996-1.000)
0.8	2	0.93 (0.90-0.97)	0.86 (0.81-0.91)	0.96 (0.95-0.98)	0.770 (0.672-0.868)	0.92 (0.88-0.95)	0.965 (0.933-0.986)
0.8	3	0.88 (0.82-0.91)	0.67 (0.61-0.72)	0.91 (0.90-0.93)	0.581 (0.470-0.662)	0.84 (0.78-0.87)	0.872 (0.810-0.909)
0.8	4	0.82 (0.77-0.85)	0.51 (0.45-0.57)	0.87 (0.86-0.88)	0.411 (0.341-0.474)	0.76 (0.71-0.79)	0.746 (0.692-0.784)
0.8	5	0.77 (0.71-0.82)	0.43 (0.37-0.49)	0.84 (0.83-0.86)	0.317 (0.279-0.354)	0.70 (0.65-0.74)	0.653 (0.619-0.689)
0.9	1	0.99 (0.97-1.00)	0.98 (0.94-1.00)	1.00 (0.99-1.00)	0.911 (0.801-0.972)	0.99 (0.97-1.00)	0.999 (0.994-1.000)
0.9	2	0.94 (0.90-0.97)	0.72 (0.65-0.80)	0.97 (0.96-0.98)	0.580 (0.438-0.714)	0.92 (0.88-0.94)	0.937 (0.883-0.968)
0.9	3	0.88 (0.82-0.92)	0.41 (0.33-0.48)	0.93 (0.92-0.94)	0.275 (0.206-0.357)	0.83 (0.78-0.87)	0.754 (0.692-0.820)
0.9	4	0.83 (0.77-0.88)	0.30 (0.22-0.38)	0.91 (0.91-0.92)	0.169 (0.138-0.214)	0.78 (0.73-0.82)	0.631 (0.581-0.686)
0.9	5	0.81 (0.73-0.85)	0.27 (0.18-0.37)	0.91 (0.90-0.91)	0.132 (0.109-0.156)	0.75 (0.70-0.79)	0.573 (0.527-0.612)
0.95	1	0.99 (0.98-1.00)	0.95 (0.88-1.00)	1.00 (0.99-1.00)	0.855 (0.695-0.962)	0.99 (0.97-1.00)	0.998 (0.990-1.000)
0.95	2	0.93 (0.87-0.96)	0.38 (0.27-0.50)	0.97 (0.96-0.97)	0.226 (0.120-0.328)	0.90 (0.84-0.93)	0.808 (0.703-0.886)
0.95	3	0.88 (0.83-0.92)	0.21 (0.12-0.32)	0.96 (0.95-0.96)	0.079 (0.054-0.110)	0.85 (0.80-0.88)	0.610 (0.550-0.685)
0.95	4	0.86 (0.80-0.91)	0.18 (0.07-0.32)	0.95 (0.95-0.96)	0.063 (0.042-0.088)	0.82 (0.77-0.87)	0.550 (0.502-0.606)
0.95	5	0.86 (0.81-0.90)	0.16 (0.07-0.27)	0.95 (0.95-0.95)	0.056 (0.037-0.074)	0.82 (0.78-0.86)	0.526 (0.463-0.583)

Strong gene expression changes (2.8-fold)							
Proportion of resistant cases	Number of resistance mechanisms	Sensitivity	Specificity	PPV	NPV	Accuracy	AUC
0.5	1	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.000 (1.000-1.000)
0.5	2	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.000 (1.000-1.000)
0.5	3	0.99 (0.97-1.00)	1.00 (0.99-1.00)	1.00 (0.99-1.00)	0.99 (0.97-1.00)	0.99 (0.98-1.00)	1.000 (0.998-1.000)
0.5	4	0.96 (0.91-0.98)	0.98 (0.97-0.99)	0.98 (0.97-0.99)	0.96 (0.91-0.98)	0.97 (0.94-0.98)	0.994 (0.984-0.998)
0.5	5	0.93 (0.89-0.96)	0.96 (0.93-0.98)	0.96 (0.93-0.98)	0.93 (0.90-0.96)	0.95 (0.91-0.97)	0.985 (0.970-0.994)
0.6	1	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.000 (1.000-1.000)
0.6	2	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.000 (1.000-1.000)
0.6	3	0.99 (0.95-1.00)	1.00 (0.99-1.00)	1.00 (0.99-1.00)	0.98 (0.93-1.00)	0.99 (0.97-1.00)	0.999 (0.996-1.000)
0.6	4	0.97 (0.94-0.98)	0.98 (0.96-0.99)	0.99 (0.97-0.99)	0.95 (0.91-0.97)	0.97 (0.95-0.98)	0.995 (0.987-0.998)
0.6	5	0.93 (0.89-0.96)	0.95 (0.91-0.97)	0.96 (0.94-0.98)	0.90 (0.85-0.94)	0.94 (0.90-0.96)	0.982 (0.963-0.991)
0.7	1	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.000 (1.000-1.000)
0.7	2	1.00 (0.99-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (0.98-1.00)	1.00 (0.99-1.00)	1.000 (1.000-1.000)
0.7	3	0.99 (0.97-1.00)	1.00 (0.98-1.00)	1.00 (0.99-1.00)	0.97 (0.94-0.99)	0.99 (0.98-1.00)	0.999 (0.998-1.000)
0.7	4	0.97 (0.93-0.98)	0.97 (0.94-0.99)	0.99 (0.97-0.99)	0.92 (0.85-0.96)	0.97 (0.93-0.98)	0.994 (0.983-0.998)
0.7	5	0.94 (0.90-0.96)	0.93 (0.88-0.96)	0.97 (0.95-0.98)	0.86 (0.79-0.91)	0.93 (0.90-0.96)	0.979 (0.958-0.989)
0.8	1	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.000 (1.000-1.000)
0.8	2	1.00 (0.99-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (0.98-1.00)	1.00 (1.00-1.00)	1.000 (1.000-1.000)
0.8	3	0.99 (0.98-1.00)	0.99 (0.98-1.00)	1.00 (1.00-1.00)	0.96 (0.92-0.99)	0.99 (0.98-1.00)	0.999 (0.997-1.000)
0.8	4	0.97 (0.94-0.98)	0.96 (0.91-0.98)	0.99 (0.98-1.00)	0.89 (0.79-0.94)	0.97 (0.93-0.98)	0.993 (0.976-0.997)
0.8	5	0.95 (0.91-0.97)	0.90 (0.84-0.94)	0.97 (0.96-0.99)	0.81 (0.71-0.89)	0.94 (0.90-0.96)	0.977 (0.953-0.989)
0.9	1	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.000 (1.000-1.000)
0.9	2	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (0.96-1.00)	1.00 (1.00-1.00)	1.000 (1.000-1.000)
0.9	3	0.99 (0.98-1.00)	0.98 (0.96-1.00)	1.00 (1.00-1.00)	0.94 (0.86-0.98)	0.99 (0.98-1.00)	0.999 (0.996-1.000)
0.9	4	0.98 (0.95-0.99)	0.91 (0.85-0.96)	0.99 (0.98-1.00)	0.82 (0.66-0.92)	0.97 (0.94-0.99)	0.990 (0.975-0.997)
0.9	5	0.96 (0.92-0.98)	0.80 (0.72-0.87)	0.98 (0.97-0.98)	0.69 (0.49-0.81)	0.94 (0.90-0.96)	0.966 (0.925-0.985)
0.95	1	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-	

**Supplementary Table S2: Performance of gene signatures according to the strength of the spiked-in gene expression changes.**

Comparison of the performance of optimal (2.0-fold), weak (1.4-fold) and strong (2.8-fold) signatures.

Proportion of resistant cases	Weak signature					Optimal signature					p-value when comparing signature strength
	Number of resistance mechanisms					Number of resistance mechanisms					
	1	2	3	4	5	1	2	3	4	5	
0.5*	0.999 (0.996-1.000)	0.968 (0.935-0.982)	0.900 (0.844-0.936)	0.818 (0.762-0.855)	0.736 (0.689-0.784)	1.000 (1.000-1.000)	1.000 (0.999-1.000)	0.992 (0.987-0.997)	0.971 (0.955-0.983)	0.931 (0.886-0.955)	< 0.0001
0.6	0.999 (0.996-1.000)	0.970 (0.949-0.984)	0.892 (0.843-0.925)	0.812 (0.747-0.855)	0.729 (0.682-0.771)	1.000 (1.000-1.000)	0.999 (0.997-1.000)	0.992 (0.985-0.996)	0.966 (0.943-0.980)	0.930 (0.882-0.954)	< 0.0001
0.7	0.999 (0.996-1.000)	0.967 (0.944-0.982)	0.895 (0.845-0.921)	0.797 (0.738-0.839)	0.708 (0.659-0.754)	1.000 (1.000-1.000)	1.000 (0.998-1.000)	0.991 (0.977-0.996)	0.967 (0.933-0.980)	0.927 (0.888-0.953)	< 0.0001
0.8	0.999 (0.996-1.000)	0.965 (0.933-0.986)	0.872 (0.810-0.909)	0.746 (0.692-0.784)	0.653 (0.619-0.689)	1.000 (1.000-1.000)	1.000 (0.998-1.000)	0.990 (0.974-0.996)	0.963 (0.933-0.980)	0.920 (0.870-0.947)	< 0.0001
0.9**	0.999 (0.994-1.000)	0.937 (0.883-0.968)	0.754 (0.692-0.820)	0.631 (0.581-0.686)	0.573 (0.527-0.612)	1.000 (1.000-1.000)	0.999 (0.998-1.000)	0.987 (0.967-0.995)	0.943 (0.898-0.967)	0.866 (0.786-0.919)	< 0.0001
0.95	0.998 (0.990-1.000)	0.808 (0.703-0.886)	0.610 (0.550-0.685)	0.550 (0.502-0.606)	0.526 (0.463-0.583)	1.000 (1.000-1.000)	0.999 (0.994-1.000)	0.951 (0.864-0.987)	0.803 (0.728-0.881)	0.687 (0.619-0.754)	< 0.0001

Proportion of resistant cases	Optimal signature					Strong signature					p-value when compare signature strength
	Number of resistance mechanisms					Number of resistance mechanisms					
	1	2	3	4	5	1	2	3	4	5	
0.5*	1.000 (1.000-1.000)	1.000 (0.999-1.000)	0.992 (0.987-0.997)	0.971 (0.955-0.983)	0.931 (0.886-0.955)	1.000 (1.000-1.000)	1.000 (1.000-1.000)	1.000 (0.998-1.000)	0.994 (0.984-0.998)	0.985 (0.970-0.994)	> 0.05
0.6	1.000 (1.000-1.000)	0.999 (0.997-1.000)	0.992 (0.985-0.996)	0.966 (0.943-0.980)	0.930 (0.882-0.954)	1.000 (1.000-1.000)	1.000 (1.000-1.000)	0.999 (0.996-1.000)	0.995 (0.987-0.998)	0.982 (0.963-0.991)	> 0.05
0.7	1.000 (1.000-1.000)	1.000 (0.998-1.000)	0.991 (0.977-0.996)	0.967 (0.933-0.980)	0.927 (0.888-0.953)	1.000 (1.000-1.000)	1.000 (1.000-1.000)	0.999 (0.998-1.000)	0.994 (0.983-0.998)	0.979 (0.958-0.989)	> 0.05
0.8	1.000 (1.000-1.000)	1.000 (0.998-1.000)	0.990 (0.974-0.996)	0.963 (0.933-0.980)	0.920 (0.870-0.947)	1.000 (1.000-1.000)	1.000 (1.000-1.000)	0.999 (0.997-1.000)	0.993 (0.976-0.997)	0.977 (0.953-0.989)	> 0.05
0.9**	1.000 (1.000-1.000)	0.999 (0.998-1.000)	0.987 (0.967-0.995)	0.943 (0.898-0.967)	0.866 (0.786-0.919)	1.000 (1.000-1.000)	1.000 (1.000-1.000)	0.999 (0.996-1.000)	0.990 (0.975-0.997)	0.966 (0.925-0.985)	> 0.05
0.95	1.000 (1.000-1.000)	0.999 (0.994-1.000)	0.951 (0.864-0.987)	0.803 (0.728-0.881)	0.687 (0.619-0.754)	1.000 (1.000-1.000)	1.000 (1.000-1.000)	0.997 (0.991-1.000)	0.959 (0.893-0.988)	0.850 (0.757-0.929)	0.005

**Supplementary Table S3: Impact of distinct mechanisms of resistance on signatures generated using superPC.**

Analysis of the impact of distinct mechanisms of resistance on the area under the curve (AUC) of receiver operating characteristic (ROC) curves derived with the predictive gene signatures generated using superPC.

Proportion of resistant cases	Optimal signature (2.0-fold)					p-value for trend
	Number of resistance mechanisms					
	1	2	3	4	5	
0.5*	0.997 (0.991-0.999)	0.991 (0.982-0.997)	0.920 (0.829-0.963)	0.640 (0.544-0.731)	0.662 (0.604-0.718)	< 0.0001
0.6	0.915 (0.912-0.919)	0.912 (0.908-0.915)	0.884 (0.831-0.907)	0.632 (0.492-0.768)	0.617 (0.554-0.686)	< 0.0001
0.7	0.856 (0.852-0.860)	0.852 (0.847-0.856)	0.831 (0.793-0.848)	0.594 (0.467-0.737)	0.587 (0.516-0.661)	< 0.0001
0.8	0.811 (0.808-0.815)	0.807 (0.803-0.812)	0.765 (0.704-0.801)	0.583 (0.437-0.738)	0.569 (0.502-0.647)	< 0.0001
0.9**	0.776 (0.773-0.780)	0.772 (0.761-0.777)	0.673 (0.588-0.741)	0.575 (0.452-0.710)	0.575 (0.506-0.629)	< 0.0001
0.95	0.761 (0.757-0.765)	0.739 (0.697-0.759)	0.627 (0.565-0.691)	0.585 (0.526-0.645)	0.564 (0.526-0.601)	< 0.0001

  

Proportion of resistant cases	Weak signature (1.4-fold)					p-value for trend
	Number of resistance mechanisms					
	1	2	3	4	5	
0.5*	0.938 (0.859-0.988)	0.763 (0.673-0.856)	0.652 (0.593-0.702)	0.623 (0.584-0.666)	0.591 (0.559-0.621)	0.0005
0.6	0.892 (0.849-0.914)	0.770 (0.654-0.855)	0.627 (0.580-0.680)	0.616 (0.576-0.656)	0.587 (0.555-0.619)	> 0.05
0.7	0.841 (0.811-0.855)	0.718 (0.632-0.808)	0.604 (0.556-0.650)	0.602 (0.567-0.641)	0.579 (0.547-0.613)	< 0.0001
0.8	0.797 (0.768-0.811)	0.674 (0.590-0.750)	0.593 (0.548-0.630)	0.582 (0.544-0.611)	0.560 (0.531-0.584)	< 0.0001
0.9**	0.753 (0.720-0.773)	0.630 (0.568-0.697)	0.570 (0.530-0.612)	0.547 (0.514-0.583)	0.529 (0.495-0.561)	< 0.0001
0.95	0.712 (0.675-0.750)	0.579 (0.530-0.639)	0.537 (0.491-0.593)	0.522 (0.483-0.570)	0.511 (0.474-0.553)	< 0.0001

  

Proportion of resistant cases	Strong signature (2.8-fold)					p-value for trend
	Number of resistance mechanisms					
	1	2	3	4	5	
0.5*	0.999 (0.999-0.999)	0.999 (0.998-0.999)	0.992 (0.980-0.997)	0.607 (0.435-0.745)	0.573 (0.501-0.663)	< 0.0001
0.6	0.915 (0.912-0.918)	0.912 (0.908-0.916)	0.910 (0.905-0.913)	0.569 (0.383-0.783)	0.537 (0.461-0.645)	< 0.0001
0.7	0.856 (0.852-0.860)	0.853 (0.848-0.857)	0.850 (0.846-0.854)	0.572 (0.370-0.830)	0.513 (0.405-0.620)	0.0013
0.8	0.812 (0.808-0.817)	0.808 (0.805-0.813)	0.805 (0.801-0.809)	0.578 (0.449-0.764)	0.515 (0.396-0.663)	0.0046
0.9**	0.777 (0.772-0.781)	0.774 (0.769-0.777)	0.768 (0.754-0.774)	0.558 (0.390-0.727)	0.519 (0.424-0.609)	0.0021
0.95	0.762 (0.758-0.765)	0.759 (0.755-0.763)	0.711 (0.655-0.746)	0.586 (0.477-0.687)	0.572 (0.502-0.625)	< 0.0001

Perturbed datasets in which s% (s%=5%, 10%, 20%, 30%, 40% or 50%) of the cases were designated to be therapy sensitive were generated. Within the 1-s% resistant cases, we allocated the cases randomly into n (n=1, 2, 3, 4, 5) equally-sized groups of resistance mechanisms. For each nth resistance mechanism, 100 genes were randomly selected as the “true” gene expression changes and were spiked-in by v (v=0.5, 1, 1.5). Classification was performed using superPC. For each combination of s, n and v, we repeated the spiking and classification 100 times. The mean value and the 95% confidence intervals of the AUCs for each combination of s, n and v are shown. For v=0.5,1,1.5, the sections are labeled “Optimal signature (2-fold)”, “Weak signature (1.4-fold)” and “Strong signature (2.8-fold)” respectively. The last column shows the p-values for the trend tests as the number of resistance mechanisms is increased from 1 to 5 for a given s%.

\*: ideal setting; \*\*: clinically-realistic setting

**Supplementary Table S4: Impact of signature strength on signature performance, when signatures are generated with SuperPC.**

Analysis of the impact of multiple mechanisms of resistance on the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and area under curve (AUC) of receiver operating characteristic (ROC) curves of the predictive gene signatures generated with superPC, where the spiked-in gene expression changes were optimal (2-fold), weak (1.4-fold) or strong (2.8-fold), and comparisons of their performances.

Optimal gene expression changes (2-fold)							
Proportion of resistant cases	Number of resistance mechanisms	Sensitivity	Specificity	PPV	NPV	Accuracy	AUC
0.5	1	1.00 (0.99-1.00)	1.00 (0.99-1.00)	1.00 (0.99-1.00)	0.998 (0.991-1.000)	1.00 (0.99-1.00)	0.997 (0.991-0.999)
0.5	2	0.99 (0.98-1.00)	0.99 (0.98-1.00)	0.99 (0.98-1.00)	0.990 (0.981-0.997)	0.99 (0.98-1.00)	0.991 (0.982-0.997)
0.5	3	0.92 (0.83-0.96)	0.92 (0.83-0.96)	0.92 (0.83-0.96)	0.920 (0.828-0.963)	0.92 (0.83-0.96)	0.920 (0.829-0.963)
0.5	4	0.65 (0.55-0.74)	0.63 (0.54-0.73)	0.64 (0.54-0.73)	0.641 (0.544-0.732)	0.64 (0.54-0.73)	0.640 (0.544-0.731)
0.5	5	0.67 (0.61-0.72)	0.66 (0.59-0.71)	0.66 (0.60-0.72)	0.663 (0.605-0.718)	0.66 (0.60-0.72)	0.662 (0.604-0.718)
0.6	1	0.83 (0.82-0.84)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	0.799 (0.792-0.805)	0.90 (0.89-0.90)	0.915 (0.912-0.919)
0.6	2	0.82 (0.82-0.83)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	0.792 (0.785-0.798)	0.89 (0.89-0.90)	0.912 (0.908-0.915)
0.6	3	0.80 (0.76-0.82)	0.97 (0.90-1.00)	0.97 (0.92-1.00)	0.765 (0.715-0.787)	0.87 (0.82-0.89)	0.884 (0.831-0.907)
0.6	4	0.61 (0.50-0.72)	0.65 (0.49-0.82)	0.73 (0.59-0.86)	0.529 (0.392-0.661)	0.63 (0.49-0.76)	0.632 (0.492-0.768)
0.6	5	0.60 (0.55-0.65)	0.64 (0.56-0.72)	0.71 (0.65-0.78)	0.513 (0.453-0.580)	0.61 (0.55-0.68)	0.617 (0.554-0.686)
0.7	1	0.71 (0.70-0.72)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	0.599 (0.592-0.606)	0.80 (0.79-0.80)	0.856 (0.852-0.860)
0.7	2	0.70 (0.69-0.71)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	0.592 (0.585-0.599)	0.79 (0.79-0.80)	0.852 (0.847-0.856)
0.7	3	0.69 (0.67-0.70)	0.97 (0.92-1.00)	0.98 (0.95-1.00)	0.574 (0.542-0.589)	0.77 (0.74-0.79)	0.831 (0.793-0.848)
0.7	4	0.56 (0.49-0.64)	0.63 (0.45-0.83)	0.78 (0.67-0.90)	0.379 (0.271-0.499)	0.58 (0.48-0.70)	0.594 (0.467-0.737)
0.7	5	0.56 (0.52-0.60)	0.62 (0.52-0.73)	0.77 (0.71-0.84)	0.374 (0.313-0.435)	0.58 (0.52-0.63)	0.587 (0.516-0.661)
0.8	1	0.62 (0.62-0.63)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	0.398 (0.394-0.403)	0.70 (0.69-0.70)	0.811 (0.808-0.815)
0.8	2	0.62 (0.61-0.62)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	0.393 (0.388-0.399)	0.69 (0.68-0.70)	0.807 (0.803-0.812)
0.8	3	0.60 (0.58-0.62)	0.93 (0.83-0.99)	0.97 (0.93-1.00)	0.367 (0.329-0.390)	0.66 (0.63-0.69)	0.765 (0.704-0.801)
0.8	4	0.54 (0.48-0.59)	0.63 (0.40-0.88)	0.85 (0.76-0.95)	0.252 (0.160-0.350)	0.55 (0.46-0.65)	0.583 (0.437-0.738)
0.8	5	0.53 (0.51-0.56)	0.61 (0.50-0.73)	0.84 (0.80-0.89)	0.243 (0.200-0.294)	0.55 (0.51-0.60)	0.569 (0.502-0.647)
0.9	1	0.55 (0.55-0.56)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	0.201 (0.198-0.203)	0.60 (0.59-0.60)	0.776 (0.773-0.780)
0.9	2	0.55 (0.54-0.55)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	0.198 (0.192-0.201)	0.59 (0.58-0.60)	0.772 (0.761-0.777)
0.9	3	0.53 (0.51-0.54)	0.82 (0.66-0.94)	0.96 (0.93-0.99)	0.163 (0.133-0.187)	0.56 (0.53-0.58)	0.673 (0.588-0.741)
0.9	4	0.52 (0.49-0.54)	0.63 (0.41-0.88)	0.93 (0.88-0.98)	0.128 (0.083-0.176)	0.53 (0.48-0.57)	0.575 (0.452-0.710)
0.9	5	0.52 (0.51-0.53)	0.63 (0.50-0.73)	0.93 (0.90-0.95)	0.128 (0.102-0.147)	0.53 (0.51-0.55)	0.575 (0.506-0.629)
0.95	1	0.52 (0.52-0.53)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	0.100 (0.099-0.102)	0.55 (0.54-0.55)	0.761 (0.757-0.765)
0.95	2	0.52 (0.51-0.52)	0.96 (0.88-1.00)	1.00 (0.99-1.00)	0.095 (0.087-0.100)	0.54 (0.53-0.55)	0.739 (0.697-0.759)
0.95	3	0.51 (0.50-0.52)	0.75 (0.63-0.86)	0.98 (0.96-0.99)	0.072 (0.060-0.083)	0.52 (0.51-0.53)	0.627 (0.565-0.691)
0.95	4	0.51 (0.50-0.51)	0.66 (0.55-0.78)	0.97 (0.95-0.98)	0.066 (0.055-0.078)	0.52 (0.51-0.53)	0.585 (0.526-0.645)
0.95	5	0.50 (0.50-0.51)	0.63 (0.55-0.70)	0.96 (0.95-0.97)	0.063 (0.055-0.070)	0.51 (0.50-0.52)	0.564 (0.526-0.601)

Weak gene expression changes (1.4-fold)							
Proportion of resistant cases	Number of resistance mechanisms	Sensitivity	Specificity	PPV	NPV	Accuracy	AUC
0.5	1	0.94 (0.86-0.99)	0.94 (0.86-0.99)	0.94 (0.86-0.99)	0.939 (0.857-0.989)	0.94 (0.86-0.99)	0.938 (0.859-0.988)
0.5	2	0.76 (0.67-0.85)	0.76 (0.67-0.86)	0.76 (0.67-0.86)	0.764 (0.674-0.854)	0.76 (0.67-0.86)	0.763 (0.673-0.856)
0.5	3	0.65 (0.59-0.71)	0.65 (0.59-0.70)	0.65 (0.59-0.70)	0.654 (0.594-0.705)	0.65 (0.59-0.70)	0.652 (0.593-0.702)
0.5	4	0.62 (0.59-0.67)	0.62 (0.58-0.66)	0.62 (0.58-0.67)	0.623 (0.584-0.666)	0.62 (0.58-0.67)	0.623 (0.584-0.666)
0.5	5	0.59 (0.56-0.63)	0.59 (0.56-0.62)	0.59 (0.56-0.62)	0.590 (0.558-0.621)	0.59 (0.56-0.62)	0.591 (0.559-0.621)
0.6	1	0.81 (0.77-0.83)	0.97 (0.92-1.00)	0.98 (0.94-1.00)	0.775 (0.732-0.797)	0.88 (0.83-0.90)	0.892 (0.849-0.914)
0.6	2	0.71 (0.62-0.78)	0.83 (0.69-0.93)	0.86 (0.75-0.94)	0.658 (0.548-0.739)	0.78 (0.65-0.84)	0.770 (0.654-0.855)
0.6	3	0.60 (0.56-0.65)	0.65 (0.60-0.72)	0.72 (0.68-0.77)	0.523 (0.477-0.573)	0.62 (0.58-0.67)	0.627 (0.580-0.680)
0.6	4	0.59 (0.56-0.63)	0.64 (0.59-0.69)	0.71 (0.67-0.75)	0.512 (0.474-0.551)	0.61 (0.57-0.65)	0.616 (0.576-0.656)
0.6	5	0.57 (0.54-0.59)	0.61 (0.56-0.64)	0.68 (0.65-0.71)	0.484 (0.453-0.515)	0.58 (0.55-0.61)	0.587 (0.555-0.619)
0.7	1	0.70 (0.68-0.71)	0.98 (0.94-1.00)	0.99 (0.96-1.00)	0.584 (0.559-0.598)	0.78 (0.76-0.80)	0.841 (0.811-0.855)
0.7	2	0.63 (0.58-0.68)	0.81 (0.69-0.94)	0.89 (0.81-0.96)	0.482 (0.410-0.556)	0.68 (0.61-0.76)	0.718 (0.632-0.808)
0.7	3	0.56 (0.53-0.59)	0.64 (0.58-0.71)	0.79 (0.75-0.83)	0.387 (0.347-0.425)	0.59 (0.55-0.63)	0.604 (0.556-0.650)
0.7	4	0.56 (0.54-0.58)	0.64 (0.59-0.69)	0.79 (0.76-0.82)	0.386 (0.356-0.419)	0.59 (0.56-0.62)	0.602 (0.567-0.641)
0.7	5	0.55 (0.53-0.56)	0.61 (0.57-0.66)	0.77 (0.74-0.80)	0.366 (0.339-0.394)	0.57 (0.54-0.59)	0.579 (0.547-0.613)
0.8	1	0.61 (0.60-0.62)	0.98 (0.93-1.00)	0.99 (0.97-1.00)	0.387 (0.371-0.398)	0.69 (0.67-0.70)	0.797 (0.768-0.811)
0.8	2	0.57 (0.54-0.60)	0.78 (0.64-0.90)	0.91 (0.86-0.96)	0.310 (0.257-0.358)	0.61 (0.56-0.66)	0.674 (0.590-0.750)
0.8	3	0.54 (0.52-0.55)	0.65 (0.58-0.71)	0.86 (0.83-0.88)	0.259 (0.230-0.282)	0.56 (0.53-0.58)	0.593 (0.548-0.630)
0.8	4	0.53 (0.52-0.54)	0.63 (0.57-0.68)	0.85 (0.83-0.87)	0.252 (0.228-0.270)	0.55 (0.53-0.57)	0.582 (0.544-0.611)
0.8	5	0.52 (0.51-0.53)	0.60 (0.55-0.64)	0.84 (0.82-0.85)	0.237 (0.219-0.253)	0.54 (0.52-0.55)	0.580 (0.531-0.584)
0.9	1	0.54 (0.53-0.55)	0.96 (0.90-1.00)	0.99 (0.98-1.00)	0.191 (0.180-0.198)	0.59 (0.57-0.60)	0.753 (0.720-0.773)
0.9	2	0.52 (0.51-0.54)	0.74 (0.63-0.86)	0.95 (0.92-0.97)	0.147 (0.125-0.172)	0.54 (0.52-0.57)	0.630 (0.568-0.697)
0.9	3	0.51 (0.50-0.52)	0.63 (0.56-0.71)	0.92 (0.91-0.94)	0.126 (0.111-0.141)	0.52 (0.51-0.54)	0.570 (0.530-0.612)
0.9	4	0.51 (0.50-0.52)	0.59 (0.52-0.65)	0.92 (0.90-0.93)	0.117 (0.105-0.130)	0.51 (0.50-0.53)	0.547 (0.514-0.583)
0.9	5	0.50 (0.49-0.51)	0.55 (0.49-0.62)	0.91 (0.90-0.92)	0.111 (0.099-0.122)	0.51 (0.49-0.52)	0.529 (0.495-0.561)
0.95	1	0.51 (0.51-0.52)	0.91 (0.84-0.99)	0.99 (0.98-1.00)	0.090 (0.083-0.097)	0.53 (0.52-0.54)	0.712 (0.675-0.750)
0.95	2	0.50 (0.49-0.51)	0.66 (0.56-0.77)	0.97 (0.96-0.98)	0.065 (0.056-0.077)	0.51 (0.50-0.52)	0.579 (0.530-0.639)
0.95	3	0.50 (0.49-0.51)	0.57 (0.48-0.68)	0.96 (0.95-0.97)	0.055 (0.047-0.065)	0.50 (0.49-0.51)	0.537 (0.491-0.593)
0.95	4	0.50 (0.49-0.51)	0.55 (0.47-0.64)	0.95 (0.95-0.96)	0.054 (0.047-0.064)	0.50 (0.49-0.51)	0.522 (0.483-0.570)
0.95	5	0.50 (0.49-0.50)	0.52 (0.45-0.60)	0.95 (0.94-0.96)	0.052 (0.045-0.060)	0.50 (0.49-0.51)	0.511 (0.474-0.553)

Strong gene expression changes (2.8-fold)							
Proportion of resistant cases	Number of resistance mechanisms	Sensitivity	Specificity	PPV	NPV	Accuracy	AUC
0.5	1	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.000 (1.000-1.000)	1.00 (1.00-1.00)	0.999 (0.999-0.999)
0.5	2	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	0.998 (0.996-0.999)	1.00 (1.00-1.00)	0.999 (0.998-0.999)
0.5	3	0.99 (0.98-1.00)	0.99 (0.98-1.00)	0.99 (0.98-1.00)	0.991 (0.979-0.996)	0.99 (0.98-1.00)	0.992 (0.980-0.997)
0.5	4	0.61 (0.44-0.75)	0.60 (0.43-0.74)	0.61 (0.44-0.75)	0.607 (0.434-0.747)	0.61 (0.44-0.75)	0.607 (0.435-0.745)
0.5	5	0.58 (0.51-0.67)	0.56 (0.49-0.66)	0.57 (0.50-0.66)	0.573 (0.500-0.663)	0.57 (0.50-0.66)	0.573 (0.501-0.663)
0.6	1	0.83 (0.82-0.84)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	0.799 (0.793-0.804)	0.90 (0.89-0.90)	0.915 (0.912-0.918)
0.6	2	0.82 (0.82-0.83)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	0.793 (0.785-0.800)	0.89 (0.89-0.90)	0.912 (0.908-0.916)
0.6	3	0.82 (0.81-0.83)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	0.788 (0.780-0.794)	0.89 (0.89-0.90)	0.910 (0.905-0.913)
0.6	4	0.56 (0.41-0.73)	0.58 (0.35-0.84)	0.67 (0.49-0.87)	0.467 (0.287-0.673)	0.57 (0.39-0.77)	0.569 (0.383-0.783)
0.6	5	0.54 (0.48-0.62)	0.54 (0.45-0.67)	0.63 (0.56-0.74)	0.436 (0.362-0.541)	0.54 (0.46-0.64)	0.537 (0.461-0.645)
0.7	1	0.71 (0.70-0.72)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	0.599 (0.592-0.605)	0.80 (0.79-0.80)	0.856 (0.852-0.860)
0.7	2	0.71 (0.70-0.71)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	0.594 (0.586-0.600)	0.79 (0.79-0.80)	0.853 (0.848-0.857)
0.7	3	0.70 (0.69-0.71)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	0.588 (0.582-0.596)	0.79 (0.78-0.80)	0.850 (0.846-0.854)
0.7	4	0.55 (0.42-0.70)	0.60 (0.32-0.96)	0.76 (0.59-0.98)	0.360 (0.190-0.577)	0.56 (0.39-0.78)	0.572 (0.370-0.830)
0.7	5	0.51 (0.45-0.58)	0.51 (0.36-0.66)	0.71 (0.62-0.80)	0.311 (0.219-0.402)	0.51 (0.42-0.60)	0.513 (0.405-0.620)
0.8	1	0.62 (0.62-0.63)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	0.399 (0.394-0.405)	0.70 (0.69-0.71)	0.812 (0.808-0.817)
0.8	2	0.62 (0.61-0.63)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	0.395 (0.390-0.400)	0.69 (0.69-0.70)	0.808 (0.805-0.813)
0.8	3	0.61 (0.60-0.62)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	0.391 (0.387-0.396)	0.69 (0.68-0.70)	0.805 (0.801-0.809)
0.8	4	0.53 (0.48-0.61)	0.62 (0.42-0.92)	0.85 (0.77-0.97)	0.249 (0.167-0.368)	0.55 (0.47-0.67)	0.578 (0.449-0.764)
0.8	5	0.51 (0.46-0.57)	0.52 (0.34-0.75)	0.81 (0.73-0.90)	0.209 (0.133-0.304)	0.51 (0.43-0.61)	0.515 (0.396-0.663)
0.9	1	0.55 (0.54-0.56)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	0.201 (0.198-0.204)	0.60 (0.59-0.61)	0.777 (0.772-0.781)
0.9	2	0.55 (0.54-0.55)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	0.198 (0.195-0.201)	0.59 (0.58-0.60)	0.774 (0.769-0.777)
0.9	3	0.54 (0.53-0.55)	0.99 (0.97-1.00)	1.00 (0.99-1.00)	0.196 (0.191-0.199)	0.59 (0.58-0.60)	0.768 (0.754-0.774)
0.9	4	0.51 (0.48-0.54)	0.60 (0.30-0.91)	0.92 (0.86-0.98)	0.122 (0.061-0.182)	0.52 (0.46-0.58)	0.558 (0.390-0.727)
0.9	5	0.51 (0.49-0.52)	0.53 (0.36-0.69)	0.91 (0.87-0.94			

**Supplementary Table S5: Impact of unevenly distributed but similarly prevalent resistance mechanisms in the training and test sets on signature performance.**

Analysis of the impact of multiple mechanisms of resistance leading to optimal (2.0-fold), weak (1.4-fold) or strong (2.8-fold) gene expression changes, where the resistance mechanisms displayed uneven frequencies but similar prevalence in training and test sets, on the predictive gene signature performance.

Optimal gene expression changes (2.0-fold)							
Proportion of resistant cases	Number of resistance mechanisms	Sensitivity	Specificity	PPV	NPV	Accuracy	AUC
0.5	2	0.84 (0.67-1.00)	1.00 (0.99-1.00)	1.00 (0.99-1.00)	0.87 (0.75-1.00)	0.92 (0.83-1.00)	0.961 (0.890-1.000)
0.5	3	0.78 (0.57-0.96)	0.99 (0.97-1.00)	0.99 (0.96-1.00)	0.82 (0.70-0.96)	0.89 (0.78-0.98)	0.929 (0.852-0.991)
0.5	4	0.74 (0.55-0.88)	0.98 (0.93-1.00)	0.97 (0.92-1.00)	0.79 (0.69-0.89)	0.86 (0.77-0.94)	0.903 (0.841-0.965)
0.5	5	0.71 (0.55-0.84)	0.95 (0.89-1.00)	0.94 (0.87-0.99)	0.77 (0.68-0.86)	0.83 (0.76-0.91)	0.882 (0.817-0.945)
0.6	2	0.83 (0.66-0.99)	1.00 (0.99-1.00)	1.00 (0.99-1.00)	0.81 (0.66-0.99)	0.90 (0.80-0.99)	0.956 (0.885-1.000)
0.6	3	0.78 (0.58-0.96)	0.99 (0.97-1.00)	0.99 (0.97-1.00)	0.76 (0.61-0.95)	0.86 (0.75-0.98)	0.928 (0.848-0.991)
0.6	4	0.73 (0.54-0.90)	0.97 (0.92-1.00)	0.98 (0.94-1.00)	0.71 (0.58-0.87)	0.83 (0.71-0.93)	0.900 (0.815-0.966)
0.6	5	0.72 (0.52-0.85)	0.94 (0.88-0.99)	0.95 (0.90-0.99)	0.70 (0.57-0.80)	0.81 (0.70-0.90)	0.882 (0.813-0.944)
0.7	2	0.84 (0.66-0.99)	1.00 (0.99-1.00)	1.00 (0.99-1.00)	0.76 (0.56-0.99)	0.89 (0.76-1.00)	0.957 (0.885-1.000)
0.7	3	0.77 (0.57-0.97)	0.99 (0.95-1.00)	0.99 (0.97-1.00)	0.66 (0.49-0.93)	0.83 (0.69-0.97)	0.923 (0.837-0.991)
0.7	4	0.75 (0.54-0.92)	0.96 (0.90-1.00)	0.98 (0.95-1.00)	0.63 (0.48-0.85)	0.81 (0.68-0.94)	0.902 (0.821-0.974)
0.7	5	0.73 (0.52-0.87)	0.94 (0.85-0.99)	0.96 (0.92-1.00)	0.60 (0.46-0.75)	0.79 (0.65-0.89)	0.880 (0.801-0.944)
0.8	2	0.85 (0.67-1.00)	1.00 (0.99-1.00)	1.00 (1.00-1.00)	0.67 (0.43-0.98)	0.88 (0.74-1.00)	0.959 (0.888-1.000)
0.8	3	0.77 (0.59-0.96)	0.98 (0.93-1.00)	0.99 (0.98-1.00)	0.55 (0.37-0.87)	0.82 (0.67-0.97)	0.925 (0.844-0.990)
0.8	4	0.75 (0.58-0.92)	0.95 (0.87-1.00)	0.99 (0.96-1.00)	0.51 (0.37-0.75)	0.79 (0.66-0.92)	0.900 (0.827-0.975)
0.8	5	0.74 (0.57-0.89)	0.91 (0.79-0.99)	0.97 (0.94-1.00)	0.48 (0.36-0.66)	0.77 (0.65-0.89)	0.878 (0.819-0.940)
0.9	2	0.85 (0.68-0.99)	1.00 (0.98-1.00)	1.00 (1.00-1.00)	0.52 (0.26-0.95)	0.86 (0.71-0.99)	0.958 (0.895-1.000)
0.9	3	0.79 (0.62-0.97)	0.97 (0.88-1.00)	1.00 (0.99-1.00)	0.39 (0.22-0.76)	0.81 (0.65-0.96)	0.925 (0.851-0.990)
0.9	4	0.77 (0.57-0.93)	0.90 (0.75-1.00)	0.99 (0.97-1.00)	0.34 (0.20-0.60)	0.79 (0.61-0.93)	0.898 (0.821-0.965)
0.9	5	0.78 (0.56-0.91)	0.82 (0.62-0.98)	0.98 (0.95-1.00)	0.31 (0.19-0.48)	0.78 (0.60-0.89)	0.872 (0.800-0.935)
0.95	2	0.85 (0.70-1.00)	0.99 (0.96-1.00)	1.00 (1.00-1.00)	0.39 (0.15-0.93)	0.86 (0.71-1.00)	0.958 (0.897-1.000)
0.95	3	0.83 (0.64-0.97)	0.89 (0.64-1.00)	0.99 (0.98-1.00)	0.26 (0.12-0.63)	0.83 (0.66-0.97)	0.917 (0.843-0.986)
0.95	4	0.83 (0.63-0.93)	0.69 (0.38-1.00)	0.98 (0.96-1.00)	0.19 (0.12-0.35)	0.82 (0.65-0.92)	0.863 (0.778-0.951)
0.95	5	0.85 (0.69-0.93)	0.49 (0.23-0.89)	0.97 (0.96-0.99)	0.15 (0.10-0.26)	0.83 (0.70-0.90)	0.802 (0.690-0.899)

Weak gene expression changes (1.4-fold)							
Proportion of resistant cases	Number of resistance mechanisms	Sensitivity	Specificity	PPV	NPV	Accuracy	AUC
0.5	2	0.83 (0.72-0.96)	0.95 (0.89-1.00)	0.94 (0.88-1.00)	0.851 (0.776-0.96)	0.89 (0.83-0.97)	0.937 (0.891-0.986)
0.5	3	0.76 (0.64-0.90)	0.89 (0.80-0.98)	0.88 (0.79-0.97)	0.791 (0.718-0.91)	0.83 (0.76-0.92)	0.886 (0.831-0.955)
0.5	4	0.73 (0.63-0.83)	0.83 (0.74-0.94)	0.82 (0.73-0.92)	0.754 (0.694-0.83)	0.78 (0.72-0.86)	0.844 (0.783-0.911)
0.5	5	0.70 (0.61-0.78)	0.78 (0.68-0.90)	0.76 (0.68-0.88)	0.721 (0.662-0.80)	0.74 (0.67-0.82)	0.803 (0.733-0.884)
0.6	2	0.85 (0.74-0.96)	0.94 (0.88-1.00)	0.96 (0.91-1.00)	0.815 (0.705-0.95)	0.89 (0.82-0.97)	0.942 (0.893-0.985)
0.6	3	0.78 (0.66-0.91)	0.88 (0.78-0.97)	0.91 (0.84-0.98)	0.733 (0.639-0.87)	0.82 (0.75-0.91)	0.891 (0.832-0.960)
0.6	4	0.75 (0.63-0.83)	0.81 (0.71-0.92)	0.86 (0.80-0.93)	0.685 (0.610-0.77)	0.77 (0.72-0.84)	0.848 (0.791-0.904)
0.6	5	0.73 (0.64-0.79)	0.74 (0.63-0.88)	0.81 (0.74-0.90)	0.646 (0.578-0.72)	0.73 (0.67-0.80)	0.805 (0.740-0.874)
0.7	2	0.85 (0.75-0.94)	0.93 (0.85-0.99)	0.97 (0.93-1.00)	0.733 (0.614-0.88)	0.87 (0.81-0.95)	0.938 (0.893-0.979)
0.7	3	0.79 (0.68-0.90)	0.85 (0.74-0.96)	0.93 (0.88-0.98)	0.645 (0.543-0.80)	0.81 (0.74-0.90)	0.887 (0.835-0.952)
0.7	4	0.77 (0.66-0.85)	0.76 (0.63-0.91)	0.88 (0.83-0.95)	0.586 (0.498-0.70)	0.76 (0.70-0.85)	0.838 (0.772-0.919)
0.7	5	0.74 (0.65-0.80)	0.68 (0.56-0.85)	0.85 (0.79-0.92)	0.534 (0.466-0.63)	0.73 (0.67-0.79)	0.788 (0.708-0.867)
0.8	2	0.86 (0.76-0.96)	0.91 (0.82-0.99)	0.98 (0.95-1.00)	0.632 (0.492-0.86)	0.87 (0.79-0.97)	0.936 (0.891-0.986)
0.8	3	0.81 (0.70-0.90)	0.80 (0.66-0.96)	0.94 (0.91-0.99)	0.525 (0.409-0.70)	0.81 (0.73-0.90)	0.881 (0.827-0.952)
0.8	4	0.79 (0.69-0.86)	0.68 (0.51-0.90)	0.91 (0.87-0.97)	0.451 (0.369-0.59)	0.77 (0.71-0.84)	0.821 (0.738-0.904)
0.8	5	0.78 (0.70-0.84)	0.57 (0.42-0.78)	0.88 (0.84-0.93)	0.392 (0.314-0.52)	0.74 (0.68-0.81)	0.760 (0.653-0.859)
0.9	2	0.87 (0.78-0.97)	0.83 (0.65-0.98)	0.98 (0.96-1.00)	0.454 (0.303-0.74)	0.87 (0.79-0.95)	0.922 (0.872-0.979)
0.9	3	0.84 (0.75-0.92)	0.61 (0.38-0.94)	0.95 (0.93-0.99)	0.304 (0.213-0.51)	0.81 (0.75-0.90)	0.828 (0.709-0.929)
0.9	4	0.83 (0.74-0.89)	0.47 (0.27-0.83)	0.93 (0.91-0.98)	0.232 (0.152-0.38)	0.79 (0.74-0.86)	0.748 (0.619-0.890)
0.9	5	0.82 (0.75-0.88)	0.36 (0.22-0.60)	0.92 (0.91-0.95)	0.183 (0.127-0.25)	0.78 (0.73-0.82)	0.673 (0.570-0.801)
0.95	2	0.89 (0.84-0.96)	0.56 (0.27-0.96)	0.97 (0.96-1.00)	0.222 (0.134-0.52)	0.87 (0.82-0.95)	0.853 (0.739-0.979)
0.95	3	0.88 (0.82-0.93)	0.33 (0.15-0.69)	0.96 (0.95-0.98)	0.124 (0.071-0.25)	0.85 (0.80-0.90)	0.717 (0.587-0.906)
0.95	4	0.87 (0.81-0.92)	0.24 (0.12-0.46)	0.96 (0.95-0.97)	0.088 (0.050-0.16)	0.84 (0.79-0.88)	0.633 (0.534-0.799)
0.95	5	0.86 (0.80-0.91)	0.20 (0.10-0.35)	0.95 (0.95-0.96)	0.069 (0.044-0.11)	0.83 (0.77-0.87)	0.579 (0.491-0.749)

Strong gene expression changes (2.8-fold)							
Proportion of resistant cases	Number of resistance mechanisms	Sensitivity	Specificity	PPV	NPV	Accuracy	AUC
0.5	2	0.83 (0.63-1.00)	1.00 (1.00-1)	1.00 (1.00-1)	0.86 (0.73-1.00)	0.91 (0.82-1.00)	0.959 (0.884-1.000)
0.5	3	0.76 (0.54-0.98)	1.00 (1.00-1)	1.00 (1.00-1)	0.81 (0.68-0.98)	0.88 (0.77-0.99)	0.931 (0.840-0.999)
0.5	4	0.72 (0.48-0.93)	1.00 (0.98-1)	1.00 (0.98-1)	0.79 (0.66-0.94)	0.86 (0.74-0.96)	0.907 (0.823-0.983)
0.5	5	0.69 (0.46-0.86)	0.99 (0.97-1)	0.99 (0.96-1)	0.77 (0.65-0.87)	0.84 (0.73-0.92)	0.889 (0.810-0.969)
0.6	2	0.82 (0.63-1.00)	1.00 (1.00-1)	1.00 (1.00-1)	0.81 (0.64-1.00)	0.89 (0.78-1.00)	0.953 (0.875-1.000)
0.6	3	0.73 (0.53-0.98)	1.00 (1.00-1)	1.00 (1.00-1)	0.73 (0.58-0.97)	0.84 (0.72-0.99)	0.923 (0.834-0.998)
0.6	4	0.70 (0.47-0.93)	1.00 (0.99-1)	1.00 (0.99-1)	0.70 (0.56-0.90)	0.82 (0.68-0.96)	0.901 (0.807-0.978)
0.6	5	0.68 (0.50-0.86)	0.99 (0.96-1)	0.99 (0.97-1)	0.68 (0.57-0.82)	0.80 (0.70-0.91)	0.881 (0.805-0.961)
0.7	2	0.82 (0.62-1.00)	1.00 (1.00-1)	1.00 (1.00-1)	0.74 (0.53-1.00)	0.87 (0.74-1.00)	0.950 (0.866-1.000)
0.7	3	0.75 (0.54-0.97)	1.00 (0.99-1)	1.00 (1.00-1)	0.65 (0.48-0.93)	0.82 (0.68-0.98)	0.922 (0.827-0.994)
0.7	4	0.71 (0.50-0.89)	1.00 (0.98-1)	1.00 (0.99-1)	0.61 (0.46-0.79)	0.79 (0.65-0.92)	0.902 (0.819-0.978)
0.7	5	0.68 (0.48-0.86)	0.99 (0.94-1)	0.99 (0.97-1)	0.58 (0.45-0.76)	0.77 (0.64-0.89)	0.881 (0.798-0.954)
0.8	2	0.82 (0.62-1.00)	1.00 (1.00-1)	1.00 (1.00-1)	0.64 (0.40-1.00)	0.85 (0.70-1.00)	0.953 (0.868-1.000)
0.8	3	0.75 (0.52-0.97)	1.00 (0.99-1)	1.00 (1.00-1)	0.53 (0.35-0.91)	0.80 (0.62-0.98)	0.922 (0.831-0.998)
0.8	4	0.71 (0.49-0.92)	0.99 (0.96-1)	1.00 (0.99-1)	0.48 (0.33-0.76)	0.77 (0.59-0.93)	0.900 (0.821-0.980)
0.8	5	0.69 (0.47-0.87)	0.98 (0.92-1)	0.99 (0.97-1)	0.46 (0.32-0.66)	0.75 (0.57-0.89)	0.883 (0.805-0.954)
0.9	2	0.81 (0.63-1.00)	1.00 (1.00-1)	1.00 (1.00-1)	0.49 (0.23-1.00)	0.83 (0.67-1.00)	0.948 (0.865-1.000)
0.9	3	0.76 (0.53-0.98)	1.00 (0.96-1)	1.00 (1.00-1)	0.37 (0.19-0.85)	0.78 (0.58-0.98)	0.922 (0.827-0.997)
0.9	4	0.72 (0.51-0.95)	0.99 (0.90-1)	1.00 (0.99-1)	0.32 (0.18-0.67)	0.75 (0.55-0.95)	0.902 (0.823-0.984)
0.9	5	0.73 (0.50-0.89)	0.96 (0.84-1)	0.99 (0.98-1)	0.30 (0.18-0.49)	0.75 (0.55-0.90)	0.890 (0.811-0.956)
0.95	2	0.82 (0.64-1.00)	1.00 (1.00-1)	1.00 (1.00-1)	0.36 (0.13-1.00)	0.83 (0.66-1.00)	0.956 (0.878-1.000)
0.95	3	0.76 (0.56-0.98)	0.99 (0.92-1)	1.00 (1.00-1)	0.24 (0.11-0.72)	0.78 (0.58-0.98)	0.928 (0.841-0.995)
0.95	4	0.77 (0.54-0.95)	0.93 (0.69-1)	1.00 (0.98-1)	0.20 (0.10-0.45)	0.77 (0.56-0.94)	0.904 (0.829-0.976)
0.95	5	0.78 (0.53-0.94)	0.80 (0.42-1)	0.99 (0.97-1)	0.18 (0.10-0.35)	0.78 (0.55-0.92)	0.871 (0.787-0.950)

Trend tests						
Optimal signature (2-fold)						
Proportion of resistant cases	2	3	4	5	p-value	
0.5*	0.961 (0.890-1.000)	0.929 (0.852-0.991)	0.903 (0.841-0.965)	0.882 (0.817-0.945)	> 0.05	
0.6	0.956 (0.885-1.000)	0.928 (0.848-0.991)	0.900 (0.815-0.966)	0.882 (0.813-0.944)	> 0.05	
0.7	0.957 (0.885-1.000)	0.923 (0.837-0.991)	0.902 (0.821-0.974)	0.880 (0.801-0.944)	> 0.05	
0.8	0.959 (0.888-1.000)	0.925 (0.844-0.990)	0.900 (0.827-0.975)	0.878 (0.819-0.940)	> 0.05	
0.9**	0.958 (0.895-1.000)	0.925 (0.851-0.990)	0.898 (0.821-0.965)	0.872 (0.800-0.935)	> 0.05	
0.95	0.958 (0.897-1.000)	0.917 (0.843-0.986)	0.863 (0.778-0.951)	0.802 (0.690-0.899)	> 0.05	
Weak signature (1.4-fold)						
Proportion of resistant cases	2	3	4	5	p-value	
0.5*	0.937 (0.891-0.986)	0.886 (0.831-0.955)	0.844 (0.783-0.911)	0.803 (0.733-0.884)	0.01	
0.6	0.942 (0.893-0.985)	0.891 (0.832-0.960)	0.848 (0.791-0.904)	0.805 (0.740-0.874)	0.005	
0.7	0.938 (0.893-0.979)	0.887 (0.835-0.952)	0.838 (0.772-0.919)	0.788 (0.708-0.867)	0.002	
0.8	0.936 (0.891-0.986)	0.881 (0.827-0.952)	0.821 (0.738-0.904)	0.760 (0.653-0.859)	0.003	
0.9**	0.922 (0.872-0.979)	0.828 (0.709-0.929)	0.748 (0.619-0.890)	0.673 (0.570-0.801)	0.0008	
0.95	0.853 (0.739-0.979)	0.717 (0.587-0.906)	0.633 (0.534-0.799)	0.579 (0.491-0.749)	0.04	
Strong signature (2.8-fold)						
Proportion of resistant cases	2	3	4	5	p-value	
0.5*	0.959 (0.884-1.000)	0.931 (0.840-0.999)	0.907 (0.823-0.983)	0.889 (0.810-0.969)	> 0.05	
0.6	0.953 (0.875-1.000)	0.923 (0.834-0.998)	0.901 (0.807-0.978)	0.881 (0.805-0.961)	> 0.05	
0.7	0.950 (0.866-1.000)	0.922 (0.827-0.994)	0.902 (0.819-0.978)	0.881 (0.798-0.954)	> 0.05	
0.8	0.953 (0.868					

**Supplementary Table S6: Impact of different distributions of resistance mechanisms in training and test sets on signature performance.**

Analysis of the impact of random and independent proportions of resistance mechanisms in training and test sets, where the gene expression changes are optimal (2-fold), weak (1.4-fold) or strong (2.8-fold) and the prevalence of resistant cases is identical in training and test sets, on the performance of the predictive gene signatures tested.

Optimal gene expression changes (2-fold)							
Proportion of resistant cases	Number of resistance mechanisms	Sensitivity	Specificity	PPV	NPV	Accuracy	AUC
0.5	2	0.66 (0.131-0.99)	1.00 (0.99-1.00)	1.00 (0.99-1.00)	0.78 (0.534-0.99)	0.83 (0.56-1.00)	0.895 (0.653-1.000)
0.5	3	0.56 (0.104-0.95)	0.99 (0.97-1.00)	0.99 (0.94-1.00)	0.71 (0.527-0.95)	0.77 (0.55-0.97)	0.835 (0.629-0.993)
0.5	4	0.50 (0.151-0.88)	0.98 (0.93-1.00)	0.95 (0.87-1.00)	0.67 (0.537-0.89)	0.74 (0.57-0.93)	0.791 (0.609-0.968)
0.5	5	0.48 (0.138-0.81)	0.96 (0.90-0.99)	0.92 (0.81-0.98)	0.66 (0.532-0.83)	0.72 (0.56-0.88)	0.767 (0.589-0.927)
0.6	2	0.69 (0.161-0.99)	1.00 (0.99-1.00)	1.00 (0.99-1.00)	0.73 (0.443-0.99)	0.81 (0.50-1.00)	0.918 (0.633-1.000)
0.6	3	0.58 (0.151-0.97)	0.99 (0.96-1.00)	0.99 (0.95-1.00)	0.64 (0.439-0.95)	0.74 (0.49-0.97)	0.844 (0.622-0.993)
0.6	4	0.52 (0.109-0.88)	0.97 (0.92-1.00)	0.97 (0.91-1.00)	0.60 (0.421-0.84)	0.70 (0.45-0.91)	0.797 (0.594-0.963)
0.6	5	0.51 (0.193-0.81)	0.95 (0.87-1.00)	0.93 (0.87-0.99)	0.58 (0.443-0.76)	0.68 (0.50-0.85)	0.780 (0.635-0.920)
0.7	2	0.64 (0.068-0.99)	1.00 (0.99-1.00)	1.00 (0.99-1.00)	0.62 (0.316-0.98)	0.75 (0.35-0.99)	0.876 (0.562-1.000)
0.7	3	0.54 (0.129-0.96)	0.99 (0.96-1.00)	0.99 (0.97-1.00)	0.52 (0.330-0.92)	0.68 (0.39-0.96)	0.824 (0.617-0.992)
0.7	4	0.53 (0.175-0.89)	0.96 (0.90-1.00)	0.97 (0.93-1.00)	0.49 (0.338-0.78)	0.66 (0.42-0.90)	0.799 (0.613-0.950)
0.7	5	0.54 (0.153-0.86)	0.93 (0.83-0.99)	0.95 (0.89-0.99)	0.48 (0.327-0.72)	0.65 (0.39-0.86)	0.784 (0.596-0.930)
0.8	2	0.66 (0.099-1.00)	1.00 (0.99-1.00)	1.00 (0.99-1.00)	0.53 (0.217-0.98)	0.73 (0.28-1.00)	0.898 (0.640-1.000)
0.8	3	0.59 (0.096-0.96)	0.98 (0.94-1.00)	0.99 (0.98-1.00)	0.43 (0.216-0.87)	0.67 (0.28-0.96)	0.843 (0.617-0.990)
0.8	4	0.53 (0.097-0.88)	0.95 (0.87-1.00)	0.98 (0.95-1.00)	0.37 (0.214-0.66)	0.62 (0.28-0.89)	0.791 (0.597-0.953)
0.8	5	0.54 (0.169-0.84)	0.91 (0.79-0.99)	0.96 (0.92-1.00)	0.35 (0.229-0.58)	0.62 (0.33-0.85)	0.777 (0.604-0.914)
0.9	2	0.68 (0.107-1.00)	1.00 (0.98-1.00)	1.00 (1.00-1.00)	0.43 (0.111-0.97)	0.71 (0.20-1.00)	0.891 (0.618-1.000)
0.9	3	0.65 (0.198-0.98)	0.97 (0.87-1.00)	0.99 (0.98-1.00)	0.32 (0.119-0.85)	0.68 (0.28-0.98)	0.853 (0.629-0.992)
0.9	4	0.60 (0.202-0.93)	0.91 (0.75-1.00)	0.98 (0.96-1.00)	0.25 (0.122-0.59)	0.63 (0.28-0.93)	0.807 (0.619-0.962)
0.9	5	0.61 (0.223-0.88)	0.81 (0.62-0.98)	0.97 (0.94-1.00)	0.21 (0.122-0.39)	0.63 (0.29-0.86)	0.770 (0.620-0.899)
0.95	2	0.68 (0.088-1.00)	0.99 (0.96-1.00)	1.00 (1.00-1.00)	0.30 (0.055-0.93)	0.70 (0.13-1.00)	0.888 (0.582-1.000)
0.95	3	0.65 (0.140-0.96)	0.89 (0.65-1.00)	0.99 (0.98-1.00)	0.18 (0.058-0.53)	0.66 (0.18-0.95)	0.832 (0.592-0.976)
0.95	4	0.69 (0.252-0.94)	0.67 (0.35-0.98)	0.98 (0.96-1.00)	0.13 (0.058-0.33)	0.69 (0.29-0.92)	0.765 (0.572-0.929)
0.95	5	0.75 (0.297-0.90)	0.47 (0.23-0.92)	0.97 (0.95-0.99)	0.10 (0.058-0.15)	0.74 (0.32-0.87)	0.705 (0.580-0.819)

Weak gene expression changes (1.4-fold)							
Proportion of resistant cases	Number of resistance mechanisms	Sensitivity	Specificity	PPV	NPV	Accuracy	AUC
0.5	2	0.65 (0.10-0.93)	0.95 (0.895-1.00)	0.92 (0.76-0.99)	0.754 (0.521-0.931)	0.80 (0.54-0.93)	0.856 (0.539-0.982)
0.5	3	0.59 (0.21-0.85)	0.90 (0.820-0.98)	0.85 (0.73-0.96)	0.697 (0.546-0.857)	0.74 (0.58-0.87)	0.798 (0.599-0.931)
0.5	4	0.55 (0.24-0.78)	0.84 (0.738-0.95)	0.78 (0.68-0.89)	0.660 (0.552-0.783)	0.70 (0.59-0.80)	0.749 (0.594-0.869)
0.5	5	0.54 (0.21-0.75)	0.79 (0.663-0.91)	0.72 (0.64-0.81)	0.638 (0.531-0.750)	0.66 (0.55-0.75)	0.713 (0.579-0.821)
0.6	2	0.71 (0.19-0.95)	0.94 (0.891-1.00)	0.94 (0.85-0.99)	0.720 (0.437-0.927)	0.80 (0.49-0.94)	0.880 (0.630-0.985)
0.6	3	0.63 (0.22-0.88)	0.88 (0.777-0.97)	0.88 (0.78-0.96)	0.634 (0.443-0.841)	0.73 (0.51-0.88)	0.809 (0.612-0.940)
0.6	4	0.59 (0.25-0.83)	0.80 (0.708-0.92)	0.82 (0.74-0.89)	0.579 (0.444-0.751)	0.67 (0.51-0.80)	0.752 (0.591-0.873)
0.6	5	0.59 (0.35-0.79)	0.74 (0.638-0.88)	0.77 (0.70-0.86)	0.554 (0.448-0.686)	0.65 (0.53-0.76)	0.717 (0.603-0.833)
0.7	2	0.70 (0.27-0.95)	0.93 (0.852-0.99)	0.96 (0.92-0.99)	0.620 (0.361-0.887)	0.77 (0.47-0.94)	0.872 (0.668-0.981)
0.7	3	0.66 (0.21-0.90)	0.84 (0.735-0.97)	0.91 (0.85-0.97)	0.545 (0.349-0.779)	0.71 (0.44-0.88)	0.812 (0.611-0.939)
0.7	4	0.62 (0.28-0.85)	0.76 (0.632-0.92)	0.86 (0.80-0.92)	0.477 (0.334-0.671)	0.66 (0.44-0.81)	0.747 (0.590-0.881)
0.7	5	0.62 (0.38-0.76)	0.68 (0.548-0.87)	0.82 (0.77-0.88)	0.441 (0.349-0.545)	0.64 (0.51-0.73)	0.704 (0.607-0.795)
0.8	2	0.70 (0.19-0.96)	0.92 (0.830-0.99)	0.97 (0.93-1.00)	0.511 (0.230-0.854)	0.74 (0.34-0.95)	0.863 (0.588-0.984)
0.8	3	0.66 (0.27-0.90)	0.80 (0.641-0.96)	0.93 (0.90-0.98)	0.409 (0.239-0.674)	0.69 (0.40-0.88)	0.794 (0.635-0.925)
0.8	4	0.66 (0.39-0.86)	0.67 (0.509-0.86)	0.89 (0.85-0.94)	0.349 (0.241-0.508)	0.66 (0.46-0.80)	0.733 (0.597-0.853)
0.8	5	0.67 (0.39-0.81)	0.56 (0.417-0.78)	0.86 (0.83-0.91)	0.308 (0.225-0.400)	0.65 (0.45-0.75)	0.676 (0.558-0.789)
0.9	2	0.72 (0.21-0.97)	0.83 (0.683-0.98)	0.97 (0.96-1.00)	0.353 (0.119-0.737)	0.73 (0.28-0.95)	0.846 (0.601-0.979)
0.9	3	0.71 (0.41-0.93)	0.62 (0.404-0.89)	0.94 (0.92-0.97)	0.220 (0.127-0.484)	0.70 (0.44-0.89)	0.742 (0.606-0.899)
0.9	4	0.74 (0.50-0.88)	0.44 (0.279-0.71)	0.92 (0.91-0.95)	0.167 (0.115-0.259)	0.71 (0.52-0.82)	0.662 (0.555-0.784)
0.9	5	0.77 (0.64-0.85)	0.34 (0.212-0.52)	0.91 (0.90-0.93)	0.141 (0.107-0.188)	0.72 (0.62-0.79)	0.605 (0.535-0.688)
0.95	2	0.77 (0.34-0.97)	0.56 (0.308-0.94)	0.97 (0.96-1.00)	0.168 (0.061-0.438)	0.76 (0.37-0.94)	0.773 (0.578-0.934)
0.95	3	0.81 (0.46-0.91)	0.33 (0.154-0.69)	0.96 (0.95-0.97)	0.089 (0.057-0.157)	0.78 (0.48-0.88)	0.651 (0.542-0.788)
0.95	4	0.83 (0.63-0.90)	0.25 (0.115-0.54)	0.95 (0.95-0.96)	0.071 (0.043-0.100)	0.80 (0.63-0.86)	0.591 (0.497-0.704)
0.95	5	0.84 (0.77-0.89)	0.20 (0.077-0.35)	0.95 (0.95-0.96)	0.062 (0.040-0.086)	0.81 (0.74-0.85)	0.556 (0.487-0.625)

Strong gene expression changes (2.8-fold)							
Proportion of resistant cases	Number of resistance mechanisms	Sensitivity	Specificity	PPV	NPV	Accuracy	AUC
0.5	2	0.65 (0.064-1.00)	1.00 (1.00-1)	1.00 (1.00-1)	0.77 (0.516-1.00)	0.83 (0.53-1.00)	0.897 (0.601-1.000)
0.5	3	0.55 (0.081-0.97)	1.00 (1.00-1)	1.00 (1.00-1)	0.71 (0.520-0.97)	0.77 (0.54-0.98)	0.849 (0.637-0.997)
0.5	4	0.49 (0.089-0.87)	1.00 (0.99-1)	1.00 (0.98-1)	0.67 (0.523-0.88)	0.74 (0.54-0.93)	0.800 (0.626-0.966)
0.5	5	0.45 (0.070-0.77)	0.99 (0.97-1)	0.99 (0.95-1)	0.65 (0.518-0.81)	0.72 (0.53-0.88)	0.780 (0.584-0.937)
0.6	2	0.60 (0.128-1.00)	1.00 (1.00-1)	1.00 (1.00-1)	0.67 (0.434-1.00)	0.76 (0.48-1.00)	0.863 (0.601-1.000)
0.6	3	0.52 (0.080-0.92)	1.00 (1.00-1)	1.00 (1.00-1)	0.61 (0.420-0.90)	0.71 (0.45-0.95)	0.823 (0.595-0.991)
0.6	4	0.49 (0.109-0.86)	1.00 (0.99-1)	1.00 (0.98-1)	0.59 (0.428-0.83)	0.69 (0.47-0.92)	0.808 (0.626-0.982)
0.6	5	0.44 (0.097-0.82)	0.99 (0.97-1)	0.99 (0.96-1)	0.55 (0.424-0.79)	0.66 (0.46-0.89)	0.773 (0.608-0.938)
0.7	2	0.65 (0.138-1.00)	1.00 (1.00-1)	1.00 (1.00-1)	0.62 (0.333-1.00)	0.75 (0.40-1.00)	0.881 (0.630-1.000)
0.7	3	0.50 (0.080-0.94)	1.00 (0.99-1)	1.00 (0.99-1)	0.50 (0.318-0.88)	0.65 (0.36-0.96)	0.813 (0.572-0.993)
0.7	4	0.45 (0.104-0.86)	1.00 (0.97-1)	1.00 (0.98-1)	0.46 (0.324-0.75)	0.62 (0.37-0.90)	0.785 (0.603-0.976)
0.7	5	0.46 (0.149-0.74)	0.99 (0.95-1)	0.99 (0.96-1)	0.45 (0.334-0.62)	0.62 (0.40-0.81)	0.773 (0.614-0.910)
0.8	2	0.64 (0.090-1.00)	1.00 (1.00-1)	1.00 (1.00-1)	0.53 (0.215-1.00)	0.71 (0.27-1.00)	0.903 (0.640-1.000)
0.8	3	0.54 (0.092-0.98)	1.00 (0.99-1)	1.00 (1.00-1)	0.41 (0.215-0.94)	0.63 (0.27-0.99)	0.835 (0.626-0.999)
0.8	4	0.49 (0.070-0.92)	0.99 (0.97-1)	1.00 (0.98-1)	0.37 (0.211-0.75)	0.59 (0.25-0.93)	0.797 (0.573-0.984)
0.8	5	0.46 (0.104-0.86)	0.98 (0.93-1)	0.99 (0.96-1)	0.33 (0.217-0.61)	0.57 (0.28-0.86)	0.782 (0.615-0.937)
0.9	2	0.62 (0.086-1.00)	1.00 (1.00-1)	1.00 (1.00-1)	0.38 (0.109-1.00)	0.66 (0.18-1.00)	0.883 (0.590-1.000)
0.9	3	0.56 (0.128-0.98)	1.00 (0.98-1)	1.00 (1.00-1)	0.27 (0.114-0.85)	0.60 (0.22-0.98)	0.839 (0.622-0.998)
0.9	4	0.50 (0.129-0.88)	0.98 (0.92-1)	1.00 (0.99-1)	0.21 (0.113-0.48)	0.55 (0.22-0.89)	0.799 (0.603-0.961)
0.9	5	0.52 (0.143-0.86)	0.95 (0.83-1)	0.99 (0.97-1)	0.20 (0.115-0.40)	0.56 (0.23-0.86)	0.790 (0.597-0.938)
0.95	2	0.63 (0.086-1.00)	1.00 (1.00-1)	1.00 (1.00-1)	0.29 (0.055-1.00)	0.65 (0.13-1.00)	0.892 (0.605-1.000)
0.95	3	0.55 (0.100-0.96)	0.99 (0.96-1)	1.00 (1.00-1)	0.15 (0.056-0.59)	0.57 (0.14-0.96)	0.836 (0.584-0.993)
0.95	4	0.54 (0.077-0.93)	0.94 (0.69-1)	1.00 (0.98-1)	0.13 (0.054-0.38)	0.56 (0.12-0.92)	0.794 (0.581-0.954)
0.95	5	0.60 (0.112-0.92)	0.81 (0.46-1)	0.99 (0.97-1)	0.12 (0.056-0.27)	0.61 (0.16-0.90)	0.772 (0.584-0.911)

Perturbed datasets in which s% (s%=5%, 10%, 20%, 30%, 40% or 50%) of the cases were designated to be therapy sensitive were generated. Within the 1-s% resistant cases, the cases were allocated randomly into n (n=2, 3, 4, 5) groups of resistance mechanisms and the case allocation for training and test datasets was performed independently. Furthermore, for each nth resistance mechanism, 100 genes were randomly selected as the "true" gene expression changes and were spiked-in by v (v=1, top; v=0.5, middle; v=1.5, bottom). Classification was performed using diagonal discriminating linear analysis (DLDA). For each combination of s and n, we repeated the spiking and classification 200 times. The mean value and the 95% confidence intervals of the performance measures for each combination of s and n are shown. Performance measures reported here are sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), accuracy and the area under curve (AUC) of the receiver operating characteristic (ROC) curves.

**Supplementary Table S7: Impact of overlapping gene signatures on signature performance.**

Analysis of the impact of overlapping gene expression changes on the predictive gene signature performance, where the optimal (2-fold), weak (1.4-fold) or strong (2.8-fold) changes in gene expression were spiked-in.

Optimal gene expression changes (2-fold)								
Proportion of resistant cases	Number of resistance mechanisms	Overlap	Sensitivity	Specificity	PPV	NPV	Accuracy	AUC
0.5	2	0	0.99 (0.98-1.00)	1.00 (0.99-1.00)	1.00 (0.99-1.00)	0.99 (0.978-1.00)	0.99 (0.99-1.00)	1.000 (0.999-1.000)
0.5	2	0.01	0.99 (0.97-1.00)	1.00 (0.99-1.00)	1.00 (0.99-1.00)	0.99 (0.969-1.00)	0.99 (0.98-1.00)	1.000 (0.998-1.000)
0.5	2	0.05	0.99 (0.98-1.00)	1.00 (0.99-1.00)	1.00 (0.99-1.00)	0.99 (0.979-1.00)	1.00 (0.99-1.00)	1.000 (0.999-1.000)
0.5	2	0.1	0.99 (0.99-1.00)	1.00 (0.99-1.00)	1.00 (0.99-1.00)	0.99 (0.986-1.00)	1.00 (0.99-1.00)	1.000 (0.999-1.000)
0.5	2	0.2	1.00 (0.99-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (0.989-1.00)	1.00 (0.99-1.00)	1.000 (1.000-1.000)
0.5	2	0.5	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (0.996-1.00)	1.00 (1.00-1.00)	1.000 (1.000-1.000)
0.5	2	0.9	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.000-1.00)	1.00 (1.00-1.00)	1.000 (1.000-1.000)
0.5	3	0	0.95 (0.93-0.97)	0.97 (0.96-0.98)	0.97 (0.96-0.98)	0.95 (0.930-0.97)	0.96 (0.94-0.98)	0.992 (0.984-0.996)
0.5	3	0.01	0.96 (0.92-0.97)	0.98 (0.95-0.99)	0.98 (0.95-0.99)	0.96 (0.924-0.98)	0.97 (0.94-0.98)	0.993 (0.984-0.997)
0.5	3	0.05	0.97 (0.95-0.99)	0.99 (0.97-1.00)	0.99 (0.97-1.00)	0.98 (0.951-0.99)	0.98 (0.96-0.99)	0.998 (0.993-1.000)
0.5	3	0.1	0.99 (0.97-1.00)	1.00 (0.98-1.00)	0.99 (0.98-1.00)	0.99 (0.966-1.00)	0.99 (0.98-1.00)	0.999 (0.997-1.000)
0.5	3	0.2	0.99 (0.98-1.00)	1.00 (0.99-1.00)	1.00 (0.99-1.00)	0.99 (0.981-1.00)	1.00 (0.99-1.00)	1.000 (0.999-1.000)
0.5	3	0.5	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (0.996-1.00)	1.00 (1.00-1.00)	1.000 (1.000-1.000)
0.5	3	0.9	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.000-1.00)	1.00 (1.00-1.00)	1.000 (1.000-1.000)
0.5	4	0	0.90 (0.87-0.94)	0.93 (0.90-0.95)	0.92 (0.90-0.95)	0.90 (0.872-0.94)	0.91 (0.89-0.94)	0.967 (0.950-0.979)
0.5	4	0.01	0.92 (0.87-0.95)	0.94 (0.89-0.97)	0.94 (0.89-0.97)	0.92 (0.871-0.95)	0.93 (0.89-0.96)	0.975 (0.952-0.990)
0.5	4	0.05	0.95 (0.91-0.98)	0.97 (0.93-0.99)	0.97 (0.93-0.99)	0.95 (0.909-0.98)	0.96 (0.92-0.98)	0.990 (0.972-0.998)
0.5	4	0.1	0.97 (0.95-0.99)	0.99 (0.97-1.00)	0.99 (0.97-1.00)	0.97 (0.949-0.99)	0.98 (0.96-0.99)	0.997 (0.992-1.000)
0.5	4	0.2	0.99 (0.98-1.00)	1.00 (0.99-1.00)	1.00 (0.99-1.00)	0.99 (0.977-1.00)	0.99 (0.98-1.00)	1.000 (0.999-1.000)
0.5	4	0.5	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (0.996-1.00)	1.00 (1.00-1.00)	1.000 (1.000-1.000)
0.5	4	0.9	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.000-1.00)	1.00 (1.00-1.00)	1.000 (1.000-1.000)
0.5	5	0	0.85 (0.81-0.89)	0.87 (0.83-0.90)	0.87 (0.82-0.90)	0.85 (0.814-0.89)	0.86 (0.82-0.89)	0.926 (0.897-0.948)
0.5	5	0.01	0.88 (0.82-0.92)	0.90 (0.85-0.94)	0.90 (0.85-0.94)	0.88 (0.829-0.93)	0.89 (0.84-0.93)	0.950 (0.909-0.975)
0.5	5	0.05	0.93 (0.88-0.96)	0.95 (0.89-0.98)	0.95 (0.89-0.98)	0.93 (0.877-0.96)	0.94 (0.89-0.97)	0.981 (0.950-0.994)
0.5	5	0.1	0.97 (0.93-0.99)	0.98 (0.95-1.00)	0.98 (0.95-1.00)	0.97 (0.930-0.99)	0.97 (0.94-0.99)	0.995 (0.986-1.000)
0.5	5	0.2	0.99 (0.97-1.00)	1.00 (0.98-1.00)	1.00 (0.98-1.00)	0.99 (0.969-1.00)	0.99 (0.97-1.00)	0.999 (0.997-1.000)
0.5	5	0.5	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (0.996-1.00)	1.00 (1.00-1.00)	1.000 (1.000-1.000)
0.5	5	0.9	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.000-1.00)	1.00 (1.00-1.00)	1.000 (1.000-1.000)
0.6	2	0	0.99 (0.98-1.00)	1.00 (0.99-1.00)	1.00 (0.99-1.00)	0.98 (0.967-1.00)	0.99 (0.98-1.00)	1.000 (0.999-1.000)
0.6	2	0.01	0.99 (0.98-1.00)	1.00 (0.99-1.00)	1.00 (0.99-1.00)	0.99 (0.965-1.00)	0.99 (0.98-1.00)	1.000 (0.998-1.000)
0.6	2	0.05	0.99 (0.98-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	0.99 (0.974-1.00)	0.99 (0.99-1.00)	1.000 (0.999-1.000)
0.6	2	0.1	1.00 (0.99-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	0.99 (0.985-1.00)	1.00 (0.99-1.00)	1.000 (1.000-1.000)
0.6	2	0.2	1.00 (0.99-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (0.987-1.00)	1.00 (0.99-1.00)	1.000 (1.000-1.000)
0.6	2	0.5	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (0.995-1.00)	1.00 (1.00-1.00)	1.000 (1.000-1.000)
0.6	2	0.9	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.000-1.00)	1.00 (1.00-1.00)	1.000 (1.000-1.000)
0.6	3	0	0.96 (0.92-0.98)	0.97 (0.94-0.99)	0.98 (0.96-0.99)	0.94 (0.893-0.96)	0.96 (0.93-0.98)	0.992 (0.982-0.996)
0.6	3	0.01	0.96 (0.93-0.98)	0.97 (0.95-0.99)	0.98 (0.96-0.99)	0.94 (0.906-0.97)	0.97 (0.94-0.98)	0.993 (0.983-0.998)
0.6	3	0.05	0.98 (0.95-0.99)	0.99 (0.96-1.00)	0.99 (0.98-1.00)	0.97 (0.928-0.99)	0.98 (0.96-0.99)	0.997 (0.991-1.000)
0.6	3	0.1	0.99 (0.97-1.00)	0.99 (0.98-1.00)	1.00 (0.99-1.00)	0.98 (0.953-1.00)	0.99 (0.97-1.00)	0.999 (0.997-1.000)
0.6	3	0.2	0.99 (0.98-1.00)	1.00 (0.99-1.00)	1.00 (0.99-1.00)	0.99 (0.974-1.00)	1.00 (0.99-1.00)	1.000 (0.999-1.000)
0.6	3	0.5	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (0.995-1.00)	1.00 (1.00-1.00)	1.000 (1.000-1.000)
0.6	3	0.9	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.000-1.00)	1.00 (1.00-1.00)	1.000 (1.000-1.000)
0.6	4	0	0.91 (0.88-0.94)	0.91 (0.87-0.94)	0.94 (0.91-0.96)	0.87 (0.828-0.91)	0.91 (0.88-0.94)	0.966 (0.945-0.978)
0.6	4	0.01	0.92 (0.88-0.95)	0.93 (0.88-0.96)	0.95 (0.92-0.98)	0.89 (0.833-0.93)	0.93 (0.88-0.96)	0.974 (0.946-0.989)
0.6	4	0.05	0.96 (0.92-0.98)	0.97 (0.93-0.99)	0.98 (0.95-0.99)	0.94 (0.888-0.98)	0.96 (0.92-0.98)	0.991 (0.978-0.998)
0.6	4	0.1	0.98 (0.95-0.99)	0.99 (0.96-1.00)	0.99 (0.98-1.00)	0.97 (0.932-0.99)	0.98 (0.96-0.99)	0.998 (0.993-1.000)
0.6	4	0.2	0.99 (0.98-1.00)	1.00 (0.99-1.00)	1.00 (0.99-1.00)	0.99 (0.968-1.00)	0.99 (0.98-1.00)	1.000 (0.998-1.000)
0.6	4	0.5	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (0.995-1.00)	1.00 (1.00-1.00)	1.000 (1.000-1.000)
0.6	4	0.9	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (0.997-1.00)	1.00 (1.00-1.00)	1.000 (1.000-1.000)
0.6	5	0	0.87 (0.83-0.90)	0.84 (0.80-0.88)	0.89 (0.86-0.92)	0.81 (0.760-0.86)	0.86 (0.82-0.89)	0.925 (0.891-0.948)
0.6	5	0.01	0.89 (0.84-0.93)	0.88 (0.82-0.93)	0.91 (0.88-0.95)	0.84 (0.781-0.90)	0.88 (0.84-0.93)	0.946 (0.912-0.976)
0.6	5	0.05	0.94 (0.90-0.98)	0.94 (0.89-0.98)	0.96 (0.93-0.99)	0.92 (0.854-0.96)	0.94 (0.90-0.97)	0.984 (0.960-0.996)
0.6	5	0.1	0.97 (0.94-0.99)	0.98 (0.95-0.99)	0.98 (0.96-1.00)	0.96 (0.916-0.98)	0.97 (0.94-0.99)	0.996 (0.985-0.999)
0.6	5	0.2	0.99 (0.98-1.00)	1.00 (0.99-1.00)	1.00 (0.99-1.00)	0.99 (0.967-1.00)	0.99 (0.98-1.00)	1.000 (0.997-1.000)
0.6	5	0.5	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (0.995-1.00)	1.00 (1.00-1.00)	1.000 (1.000-1.000)
0.6	5	0.9	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.000-1.00)	1.00 (1.00-1.00)	1.000 (1.000-1.000)
0.7	2	0	0.99 (0.98-1.00)	1.00 (0.99-1.00)	1.00 (1.00-1.00)	0.98 (0.957-0.99)	0.99 (0.98-1.00)	1.000 (0.999-1.000)
0.7	2	0.01	0.99 (0.98-1.00)	1.00 (0.99-1.00)	1.00 (0.99-1.00)	0.98 (0.953-0.99)	0.99 (0.98-1.00)	1.000 (0.998-1.000)
0.7	2	0.05	0.99 (0.98-1.00)	1.00 (0.99-1.00)	1.00 (0.99-1.00)	0.98 (0.962-0.99)	0.99 (0.98-1.00)	1.000 (0.999-1.000)
0.7	2	0.1	1.00 (0.99-1.00)	1.00 (0.99-1.00)	1.00 (1.00-1.00)	0.99 (0.968-1.00)	1.00 (0.99-1.00)	1.000 (0.999-1.000)
0.7	2	0.2	1.00 (0.99-1.00)	1.00 (0.99-1.00)	1.00 (1.00-1.00)	0.99 (0.979-1.00)	1.00 (0.99-1.00)	1.000 (1.000-1.000)
0.7	2	0.5	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (0.994-1.00)	1.00 (1.00-1.00)	1.000 (1.000-1.000)
0.7	2	0.9	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.000-1.00)	1.00 (1.00-1.00)	1.000 (1.000-1.000)
0.7	3	0	0.96 (0.94-0.98)	0.96 (0.92-0.98)	0.98 (0.96-0.99)	0.91 (0.857-0.95)	0.96 (0.93-0.98)	0.991 (0.978-0.996)
0.7	3	0.01	0.96 (0.93-0.98)	0.96 (0.93-0.99)	0.98 (0.97-0.99)	0.92 (0.851-0.96)	0.96 (0.93-0.98)	0.992 (0.980-0.997)
0.7	3	0.05	0.98 (0.96-0.99)	0.98 (0.95-0.99)	0.99 (0.98-1.00)	0.95 (0.918-0.98)	0.96 (0.96-0.99)	0.997 (0.992-1.000)
0.7	3	0.1	0.99 (0.98-1.00)	0.99 (0.98-1.00)	1.00 (0.99-1.00)	0.97 (0.951-0.99)	0.99 (0.98-1.00)	0.999 (0.998-1.000)
0.7	3	0.2	0.99 (0.98-1.00)	1.00 (0.99-1.00)	1.00 (0.99-1.00)	0.99 (0.958-1.00)	1.00 (0.98-1.00)	1.000 (0.999-1.000)
0.7	3	0.5	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (0.990-1.00)	1.00 (1.00-1.00)	1.000 (1.000-1.000)
0.7	3	0.9	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.000-1.00)	1.00 (1.00-1.00)	1.000 (1.000-1.000)

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0.7	4	0	0.92 (0.88-0.95)	0.89 (0.84-0.92)	0.95 (0.93-0.96)	0.82 (0.748-0.88)	0.91 (0.87-0.94)	0.962 (0.927-0.977)
0.7	4	0.01	0.93 (0.88-0.96)	0.91 (0.84-0.95)	0.96 (0.93-0.98)	0.85 (0.754-0.92)	0.92 (0.87-0.96)	0.972 (0.936-0.988)
0.7	4	0.05	0.96 (0.93-0.98)	0.95 (0.91-0.98)	0.98 (0.96-0.99)	0.91 (0.846-0.96)	0.96 (0.93-0.98)	0.990 (0.975-0.996)
0.7	4	0.1	0.98 (0.97-0.99)	0.98 (0.96-0.99)	0.99 (0.98-1.00)	0.96 (0.926-0.98)	0.98 (0.97-0.99)	0.998 (0.994-1.000)
0.7	4	0.2	0.99 (0.98-1.00)	1.00 (0.98-1.00)	1.00 (0.99-1.00)	0.98 (0.952-1.00)	0.99 (0.98-1.00)	1.000 (0.998-1.000)
0.7	4	0.5	1.00 (0.99-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (0.987-1.00)	1.00 (1.00-1.00)	1.000 (1.000-1.000)
0.7	4	0.9	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.000-1.00)	1.00 (1.00-1.00)	1.000 (1.000-1.000)
0.7	5	0	0.88 (0.83-0.92)	0.81 (0.75-0.85)	0.91 (0.89-0.94)	0.74 (0.662-0.81)	0.86 (0.81-0.90)	0.920 (0.876-0.950)
0.7	5	0.01	0.90 (0.84-0.94)	0.85 (0.78-0.90)	0.93 (0.90-0.96)	0.78 (0.673-0.87)	0.88 (0.82-0.93)	0.942 (0.880-0.972)
0.7	5	0.05	0.95 (0.91-0.97)	0.93 (0.86-0.97)	0.97 (0.94-0.99)	0.89 (0.807-0.94)	0.94 (0.89-0.97)	0.982 (0.953-0.994)
0.7	5	0.1	0.98 (0.96-0.99)	0.97 (0.94-0.99)	0.99 (0.97-1.00)	0.95 (0.904-0.98)	0.98 (0.95-0.99)	0.996 (0.990-0.999)
0.7	5	0.2	0.99 (0.98-1.00)	0.99 (0.98-1.00)	1.00 (0.99-1.00)	0.98 (0.944-1.00)	0.99 (0.98-1.00)	1.000 (0.998-1.000)
0.7	5	0.5	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (0.990-1.00)	1.00 (1.00-1.00)	1.000 (1.000-1.000)
0.7	5	0.9	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.000-1.00)	1.00 (1.00-1.00)	1.000 (1.000-1.000)
0.8	2	0	0.99 (0.98-1.00)	1.00 (0.98-1.00)	1.00 (1.00-1.00)	0.97 (0.927-0.99)	0.99 (0.98-1.00)	1.000 (0.998-1.000)
0.8	2	0.01	0.99 (0.98-1.00)	1.00 (0.98-1.00)	1.00 (1.00-1.00)	0.97 (0.932-0.99)	0.99 (0.98-1.00)	1.000 (0.998-1.000)
0.8	2	0.05	0.99 (0.98-1.00)	1.00 (0.98-1.00)	1.00 (1.00-1.00)	0.98 (0.926-1.00)	0.99 (0.98-1.00)	1.000 (0.999-1.000)
0.8	2	0.1	1.00 (0.99-1.00)	1.00 (0.99-1.00)	1.00 (1.00-1.00)	0.98 (0.945-1.00)	1.00 (0.99-1.00)	1.000 (0.999-1.000)
0.8	2	0.2	1.00 (0.99-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	0.99 (0.972-1.00)	1.00 (0.99-1.00)	1.000 (1.000-1.000)
0.8	2	0.5	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (0.990-1.00)	1.00 (1.00-1.00)	1.000 (1.000-1.000)
0.8	2	0.9	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.000-1.00)	1.00 (1.00-1.00)	1.000 (1.000-1.000)
0.8	3	0	0.97 (0.94-0.98)	0.95 (0.91-0.97)	0.99 (0.98-0.99)	0.88 (0.782-0.92)	0.96 (0.93-0.98)	0.990 (0.978-0.995)
0.8	3	0.01	0.97 (0.95-0.99)	0.95 (0.92-0.98)	0.99 (0.98-1.00)	0.89 (0.821-0.95)	0.97 (0.95-0.98)	0.992 (0.986-0.998)
0.8	3	0.05	0.98 (0.96-1.00)	0.98 (0.94-1.00)	0.99 (0.98-1.00)	0.93 (0.847-0.98)	0.98 (0.96-1.00)	0.997 (0.991-1.000)
0.8	3	0.1	0.99 (0.98-1.00)	0.99 (0.97-1.00)	1.00 (0.99-1.00)	0.96 (0.910-0.99)	0.99 (0.97-1.00)	0.999 (0.996-1.000)
0.8	3	0.2	1.00 (0.99-1.00)	1.00 (0.99-1.00)	1.00 (1.00-1.00)	0.98 (0.953-1.00)	1.00 (0.99-1.00)	1.000 (0.999-1.000)
0.8	3	0.5	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (0.990-1.00)	1.00 (1.00-1.00)	1.000 (1.000-1.000)
0.8	3	0.9	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (0.997-1.00)	1.00 (1.00-1.00)	1.000 (1.000-1.000)
0.8	4	0	0.93 (0.89-0.96)	0.86 (0.81-0.90)	0.96 (0.95-0.98)	0.76 (0.653-0.84)	0.92 (0.88-0.94)	0.961 (0.933-0.977)
0.8	4	0.01	0.94 (0.91-0.97)	0.88 (0.81-0.93)	0.97 (0.95-0.98)	0.79 (0.693-0.88)	0.93 (0.89-0.96)	0.969 (0.942-0.988)
0.8	4	0.05	0.97 (0.93-0.99)	0.94 (0.87-0.99)	0.98 (0.97-1.00)	0.87 (0.766-0.95)	0.96 (0.92-0.99)	0.989 (0.966-0.998)
0.8	4	0.1	0.98 (0.96-0.99)	0.97 (0.93-1.00)	0.99 (0.98-1.00)	0.93 (0.852-0.98)	0.98 (0.96-0.99)	0.997 (0.989-1.000)
0.8	4	0.2	0.99 (0.98-1.00)	1.00 (0.98-1.00)	1.00 (0.99-1.00)	0.98 (0.933-1.00)	0.99 (0.98-1.00)	1.000 (0.998-1.000)
0.8	4	0.5	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (0.990-1.00)	1.00 (1.00-1.00)	1.000 (1.000-1.000)
0.8	4	0.9	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.000-1.00)	1.00 (1.00-1.00)	1.000 (1.000-1.000)
0.8	5	0	0.90 (0.86-0.93)	0.75 (0.70-0.80)	0.93 (0.92-0.95)	0.65 (0.562-0.74)	0.87 (0.83-0.90)	0.915 (0.881-0.942)
0.8	5	0.01	0.91 (0.87-0.95)	0.79 (0.72-0.87)	0.95 (0.93-0.97)	0.70 (0.576-0.80)	0.89 (0.84-0.93)	0.934 (0.885-0.970)
0.8	5	0.05	0.96 (0.91-0.98)	0.90 (0.82-0.97)	0.98 (0.95-0.99)	0.84 (0.684-0.93)	0.95 (0.89-0.98)	0.980 (0.942-0.997)
0.8	5	0.1	0.98 (0.94-0.99)	0.96 (0.89-1.00)	0.99 (0.97-1.00)	0.91 (0.780-0.96)	0.97 (0.93-0.99)	0.994 (0.973-0.999)
0.8	5	0.2	0.99 (0.98-1.00)	0.99 (0.97-1.00)	1.00 (0.99-1.00)	0.97 (0.918-1.00)	0.99 (0.98-1.00)	0.999 (0.997-1.000)
0.8	5	0.5	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (0.985-1.00)	1.00 (1.00-1.00)	1.000 (1.000-1.000)
0.8	5	0.9	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (0.990-1.00)	1.00 (1.00-1.00)	1.000 (1.000-1.000)
0.9	2	0	0.99 (0.98-1.00)	0.99 (0.96-1.00)	1.00 (1.00-1.00)	0.94 (0.850-0.98)	0.99 (0.98-1.00)	0.999 (0.998-1.000)
0.9	2	0.01	0.99 (0.98-1.00)	0.99 (0.97-1.00)	1.00 (1.00-1.00)	0.94 (0.854-0.98)	0.99 (0.98-1.00)	1.000 (0.998-1.000)
0.9	2	0.05	1.00 (0.99-1.00)	1.00 (0.98-1.00)	1.00 (1.00-1.00)	0.96 (0.894-0.99)	0.99 (0.99-1.00)	1.000 (0.999-1.000)
0.9	2	0.1	1.00 (0.99-1.00)	1.00 (0.98-1.00)	1.00 (1.00-1.00)	0.97 (0.900-1.00)	1.00 (0.99-1.00)	1.000 (0.999-1.000)
0.9	2	0.2	1.00 (0.99-1.00)	1.00 (0.99-1.00)	1.00 (1.00-1.00)	0.99 (0.936-1.00)	1.00 (0.99-1.00)	1.000 (1.000-1.000)
0.9	2	0.5	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (0.990-1.00)	1.00 (1.00-1.00)	1.000 (1.000-1.000)
0.9	2	0.9	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.000-1.00)	1.00 (1.00-1.00)	1.000 (1.000-1.000)
0.9	3	0	0.97 (0.94-0.99)	0.90 (0.83-0.96)	0.99 (0.98-1.00)	0.78 (0.603-0.89)	0.96 (0.93-0.98)	0.986 (0.963-0.995)
0.9	3	0.01	0.97 (0.95-0.99)	0.92 (0.86-0.97)	0.99 (0.98-1.00)	0.80 (0.666-0.90)	0.97 (0.94-0.98)	0.990 (0.972-0.997)
0.9	3	0.05	0.98 (0.97-1.00)	0.96 (0.90-1.00)	1.00 (0.99-1.00)	0.88 (0.766-0.96)	0.98 (0.96-0.99)	0.996 (0.987-1.000)
0.9	3	0.1	0.99 (0.97-1.00)	0.98 (0.93-1.00)	1.00 (0.99-1.00)	0.93 (0.788-0.98)	0.99 (0.97-1.00)	0.999 (0.992-1.000)
0.9	3	0.2	1.00 (0.98-1.00)	1.00 (0.96-1.00)	1.00 (1.00-1.00)	0.97 (0.879-1.00)	1.00 (0.98-1.00)	1.000 (0.998-1.000)
0.9	3	0.5	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (0.981-1.00)	1.00 (1.00-1.00)	1.000 (1.000-1.000)
0.9	3	0.9	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.000-1.00)	1.00 (1.00-1.00)	1.000 (1.000-1.000)
0.9	4	0	0.94 (0.89-0.97)	0.72 (0.64-0.77)	0.97 (0.96-0.97)	0.59 (0.404-0.71)	0.92 (0.87-0.95)	0.939 (0.884-0.969)
0.9	4	0.01	0.95 (0.91-0.97)	0.77 (0.70-0.88)	0.97 (0.96-0.99)	0.64 (0.462-0.78)	0.93 (0.89-0.96)	0.954 (0.904-0.984)
0.9	4	0.05	0.97 (0.94-0.99)	0.89 (0.79-0.96)	0.99 (0.98-1.00)	0.79 (0.600-0.92)	0.96 (0.93-0.99)	0.986 (0.953-0.998)
0.9	4	0.1	0.98 (0.95-1.00)	0.95 (0.87-0.99)	0.99 (0.98-1.00)	0.88 (0.691-0.96)	0.98 (0.95-0.99)	0.995 (0.981-1.000)
0.9	4	0.2	0.99 (0.98-1.00)	0.99 (0.96-1.00)	1.00 (1.00-1.00)	0.96 (0.853-1.00)	0.99 (0.98-1.00)	1.000 (0.997-1.000)
0.9	4	0.5	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (0.981-1.00)	1.00 (1.00-1.00)	1.000 (1.000-1.000)
0.9	4	0.9	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.000-1.00)	1.00 (1.00-1.00)	1.000 (1.000-1.000)
0.9	5	0	0.91 (0.84-0.94)	0.54 (0.44-0.62)	0.95 (0.94-0.96)	0.41 (0.268-0.50)	0.87 (0.81-0.90)	0.855 (0.783-0.905)
0.9	5	0.01	0.92 (0.87-0.96)	0.61 (0.50-0.75)	0.95 (0.94-0.97)	0.47 (0.300-0.69)	0.89 (0.83-0.94)	0.889 (0.806-0.963)
0.9	5	0.05	0.96 (0.92-0.99)	0.80 (0.67-0.92)	0.98 (0.96-0.99)	0.71 (0.493-0.89)	0.95 (0.90-0.98)	0.966 (0.905-0.996)
0.9	5	0.1	0.98 (0.95-0.99)	0.90 (0.80-0.97)	0.99 (0.98-1.00)	0.83 (0.632-0.95)	0.97 (0.93-0.99)	0.988 (0.958-0.999)
0.9	5	0.2	0.99 (0.98-1.00)	0.99 (0.95-1.00)	1.00 (0.99-1.00)	0.95 (0.845-0.99)	0.99 (0.98-1.00)	0.999 (0.996-1.000)
0.9	5	0.5	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (0.981-1.00)	1.00 (1.00-1.00)	1.000 (1.000-1.000)
0.9	5	0.9	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.000-1.00)	1.00 (1.00-1.00)	1.000 (1.000-1.000)
0.95	2	0	0.99 (0.98-1.00)	0.98 (0.92-1.00)	1.00 (1.00-1.00)	0.89 (0.743-0.96)	0.99 (0.98-1.00)	0.999 (0.996-1.000)
0.95	2	0.01	0.99 (0.98-1.00)	0.98 (0.92-1.00)	1.00 (1.00-1.00)	0.90 (0.743-0.96)	0.99 (0.98-1.00)	0.999 (0.996-1.000)
0.95	2	0.05	1.00 (0.99-1.00)	0.99 (0.96-1.00)	1.00 (1.00-1.00)	0.92 (0.788-1.00)	0.99 (0.99-1.00)	1.000 (0.998-1.000)
0.95	2	0.1	1.00 (0.99-1.00)	0.99 (0.96-1.00)	1.00 (1.00-1.00)	0.95 (0.846-1.00)	1.00 (0.99-1.00)	1.000 (0.999-1.000)
0.95	2	0.2	1.00 (0.99-1.00)	1.00 (0.96-1.00)	1.00 (1.00-1.00)	0.98 (0.896-1.00)	1.00 (0.99-1.00)	1.000 (1.000-1.000)
0.95	2	0.5	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (0.963-1.00)	1.00 (1.00-1.00)	1.000 (1.000-1.000)
0.95	2	0.9	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.000-1.00)	1.00 (1.00-1.00)	1.000 (1.000-1.000)
0.95	3	0	0.96 (0.91-0.99)	0.66 (0.52-0.77)	0.98 (0.97-0.99)	0.51 (0.246-0.73)	0.95 (0.90-0.97)	0.950 (0.872-0.982)
0.95	3	0.01	0.97 (0.94-0.99)	0.70 (0.55-0.83)	0.98 (0.98-0.99)	0.57 (0.323-0.77)	0.96 (0.92-0.98)	0.961 (0.891-0.989)
0.95	3	0.05	0.98 (0.96-0.99)	0.83 (0.72-0.94)	0.99 (0.99-1.00)	0.72 (0.517-0.88)	0.98 (0.95-0.99)	0.986 (0.953-0.997)



Supplementary Table S7  
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0.95	3	0.1	0.99 (0.96-1.00)	0.92 (0.80-1.00)	1.00 (0.99-1.00)	0.83 (0.533-0.96)	0.99 (0.96-1.00)	0.995 (0.970-1.000)
0.95	3	0.2	1.00 (0.98-1.00)	0.98 (0.92-1.00)	1.00 (1.00-1.00)	0.92 (0.731-1.00)	0.99 (0.98-1.00)	0.999 (0.995-1.000)
0.95	3	0.5	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (0.962-1.00)	1.00 (1.00-1.00)	1.000 (1.000-1.000)
0.95	3	0.9	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.000-1.00)	1.00 (1.00-1.00)	1.000 (1.000-1.000)
0.95	4	0	0.92 (0.84-0.96)	0.35 (0.23-0.46)	0.96 (0.96-0.97)	0.21 (0.115-0.35)	0.89 (0.82-0.93)	0.788 (0.696-0.876)
0.95	4	0.01	0.93 (0.87-0.97)	0.39 (0.27-0.54)	0.97 (0.96-0.97)	0.24 (0.130-0.41)	0.90 (0.85-0.94)	0.816 (0.722-0.900)
0.95	4	0.05	0.96 (0.93-0.98)	0.58 (0.40-0.73)	0.98 (0.97-0.99)	0.46 (0.248-0.68)	0.94 (0.91-0.97)	0.924 (0.843-0.976)
0.95	4	0.1	0.98 (0.94-1.00)	0.75 (0.57-0.88)	0.99 (0.98-0.99)	0.68 (0.352-0.91)	0.97 (0.92-0.99)	0.974 (0.899-0.996)
0.95	4	0.2	0.99 (0.97-1.00)	0.93 (0.85-1.00)	1.00 (0.99-1.00)	0.88 (0.613-1.00)	0.99 (0.97-1.00)	0.997 (0.986-1.000)
0.95	4	0.5	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (0.963-1.00)	1.00 (1.00-1.00)	1.000 (1.000-1.000)
0.95	4	0.9	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.000-1.00)	1.00 (1.00-1.00)	1.000 (1.000-1.000)
0.95	5	0	0.90 (0.83-0.94)	0.24 (0.15-0.35)	0.96 (0.95-0.96)	0.11 (0.073-0.16)	0.86 (0.80-0.90)	0.664 (0.594-0.734)
0.95	5	0.01	0.90 (0.86-0.95)	0.28 (0.18-0.38)	0.96 (0.95-0.97)	0.14 (0.086-0.22)	0.87 (0.83-0.91)	0.714 (0.634-0.808)
0.95	5	0.05	0.94 (0.90-0.98)	0.45 (0.31-0.62)	0.97 (0.96-0.98)	0.32 (0.159-0.56)	0.92 (0.88-0.96)	0.860 (0.773-0.939)
0.95	5	0.1	0.97 (0.93-0.99)	0.64 (0.46-0.85)	0.98 (0.97-0.99)	0.59 (0.282-0.86)	0.98 (0.91-0.98)	0.951 (0.860-0.994)
0.95	5	0.2	0.99 (0.97-1.00)	0.89 (0.77-0.98)	0.99 (0.99-1.00)	0.86 (0.630-0.97)	0.99 (0.97-1.00)	0.994 (0.975-1.000)
0.95	5	0.5	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (0.963-1.00)	1.00 (1.00-1.00)	1.000 (1.000-1.000)
0.95	5	0.9	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.000-1.00)	1.00 (1.00-1.00)	1.000 (1.000-1.000)

Weak gene expression changes (1.4-fold)

Proportion of resistant cases	Number of resistance mechanisms	Overlap	Sensitivity	Specificity	PPV	NPV	Accuracy	AUC
0.5	2	0	0.91 (0.88-0.94)	0.92 (0.879-0.95)	0.92 (0.88-0.95)	0.909 (0.879-0.940)	0.91 (0.88-0.94)	0.969 (0.943-0.984)
0.5	2	0.01	0.91 (0.87-0.94)	0.92 (0.887-0.95)	0.92 (0.89-0.95)	0.910 (0.876-0.942)	0.92 (0.88-0.94)	0.970 (0.948-0.986)
0.5	2	0.05	0.92 (0.88-0.95)	0.93 (0.891-0.97)	0.93 (0.89-0.96)	0.921 (0.885-0.950)	0.93 (0.89-0.96)	0.976 (0.956-0.989)
0.5	2	0.1	0.93 (0.90-0.96)	0.94 (0.901-0.97)	0.94 (0.90-0.97)	0.931 (0.900-0.957)	0.94 (0.90-0.96)	0.981 (0.963-0.992)
0.5	2	0.2	0.94 (0.90-0.97)	0.95 (0.915-0.98)	0.95 (0.91-0.98)	0.943 (0.903-0.969)	0.95 (0.91-0.97)	0.986 (0.966-0.996)
0.5	2	0.5	0.97 (0.94-0.99)	0.98 (0.950-1.00)	0.98 (0.95-1.00)	0.968 (0.942-0.987)	0.97 (0.94-0.99)	0.996 (0.987-1.000)
0.5	2	0.9	0.98 (0.96-1.00)	0.99 (0.970-1.00)	0.99 (0.97-1.00)	0.983 (0.964-0.996)	0.99 (0.97-1.00)	0.999 (0.995-1.000)
0.5	3	0	0.82 (0.78-0.86)	0.82 (0.780-0.86)	0.82 (0.78-0.86)	0.824 (0.781-0.866)	0.82 (0.78-0.86)	0.897 (0.857-0.925)
0.5	3	0.01	0.83 (0.78-0.87)	0.83 (0.766-0.88)	0.83 (0.77-0.88)	0.830 (0.780-0.871)	0.83 (0.78-0.87)	0.903 (0.851-0.935)
0.5	3	0.05	0.85 (0.81-0.89)	0.86 (0.811-0.91)	0.86 (0.81-0.90)	0.856 (0.808-0.894)	0.86 (0.81-0.90)	0.927 (0.883-0.960)
0.5	3	0.1	0.88 (0.84-0.92)	0.89 (0.841-0.93)	0.88 (0.84-0.93)	0.879 (0.841-0.918)	0.88 (0.84-0.92)	0.947 (0.910-0.970)
0.5	3	0.2	0.91 (0.87-0.95)	0.92 (0.877-0.96)	0.92 (0.88-0.96)	0.915 (0.871-0.950)	0.92 (0.87-0.95)	0.971 (0.940-0.987)
0.5	3	0.5	0.96 (0.93-0.99)	0.97 (0.932-0.99)	0.97 (0.93-0.99)	0.963 (0.928-0.986)	0.97 (0.93-0.99)	0.994 (0.980-0.999)
0.5	3	0.9	0.98 (0.96-1.00)	0.99 (0.961-1.00)	0.99 (0.96-1.00)	0.983 (0.961-0.996)	0.99 (0.96-1.00)	0.999 (0.993-1.000)
0.5	4	0	0.74 (0.70-0.79)	0.74 (0.683-0.78)	0.74 (0.69-0.78)	0.741 (0.700-0.783)	0.74 (0.70-0.78)	0.810 (0.764-0.847)
0.5	4	0.01	0.76 (0.71-0.80)	0.75 (0.688-0.80)	0.75 (0.70-0.80)	0.755 (0.703-0.801)	0.75 (0.70-0.80)	0.827 (0.755-0.870)
0.5	4	0.05	0.80 (0.75-0.86)	0.80 (0.744-0.85)	0.80 (0.75-0.85)	0.798 (0.743-0.854)	0.80 (0.75-0.85)	0.874 (0.817-0.925)
0.5	4	0.1	0.84 (0.80-0.89)	0.84 (0.788-0.90)	0.84 (0.79-0.89)	0.842 (0.795-0.887)	0.84 (0.80-0.89)	0.915 (0.870-0.951)
0.5	4	0.2	0.90 (0.86-0.93)	0.90 (0.851-0.95)	0.90 (0.85-0.95)	0.896 (0.854-0.933)	0.90 (0.85-0.94)	0.959 (0.925-0.982)
0.5	4	0.5	0.96 (0.93-0.98)	0.97 (0.928-0.99)	0.97 (0.93-0.99)	0.961 (0.927-0.985)	0.97 (0.93-0.98)	0.993 (0.980-0.999)
0.5	4	0.9	0.98 (0.97-1.00)	0.99 (0.967-1.00)	0.99 (0.97-1.00)	0.982 (0.966-0.996)	0.99 (0.97-1.00)	0.999 (0.995-1.000)
0.5	5	0	0.67 (0.62-0.71)	0.66 (0.616-0.70)	0.67 (0.63-0.71)	0.669 (0.625-0.706)	0.67 (0.62-0.70)	0.724 (0.674-0.763)
0.5	5	0.01	0.69 (0.65-0.74)	0.68 (0.635-0.73)	0.69 (0.64-0.73)	0.690 (0.646-0.736)	0.69 (0.65-0.73)	0.751 (0.692-0.804)
0.5	5	0.05	0.75 (0.67-0.82)	0.75 (0.680-0.81)	0.75 (0.69-0.81)	0.749 (0.676-0.818)	0.75 (0.68-0.81)	0.821 (0.751-0.891)
0.5	5	0.1	0.81 (0.75-0.86)	0.81 (0.738-0.86)	0.81 (0.75-0.86)	0.808 (0.753-0.859)	0.81 (0.75-0.86)	0.882 (0.821-0.931)
0.5	5	0.2	0.88 (0.83-0.92)	0.89 (0.834-0.93)	0.89 (0.84-0.93)	0.884 (0.837-0.923)	0.89 (0.84-0.92)	0.950 (0.914-0.976)
0.5	5	0.5	0.96 (0.92-0.98)	0.97 (0.924-0.99)	0.97 (0.92-0.99)	0.961 (0.920-0.984)	0.96 (0.92-0.99)	0.993 (0.978-0.999)
0.5	5	0.9	0.98 (0.96-1.00)	0.99 (0.969-1.00)	0.99 (0.97-1.00)	0.983 (0.964-0.996)	0.99 (0.97-1.00)	0.999 (0.995-1.000)
0.6	2	0	0.92 (0.89-0.94)	0.91 (0.878-0.95)	0.94 (0.92-0.96)	0.883 (0.844-0.911)	0.92 (0.89-0.94)	0.970 (0.950-0.982)
0.6	2	0.01	0.92 (0.88-0.94)	0.91 (0.862-0.94)	0.94 (0.91-0.96)	0.880 (0.830-0.916)	0.91 (0.87-0.94)	0.969 (0.940-0.984)
0.6	2	0.05	0.92 (0.89-0.95)	0.92 (0.867-0.96)	0.94 (0.91-0.97)	0.889 (0.838-0.935)	0.92 (0.88-0.96)	0.973 (0.945-0.990)
0.6	2	0.1	0.94 (0.90-0.96)	0.93 (0.883-0.97)	0.95 (0.92-0.98)	0.909 (0.855-0.945)	0.94 (0.90-0.96)	0.981 (0.959-0.993)
0.6	2	0.2	0.95 (0.91-0.97)	0.95 (0.912-0.98)	0.96 (0.94-0.99)	0.923 (0.877-0.958)	0.95 (0.91-0.97)	0.987 (0.968-0.996)
0.6	2	0.5	0.97 (0.93-0.99)	0.97 (0.944-1.00)	0.98 (0.96-1.00)	0.954 (0.904-0.984)	0.97 (0.94-0.99)	0.995 (0.985-0.999)
0.6	2	0.9	0.98 (0.97-1.00)	0.99 (0.966-1.00)	0.99 (0.98-1.00)	0.975 (0.953-0.995)	0.99 (0.97-1.00)	0.999 (0.995-1.000)
0.6	3	0	0.84 (0.80-0.87)	0.79 (0.750-0.83)	0.86 (0.82-0.88)	0.771 (0.708-0.811)	0.82 (0.77-0.85)	0.895 (0.840-0.921)
0.6	3	0.01	0.85 (0.80-0.88)	0.80 (0.748-0.85)	0.86 (0.83-0.89)	0.776 (0.711-0.827)	0.83 (0.78-0.87)	0.899 (0.847-0.930)
0.6	3	0.05	0.87 (0.83-0.91)	0.83 (0.784-0.89)	0.89 (0.85-0.92)	0.809 (0.759-0.861)	0.85 (0.81-0.89)	0.924 (0.883-0.955)
0.6	3	0.1	0.90 (0.87-0.93)	0.87 (0.821-0.91)	0.91 (0.88-0.94)	0.848 (0.803-0.891)	0.89 (0.85-0.92)	0.949 (0.922-0.972)
0.6	3	0.2	0.92 (0.88-0.95)	0.91 (0.861-0.96)	0.94 (0.91-0.97)	0.890 (0.828-0.931)	0.92 (0.87-0.96)	0.972 (0.940-0.988)
0.6	3	0.5	0.97 (0.94-0.99)	0.97 (0.932-0.99)	0.98 (0.95-1.00)	0.951 (0.907-0.979)	0.97 (0.94-0.99)	0.994 (0.984-0.999)
0.6	3	0.9	0.98 (0.97-1.00)	0.99 (0.964-1.00)	0.99 (0.98-1.00)	0.976 (0.951-0.995)	0.99 (0.97-1.00)	0.999 (0.995-1.000)
0.6	4	0	0.77 (0.72-0.80)	0.69 (0.647-0.73)	0.79 (0.76-0.81)	0.669 (0.608-0.710)	0.74 (0.69-0.77)	0.803 (0.742-0.841)
0.6	4	0.01	0.79 (0.73-0.83)	0.71 (0.654-0.75)	0.80 (0.76-0.83)	0.689 (0.621-0.745)	0.76 (0.70-0.80)	0.821 (0.753-0.866)
0.6	4	0.05	0.82 (0.76-0.87)	0.76 (0.691-0.82)	0.84 (0.79-0.88)	0.744 (0.670-0.811)	0.80 (0.74-0.85)	0.870 (0.809-0.919)
0.6	4	0.1	0.86 (0.82-0.90)	0.82 (0.763-0.87)	0.88 (0.84-0.91)	0.801 (0.738-0.853)	0.84 (0.80-0.89)	0.915 (0.866-0.952)
0.6	4	0.2	0.91 (0.85-0.94)	0.88 (0.817-0.93)	0.92 (0.88-0.95)	0.865 (0.788-0.917)	0.90 (0.84-0.94)	0.957 (0.912-0.980)
0.6	4	0.5	0.97 (0.93-0.99)	0.97 (0.926-0.99)	0.98 (0.95-0.99)	0.950 (0.895-0.981)	0.97 (0.93-0.99)	0.994 (0.981-0.999)
0.6	4	0.9	0.98 (0.96-1.00)	0.99 (0.966-1.00)	0.99 (0.98-1.00)	0.976 (0.943-0.995)	0.99 (0.96-1.00)	0.999 (0.995-1.000)
0.6	5	0	0.71 (0.66-0.75)	0.61 (0.568-0.65)	0.73 (0.70-0.76)	0.586 (0.536-0.627)	0.67 (0.63-0.71)	0.718 (0.670-0.757)
0.6	5	0.01	0.73 (0.66-0.78)	0.63 (0.578-0.67)	0.75 (0.71-0.78)	0.613 (0.539-0.663)	0.69 (0.63-0.74)	0.745 (0.660-0.795)
0.6	5	0.05	0.78 (0.72-0.83)	0.70 (0.624-0.76)	0.79 (0.75-0.84)	0.680 (0.600-0.747)	0.75 (0.68-0.80)	0.811 (0.746-0.869)
0.6	5	0.1	0.83 (0.78-0.89)	0.77 (0.708-0.85)	0.85 (0.80-0.90)	0.757 (0.680-0.839)	0.81 (0.75-0.87)	0.881 (0.819-0.939)
0.6	5	0.2	0.89 (0.83-0.94)	0.86 (0.789-0.91)	0.90 (0.85-0.94)	0.842 (0.765-0.902)	0.88 (0.82-0.93)	0.943 (0.888-0.974)
0.6	5	0.5	0.96 (0.93-0.98)	0.97 (0.923-0.99)	0.98 (0.95-0.99)	0.948 (0.896-0.976)	0.96 (0.93-0.99)	0.993 (0.977-0.999)
0.6	5	0.9	0.98 (0.96-1.00)	0.99 (0.961-1.00)	0.99 (0.97-1.00)	0.976 (0.945-0.995)	0.99 (0.96-1.00)	0.999 (0.994-1.000)

Supplementary Table S7  
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0.7	2	0	0.93 (0.89-0.96)	0.89 (0.845-0.94)	0.95 (0.93-0.97)	0.842 (0.773-0.895)	0.92 (0.88-0.94)	0.968 (0.942-0.983)
0.7	2	0.01	0.93 (0.90-0.96)	0.90 (0.852-0.93)	0.95 (0.93-0.97)	0.845 (0.787-0.902)	0.92 (0.89-0.95)	0.970 (0.951-0.985)
0.7	2	0.05	0.93 (0.89-0.96)	0.90 (0.843-0.95)	0.96 (0.93-0.98)	0.854 (0.766-0.917)	0.92 (0.88-0.96)	0.974 (0.943-0.990)
0.7	2	0.1	0.94 (0.90-0.97)	0.92 (0.873-0.95)	0.97 (0.94-0.98)	0.870 (0.796-0.922)	0.93 (0.89-0.96)	0.980 (0.958-0.990)
0.7	2	0.2	0.96 (0.92-0.98)	0.94 (0.898-0.97)	0.98 (0.95-0.99)	0.901 (0.824-0.947)	0.95 (0.91-0.97)	0.988 (0.967-0.996)
0.7	2	0.5	0.97 (0.95-0.99)	0.97 (0.934-1.00)	0.99 (0.97-1.00)	0.941 (0.883-0.975)	0.97 (0.94-0.99)	0.996 (0.986-0.999)
0.7	2	0.9	0.98 (0.97-0.99)	0.99 (0.961-1.00)	0.99 (0.98-1.00)	0.963 (0.925-0.987)	0.98 (0.97-1.00)	0.999 (0.995-1.000)
0.7	3	0	0.86 (0.81-0.90)	0.75 (0.702-0.79)	0.89 (0.87-0.91)	0.697 (0.626-0.763)	0.83 (0.79-0.86)	0.888 (0.835-0.920)
0.7	3	0.01	0.87 (0.83-0.90)	0.76 (0.718-0.81)	0.90 (0.87-0.92)	0.713 (0.652-0.770)	0.84 (0.80-0.87)	0.898 (0.859-0.930)
0.7	3	0.05	0.89 (0.85-0.92)	0.80 (0.745-0.86)	0.91 (0.89-0.94)	0.752 (0.678-0.823)	0.86 (0.82-0.90)	0.921 (0.878-0.958)
0.7	3	0.1	0.90 (0.86-0.94)	0.84 (0.774-0.90)	0.93 (0.90-0.95)	0.785 (0.699-0.860)	0.88 (0.83-0.92)	0.942 (0.895-0.968)
0.7	3	0.2	0.93 (0.89-0.96)	0.90 (0.837-0.94)	0.96 (0.93-0.97)	0.854 (0.766-0.914)	0.92 (0.88-0.96)	0.972 (0.939-0.990)
0.7	3	0.5	0.97 (0.94-0.99)	0.96 (0.923-0.99)	0.98 (0.97-1.00)	0.931 (0.874-0.968)	0.97 (0.94-0.99)	0.994 (0.982-0.999)
0.7	3	0.9	0.98 (0.97-1.00)	0.99 (0.961-1.00)	0.99 (0.98-1.00)	0.962 (0.925-0.991)	0.98 (0.96-1.00)	0.998 (0.993-1.000)
0.7	4	0	0.80 (0.75-0.84)	0.62 (0.573-0.67)	0.83 (0.81-0.85)	0.577 (0.505-0.641)	0.75 (0.70-0.78)	0.793 (0.745-0.835)
0.7	4	0.01	0.81 (0.77-0.85)	0.64 (0.592-0.69)	0.84 (0.82-0.87)	0.587 (0.531-0.663)	0.76 (0.72-0.80)	0.802 (0.758-0.857)
0.7	4	0.05	0.84 (0.78-0.89)	0.70 (0.622-0.77)	0.87 (0.83-0.90)	0.656 (0.558-0.745)	0.80 (0.74-0.85)	0.857 (0.791-0.909)
0.7	4	0.1	0.87 (0.80-0.91)	0.76 (0.675-0.83)	0.89 (0.85-0.93)	0.715 (0.605-0.801)	0.84 (0.77-0.88)	0.897 (0.821-0.942)
0.7	4	0.2	0.92 (0.87-0.95)	0.85 (0.776-0.92)	0.94 (0.90-0.96)	0.818 (0.715-0.893)	0.90 (0.84-0.94)	0.954 (0.903-0.984)
0.7	4	0.5	0.97 (0.93-0.99)	0.96 (0.916-0.98)	0.98 (0.96-0.99)	0.924 (0.857-0.968)	0.96 (0.93-0.98)	0.992 (0.974-0.998)
0.7	4	0.9	0.98 (0.97-0.99)	0.99 (0.964-1.00)	0.99 (0.98-1.00)	0.965 (0.922-0.987)	0.99 (0.97-1.00)	0.999 (0.994-1.000)
0.7	5	0	0.75 (0.70-0.79)	0.53 (0.477-0.58)	0.79 (0.77-0.81)	0.473 (0.425-0.519)	0.68 (0.65-0.71)	0.697 (0.652-0.749)
0.7	5	0.01	0.76 (0.70-0.81)	0.55 (0.495-0.60)	0.80 (0.77-0.82)	0.494 (0.435-0.563)	0.70 (0.65-0.74)	0.716 (0.661-0.777)
0.7	5	0.05	0.80 (0.73-0.86)	0.62 (0.561-0.71)	0.83 (0.80-0.87)	0.580 (0.477-0.672)	0.75 (0.68-0.80)	0.793 (0.720-0.861)
0.7	5	0.1	0.84 (0.76-0.89)	0.70 (0.622-0.77)	0.87 (0.83-0.90)	0.660 (0.531-0.754)	0.80 (0.72-0.85)	0.857 (0.767-0.917)
0.7	5	0.2	0.90 (0.85-0.95)	0.82 (0.745-0.89)	0.92 (0.89-0.95)	0.786 (0.677-0.874)	0.88 (0.82-0.93)	0.935 (0.880-0.976)
0.7	5	0.5	0.97 (0.92-0.99)	0.95 (0.903-0.98)	0.98 (0.96-0.99)	0.924 (0.836-0.968)	0.96 (0.92-0.98)	0.991 (0.968-0.998)
0.7	5	0.9	0.98 (0.97-0.99)	0.99 (0.964-1.00)	0.99 (0.98-1.00)	0.966 (0.928-0.987)	0.99 (0.97-1.00)	0.999 (0.995-1.000)
0.8	2	0	0.94 (0.90-0.96)	0.86 (0.808-0.90)	0.96 (0.95-0.98)	0.775 (0.676-0.851)	0.92 (0.89-0.95)	0.966 (0.935-0.982)
0.8	2	0.01	0.94 (0.91-0.96)	0.86 (0.798-0.91)	0.97 (0.95-0.98)	0.771 (0.690-0.857)	0.92 (0.89-0.95)	0.966 (0.940-0.984)
0.8	2	0.05	0.94 (0.91-0.97)	0.88 (0.820-0.94)	0.97 (0.95-0.98)	0.789 (0.689-0.881)	0.93 (0.89-0.96)	0.971 (0.942-0.989)
0.8	2	0.1	0.95 (0.91-0.97)	0.90 (0.835-0.94)	0.97 (0.96-0.99)	0.816 (0.710-0.888)	0.94 (0.90-0.96)	0.978 (0.950-0.992)
0.8	2	0.2	0.96 (0.93-0.98)	0.93 (0.874-0.96)	0.98 (0.97-0.99)	0.850 (0.765-0.922)	0.95 (0.92-0.98)	0.986 (0.970-0.995)
0.8	2	0.5	0.98 (0.95-0.99)	0.97 (0.932-0.99)	0.99 (0.98-1.00)	0.915 (0.827-0.967)	0.98 (0.95-0.99)	0.996 (0.986-0.999)
0.8	2	0.9	0.99 (0.97-1.00)	0.99 (0.956-1.00)	1.00 (0.99-1.00)	0.947 (0.879-0.990)	0.99 (0.97-1.00)	0.999 (0.994-1.000)
0.8	3	0	0.88 (0.83-0.91)	0.67 (0.616-0.72)	0.91 (0.90-0.93)	0.585 (0.469-0.671)	0.84 (0.78-0.87)	0.872 (0.815-0.911)
0.8	3	0.01	0.88 (0.83-0.92)	0.68 (0.631-0.75)	0.92 (0.90-0.93)	0.592 (0.486-0.699)	0.84 (0.79-0.88)	0.879 (0.823-0.925)
0.8	3	0.05	0.90 (0.85-0.93)	0.73 (0.650-0.80)	0.93 (0.91-0.95)	0.645 (0.532-0.740)	0.87 (0.82-0.90)	0.906 (0.852-0.947)
0.8	3	0.1	0.91 (0.85-0.94)	0.78 (0.694-0.84)	0.94 (0.92-0.96)	0.693 (0.533-0.789)	0.89 (0.82-0.92)	0.930 (0.867-0.964)
0.8	3	0.2	0.94 (0.90-0.97)	0.86 (0.796-0.91)	0.96 (0.95-0.98)	0.784 (0.666-0.870)	0.92 (0.88-0.95)	0.966 (0.929-0.986)
0.8	3	0.5	0.97 (0.94-0.99)	0.95 (0.905-0.98)	0.99 (0.98-1.00)	0.899 (0.796-0.953)	0.97 (0.94-0.99)	0.994 (0.979-0.999)
0.8	3	0.9	0.99 (0.97-1.00)	0.99 (0.961-1.00)	1.00 (0.99-1.00)	0.948 (0.897-0.988)	0.99 (0.97-1.00)	0.999 (0.996-1.000)
0.8	4	0	0.82 (0.75-0.87)	0.50 (0.442-0.56)	0.87 (0.85-0.88)	0.414 (0.328-0.492)	0.76 (0.70-0.80)	0.745 (0.683-0.800)
0.8	4	0.01	0.82 (0.76-0.88)	0.52 (0.459-0.59)	0.87 (0.86-0.89)	0.429 (0.352-0.541)	0.76 (0.72-0.82)	0.759 (0.697-0.828)
0.8	4	0.05	0.86 (0.80-0.91)	0.61 (0.529-0.70)	0.90 (0.87-0.92)	0.528 (0.413-0.648)	0.81 (0.75-0.86)	0.832 (0.754-0.897)
0.8	4	0.1	0.88 (0.80-0.93)	0.67 (0.583-0.75)	0.91 (0.89-0.93)	0.590 (0.444-0.716)	0.84 (0.77-0.89)	0.872 (0.793-0.931)
0.8	4	0.2	0.93 (0.89-0.96)	0.79 (0.721-0.87)	0.95 (0.93-0.97)	0.738 (0.617-0.839)	0.90 (0.86-0.94)	0.946 (0.899-0.977)
0.8	4	0.5	0.97 (0.95-0.99)	0.94 (0.883-0.98)	0.99 (0.97-1.00)	0.896 (0.799-0.953)	0.97 (0.93-0.99)	0.992 (0.975-0.998)
0.8	4	0.9	0.99 (0.97-1.00)	0.99 (0.961-1.00)	1.00 (0.99-1.00)	0.949 (0.899-0.981)	0.99 (0.97-1.00)	0.999 (0.996-1.000)
0.8	5	0	0.77 (0.70-0.82)	0.41 (0.339-0.47)	0.84 (0.83-0.85)	0.312 (0.270-0.364)	0.70 (0.66-0.74)	0.646 (0.600-0.692)
0.8	5	0.01	0.78 (0.72-0.84)	0.44 (0.362-0.50)	0.85 (0.83-0.87)	0.336 (0.288-0.422)	0.71 (0.67-0.77)	0.673 (0.627-0.749)
0.8	5	0.05	0.83 (0.76-0.88)	0.52 (0.442-0.61)	0.87 (0.85-0.90)	0.429 (0.338-0.551)	0.76 (0.71-0.82)	0.756 (0.678-0.842)
0.8	5	0.1	0.86 (0.79-0.91)	0.59 (0.519-0.68)	0.89 (0.87-0.92)	0.514 (0.396-0.657)	0.80 (0.75-0.86)	0.820 (0.730-0.896)
0.8	5	0.2	0.91 (0.85-0.95)	0.75 (0.643-0.82)	0.94 (0.91-0.96)	0.689 (0.514-0.805)	0.88 (0.81-0.92)	0.922 (0.843-0.963)
0.8	5	0.5	0.97 (0.93-0.99)	0.93 (0.871-0.98)	0.98 (0.97-0.99)	0.891 (0.766-0.957)	0.96 (0.92-0.99)	0.990 (0.965-0.998)
0.8	5	0.9	0.99 (0.97-1.00)	0.98 (0.961-1.00)	1.00 (0.99-1.00)	0.945 (0.892-0.981)	0.99 (0.97-1.00)	0.999 (0.996-1.000)
0.9	2	0	0.94 (0.90-0.97)	0.72 (0.639-0.81)	0.97 (0.96-0.98)	0.594 (0.444-0.725)	0.92 (0.88-0.95)	0.941 (0.888-0.969)
0.9	2	0.01	0.94 (0.90-0.97)	0.72 (0.601-0.81)	0.97 (0.95-0.98)	0.591 (0.418-0.725)	0.92 (0.87-0.95)	0.939 (0.877-0.972)
0.9	2	0.05	0.95 (0.91-0.97)	0.76 (0.654-0.84)	0.97 (0.96-0.98)	0.635 (0.441-0.767)	0.93 (0.88-0.96)	0.952 (0.892-0.978)
0.9	2	0.1	0.96 (0.92-0.98)	0.80 (0.692-0.88)	0.98 (0.96-0.99)	0.674 (0.487-0.815)	0.94 (0.90-0.97)	0.964 (0.919-0.987)
0.9	2	0.2	0.96 (0.93-0.98)	0.84 (0.750-0.92)	0.98 (0.97-0.99)	0.732 (0.559-0.852)	0.95 (0.92-0.97)	0.976 (0.945-0.992)
0.9	2	0.5	0.98 (0.96-0.99)	0.94 (0.875-0.98)	0.99 (0.99-1.00)	0.845 (0.693-0.952)	0.98 (0.95-0.99)	0.994 (0.980-0.999)
0.9	2	0.9	0.99 (0.97-1.00)	0.98 (0.942-1.00)	1.00 (0.99-1.00)	0.908 (0.811-0.972)	0.99 (0.97-1.00)	0.998 (0.995-1.000)
0.9	3	0	0.87 (0.80-0.92)	0.41 (0.327-0.48)	0.93 (0.92-0.94)	0.271 (0.188-0.354)	0.83 (0.77-0.86)	0.752 (0.674-0.812)
0.9	3	0.01	0.87 (0.80-0.92)	0.42 (0.327-0.50)	0.93 (0.92-0.94)	0.279 (0.194-0.378)	0.83 (0.77-0.87)	0.757 (0.687-0.823)
0.9	3	0.05	0.89 (0.83-0.94)	0.48 (0.404-0.57)	0.94 (0.93-0.95)	0.348 (0.230-0.452)	0.85 (0.79-0.89)	0.813 (0.726-0.878)
0.9	3	0.1	0.91 (0.84-0.95)	0.54 (0.462-0.65)	0.95 (0.94-0.96)	0.425 (0.264-0.570)	0.88 (0.81-0.91)	0.859 (0.767-0.922)
0.9	3	0.2	0.94 (0.89-0.97)	0.67 (0.558-0.78)	0.96 (0.95-0.97)	0.559 (0.362-0.721)	0.91 (0.86-0.95)	0.919 (0.842-0.969)
0.9	3	0.5	0.98 (0.95-0.99)	0.90 (0.826-0.94)	0.99 (0.98-0.99)	0.824 (0.672-0.922)	0.97 (0.94-0.98)	0.989 (0.969-0.997)
0.9	3	0.9	0.99 (0.97-1.00)	0.98 (0.942-1.00)	1.00 (0.99-1.00)	0.901 (0.777-0.981)	0.99 (0.97-1.00)	0.998 (0.991-1.000)
0.9	4	0	0.83 (0.76-0.88)	0.30 (0.231-0.38)	0.91 (0.91-0.92)	0.163 (0.129-0.197)	0.77 (0.72-0.82)	0.623 (0.579-0.670)
0.9	4	0.01	0.83 (0.77-0.89)	0.31 (0.206-0.40)	0.92 (0.91-0.92)	0.174 (0.140-0.219)	0.78 (0.74-0.82)	0.638 (0.585-0.700)
0.9	4	0.05	0.86 (0.80-0.91)	0.37 (0.278-0.48)	0.92 (0.91-0.93)	0.235 (0.172-0.307)	0.81 (0.76-0.85)	0.710 (0.636-0.774)
0.9	4	0.1	0.89 (0.83-0.93)	0.43 (0.341-0.53)	0.93 (0.92-0.95)	0.305 (0.204-0.441)	0.84 (0.78-0.88)	0.774 (0.695-0.857)
0.9	4	0.2	0.92 (0.85-0.96)	0.57 (0.481-0.66)	0.95 (0.94-0.96)	0.471 (0.272-0.638)	0.89 (0.81-0.93)	0.876 (0.777-0.939)
0.9	4	0.5	0.98 (0.95-0.99)	0.87 (0.803-0.94)	0.99 (0.98-0.99)	0.813 (0.666-0.926)	0.97 (0.94-0.99)	0.986 (0.964-0.997)
0.9	4	0.9	0.99 (0.97-1.00)	0.97 (0.942-1.00)	1.00 (0.99-1.00)	0.904 (0.758-0.981)	0.99 (0.96-1.00)	0.998 (0.990-1.000)
0.9	5	0	0.80 (0.75-0.86)	0.26 (0.192-0.39)	0.91 (0.90-0.92)	0.130 (0.106-0.151)	0.75 (0.71-0.79)	0.566 (0.520-0.615)
0.9	5	0.01	0.81 (0.75-0.86)	0.28 (0.192-0.37)	0.91 (0.90-0.92)	0.143 (0.111-0.179)	0.76 (0.70-0.80)	0.588 (0.534-0.648)
0.9	5	0.05	0.84 (0.79-0.89)	0.32 (0.235-0.42)	0.92 (0.91-0.93)	0.190 (0.148-0.239)	0.79 (0.75-0.83)	0.657 (0.593-0.710)





Supplementary Table S7  
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0.9	3	0.1	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	0.99 (0.96-1.00)	1.00 (1.00-1.00)	1.000 (1.000-1.000)
0.9	3	0.2	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.000 (1.000-1.000)
0.9	3	0.5	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.000 (1.000-1.000)
0.9	3	0.9	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.000 (1.000-1.000)
0.9	4	0	0.97 (0.95-0.99)	0.90 (0.84-0.96)	0.99 (0.98-1.00)	0.81 (0.63-0.90)	0.97 (0.93-0.98)	0.988 (0.962-0.996)
0.9	4	0.01	0.98 (0.95-0.99)	0.94 (0.87-0.99)	0.99 (0.98-1.00)	0.86 (0.67-0.95)	0.98 (0.95-0.99)	0.994 (0.981-1.000)
0.9	4	0.05	0.99 (0.98-1.00)	0.99 (0.96-1.00)	1.00 (1.00-1.00)	0.95 (0.86-1.00)	0.99 (0.98-1.00)	0.999 (0.997-1.000)
0.9	4	0.1	1.00 (0.99-1.00)	1.00 (0.98-1.00)	1.00 (1.00-1.00)	0.99 (0.94-1.00)	1.00 (0.99-1.00)	1.000 (0.999-1.000)
0.9	4	0.2	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (0.98-1.00)	1.00 (1.00-1.00)	1.000 (1.000-1.000)
0.9	4	0.5	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.000 (1.000-1.000)
0.9	4	0.9	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.000 (1.000-1.000)
0.9	5	0	0.95 (0.92-0.98)	0.78 (0.71-0.85)	0.97 (0.97-0.98)	0.66 (0.50-0.79)	0.94 (0.90-0.96)	0.960 (0.916-0.984)
0.9	5	0.01	0.97 (0.91-0.99)	0.86 (0.76-0.96)	0.98 (0.97-1.00)	0.76 (0.51-0.89)	0.96 (0.90-0.98)	0.979 (0.942-0.996)
0.9	5	0.05	0.99 (0.97-1.00)	0.97 (0.90-1.00)	1.00 (0.99-1.00)	0.92 (0.80-1.00)	0.99 (0.97-1.00)	0.998 (0.989-1.000)
0.9	5	0.1	1.00 (0.99-1.00)	1.00 (0.98-1.00)	1.00 (1.00-1.00)	0.98 (0.90-1.00)	1.00 (0.99-1.00)	1.000 (0.999-1.000)
0.9	5	0.2	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (0.98-1.00)	1.00 (1.00-1.00)	1.000 (1.000-1.000)
0.9	5	0.5	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.000 (1.000-1.000)
0.9	5	0.9	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.000 (1.000-1.000)
0.95	2	0	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	0.99 (0.96-1.00)	1.00 (1.00-1.00)	1.000 (1.000-1.000)
0.95	2	0.01	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	0.99 (0.95-1.00)	1.00 (1.00-1.00)	1.000 (1.000-1.000)
0.95	2	0.05	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (0.96-1.00)	1.00 (1.00-1.00)	1.000 (1.000-1.000)
0.95	2	0.1	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (0.96-1.00)	1.00 (1.00-1.00)	1.000 (1.000-1.000)
0.95	2	0.2	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.000 (1.000-1.000)
0.95	2	0.5	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.000 (1.000-1.000)
0.95	2	0.9	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.000 (1.000-1.000)
0.95	3	0	0.99 (0.98-1.00)	0.94 (0.88-1.00)	1.00 (0.99-1.00)	0.85 (0.67-0.96)	0.99 (0.97-1.00)	0.997 (0.990-1.000)
0.95	3	0.01	0.99 (0.98-1.00)	0.96 (0.88-1.00)	1.00 (0.99-1.00)	0.89 (0.71-0.96)	0.99 (0.98-1.00)	0.998 (0.994-1.000)
0.95	3	0.05	1.00 (0.99-1.00)	1.00 (0.96-1.00)	1.00 (1.00-1.00)	0.96 (0.83-1.00)	1.00 (0.99-1.00)	1.000 (0.999-1.000)
0.95	3	0.1	1.00 (0.99-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	0.98 (0.90-1.00)	1.00 (0.99-1.00)	1.000 (1.000-1.000)
0.95	3	0.2	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.000 (1.000-1.000)
0.95	3	0.5	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.000 (1.000-1.000)
0.95	3	0.9	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.000 (1.000-1.000)
0.95	4	0	0.97 (0.94-0.99)	0.66 (0.54-0.77)	0.98 (0.98-0.99)	0.57 (0.32-0.77)	0.96 (0.92-0.98)	0.957 (0.904-0.987)
0.95	4	0.01	0.98 (0.94-0.99)	0.76 (0.59-0.88)	0.99 (0.98-0.99)	0.67 (0.38-0.87)	0.97 (0.93-0.99)	0.975 (0.921-0.997)
0.95	4	0.05	0.99 (0.97-1.00)	0.95 (0.85-1.00)	1.00 (0.99-1.00)	0.90 (0.63-1.00)	0.99 (0.97-1.00)	0.997 (0.985-1.000)
0.95	4	0.1	1.00 (0.99-1.00)	0.99 (0.93-1.00)	1.00 (1.00-1.00)	0.97 (0.86-1.00)	1.00 (0.99-1.00)	1.000 (0.998-1.000)
0.95	4	0.2	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (0.97-1.00)	1.00 (1.00-1.00)	1.000 (1.000-1.000)
0.95	4	0.5	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.000 (1.000-1.000)
0.95	4	0.9	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.000 (1.000-1.000)
0.95	5	0	0.93 (0.87-0.97)	0.39 (0.27-0.50)	0.97 (0.96-0.97)	0.25 (0.14-0.40)	0.91 (0.85-0.94)	0.832 (0.759-0.897)
0.95	5	0.01	0.95 (0.89-0.99)	0.52 (0.38-0.76)	0.97 (0.97-0.99)	0.40 (0.19-0.70)	0.93 (0.87-0.97)	0.899 (0.803-0.978)
0.95	5	0.05	0.99 (0.96-1.00)	0.84 (0.64-0.98)	0.99 (0.98-1.00)	0.80 (0.48-0.99)	0.98 (0.95-1.00)	0.987 (0.944-1.000)
0.95	5	0.1	1.00 (0.98-1.00)	0.96 (0.85-1.00)	1.00 (0.99-1.00)	0.94 (0.71-1.00)	0.99 (0.97-1.00)	0.999 (0.990-1.000)
0.95	5	0.2	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (0.96-1.00)	1.00 (1.00-1.00)	1.000 (1.000-1.000)
0.95	5	0.5	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.000 (1.000-1.000)
0.95	5	0.9	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.000 (1.000-1.000)

Perturbed datasets in which  $s\%$  ( $s\%=5\%, 10\%, 20\%, 30\%, 40\%$  or  $50\%$ ) of the cases were designated to be therapy sensitive were generated. Within the  $1-s\%$  resistant cases,  $w$  allocated the cases randomly into  $n$  ( $n=2, 3, 4, 5$ ) equally sized groups of resistance mechanisms. For each  $n$ th resistance mechanism, 100 genes were selected as the "true" signatures, of which  $o\%$  ( $o\%=0\%, 1\%, 5\%, 10\%, 20\%, 50\%, 90\%$ ) of the 100 genes were common to all  $n$  mechanisms. The selected genes were then spiked-in by  $v$  ( $v=1$ , top;  $v=0.5$ , middle;  $v=1.5$ , bottom). Classification was performed using diagonal discriminant linear analysis (DLDA). For each combination of  $s$ ,  $n$  and  $o$ , we repeated the spiking and classification 100 times. The mean value and the 95% confidence intervals of the performance measures for each combination of  $s$ ,  $n$  and  $o$  are shown. Performance measures reported here are sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), accuracy and the area under curve (AUC) of the receiver operating characteristic (ROC) curves.