

Min-Max, Min-Max-Median, and Min-Max-IQR in Deciding Optimal Diagnostic Thresholds: Performances of a Logistic Regression Approach on Simulated and Real Data

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Table S1. Youden index and AUCs (averages \pm standard deviation) for 100 random samples with normally distributed biomarkers with the same mean: four biomarkers (CM=Covariance matrix).

CM	N/N	Method	Metric	Four biomarkers			
				LR	LR(MM)	LR(MMM)	LR(MMIQR)
$\Sigma_1=\Sigma_2=I$	30/30	Resubstitution	Youden	0.747 \pm 0.041	0.711 \pm 0.053	0.758 \pm 0.042	0.764 \pm 0.041
			AUC	0.925 \pm 0.008	0.909 \pm 0.017	0.931 \pm 0.008	0.934 \pm 0.010
	100/100	Resubstitution	Youden	0.714 \pm 0.028	0.669 \pm 0.029	0.717 \pm 0.027	0.721 \pm 0.027
			AUC	0.922 \pm 0.004	0.902 \pm 0.008	0.924 \pm 0.004	0.925 \pm 0.005
	500/500	Resubstitution	Youden	0.692 \pm 0.011	0.652 \pm 0.014	0.692 \pm 0.011	0.694 \pm 0.011
			AUC	0.921 \pm 0.001	0.902 \pm 0.004	0.921 \pm 0.001	0.921 \pm 0.001
	30/30	Cross-validation	Youden	0.659 \pm 0.040	0.664 \pm 0.051	0.692 \pm 0.042	0.683 \pm 0.043
			AUC	0.883 \pm 0.011	0.885 \pm 0.019	0.899 \pm 0.010	0.893 \pm 0.012
	100/100	Cross-validation	Youden	0.683 \pm 0.027	0.652 \pm 0.029	0.693 \pm 0.027	0.690 \pm 0.026
			AUC	0.911 \pm 0.004	0.895 \pm 0.008	0.915 \pm 0.005	0.914 \pm 0.005
	500/500	Cross-validation	Youden	0.684 \pm 0.011	0.647 \pm 0.014	0.686 \pm 0.011	0.686 \pm 0.011
			AUC	0.919 \pm 0.001	0.901 \pm 0.004	0.919 \pm 0.001	0.919 \pm 0.001
$\Sigma_1=\Sigma_2=0.5I+0.5J$	30/30	Resubstitution	Youden	0.545 \pm 0.050	0.542 \pm 0.055	0.558 \pm 0.053	0.571 \pm 0.053
			AUC	0.814 \pm 0.009	0.813 \pm 0.015	0.824 \pm 0.015	0.832 \pm 0.018
	100/100	Resubstitution	Youden	0.512 \pm 0.026	0.506 \pm 0.031	0.518 \pm 0.025	0.520 \pm 0.027
			AUC	0.815 \pm 0.004	0.811 \pm 0.008	0.818 \pm 0.005	0.820 \pm 0.005
	500/500	Resubstitution	Youden	0.488 \pm 0.014	0.479 \pm 0.014	0.489 \pm 0.012	0.489 \pm 0.013
			AUC	0.814 \pm 0.001	0.810 \pm 0.003	0.815 \pm 0.001	0.815 \pm 0.002
	30/30	Cross-validation	Youden	0.425 \pm 0.049	0.487 \pm 0.055	0.473 \pm 0.054	0.462 \pm 0.058
			AUC	0.749 \pm 0.011	0.783 \pm 0.016	0.777 \pm 0.018	0.771 \pm 0.022
	100/100	Cross-validation	Youden	0.472 \pm 0.026	0.485 \pm 0.031	0.488 \pm 0.025	0.481 \pm 0.027
			AUC	0.797 \pm 0.004	0.802 \pm 0.008	0.805 \pm 0.006	0.802 \pm 0.006
	500/500	Cross-validation	Youden	0.477 \pm 0.014	0.473 \pm 0.014	0.481 \pm 0.012	0.479 \pm 0.013
			AUC	0.811 \pm 0.001	0.808 \pm 0.003	0.812 \pm 0.001	0.812 \pm 0.002
$\Sigma_1=0.3I+0.7J$ $\Sigma_2=0.7I+0.3J$	30/30	Resubstitution	Youden	0.555 \pm 0.048	0.636 \pm 0.058	0.644 \pm 0.056	0.653 \pm 0.055
			AUC	0.814 \pm 0.010	0.873 \pm 0.022	0.880 \pm 0.021	0.884 \pm 0.021
	100/100	Resubstitution	Youden	0.520 \pm 0.025	0.598 \pm 0.030	0.606 \pm 0.029	0.610 \pm 0.030
			AUC	0.815 \pm 0.005	0.867 \pm 0.011	0.871 \pm 0.010	0.873 \pm 0.010
	500/500	Resubstitution	Youden	0.498 \pm 0.014	0.579 \pm 0.015	0.584 \pm 0.015	0.585 \pm 0.015
			AUC	0.814 \pm 0.002	0.867 \pm 0.005	0.870 \pm 0.005	0.871 \pm 0.005
	30/30	Cross-validation	Youden	0.435 \pm 0.048	0.587 \pm 0.060	0.574 \pm 0.059	0.562 \pm 0.061
			AUC	0.752 \pm 0.011	0.848 \pm 0.024	0.843 \pm 0.024	0.836 \pm 0.026
	100/100	Cross-validation	Youden	0.481 \pm 0.026	0.579 \pm 0.031	0.580 \pm 0.030	0.578 \pm 0.030
			AUC	0.798 \pm 0.005	0.860 \pm 0.011	0.860 \pm 0.010	0.859 \pm 0.011
	500/500	Cross-validation	Youden	0.488 \pm 0.014	0.574 \pm 0.015	0.577 \pm 0.016	0.577 \pm 0.015
			AUC	0.811 \pm 0.002	0.866 \pm 0.005	0.868 \pm 0.005	0.868 \pm 0.005
$\Sigma_1=0.5I+0.5J$ $\Sigma_2=I$	30/30	Resubstitution	Youden	0.644 \pm 0.048	0.667 \pm 0.056	0.690 \pm 0.054	0.701 \pm 0.050
			AUC	0.859 \pm 0.011	0.886 \pm 0.021	0.897 \pm 0.018	0.901 \pm 0.017
	100/100	Resubstitution	Youden	0.612 \pm 0.026	0.635 \pm 0.029	0.650 \pm 0.029	0.653 \pm 0.027
			AUC	0.858 \pm 0.006	0.880 \pm 0.010	0.888 \pm 0.009	0.889 \pm 0.009
	500/500	Resubstitution	Youden	0.591 \pm 0.010	0.612 \pm 0.013	0.629 \pm 0.012	0.630 \pm 0.013
			AUC	0.857 \pm 0.002	0.879 \pm 0.004	0.887 \pm 0.004	0.887 \pm 0.004
	30/30	Cross-validation	Youden	0.543 \pm 0.050	0.623 \pm 0.059	0.623 \pm 0.058	0.613 \pm 0.053
			AUC	0.809 \pm 0.013	0.862 \pm 0.023	0.863 \pm 0.020	0.856 \pm 0.020
	100/100	Cross-validation	Youden	0.579 \pm 0.025	0.616 \pm 0.029	0.626 \pm 0.029	0.622 \pm 0.027
			AUC	0.845 \pm 0.007	0.873 \pm 0.011	0.879 \pm 0.009	0.087 \pm 0.009
	500/500	Cross-validation	Youden	0.583 \pm 0.011	0.607 \pm 0.013	0.623 \pm 0.012	0.623 \pm 0.013
			AUC	0.855 \pm 0.002	0.878 \pm 0.004	0.885 \pm 0.004	0.885 \pm 0.004

Table S2. Youden index and AUCs (average \pm standard deviation) for 100 random samples with normally distributed biomarkers with the same mean: ten biomarkers (CM=Covariance matrix).

CM	N/N	Method	Metric	Ten biomarkers			
				LR	LR(MM)	LR(MMM)	LR(MMIQR)
$\Sigma_1=$ $\Sigma_2=$ I	30/30	Resubstitution	Youden	0.983 \pm 0.031	0.820 \pm 0.064	0.923 \pm 0.040	0.960 \pm 0.035
			AUC	0.996 \pm 0.008	0.955 \pm 0.020	0.988 \pm 0.007	0.994 \pm 0.005
	100/100	Resubstitution	Youden	0.915 \pm 0.018	0.785 \pm 0.031	0.891 \pm 0.019	0.910 \pm 0.020
			AUC	0.989 \pm 0.003	0.951 \pm 0.009	0.984 \pm 0.003	0.989 \pm 0.003
	500/500	Resubstitution	Youden	0.897 \pm 0.008	0.770 \pm 0.014	0.876 \pm 0.009	0.894 \pm 0.009
			AUC	0.988 \pm 0.001	0.950 \pm 0.004	0.983 \pm 0.001	0.987 \pm 0.001
	30/30	Cross-validation	Youden	0.718 \pm 0.060	0.777 \pm 0.069	0.862 \pm 0.039	0.842 \pm 0.041
			AUC	0.872 \pm 0.052	0.934 \pm 0.022	0.950 \pm 0.015	0.927 \pm 0.030
	100/100	Cross-validation	Youden	0.853 \pm 0.018	0.769 \pm 0.030	0.873 \pm 0.020	0.882 \pm 0.019
			AUC	0.973 \pm 0.004	0.945 \pm 0.010	0.980 \pm 0.004	0.981 \pm 0.003
	500/500	Cross-validation	Youden	0.884 \pm 0.008	0.766 \pm 0.014	0.871 \pm 0.009	0.887 \pm 0.009
			AUC	0.986 \pm 0.001	0.949 \pm 0.004	0.983 \pm 0.001	0.986 \pm 0.001
$\Sigma_1=$ $\Sigma_2=$ 0.5I+0.5J	30/30	Resubstitution	Youden	0.575 \pm 0.046	0.564 \pm 0.054	0.584 \pm 0.044	0.597 \pm 0.052
			AUC	0.832 \pm 0.009	0.826 \pm 0.017	0.839 \pm 0.013	0.849 \pm 0.016
	100/100	Resubstitution	Youden	0.532 \pm 0.029	0.517 \pm 0.033	0.536 \pm 0.028	0.543 \pm 0.030
			AUC	0.830 \pm 0.004	0.821 \pm 0.009	0.831 \pm 0.005	0.836 \pm 0.005
	500/500	Resubstitution	Youden	0.514 \pm 0.012	0.498 \pm 0.015	0.513 \pm 0.012	0.515 \pm 0.013
			AUC	0.830 \pm 0.001	0.821 \pm 0.003	0.829 \pm 0.002	0.831 \pm 0.002
	30/30	Cross-validation	Youden	0.286 \pm 0.040	0.509 \pm 0.052	0.502 \pm 0.047	0.468 \pm 0.058
			AUC	0.663 \pm 0.014	0.797 \pm 0.018	0.796 \pm 0.015	0.778 \pm 0.021
	100/100	Cross-validation	Youden	0.445 \pm 0.029	0.498 \pm 0.033	0.505 \pm 0.028	0.499 \pm 0.029
			AUC	0.785 \pm 0.005	0.812 \pm 0.010	0.818 \pm 0.005	0.815 \pm 0.006
	500/500	Cross-validation	Youden	0.493 \pm 0.012	0.492 \pm 0.015	0.505 \pm 0.012	0.504 \pm 0.013
			AUC	0.821 \pm 0.002	0.819 \pm 0.004	0.827 \pm 0.002	0.827 \pm 0.002
$\Sigma_1=$ $\Sigma_2=$ 0.3I+0.7J	30/30	Resubstitution	Youden	0.583 \pm 0.045	0.810 \pm 0.055	0.821 \pm 0.059	0.863 \pm 0.066
			AUC	0.832 \pm 0.010	0.952 \pm 0.019	0.957 \pm 0.018	0.970 \pm 0.017
	100/100	Resubstitution	Youden	0.550 \pm 0.028	0.737 \pm 0.035	0.744 \pm 0.035	0.766 \pm 0.031
			AUC	0.829 \pm 0.005	0.933 \pm 0.011	0.936 \pm 0.011	0.946 \pm 0.009
	500/500	Resubstitution	Youden	0.531 \pm 0.014	0.711 \pm 0.016	0.715 \pm 0.016	0.733 \pm 0.014
			AUC	0.829 \pm 0.002	0.929 \pm 0.005	0.931 \pm 0.005	0.939 \pm 0.004
	30/30	Cross-validation	Youden	0.296 \pm 0.039	0.768 \pm 0.059	0.768 \pm 0.062	0.764 \pm 0.069
			AUC	0.666 \pm 0.014	0.933 \pm 0.020	0.929 \pm 0.019	0.920 \pm 0.021
	100/100	Cross-validation	Youden	0.463 \pm 0.029	0.721 \pm 0.037	0.721 \pm 0.034	0.730 \pm 0.032
			AUC	0.788 \pm 0.006	0.927 \pm 0.012	0.929 \pm 0.011	0.934 \pm 0.010
	500/500	Cross-validation	Youden	0.512 \pm 0.014	0.706 \pm 0.016	0.709 \pm 0.016	0.725 \pm 0.014
			AUC	0.822 \pm 0.002	0.928 \pm 0.005	0.930 \pm 0.005	0.936 \pm 0.004
$\Sigma_1=$ $\Sigma_2=$ 0.5I+0.5J	30/30	Resubstitution	Youden	0.744 \pm 0.048	0.799 \pm 0.064	0.827 \pm 0.056	0.858 \pm 0.060
			AUC	0.899 \pm 0.015	0.949 \pm 0.018	0.958 \pm 0.016	0.970 \pm 0.015
	100/100	Resubstitution	Youden	0.716 \pm 0.025	0.750 \pm 0.026	0.777 \pm 0.029	0.788 \pm 0.027
			AUC	0.893 \pm 0.008	0.934 \pm 0.010	0.944 \pm 0.009	0.950 \pm 0.008
	500/500	Resubstitution	Youden	0.702 \pm 0.012	0.727 \pm 0.014	0.755 \pm 0.012	0.764 \pm 0.012
			AUC	0.892 \pm 0.004	0.931 \pm 0.005	0.939 \pm 0.004	0.944 \pm 0.004
	30/30	Cross-validation	Youden	0.518 \pm 0.041	0.759 \pm 0.065	0.769 \pm 0.061	0.756 \pm 0.057
			AUC	0.791 \pm 0.018	0.929 \pm 0.020	0.930 \pm 0.018	0.920 \pm 0.015
	100/100	Cross-validation	Youden	0.654 \pm 0.025	0.734 \pm 0.026	0.756 \pm 0.028	0.757 \pm 0.027
			AUC	0.868 \pm 0.009	0.929 \pm 0.010	0.936 \pm 0.009	0.940 \pm 0.009
	500/500	Cross-validation	Youden	0.689 \pm 0.012	0.722 \pm 0.014	0.749 \pm 0.011	0.756 \pm 0.012
			AUC	0.887 \pm 0.004	0.930 \pm 0.005	0.938 \pm 0.004	0.942 \pm 0.004

Table S3. Youden index and AUC (averages \pm standard deviation) for 100 random samples with different means of normally distributed biomarkers: four biomarkers (CM = covariance matrix).

CM	N/N	Method	Metric	Regression model			
				LR	LR(MM)	LR(MMM)	LR(MMIQR)
$\Sigma_1=\Sigma_2=I$	30/30	Resubstitution	Youden	0.564 \pm 0.042	0.502 \pm 0.065	0.544 \pm 0.046	0.558 \pm 0.045
			AUC	0.829 \pm 0.008	0.789 \pm 0.026	0.816 \pm 0.014	0.824 \pm 0.016
	100/100	Resubstitution	Youden	0.534 \pm 0.030	0.456 \pm 0.036	0.494 \pm 0.025	0.503 \pm 0.027
			AUC	0.828 \pm 0.004	0.779 \pm 0.013	0.806 \pm 0.005	0.809 \pm 0.007
	500/500	Resubstitution	Youden	0.508 \pm 0.013	0.434 \pm 0.014	0.468 \pm 0.014	0.469 \pm 0.014
			AUC	0.827 \pm 0.002	0.782 \pm 0.005	0.803 \pm 0.001	0.804 \pm 0.001
	30/30	Cross-validation	Youden	0.454 \pm 0.044	0.444 \pm 0.064	0.459 \pm 0.045	0.440 \pm 0.047
			AUC	0.768 \pm 0.012	0.755 \pm 0.028	0.769 \pm 0.016	0.760 \pm 0.020
	100/100	Cross-validation	Youden	0.495 \pm 0.030	0.431 \pm 0.039	0.465 \pm 0.023	0.463 \pm 0.024
			AUC	0.811 \pm 0.005	0.769 \pm 0.014	0.792 \pm 0.006	0.790 \pm 0.007
	500/500	Cross-validation	Youden	0.498 \pm 0.013	0.428 \pm 0.015	0.460 \pm 0.014	0.458 \pm 0.014
			AUC	0.823 \pm 0.002	0.780 \pm 0.005	0.800 \pm 0.001	0.800 \pm 0.002
$\Sigma_1=\Sigma_2=0.5I+0.5J$	30/30	Resubstitution	Youden	0.508 \pm 0.047	0.395 \pm 0.053	0.406 \pm 0.051	0.427 \pm 0.048
			AUC	0.789 \pm 0.010	0.710 \pm 0.020	0.723 \pm 0.019	0.736 \pm 0.023
	100/100	Resubstitution	Youden	0.462 \pm 0.028	0.353 \pm 0.033	0.362 \pm 0.032	0.369 \pm 0.031
			AUC	0.786 \pm 0.005	0.710 \pm 0.010	0.717 \pm 0.008	0.720 \pm 0.008
	500/500	Resubstitution	Youden	0.443 \pm 0.016	0.322 \pm 0.017	0.328 \pm 0.015	0.327 \pm 0.015
			AUC	0.786 \pm 0.002	0.710 \pm 0.004	0.714 \pm 0.003	0.715 \pm 0.003
	30/30	Cross-validation	Youden	0.381 \pm 0.043	0.319 \pm 0.058	0.302 \pm 0.056	0.287 \pm 0.059
			AUC	0.718 \pm 0.011	0.667 \pm 0.022	0.659 \pm 0.023	0.649 \pm 0.030
	100/100	Cross-validation	Youden	0.417 \pm 0.025	0.325 \pm 0.031	0.323 \pm 0.031	0.315 \pm 0.031
			AUC	0.765 \pm 0.005	0.697 \pm 0.011	0.698 \pm 0.009	0.693 \pm 0.010
	500/500	Cross-validation	Youden	0.432 \pm 0.016	0.315 \pm 0.017	0.317 \pm 0.015	0.314 \pm 0.015
			AUC	0.782 \pm 0.002	0.707 \pm 0.004	0.710 \pm 0.003	0.709 \pm 0.003
$\Sigma_1=0.3I+0.7J$ $\Sigma_2=0.7I+0.3J$	30/30	Resubstitution	Youden	0.503 \pm 0.047	0.573 \pm 0.065	0.586 \pm 0.068	0.595 \pm 0.066
			AUC	0.787 \pm 0.010	0.834 \pm 0.026	0.841 \pm 0.028	0.848 \pm 0.030
	100/100	Resubstitution	Youden	0.464 \pm 0.028	0.531 \pm 0.036	0.534 \pm 0.036	0.539 \pm 0.037
			AUC	0.786 \pm 0.005	0.829 \pm 0.016	0.831 \pm 0.015	0.834 \pm 0.016
	500/500	Resubstitution	Youden	0.444 \pm 0.014	0.511 \pm 0.018	0.512 \pm 0.017	0.516 \pm 0.018
			AUC	0.786 \pm 0.002	0.830 \pm 0.007	0.831 \pm 0.007	0.832 \pm 0.006
	30/30	Cross-validation	Youden	0.381 \pm 0.047	0.519 \pm 0.069	0.504 \pm 0.070	0.491 \pm 0.075
			AUC	0.715 \pm 0.013	0.806 \pm 0.028	0.800 \pm 0.031	0.795 \pm 0.035
	100/100	Cross-validation	Youden	0.422 \pm 0.028	0.511 \pm 0.038	0.505 \pm 0.037	0.503 \pm 0.038
			AUC	0.766 \pm 0.005	0.820 \pm 0.016	0.819 \pm 0.016	0.818 \pm 0.016
	500/500	Cross-validation	Youden	0.434 \pm 0.014	0.505 \pm 0.018	0.505 \pm 0.017	0.506 \pm 0.017
			AUC	0.782 \pm 0.002	0.828 \pm 0.007	0.829 \pm 0.007	0.829 \pm 0.006
$\Sigma_1=\Sigma_2=\rho= -0.1$	30/30	Resubstitution	Youden	0.626 \pm 0.045	0.550 \pm 0.071	0.607 \pm 0.044	0.613 \pm 0.051
			AUC	0.863 \pm 0.008	0.814 \pm 0.032	0.856 \pm 0.013	0.861 \pm 0.015
	100/100	Resubstitution	Youden	0.594 \pm 0.029	0.510 \pm 0.041	0.567 \pm 0.026	0.568 \pm 0.027
			AUC	0.862 \pm 0.004	0.813 \pm 0.016	0.848 \pm 0.004	0.850 \pm 0.005
	500/500	Resubstitution	Youden	0.570 \pm 0.013	0.486 \pm 0.019	0.543 \pm 0.013	0.544 \pm 0.014
			AUC	0.861 \pm 0.001	0.813 \pm 0.008	0.846 \pm 0.001	0.846 \pm 0.001
	30/30	Cross-validation	Youden	0.522 \pm 0.047	0.495 \pm 0.075	0.527 \pm 0.044	0.512 \pm 0.048
			AUC	0.809 \pm 0.011	0.783 \pm 0.035	0.815 \pm 0.015	0.806 \pm 0.018
	100/100	Cross-validation	Youden	0.558 \pm 0.027	0.489 \pm 0.041	0.538 \pm 0.026	0.533 \pm 0.027
			AUC	0.847 \pm 0.004	0.804 \pm 0.017	0.836 \pm 0.005	0.834 \pm 0.005
	500/500	Cross-validation	Youden	0.561 \pm 0.012	0.480 \pm 0.019	0.536 \pm 0.013	0.535 \pm 0.013
			AUC	0.858 \pm 0.001	0.811 \pm 0.008	0.844 \pm 0.001	0.843 \pm 0.001

Table S4. Youden index and AUC (averages \pm standard deviation) for 100 random samples with different means of normally distributed biomarkers: ten biomarkers.

CM	N/N	Method	Metric	Regression model				
				LR	LR(MM)	LR(MMM)	LR(MMIQR)	
$\Sigma_1=\Sigma_2=I$	30/30	Resubstitution	Youden	1 \pm 0	0.856 \pm 0.054	0.959 \pm 0.033	0.985 \pm 0.025	
			AUC	1 \pm 0	0.969 \pm 0.015	0.995 \pm 0.004	0.998 \pm 0.003	
	100/100	Resubstitution	Youden	0.982 \pm 0.018	0.828 \pm 0.029	0.927 \pm 0.017	0.945 \pm 0.016	
			AUC	0.998 \pm 0.001	0.964 \pm 0.008	0.992 \pm 0.002	0.994 \pm 0.002	
	500/500	Resubstitution	Youden	0.959 \pm 0.006	0.812 \pm 0.014	0.912 \pm 0.009	0.930 \pm 0.008	
			AUC	0.997 \pm 0.001	0.965 \pm 0.003	0.991 \pm 0.001	0.993 \pm 0.001	
	30/30	Cross-validation	Youden	0.832 \pm 0.071	0.818 \pm 0.060	0.893 \pm 0.037	0.871 \pm 0.047	
			AUC	0.949 \pm 0.038	0.950 \pm 0.016	0.951 \pm 0.022	0.943 \pm 0.040	
	100/100	Cross-validation	Youden	0.909 \pm 0.017	0.813 \pm 0.029	0.908 \pm 0.018	0.916 \pm 0.017	
			AUC	0.966 \pm 0.012	0.959 \pm 0.009	0.987 \pm 0.003	0.986 \pm 0.003	
	500/500	Cross-validation	Youden	0.949 \pm 0.006	0.808 \pm 0.014	0.908 \pm 0.009	0.924 \pm 0.008	
			AUC	0.996 \pm 0.001	0.964 \pm 0.003	0.990 \pm 0.001	0.993 \pm 0.001	
	$\Sigma_1=\Sigma_2=0.5I+0.5J$	30/30	Resubstitution	Youden	0.950 \pm 0.054	0.725 \pm 0.058	0.746 \pm 0.053	0.773 \pm 0.052
				AUC	0.990 \pm 0.015	0.914 \pm 0.018	0.922 \pm 0.017	0.935 \pm 0.016
100/100		Resubstitution	Youden	0.890 \pm 0.017	0.663 \pm 0.033	0.680 \pm 0.033	0.699 \pm 0.031	
			AUC	0.984 \pm 0.003	0.899 \pm 0.010	0.906 \pm 0.008	0.917 \pm 0.008	
500/500		Resubstitution	Youden	0.871 \pm 0.010	0.645 \pm 0.014	0.657 \pm 0.014	0.676 \pm 0.014	
			AUC	0.982 \pm 0.001	0.898 \pm 0.004	0.904 \pm 0.004	0.912 \pm 0.004	
30/30		Cross-validation	Youden	0.680 \pm 0.042	0.678 \pm 0.058	0.676 \pm 0.053	0.667 \pm 0.052	
			AUC	0.840 \pm 0.041	0.891 \pm 0.020	0.891 \pm 0.020	0.885 \pm 0.019	
100/100		Cross-validation	Youden	0.830 \pm 0.019	0.645 \pm 0.034	0.655 \pm 0.033	0.662 \pm 0.032	
			AUC	0.968 \pm 0.004	0.892 \pm 0.010	0.897 \pm 0.009	0.903 \pm 0.009	
500/500		Cross-validation	Youden	0.859 \pm 0.010	0.640 \pm 0.014	0.651 \pm 0.014	0.667 \pm 0.015	
			AUC	0.980 \pm 0.001	0.897 \pm 0.004	0.902 \pm 0.004	0.909 \pm 0.004	
$\Sigma_1=0.3I+0.7J$ $\Sigma_2=0.7I+0.3J$		30/30	Resubstitution	Youden	0.962 \pm 0.048	0.925 \pm 0.040	0.931 \pm 0.041	0.962 \pm 0.037
				AUC	0.993 \pm 0.010	0.986 \pm 0.008	0.988 \pm 0.008	0.993 \pm 0.006
	100/100	Resubstitution	Youden	0.894 \pm 0.020	0.870 \pm 0.028	0.873 \pm 0.028	0.896 \pm 0.025	
			AUC	0.985 \pm 0.003	0.980 \pm 0.005	0.981 \pm 0.005	0.986 \pm 0.004	
	500/500	Resubstitution	Youden	0.874 \pm 0.009	0.853 \pm 0.012	0.857 \pm 0.012	0.876 \pm 0.012	
			AUC	0.982 \pm 0.001	0.978 \pm 0.002	0.978 \pm 0.002	0.983 \pm 0.002	
	30/30	Cross-validation	Youden	0.691 \pm 0.050	0.887 \pm 0.041	0.876 \pm 0.044	0.860 \pm 0.049	
			AUC	0.846 \pm 0.041	0.960 \pm 0.013	0.954 \pm 0.015	0.935 \pm 0.032	
	100/100	Cross-validation	Youden	0.834 \pm 0.019	0.857 \pm 0.029	0.855 \pm 0.029	0.865 \pm 0.024	
			AUC	0.966 \pm 0.005	0.976 \pm 0.006	0.976 \pm 0.006	0.979 \pm 0.005	
	500/500	Cross-validation	Youden	0.862 \pm 0.009	0.849 \pm 0.012	0.852 \pm 0.013	0.869 \pm 0.012	
			AUC	0.979 \pm 0.001	0.977 \pm 0.002	0.978 \pm 0.002	0.981 \pm 0.002	
	$\Sigma_1=\Sigma_2=\rho=-0.1$	30/30	Resubstitution	Youden	1 \pm 0	0.940 \pm 0.043	1 \pm 0	1 \pm 0
				AUC	1 \pm 0	0.991 \pm 0.009	1 \pm 0	1 \pm 0
100/100		Resubstitution	Youden	1 \pm 0	0.921 \pm 0.021	1 \pm 0	1 \pm 0	
			AUC	1 \pm 0	0.989 \pm 0.004	1 \pm 0	1 \pm 0	
500/500		Resubstitution	Youden	1 \pm 0	0.906 \pm 0.012	0.999 \pm 0.001	1 \pm 0	
			AUC	1 \pm 0	0.988 \pm 0.002	0.999 \pm 0.001	1 \pm 0	
30/30		Cross-validation	Youden	1 \pm 0	0.903 \pm 0.046	0.999 \pm 0.002	1 \pm 0	
			AUC	1 \pm 0	0.962 \pm 0.017	0.999 \pm 0.001	1 \pm 0	
100/100		Cross-validation	Youden	1 \pm 0	0.910 \pm 0.022	0.999 \pm 0.001	0.999 \pm 0.001	
			AUC	1 \pm 0	0.985 \pm 0.005	0.999 \pm 0.001	0.999 \pm 0.001	
500/500		Cross-validation	Youden	1 \pm 0	0.903 \pm 0.012	0.999 \pm 0.001	1 \pm 0	
			AUC	1 \pm 0	0.987 \pm 0.002	0.999 \pm 0.001	1 \pm 0	

CM = covariance matrix

Table S5. Youden index and AUC (average \pm standard deviation) for 100 random samples with equal means of 100 normally distributed biomarkers (CM = covariance matrix).

CM	N/N	Method	Metric	LR	LR(MM)	LR(MMM)	LR(MMIQR)
$\Sigma_1=\Sigma_2=I$	30/30	Resubstitution	Youden	1 \pm 0	0.938 \pm 0.046	1 \pm 0	1 \pm 0
			AUC	1 \pm 0	0.991 \pm 0.008	1 \pm 0	1 \pm 0
	30/30	Cross-validation	Youden	0.297 \pm 0.098	0.899 \pm 0.051	1 \pm 0	1 \pm 0
			AUC	0.659 \pm 0.056	0.962 \pm 0.021	1 \pm 0	1 \pm 0
$\Sigma_1=0.5I+0.5J$ $\Sigma_2=I$	30/30	Resubstitution	Youden	1 \pm 0	0.959 \pm 0.034	0.977 \pm 0.032	0.999 \pm 0.004
			AUC	1 \pm 0	0.994 \pm 0.005	0.996 \pm 0.005	0.999 \pm 0.001
	30/30	Cross-validation	Youden	0.089 \pm 0.052	0.920 \pm 0.037	0.919 \pm 0.042	0.945 \pm 0.047
			AUC	0.535 \pm 0.028	0.962 \pm 0.019	0.965 \pm 0.027	0.986 \pm 0.022