Combining Multiple Biomarkers Linearly to Minimize the Euclidean Distance of the Closest Point on the ROC Surface to the Perfection Corner in Trichotomous Settings

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Web -Appendix A (Proof for a Dominant ROC Surface.)

Proof. Let X_{1i}, X_{2j}, and X_{3k} be the marker values for each of the three groups. Suppose they are multivariate normally distributed, so that $X_1 \sim N(\boldsymbol{\mu}_1, \boldsymbol{\Sigma})$, $X_2 \sim N(\boldsymbol{\mu}_2, \boldsymbol{\Sigma})$, $X_3 \sim N(\boldsymbol{\mu}_3, \boldsymbol{\Sigma})$ and $\boldsymbol{\mu}_2 - \boldsymbol{\mu}_1 = \boldsymbol{\mu}_3 - \boldsymbol{\mu}_2 = \boldsymbol{\delta}$.

Then, when comparing groups 1 vs 2, 2 vs 3, and 1 vs 3, the best linear combination coefficient is $\boldsymbol{\beta} \propto \boldsymbol{\delta}^T \boldsymbol{\Sigma}^{-1}$, (Su 1993). The best linear combination implies that for every value of a given specificity, the sensitivity is higher than (or equal to) the sensitivity obtained by any other linear combination. Similarly, for a given value of specificity.

Let F_1, F_2, and F_3 be the CDFs of the combined scores using the best linear combination. Let F_1^*, F_2^*, and F_3^* represent the CDFs of any other linear combination of the scores. Note that when focus is on the two class setting with random variables X and Y for the healthy and the diseased groups respectively, then functional form of the ROC curve is $S_Y(S_X^{-1}(t))$. We assume there is stochastic ordering $Y > X$. An ROC curve is dominant if

$$S_Y(S_X^{-1}(t)) \geq S_Y^*(S_X^{*-1}(t)), \tag{1}$$

for all t, or equivalently, if

$$F_X(F_Y^{-1}(1-t)) \geq F_X^*(F_Y^{*-1}(1-t)) \tag{2}$$

for all t.

Turning now to the three class setting we have (by using (1)) that for all p:

$$1 - F_2\Big(F_1^{-1}(p)\Big) \geq 1 - F_2^*\Big(F_1^{*-1}(p)\Big)$$

and so,

$$F_2\Big(F_1^{-1}(TCR_1)\Big) \leq F_2^*\Big(F_1^{*-1}(TCR_1)\Big).$$

Note that for all p, we have that (using (2)):

$$F_2\Big(F_3^{-1}(1-p)\Big) \geq F_2^*\Big(F_3^{*-1}(1-p)\Big)$$

and so,

$$F_2\Big(F_3^{-1}(1-TCR_3)\Big) \geq F_2^*\Big(F_3^{*-1}(1-TCR_3)\Big)$$

Note that the functional form of the ROC surface is $S = F_2(F_3^{-1}(1-TCR_3)) - F_2(F_1^{-1}(TCR_1))$.

Therefore,

$$S = \left(F_2\Big(F_3^{-1}(1-TCR_3)\Big) - F_2\Big(F_1^{-1}(TCR_1)\Big)\right) \geq \left(F_2^*\Big(F_3^{*-1}(1-TCR_3)\Big) - F_2\Big(F_1^{*-1}(TCR_1)\Big)\right),$$

and so $\boldsymbol{\beta} \propto \boldsymbol{\delta}^T \boldsymbol{\Sigma}^{-1}$ provides a linear combination of biomarker scores with a dominant ROC surface.

Web -Appendix B (Simulation Results for Scenarios Generated from Normal Distributions with a Dominant ROC Surface)

Table B.1

The table provides results for the normal scenarios with $\Sigma = 0.5I + 0.5J$. The table provides the bias, variance, and MSE for β_1, β_2 and β_3 for each of the explored approaches when using the Euclidean distance as the objective function.

Method	Approach	n_1, n_2, n_3	β_1 Bias	Variance	MSE	β_2 Bias	Variance	MSE	β_3 Bias	Variance	MSE
Euclidean	Logistic	30,30,30	-0.0173	0.1094	0.1097	-0.0365	0.0873	0.0886	-0.1129	0.0420	0.0547
		50,50,50	0.0056	0.0821	0.0821	-0.0255	0.0691	0.0697	-0.0707	0.0225	0.0275
		100,100,100	0.0008	0.0468	0.0468	0.0058	0.0430	0.0430	-0.0287	0.0062	0.0070
		200,200,200	0.0071	0.0253	0.0254	0.0104	0.0269	0.0270	-0.0089	0.0013	0.0014
		200,50,50	0.0122	0.0567	0.0569	-0.0105	0.0492	0.0493	-0.0363	0.0090	0.0103
	Yan	30,30,30	-0.0440	0.2071	0.2090	-0.1329	0.1679	0.1856	-0.2145	0.1051	0.1511
		50,50,50	-0.0003	0.1768	0.1768	-0.0654	0.1337	0.1380	-0.1677	0.0721	0.1003
		100,100,100	-0.0083	0.1179	0.1180	-0.0122	0.0850	0.0852	-0.0900	0.0330	0.0411
		200,200,200	0.0254	0.0768	0.0775	0.0264	0.0620	0.0627	-0.0487	0.0139	0.0162
		200,50,50	0.0030	0.1608	0.1608	-0.0554	0.1200	0.1231	-0.1430	0.0678	0.0883
	Normal	30,30,30	-0.0183	0.1185	0.1188	-0.0529	0.0976	0.1004	-0.1329	0.0505	0.0682
		50,50,50	0.0015	0.0925	0.0925	-0.0344	0.0777	0.0788	-0.0836	0.0275	0.0345
		100,100,100	-0.0013	0.0522	0.0522	0.0051	0.0473	0.0474	-0.0334	0.0075	0.0087
		200,200,200	0.0060	0.0295	0.0296	0.0083	0.0289	0.0290	-0.0116	0.0019	0.0021
		200,50,50	0.0106	0.0793	0.0794	-0.0319	0.0671	0.0681	-0.0614	0.0174	0.0211
	Stepwise	30,30,30	-0.2779	0.1794	0.2566	-0.3183	0.1814	0.2827	-0.2988	0.1480	0.2373
		50,50,50	-0.2657	0.1629	0.2335	-0.2421	0.1537	0.2123	-0.2468	0.1108	0.1717
		100,100,100	-0.2393	0.1510	0.2083	-0.2019	0.1319	0.1727	-0.1754	0.0707	0.1014
		200,200,200	-0.2071	0.1342	0.1771	-0.1634	0.1011	0.1278	-0.1205	0.0394	0.0539
		200,50,50	-0.2622	0.1624	0.2311	-0.2315	0.1548	0.2084	-0.2289	0.0972	0.1496
Youden	Logistic	30,30,30	-0.0173	0.1094	0.1097	-0.0365	0.0873	0.0886	-0.1129	0.0420	0.0547
		50,50,50	0.0056	0.0821	0.0821	-0.0255	0.0691	0.0697	-0.0707	0.0225	0.0275
		100,100,100	0.0008	0.0468	0.0468	0.0058	0.0430	0.0430	-0.0287	0.0062	0.0070
		200,200,200	0.0071	0.0253	0.0254	0.0104	0.0269	0.0270	-0.0089	0.0013	0.0014
		200,50,50	0.0122	0.0567	0.0569	-0.0105	0.0492	0.0493	-0.0363	0.0090	0.0103
	Yan	30,30,30	-0.0278	0.1939	0.1947	-0.1044	0.1622	0.1731	-0.2233	0.1053	0.1551
		50,50,50	0.0069	0.1644	0.1645	-0.0703	0.1262	0.1311	-0.1612	0.0692	0.0952
		100,100,100	-0.0042	0.1125	0.1125	-0.0080	0.0813	0.0813	-0.0857	0.0305	0.0378
		200,200,200	0.0217	0.0771	0.0775	0.0267	0.0596	0.0603	-0.0483	0.0139	0.0162
		200,50,50	-0.2042	0.1512	0.1929	-0.1504	0.1216	0.1443	-0.1268	0.0575	0.0736
	Normal	30,30,30	-0.0128	0.1162	0.1164	-0.0416	0.0912	0.0929	-0.1206	0.0445	0.0591
		50,50,50	0.0055	0.0856	0.0856	-0.0286	0.0727	0.0735	-0.0742	0.0237	0.0292
		100,100,100	-0.0010	0.0475	0.0475	0.0054	0.0447	0.0448	-0.0289	0.0062	0.0071
		200,200,200	0.0061	0.0260	0.0260	0.0106	0.0270	0.0271	-0.0095	0.0015	0.0016
		200,50,50	0.0146	0.0701	0.0703	-0.0231	0.0594	0.0599	-0.0499	0.0137	0.0162
	Stepwise	30,30,30	-0.1707	0.1857	0.2149	-0.2207	0.1808	0.2295	-0.2828	0.1371	0.2170
		50,50,50	-0.1191	0.1698	0.1840	-0.1709	0.1551	0.1843	-0.2508	0.1088	0.1717
		100,100,100	-0.1245	0.1285	0.1440	-0.1044	0.1124	0.1233	-0.1411	0.0563	0.0762
		200,200,200	-0.0914	0.1048	0.1131	-0.0432	0.0824	0.0843	-0.0959	0.0305	0.0397
		200,50,50	-0.1084	0.1544	0.1661	-0.1220	0.1332	0.1481	-0.1965	0.0809	0.1195

Table B.2
The table provides results for the normal scenarios with $\Sigma = 0.3I + 0.7J$. The table provides the bias, variance, and MSE
for β_1, β_2 and β_3 for each of the explored approaches when using the Euclidean distance as the objective function.

Method	Approach	n_1, n_2, n_3	β_1 Bias	β_1 Variance	β_1 MSE	β_2 Bias	β_2 Variance	β_2 MSE	β_3 Bias	β_3 Variance	β_3 MSE
Euclidean	Logistic	30,30,30	0.0316	0.1424	0.1434	0.0089	0.1228	0.1229	-0.0975	0.0447	0.0542
		50,50,50	0.0403	0.1026	0.1042	0.0083	0.0979	0.0979	-0.0554	0.0217	0.0248
		100,100,100	0.0123	0.0523	0.0524	0.0296	0.0618	0.0627	-0.0168	0.0042	0.0045
		200,200,200	0.0093	0.0252	0.0253	0.0205	0.0358	0.0362	-0.0032	0.0005	0.0005
		200,50,50	0.0295	0.0664	0.0673	0.0148	0.0700	0.0702	-0.0236	0.0070	0.0075
	Yan	30,30,30	0.0453	0.2753	0.2774	-0.0784	0.2340	0.2402	-0.2136	0.1186	0.1643
		50,50,50	0.0732	0.2399	0.2453	-0.0277	0.1988	0.1995	-0.1588	0.0867	0.1120
		100,100,100	0.0305	0.1598	0.1608	0.0334	0.1248	0.1259	-0.0800	0.0353	0.0417
		200,200,200	0.0494	0.1050	0.1075	0.0744	0.0979	0.1035	-0.0386	0.0133	0.0148
		200,50,50	0.0634	0.2370	0.2410	-0.0037	0.1860	0.1860	-0.1375	0.0763	0.0952
	Normal	30,30,30	0.0370	0.1560	0.1574	-0.0062	0.1386	0.1386	-0.1215	0.0562	0.0710
		50,50,50	0.0420	0.1187	0.1205	0.0031	0.1111	0.1111	-0.0690	0.0279	0.0326
		100,100,100	0.0119	0.0598	0.0600	0.0307	0.0681	0.0691	-0.0217	0.0057	0.0061
		200,200,200	0.0097	0.0310	0.0311	0.0196	0.0396	0.0400	-0.0052	0.0009	0.0010
		200,50,50	0.0428	0.1015	0.1033	0.0017	0.0968	0.0968	-0.0453	0.0159	0.0179
	Stepwise	30,30,30	-0.4159	0.1944	0.3673	-0.4376	0.2396	0.4310	-0.3225	0.1896	0.2936
		50,50,50	-0.4280	0.1736	0.3568	-0.3383	0.2104	0.3248	-0.2723	0.1507	0.2249
		100,100,100	-0.4140	0.1616	0.3331	-0.3139	0.1765	0.2750	-0.1959	0.0984	0.1368
		200,200,200	-0.4333	0.1306	0.3183	-0.2877	0.1425	0.2253	-0.1219	0.0574	0.0723
		200,50,50	-0.3936	0.1869	0.3419	-0.3644	0.2013	0.3341	-0.2376	0.1276	0.1841
Youden	Logistic	30,30,30	0.0316	0.1424	0.1434	0.0089	0.1228	0.1229	-0.0975	0.0447	0.0542
		50,50,50	0.0403	0.1026	0.1042	0.0083	0.0979	0.0979	-0.0554	0.0217	0.0248
		100,100,100	0.0123	0.0523	0.0524	0.0296	0.0618	0.0627	-0.0168	0.0042	0.0045
		200,200,200	0.0093	0.0252	0.0253	0.0205	0.0358	0.0362	-0.0032	0.0005	0.0005
		200,50,50	0.0295	0.0664	0.0673	0.0148	0.0700	0.0702	-0.0236	0.0070	0.0075
	Yan	30,30,30	0.0576	0.2699	0.2732	-0.0377	0.2193	0.2208	-0.2219	0.1185	0.1678
		50,50,50	0.0734	0.2206	0.2269	-0.0131	0.1869	0.1871	-0.1479	0.0771	0.0990
		100,100,100	0.0204	0.1460	0.1464	0.0368	0.1233	0.1247	-0.0718	0.0300	0.0352
		200,200,200	0.0495	0.1021	0.1045	0.0705	0.0963	0.1013	-0.0372	0.0122	0.0136
		200,50,50	0.0672	0.2203	0.2248	0.0026	0.1703	0.1703	-0.1215	0.0657	0.0805
	Normal	30,30,30	0.0384	0.1537	0.1551	0.0050	0.1292	0.1292	-0.1068	0.0484	0.0598
		50,50,50	0.0420	0.1086	0.1103	0.0065	0.1030	0.1030	-0.0596	0.0233	0.0269
		100,100,100	0.0105	0.0531	0.0532	0.0284	0.0637	0.0645	-0.0177	0.0043	0.0047
		200,200,200	0.0083	0.0262	0.0263	0.0211	0.0362	0.0367	-0.0037	0.0006	0.0006
		200,50,50	0.0409	0.0868	0.0885	0.0061	0.0842	0.0843	-0.0348	0.0120	0.0132
	Stepwise	30,30,30	-0.0016	0.1896	0.1896	-0.1740	0.2236	0.2539	-0.2962	0.1661	0.2538
		50,50,50	0.0424	0.1730	0.1748	-0.1304	0.2036	0.2206	-0.2329	0.1240	0.1782
		100,100,100	-0.0090	0.1192	0.1193	-0.0751	0.1560	0.1616	-0.1367	0.0683	0.0870
		200,200,200	-0.0047	0.0862	0.0863	-0.0220	0.1241	0.1246	-0.0829	0.0335	0.0404
		200,50,50	0.0407	0.1487	0.1504	-0.0823	0.1723	0.1790	-0.1828	0.0963	0.1297

Table B.3

The table provides results for the normal scenarios with $\Sigma = 0.5I + 0.5J$. The table provides the bias, variance, and MSE for the cutoff values, c_1 and c_2, for each of the explored approaches when using the Euclidean distance as the objective function.

Method	Approach	n_1, n_2, n_3	c_1 Bias	c_1 Variance	c_1 MSE	c_2 Bias	c_2 Variance	c_2 MSE
Euclidean	Logistic	30,30,30	-0.0992	0.2195	0.2293	-0.3996	0.5650	0.7246
		50,50,50	-0.0448	0.1565	0.1585	-0.2066	0.4009	0.4436
		100,100,100	-0.0113	0.1066	0.1067	-0.0843	0.3011	0.3082
		200,200,200	0.0011	0.0599	0.0599	-0.0087	0.1917	0.1918
		200,50,50	0.0714	0.1227	0.1278	-0.1121	0.3936	0.4062
	Yan	30,30,30	-0.1837	0.1093	0.1431	-0.6827	0.6450	1.1111
		50,50,50	-0.1259	0.0796	0.0954	-0.4053	0.5824	0.7467
		100,100,100	-0.0698	0.0505	0.0554	-0.1811	0.4303	0.4631
		200,200,200	-0.0256	0.0337	0.0344	0.0131	0.3360	0.3361
		200,50,50	-0.0752	0.0636	0.0692	-0.3239	0.5621	0.6670
	Normal	30,30,30	-0.0818	0.0592	0.0659	-0.3682	0.4081	0.5437
		50,50,50	-0.0552	0.0403	0.0434	-0.2101	0.3318	0.3760
		100,100,100	-0.0179	0.0233	0.0236	-0.0547	0.2398	0.2428
		200,200,200	-0.0055	0.0136	0.0136	0.0001	0.1600	0.1600
		200,50,50	-0.0233	0.0273	0.0278	-0.1449	0.3056	0.3266
	Stepwise	30,30,30	-0.2191	0.1426	0.1906	-1.0821	0.5195	1.6904
		50,50,50	-0.1518	0.1099	0.1330	-0.8256	0.5059	1.1876
		100,100,100	0.0185	0.0708	0.0711	-0.5286	0.4490	0.7284
		200,200,200	0.0292	0.0546	0.0555	-0.3103	0.4004	0.4967
		200,50,50	0.0662	0.0695	0.0739	-0.7092	0.4916	0.9946
Youden	Logistic	30,30,30	-0.2996	0.4115	0.5012	-0.3982	0.6398	0.7984
		50,50,50	-0.1917	0.3195	0.3563	-0.2436	0.4753	0.5347
		100,100,100	-0.0890	0.2165	0.2244	-0.0877	0.3642	0.3719
		200,200,200	-0.0533	0.1424	0.1453	-0.0114	0.2583	0.2584
		200,50,50	-0.0137	0.2488	0.2490	-0.1212	0.5010	0.5157
	Yan	30,30,30	-0.2737	0.2409	0.3158	-0.5371	0.6716	0.9601
		50,50,50	-0.1818	0.1933	0.2264	-0.3492	0.5366	0.6586
		100,100,100	-0.0776	0.1167	0.1227	-0.1545	0.3925	0.4164
		200,200,200	-0.0153	0.0786	0.0788	-0.0060	0.3020	0.3021
		200,50,50	-0.1045	0.1561	0.1670	-0.2640	0.5466	0.6163
	Normal	30,30,30	-0.1393	0.1071	0.1265	-0.2499	0.3790	0.4414
		50,50,50	-0.0946	0.0748	0.0837	-0.1419	0.2858	0.3059
		100,100,100	-0.0318	0.0438	0.0449	-0.0319	0.1957	0.1967
		200,200,200	-0.0079	0.0247	0.0247	0.0123	0.1298	0.1300
		200,50,50	-0.0527	0.0553	0.0581	-0.0735	0.2649	0.2703
	Stepwise	30,30,30	-0.4085	0.2215	0.3884	-1.0540	0.5327	1.6436
		50,50,50	-0.3214	0.2031	0.3064	-0.8372	0.4776	1.1785
		100,100,100	-0.1972	0.1770	0.2159	-0.5567	0.4373	0.7473
		200,200,200	-0.1268	0.1246	0.1407	-0.3605	0.3668	0.4967
		200,50,50	-0.1877	0.1743	0.2095	-0.6699	0.4835	0.9324

Table B.4

The table provides results for the normal scenarios with $\Sigma = 0.3I + 0.7J$. The table provides the bias, variance, and MSE for the cutoff values, c_1 and c_2, for each of the explored approaches when using the Euclidean distance as the objective function.

Method	Approach	n_1, n_2, n_3	c_1 Bias	c_1 Variance	c_1 MSE	c_2 Bias	c_2 Variance	c_2 MSE
		30,30,30	-0.0736	0.1704	0.1758	-0.2069	0.6294	0.6722
		50,50,50	-0.0229	0.1399	0.1404	-0.0751	0.4422	0.4478
	Logistic	100,100,100	0.0156	0.0836	0.0838	0.0067	0.3153	0.3154
		200,200,200	0.0072	0.0544	0.0544	0.0196	0.1954	0.1958
		200,50,50	0.0656	0.0978	0.1021	-0.0162	0.4096	0.4099
		30,30,30	-0.1309	0.0928	0.1100	-0.4574	0.7453	0.9545
		50,50,50	-0.0965	0.0705	0.0798	-0.2287	0.6693	0.7216
	Yan	100,100,100	-0.0389	0.0458	0.0473	-0.0299	0.4997	0.5006
		200,200,200	-0.0027	0.0340	0.0340	0.1462	0.4677	0.4891
		200,50,50	-0.0393	0.0680	0.0695	-0.1348	0.7693	0.7875
Euclidean								
		30,30,30	-0.0435	0.0522	0.0541	-0.1839	0.4732	0.5070
		50,50,50	-0.0257	0.0347	0.0353	-0.0606	0.3903	0.3940
	Normal	100,100,100	-0.0009	0.0203	0.0203	0.0306	0.2798	0.2807
		200,200,200	0.0019	0.0114	0.0114	0.0374	0.1739	0.1753
		200,50,50	0.0022	0.0257	0.0257	-0.0107	0.3804	0.3805
		30,30,30	-0.1355	0.1232	0.1416	-0.7874	0.5222	1.1422
		50,50,50	-0.0855	0.1007	0.1080	-0.5422	0.4990	0.7930
	Stepwise	100,100,100	0.0711	0.0551	0.0601	-0.2685	0.4752	0.5473
		200,200,200	0.0673	0.0454	0.0499	-0.1139	0.4098	0.4228
		200,50,50	0.1316	0.0662	0.0835	-0.4149	0.5379	0.7101
		30,30,30	-0.2082	0.3665	0.4099	-0.2135	0.6595	0.7051
		50,50,50	-0.1501	0.2900	0.3125	-0.1021	0.4882	0.4986
	Logistic	100,100,100	-0.0569	0.1908	0.1940	-0.0078	0.3570	0.3571
		200,200,200	-0.0377	0.1233	0.1247	0.0028	0.2273	0.2273
		200,50,50	0.0111	0.2045	0.2046	-0.0597	0.4706	0.4742
		30,30,30	-0.2223	0.2400	0.2894	-0.3130	0.7577	0.8557
		50,50,50	-0.1293	0.2082	0.2249	-0.1471	0.5963	0.6179
	Yan	100,100,100	-0.0439	0.1242	0.1262	-0.0225	0.4652	0.4657
		200,200,200	0.0240	0.0917	0.0923	0.1209	0.3894	0.4040
		200,50,50	-0.0524	0.1705	0.1732	-0.0706	0.6249	0.6299
Youden								
		30,30,30	-0.0860	0.1086	0.1160	-0.0865	0.4418	0.4492
		50,50,50	-0.0534	0.0737	0.0765	-0.0154	0.3275	0.3277
	Normal	100,100,100	-0.0071	0.0440	0.0440	0.0371	0.2194	0.2208
		200,200,200	0.0026	0.0233	0.0233	0.0409	0.1351	0.1368
		200,50,50	-0.0194	0.0569	0.0573	0.0319	0.3145	0.3155
		30,30,30	-0.3109	0.1918	0.2885	-0.7594	0.4405	1.0172
		50,50,50	-0.2193	0.1980	0.2461	-0.5267	0.4866	0.7640
	Stepwise	100,100,100	-0.1245	0.1671	0.1826	-0.3642	0.4432	0.5759
		200,200,200	-0.0655	0.1148	0.1191	-0.1823	0.3819	0.4151
		200,50,50	-0.0985	0.1615	0.1712	-0.3721	0.5089	0.6473

Table B.5

The table provides results for the normal scenarios with $\Sigma = 0.5I + 0.5J$. The table provides the bias, variance, and MSE for TCR_1, TCR_2, and TCR_3 for each of the explored approaches when using the Euclidean distance as the objective function.

| Method	Approach	n_1, n_2, n_3	TCR_1 Bias	Variance	MSE	TCR_2 Bias	Variance	MSE	TCR_3 Bias	Variance	MSE	$Sum(TCRs)$ Mean
		30,30,30	0.0030	0.0094	0.0095	-0.0175	0.0082	0.0085	0.0351	0.0084	0.0096	1.8736
		50,50,50	0.0119	0.0061	0.0063	-0.0002	0.0049	0.0049	0.0236	0.0056	0.0062	1.8884
	Logistic	100,100,100	0.0165	0.0040	0.0043	0.0055	0.0032	0.0032	0.0256	0.0038	0.0045	1.9006
		200,200,200	0.0183	0.0022	0.0026	0.0136	0.0019	0.0021	0.0224	0.0024	0.0029	1.9073
		200,50,50	0.0334	0.0043	0.0054	-0.0134	0.0046	0.0048	0.0247	0.0065	0.0072	1.8977
		30,30,30	-0.0037	0.0047	0.0047	-0.0070	0.0035	0.0036	0.0088	0.0043	0.0043	1.8511
		50,50,50	0.0028	0.0028	0.0028	0.0075	0.0021	0.0021	0.0100	0.0025	0.0026	1.8733
	Yan	100,100,100	0.0097	0.0014	0.0015	0.0175	0.0010	0.0013	0.0131	0.0014	0.0015	1.8932
		200,200,200	0.0129	0.0008	0.0009	0.0232	0.0005	0.0011	0.0139	0.0007	0.0009	1.9030
		200,50,50	0.0120	0.0019	0.0020	0.0067	0.0017	0.0017	0.0081	0.0026	0.0027	1.8798
Euclidean												
		30,30,30	0.0133	0.0021	0.0023	0.0052	0.0015	0.0015	0.0175	0.0021	0.0024	1.8890
		50,50,50	0.0145	0.0012	0.0014	0.0136	0.0008	0.0010	0.0174	0.0012	0.0015	1.8985
	Normal	100,100,100	0.0175	0.0006	0.0009	0.0186	0.0004	0.0007	0.0188	0.0006	0.0010	1.9079
		200,200,200	0.0183	0.0003	0.0006	0.0207	0.0002	0.0006	0.0198	0.0003	0.0007	1.9119
		200,50,50	0.0195	0.0006	0.0010	0.0138	0.0005	0.0007	0.0166	0.0012	0.0015	1.9029
		30,30,30	0.0010	0.0081	0.0081	-0.0399	0.0076	0.0092	0.0209	0.0075	0.0079	1.8350
		50,50,50	0.0116	0.0053	0.0054	-0.0246	0.0051	0.0057	0.0180	0.0053	0.0056	1.8580
	Stepwise	100,100,100	0.0425	0.0019	0.0037	-0.0219	0.0027	0.0032	0.0114	0.0031	0.0032	1.8850
		200,200,200	0.0367	0.0014	0.0027	-0.0061	0.0019	0.0019	0.0120	0.0019	0.0020	1.8956
		200,50,50	0.0624	0.0016	0.0055	-0.0499	0.0041	0.0066	0.0058	0.0049	0.0049	1.8713
		30,30,30	-0.0434	0.0158	0.0177	0.0101	0.0217	0.0218	0.0250	0.0119	0.0125	1.8593
		50,50,50	-0.0238	0.0113	0.0119	0.0152	0.0170	0.0172	0.0209	0.0092	0.0096	1.8799
	Logistic	100,100,100	-0.0061	0.0070	0.0070	0.0212	0.0112	0.0116	0.0170	0.0063	0.0066	1.8998
		200,200,200	0.0003	0.0045	0.0045	0.0279	0.0081	0.0088	0.0146	0.0047	0.0049	1.9104
		200,50,50	0.0078	0.0074	0.0075	-0.0010	0.0142	0.0142	0.0164	0.0097	0.0100	1.8909
		30,30,30	-0.0242	0.0085	0.0091	0.0206	0.0106	0.0110	-0.0091	0.0078	0.0079	1.8549
		50,50,50	-0.0111	0.0061	0.0062	0.0232	0.0073	0.0079	0.0003	0.0048	0.0048	1.8800
	Yan	100,100,100	0.0036	0.0030	0.0030	0.0239	0.0040	0.0046	0.0081	0.0030	0.0030	1.9033
		200,200,200	0.0095	0.0017	0.0018	0.0269	0.0024	0.0031	0.0110	0.0016	0.0017	1.9150
		200,50,50	0.0020	0.0041	0.0041	0.0189	0.0051	0.0055	-0.0001	0.0051	0.0051	1.8875
Youden												
		30,30,30	-0.0016	0.0030	0.0030	0.0314	0.0043	0.0053	0.0021	0.0029	0.0029	1.8995
		50,50,50	0.0026	0.0018	0.0018	0.0334	0.0025	0.0036	0.0077	0.0016	0.0017	1.9112
	Normal	100,100,100	0.0100	0.0009	0.0010	0.0323	0.0014	0.0024	0.0115	0.0008	0.0009	1.9214
		200,200,200	0.0125	0.0004	0.0006	0.0318	0.0007	0.0017	0.0139	0.0004	0.0006	1.9258
		200,50,50	0.0081	0.0011	0.0011	0.0329	0.0019	0.0030	0.0071	0.0017	0.0017	1.9158
		30,30,30	-0.0274	0.0129	0.0137	-0.0156	0.0191	0.0193	-0.0065	0.0121	0.0121	1.8180
		50,50,50	-0.0160	0.0096	0.0099	-0.0004	0.0159	0.0159	-0.0049	0.0094	0.0094	1.8463
	Stepwise	100,100,100	-0.0009	0.0064	0.0064	0.0095	0.0105	0.0106	0.0026	0.0061	0.0061	1.8788
		200,200,200	0.0052	0.0038	0.0038	0.0148	0.0067	0.0069	0.0105	0.0038	0.0039	1.8982
		200,50,50	0.0065	0.0063	0.0064	-0.0107	0.0125	0.0126	0.0010	0.0087	0.0087	1.8644
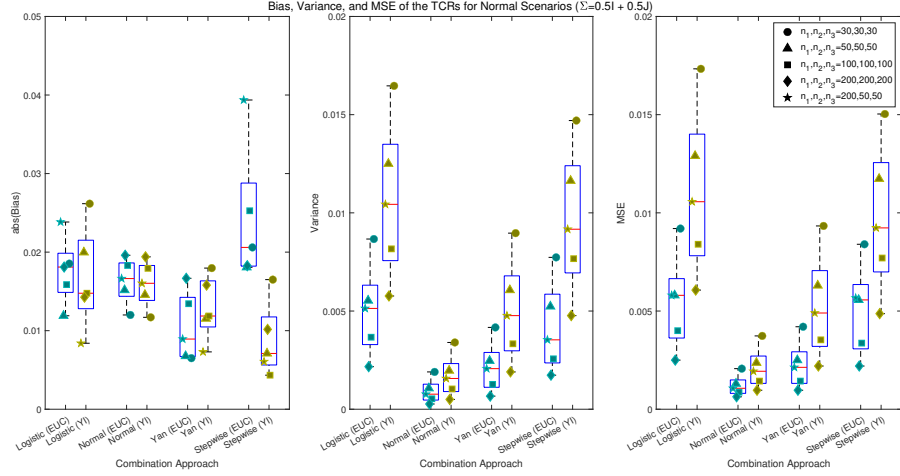
Figure 1: The plot displays the bias, variance, and MSE of $\widehat{TCR_1}$, $\widehat{TCR_2}$, and $\widehat{TCR_3}$ for each sample size explored. We see that for most scenarios, the Euclidean method had smaller bias than the Youden index. For all scenarios, the Euclidean method had smaller variance and MSE.
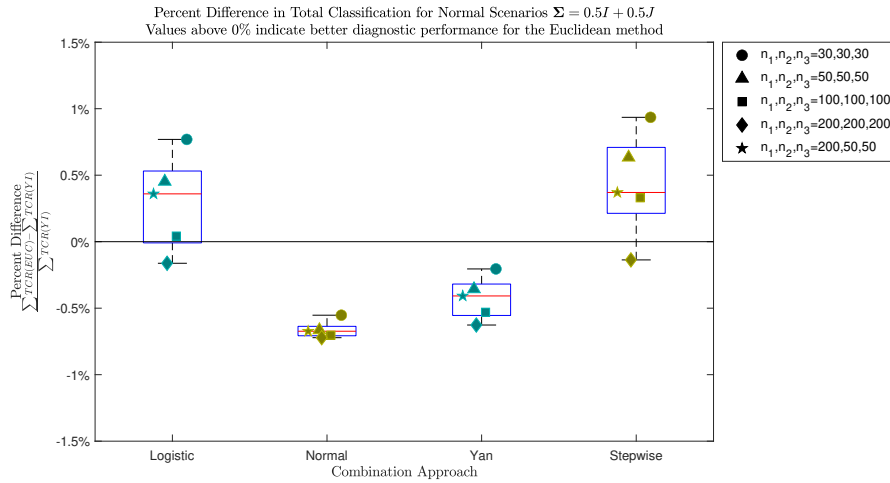

Figure 2: The plot displays the percent difference in $\sum_i TCR_i$, $i = 1, 2, 3$, i.e. total classification, for the Euclidean method (EUC) versus the Youden index (YI) for each of the combination approaches and sample sizes, where $\Sigma = 0.7I + 0.3J$. The percent difference is calculated by $\frac{\Sigma TCR(EUC) - \Sigma TCR(YI)}{\Sigma TCR(YI)}$. Values above 0% correspond to a higher total classification for the Euclidean method than the Youden index, indicating better diagnostic performance for the Euclidean method. Both logistic regression and the stepwise procedure saw higher total classification than the Youden index for all sample sizes except when $(n_1, n_2, n_3) = (200, 200, 200)$. For the normality assumption and Yan's method, the Youden index saw higher total classification that was less than 1% higher than that of the Euclidean method.

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Table B.6

The table provides results for the normal scenarios with $\Sigma = 0.3I + 0.7J$. The table provides the bias, variance, and MSE for TCR_1, TCR_2, and TCR_3 for each of the explored approaches when using the Euclidean distance as the objective function.

| Method	Approach	n_1, n_2, n_3	TCR_1 Bias	Variance	MSE	TCR_2 Bias	Variance	MSE	TCR_3 Bias	Variance	MSE	$Sum(TCRs)$ Mean
Euclidean	Logistic	30,30,30	-0.0195	0.0091	0.0095	-0.0364	0.0083	0.0097	0.0151	0.0088	0.0091	1.8122
		50,50,50	-0.0095	0.0069	0.0070	-0.0240	0.0056	0.0061	0.0054	0.0063	0.0064	1.8248
		100,100,100	-0.0009	0.0040	0.0040	-0.0175	0.0033	0.0036	0.0033	0.0044	0.0044	1.8378
		200,200,200	-0.0024	0.0026	0.0026	-0.0100	0.0021	0.0022	0.0036	0.0026	0.0026	1.8442
		200,50,50	0.0107	0.0047	0.0049	-0.0340	0.0047	0.0059	0.0052	0.0069	0.0070	1.8349
	Yan	30,30,30	-0.0247	0.0047	0.0053	-0.0292	0.0036	0.0045	-0.0122	0.0045	0.0046	1.7869
		50,50,50	-0.0224	0.0031	0.0036	-0.0147	0.0022	0.0024	-0.0096	0.0028	0.0029	1.8063
		100,100,100	-0.0120	0.0016	0.0017	-0.0044	0.0011	0.0011	-0.0075	0.0015	0.0015	1.8291
		200,200,200	-0.0091	0.0009	0.0010	0.0013	0.0006	0.0006	-0.0067	0.0008	0.0009	1.8385
		200,50,50	-0.0111	0.0022	0.0023	-0.0156	0.0018	0.0020	-0.0141	0.0028	0.0030	1.8122
	Normal	30,30,30	-0.0075	0.0022	0.0022	-0.0167	0.0014	0.0017	-0.0033	0.0022	0.0022	1.8256
		50,50,50	-0.0065	0.0013	0.0013	-0.0081	0.0008	0.0009	-0.0032	0.0013	0.0013	1.8352
		100,100,100	-0.0030	0.0006	0.0006	-0.0035	0.0004	0.0004	-0.0020	0.0006	0.0006	1.8446
		200,200,200	-0.0021	0.0003	0.0003	-0.0015	0.0002	0.0002	-0.0006	0.0003	0.0003	1.8488
		200,50,50	-0.0012	0.0007	0.0007	-0.0082	0.0005	0.0006	-0.0040	0.0012	0.0013	1.8396
	Stepwise	30,30,30	-0.0147	0.0083	0.0085	-0.0639	0.0077	0.0118	0.0022	0.0080	0.0080	1.7766
		50,50,50	-0.0079	0.0058	0.0059	-0.0474	0.0055	0.0077	0.0026	0.0056	0.0056	1.8002
		100,100,100	0.0267	0.0019	0.0026	-0.0440	0.0028	0.0047	-0.0089	0.0032	0.0032	1.8268
		200,200,200	0.0195	0.0015	0.0019	-0.0275	0.0020	0.0028	-0.0095	0.0022	0.0023	1.8356
		200,50,50	0.0478	0.0018	0.0041	-0.0768	0.0040	0.0099	-0.0092	0.0048	0.0049	1.8148
Youden	Logistic	30,30,30	-0.0560	0.0169	0.0201	-0.0217	0.0236	0.0241	0.0085	0.0131	0.0132	1.7984
		50,50,50	-0.0431	0.0128	0.0147	-0.0118	0.0196	0.0197	0.0039	0.0103	0.0103	1.8165
		100,100,100	-0.0227	0.0078	0.0083	-0.0085	0.0137	0.0138	-0.0003	0.0076	0.0076	1.8360
		200,200,200	-0.0159	0.0052	0.0055	-0.0065	0.0093	0.0094	0.0025	0.0050	0.0050	1.8477
		200,50,50	-0.0073	0.0084	0.0084	-0.0384	0.0172	0.0187	0.0055	0.0109	0.0110	1.8273
	Yan	30,30,30	-0.0496	0.0102	0.0127	-0.0011	0.0120	0.0120	-0.0278	0.0091	0.0099	1.7891
		50,50,50	-0.0338	0.0076	0.0087	-0.0020	0.0087	0.0087	-0.0174	0.0055	0.0058	1.8144
		100,100,100	-0.0157	0.0039	0.0041	-0.0033	0.0051	0.0051	-0.0095	0.0033	0.0034	1.8391
		200,200,200	-0.0079	0.0023	0.0024	-0.0032	0.0030	0.0030	-0.0059	0.0020	0.0020	1.8507
		200,50,50	-0.0184	0.0051	0.0055	-0.0082	0.0064	0.0065	-0.0191	0.0059	0.0062	1.8219
	Normal	30,30,30	-0.0192	0.0036	0.0040	0.0021	0.0057	0.0057	-0.0149	0.0035	0.0037	1.8356
		50,50,50	-0.0145	0.0022	0.0024	0.0036	0.0034	0.0034	-0.0088	0.0019	0.0020	1.8479
		100,100,100	-0.0059	0.0010	0.0011	0.0015	0.0018	0.0018	-0.0047	0.0010	0.0010	1.8585
		200,200,200	-0.0033	0.0005	0.0005	0.0007	0.0009	0.0009	-0.0019	0.0005	0.0005	1.8632
		200,50,50	-0.0086	0.0013	0.0014	0.0032	0.0025	0.0026	-0.0094	0.0020	0.0021	1.8527
	Stepwise	30,30,30	-0.0428	0.0138	0.0157	-0.0355	0.0209	0.0222	-0.0260	0.0136	0.0142	1.7633
		50,50,50	-0.0314	0.0108	0.0118	-0.0270	0.0160	0.0167	-0.0171	0.0097	0.0100	1.7921
		100,100,100	-0.0151	0.0071	0.0073	-0.0244	0.0133	0.0139	-0.0094	0.0072	0.0073	1.8187
		200,200,200	-0.0089	0.0045	0.0045	-0.0153	0.0078	0.0080	-0.0059	0.0046	0.0046	1.8375
		200,50,50	-0.0078	0.0071	0.0071	-0.0364	0.0138	0.0152	-0.0152	0.0096	0.0098	1.8082
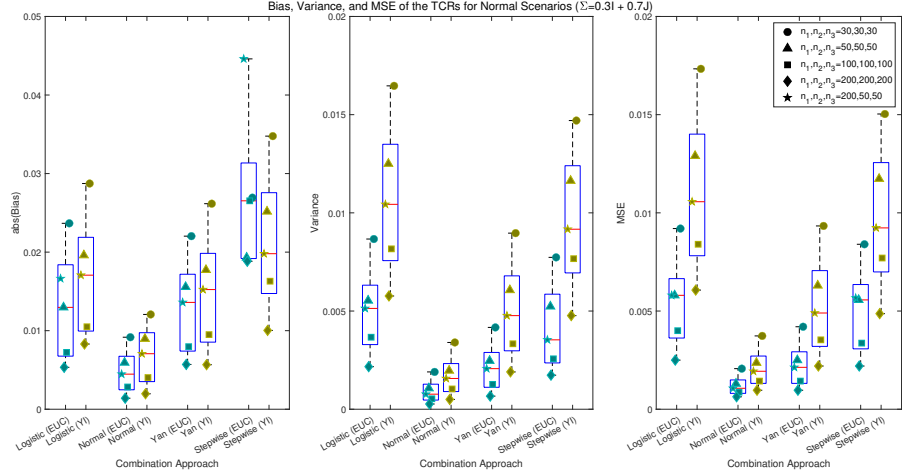
Figure 3: The plot displays the bias, variance, and MSE of $\widehat{TCR_1}$, $\widehat{TCR_2}$, and $\widehat{TCR_3}$ for each sample size explored. We see that for most scenarios, the Euclidean method had smaller bias than the Youden index. For all scenarios, the Euclidean method had smaller variance and MSE.
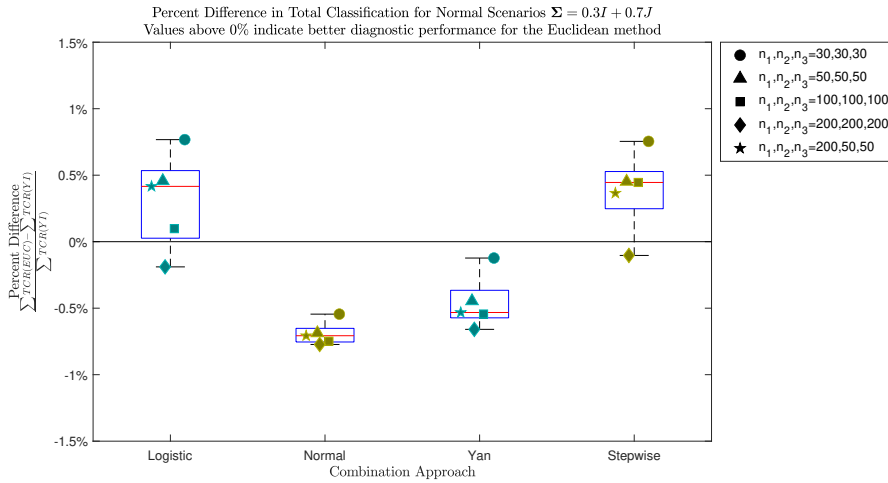

Figure 4: The plot displays the percent difference in $\sum_i TCR_i$, $i = 1, 2, 3$, i.e. total classification, for the Euclidean method (EUC) versus the Youden index (YI) for each of the combination approaches and sample sizes, where $\Sigma = 0.7I + 0.3J$. The percent difference is calculated by $\frac{\Sigma TCR(EUC) - \Sigma TCR(YI)}{\Sigma TCR(YI)}$. Values above 0% correspond to a higher total classification for the Euclidean method than the Youden index, indicating better diagnostic performance for the Euclidean method. Both logistic regression and the stepwise procedure saw higher total classification than the Youden index for all sample sizes except when $(n_1, n_2, n_3) = (200, 200, 200)$. For the normality assumption and Yan's method, the Youden index saw higher total classification that was less than 1% higher than that of the Euclidean method.

Table B.7

The table provides results based on training data for the normal scenarios with $\Sigma = 0.7I + 0.3J$. The table provides the bias, variance, and MSE for TCR_1, TCR_2, and TCR_3 for each of the explored approaches when using the Euclidean distance as the objective function.

Method	Approach	n_1, n_2, n_3	TCR_1 Bias	Variance	MSE	TCR_2 Bias	Variance	MSE	TCR_3 Bias	Variance	MSE	$Sum(TCRs)$ Mean
		30,30,30	0.0484	0.0075	0.0099	0.0621	0.0069	0.0107	0.0510	0.0076	0.0102	2.1676
		50,50,50	0.0332	0.0055	0.0066	0.0467	0.0046	0.0068	0.0382	0.0053	0.0068	2.1243
	Logistic	100,100,100	0.0242	0.0033	0.0039	0.0303	0.0028	0.0037	0.0252	0.0033	0.0039	2.0859
		200,200,200	0.0151	0.0021	0.0024	0.0200	0.0016	0.0020	0.0144	0.0022	0.0024	2.0558
		200,50,50	0.0285	0.0038	0.0046	0.0413	0.0041	0.0058	0.0348	0.0055	0.0067	2.1107
		30,30,30	0.0174	0.0052	0.0055	0.0505	0.0050	0.0075	0.0185	0.0057	0.0060	2.0926
		50,50,50	0.0092	0.0033	0.0034	0.0340	0.0032	0.0044	0.0124	0.0031	0.0033	2.0618
	Yan	100,100,100	0.0048	0.0018	0.0018	0.0227	0.0017	0.0022	0.0067	0.0016	0.0016	2.0404
		200,200,200	0.0021	0.0009	0.0009	0.0138	0.0008	0.0010	0.0004	0.0009	0.0009	2.0225
		200,50,50	0.0021	0.0016	0.0016	0.0312	0.0029	0.0039	0.0121	0.0033	0.0034	2.0516
Euclidean		30,30,30	0.0083	0.0046	0.0047	0.0112	0.0067	0.0068	0.0074	0.0050	0.0050	2.0331
		50,50,50	0.0026	0.0028	0.0028	0.0068	0.0042	0.0043	0.0084	0.0024	0.0025	2.0240
	Normal	100,100,100	0.0034	0.0013	0.0013	0.0059	0.0022	0.0022	0.0032	0.0013	0.0013	2.0188
		200,200,200	0.0030	0.0007	0.0007	0.0010	0.0010	0.0010	0.0007	0.0007	0.0007	2.0110
		200,50,50	0.0014	0.0010	0.0010	0.0057	0.0039	0.0039	0.0063	0.0027	0.0028	2.0217
		30,30,30	0.0636	0.0056	0.0096	0.0883	0.0056	0.0134	0.0657	0.0057	0.0100	2.2238
		50,50,50	0.0457	0.0041	0.0062	0.0635	0.0040	0.0080	0.0483	0.0038	0.0062	2.1637
	Stepwise	100,100,100	0.0466	0.0021	0.0042	0.0238	0.0025	0.0031	0.0229	0.0027	0.0033	2.0995
		200,200,200	0.0349	0.0013	0.0025	0.0128	0.0016	0.0018	0.0107	0.0017	0.0018	2.0646
		200,50,50	0.0513	0.0018	0.0045	0.0371	0.0040	0.0054	0.0390	0.0042	0.0057	2.1337
		30,30,30	0.0157	0.0131	0.0133	0.0947	0.0243	0.0333	0.0598	0.0116	0.0152	2.1897
		50,50,50	0.0145	0.0092	0.0094	0.0615	0.0181	0.0218	0.0490	0.0081	0.0105	2.1444
	Logistic	100,100,100	0.0089	0.0064	0.0065	0.0480	0.0110	0.0133	0.0276	0.0054	0.0062	2.1040
		200,200,200	0.0033	0.0039	0.0039	0.0313	0.0076	0.0086	0.0178	0.0040	0.0044	2.0720
		200,50,50	0.0140	0.0064	0.0064	0.0555	0.0162	0.0193	0.0401	0.0091	0.0107	2.1292
		30,30,30	0.0079	0.0104	0.0105	0.0759	0.0189	0.0246	0.0150	0.0105	0.0107	2.1183
		50,50,50	0.0075	0.0068	0.0068	0.0466	0.0125	0.0147	0.0145	0.0057	0.0059	2.0881
	Yan	100,100,100	0.0063	0.0035	0.0035	0.0269	0.0064	0.0072	0.0100	0.0031	0.0032	2.0627
		200,200,200	0.0044	0.0019	0.0019	0.0138	0.0034	0.0036	0.0040	0.0018	0.0018	2.0417
		200,50,50	0.0008	0.0034	0.0034	0.0430	0.0103	0.0121	0.0152	0.0059	0.0061	2.0785
Youden		30,30,30	0.0014	0.0064	0.0064	0.0284	0.0141	0.0149	-0.0012	0.0068	0.0068	2.0481
		50,50,50	-0.0022	0.0037	0.0037	0.0173	0.0088	0.0091	0.0053	0.0033	0.0033	2.0398
	Normal	100,100,100	0.0006	0.0017	0.0018	0.0108	0.0047	0.0048	0.0010	0.0017	0.0017	2.0319
		200,200,200	0.0011	0.0009	0.0009	0.0041	0.0022	0.0022	0.0002	0.0008	0.0008	2.0249
		200,50,50	-0.0024	0.0014	0.0014	0.0139	0.0081	0.0082	0.0038	0.0037	0.0037	2.0348
		30,30,30	0.0464	0.0109	0.0130	0.1179	0.0201	0.0340	0.0520	0.0101	0.0128	2.2359
		50,50,50	0.0365	0.0079	0.0092	0.0909	0.0151	0.0234	0.0375	0.0078	0.0093	2.1844
	Stepwise	100,100,100	0.0267	0.0057	0.0064	0.0522	0.0105	0.0133	0.0302	0.0051	0.0060	2.1286
		200,200,200	0.0140	0.0036	0.0038	0.0380	0.0072	0.0087	0.0159	0.0037	0.0039	2.0875
		200,50,50	0.0170	0.0050	0.0064	0.0872	0.0123	0.0199	0.0443	0.0077	0.0097	2.1679

Table B.8

The table provides results based on training data for the normal scenarios with $\Sigma = 0.5I + 0.5J$. The table provides the bias, variance, and MSE for TCR_1, TCR_2, and TCR_3 for each of the explored approaches when using the Euclidean distance as the objective function.

Method	Approach	n_1, n_2, n_3	TCR_1 Bias	Variance	MSE	TCR_2 Bias	Variance	MSE	TCR_3 Bias	Variance	MSE	$Sum(TCRs)$ Mean
		30,30,30	0.0488	0.0086	0.0110	0.0657	0.0078	0.0121	0.0546	0.0087	0.0117	2.0850
		50,50,50	0.0367	0.0062	0.0076	0.0490	0.0049	0.0073	0.0381	0.0054	0.0068	2.0398
	Logistic	100,100,100	0.0239	0.0037	0.0043	0.0306	0.0031	0.0040	0.0266	0.0035	0.0042	1.9971
		200,200,200	0.0159	0.0023	0.0026	0.0198	0.0018	0.0022	0.0154	0.0023	0.0026	1.9670
		200,50,50	0.0282	0.0041	0.0049	0.0434	0.0048	0.0066	0.0361	0.0062	0.0075	2.0235
		30,30,30	0.0154	0.0060	0.0063	0.0584	0.0051	0.0086	0.0210	0.0063	0.0067	2.0107
		50,50,50	0.0074	0.0036	0.0036	0.0393	0.0034	0.0049	0.0147	0.0034	0.0036	1.9772
	Yan	100,100,100	0.0034	0.0018	0.0018	0.0246	0.0018	0.0024	0.0064	0.0017	0.0017	1.9503
		200,200,200	0.0020	0.0011	0.0011	0.0152	0.0009	0.0011	-0.0002	0.0010	0.0010	1.9330
		200,50,50	0.0007	0.0019	0.0019	0.0377	0.0028	0.0042	0.0128	0.0036	0.0038	1.9670
Euclidean		30,30,30	0.0080	0.0050	0.0051	0.0122	0.0071	0.0073	0.0060	0.0051	0.0051	1.9421
		50,50,50	0.0032	0.0029	0.0029	0.0080	0.0045	0.0046	0.0093	0.0027	0.0028	1.9364
	Normal	100,100,100	0.0017	0.0014	0.0014	0.0060	0.0023	0.0023	0.0021	0.0014	0.0014	1.9256
		200,200,200	0.0026	0.0007	0.0007	0.0017	0.0011	0.0011	0.0012	0.0007	0.0007	1.9214
		200,50,50	0.0033	0.0011	0.0011	0.0076	0.0043	0.0043	0.0056	0.0031	0.0031	1.9325
		30,30,30	0.0018	0.0064	0.0064	0.0972	0.0062	0.0156	0.0697	0.0066	0.0115	2.1495
		50,50,50	-0.0140	0.0046	0.0048	0.0692	0.0043	0.0091	0.0551	0.0043	0.0073	2.0910
	Stepwise	100,100,100	-0.0133	0.0022	0.0023	0.0255	0.0029	0.0035	0.0264	0.0029	0.0036	2.0194
		200,200,200	-0.0269	0.0016	0.0023	0.0149	0.0017	0.0019	0.0124	0.0018	0.0020	1.9812
		200,50,50	-0.0077	0.0018	0.0019	0.0407	0.0041	0.0058	0.0418	0.0046	0.0063	2.0556
		30,30,30	0.0161	0.0150	0.0153	0.1029	0.0273	0.0379	0.0603	0.0136	0.0172	2.1094
		50,50,50	0.0137	0.0113	0.0115	0.0692	0.0210	0.0258	0.0485	0.0092	0.0116	2.0616
	Logistic	100,100,100	0.0117	0.0069	0.0071	0.0465	0.0133	0.0155	0.0289	0.0067	0.0076	2.0172
		200,200,200	0.0061	0.0046	0.0046	0.0322	0.0090	0.0101	0.0164	0.0050	0.0052	1.9848
		200,50,50	0.0095	0.0075	0.0076	0.0637	0.0178	0.0218	0.0401	0.0102	0.0118	2.0434
		30,30,30	0.0070	0.0121	0.0121	0.0869	0.0228	0.0303	0.0154	0.0122	0.0125	2.0394
		50,50,50	0.0033	0.0087	0.0086	0.0537	0.0145	0.0173	0.0172	0.0066	0.0069	2.0043
	Yan	100,100,100	0.0048	0.0042	0.0042	0.0307	0.0081	0.0090	0.0105	0.0039	0.0040	1.9761
		200,200,200	0.0052	0.0023	0.0023	0.0163	0.0043	0.0045	0.0040	0.0021	0.0022	1.9556
		200,50,50	-0.0030	0.0045	0.0045	0.0508	0.0130	0.0156	0.0144	0.0073	0.0075	1.9923
Youden		30,30,30	0.0003	0.0075	0.0075	0.0326	0.0168	0.0179	-0.0010	0.0078	0.0078	1.9619
		50,50,50	-0.0036	0.0043	0.0043	0.0187	0.0101	0.0105	0.0059	0.0037	0.0038	1.9511
	Normal	100,100,100	0.0005	0.0020	0.0020	0.0111	0.0054	0.0055	0.0013	0.0019	0.0019	1.9430
		200,200,200	0.0011	0.0011	0.0011	0.0043	0.0026	0.0026	0.0000	0.0009	0.0009	1.9355
		200,50,50	-0.0036	0.0017	0.0017	0.0143	0.0096	0.0098	0.0038	0.0044	0.0044	1.9440
		30,30,30	0.0462	0.0123	0.0149	0.1314	0.0235	0.0407	0.0575	0.0122	0.0155	2.1705
		50,50,50	0.0367	0.0095	0.0108	0.0975	0.0184	0.0279	0.0464	0.0092	0.0113	2.1101
	Stepwise	100,100,100	0.0275	0.0062	0.0070	0.0637	0.0118	0.0159	0.0288	0.0063	0.0071	2.0505
		200,200,200	0.0164	0.0038	0.0041	0.0367	0.0076	0.0089	0.0198	0.0039	0.0043	2.0060
		200,50,50	0.0256	0.0062	0.0064	0.0982	0.0139	0.0236	0.0498	0.0088	0.0113	2.0917

Table B.9

The table provides results based on training data for the normal scenarios with $\Sigma = 0.3I + 0.7J$. The table provides the bias, variance, and MSE for TCR_1, TCR_2, and TCR_3 for each of the explored approaches when using the Euclidean distance as the objective function.

Method	Approach	n_1, n_2, n_3	TCR_1 Bias	TCR_1 Variance	TCR_1 MSE	TCR_2 Bias	TCR_2 Variance	TCR_2 MSE	TCR_3 Bias	TCR_3 Variance	TCR_3 MSE	$Sum(TCRs)$ Mean
		30,30,30	0.0462	0.0089	0.0110	0.0689	0.0079	0.0079	0.0555	0.0097	0.0128	2.0236
		50,50,50	0.0367	0.0069	0.0082	0.0506	0.0055	0.0055	0.0414	0.0061	0.0078	1.9817
	Logistic	100,100,100	0.0275	0.0039	0.0047	0.0305	0.0036	0.0036	0.0258	0.0039	0.0046	1.9368
		200,200,200	0.0164	0.0027	0.0030	0.0194	0.0020	0.0020	0.0170	0.0027	0.0030	1.9058
		200,50,50	0.0256	0.0048	0.0055	0.0456	0.0046	0.0067	0.0247	0.0067	0.0081	1.9617
		30,30,30	0.0156	0.0063	0.0066	0.0622	0.0053	0.0092	0.0214	0.0067	0.0071	1.9522
		50,50,50	0.0057	0.0038	0.0039	0.0438	0.0034	0.0053	0.0182	0.0036	0.0039	1.9207
	Yan	100,100,100	0.0022	0.0019	0.0019	0.0268	0.0019	0.0026	0.0059	0.0018	0.0018	1.8879
		200,200,200	0.0006	0.0012	0.0012	0.0163	0.0010	0.0013	-0.0001	0.0011	0.0011	1.8698
		200,50,50	-0.0017	0.0023	0.0023	0.0420	0.0029	0.0047	0.0120	0.0039	0.0041	1.9053
Euclidean		30,30,30	0.0089	0.0053	0.0054	0.0120	0.0077	0.0078	0.0058	0.0054	0.0055	1.8796
		50,50,50	0.0037	0.0031	0.0031	0.0077	0.0047	0.0048	0.0096	0.0029	0.0030	1.8739
	Normal	100,100,100	0.0022	0.0015	0.0015	0.0058	0.0024	0.0024	0.0017	0.0015	0.0015	1.8626
		200,200,200	0.0021	0.0008	0.0008	0.0019	0.0012	0.0012	0.0009	0.0008	0.0008	1.8579
		200,50,50	0.0031	0.0011	0.0011	0.0071	0.0044	0.0044	0.0060	0.0032	0.0032	1.8691
		30,30,30	0.0682	0.0067	0.0114	0.0987	0.0064	0.0161	0.0735	0.0073	0.0127	2.0934
		50,50,50	0.0527	0.0051	0.0079	0.0706	0.0047	0.0097	0.0619	0.0047	0.0085	2.0381
	Stepwise	100,100,100	0.0566	0.0022	0.0055	0.0254	0.0031	0.0038	0.0259	0.0029	0.0036	1.9609
		200,200,200	0.0412	0.0015	0.0032	0.0164	0.0021	0.0021	0.0128	0.0021	0.0023	1.9235
		200,50,50	0.0617	0.0021	0.0060	0.0374	0.0059	0.0059	0.0447	0.0047	0.0067	1.9967
		30,30,30	0.0204	0.0164	0.0168	0.1019	0.0308	0.0412	0.0598	0.0153	0.0189	2.0497
		50,50,50	0.0124	0.0126	0.0128	0.0754	0.0240	0.0297	0.0491	0.0104	0.0128	2.0045
	Logistic	100,100,100	0.0113	0.0078	0.0079	0.0502	0.0161	0.0186	0.0286	0.0084	0.0092	1.9577
		200,200,200	0.0064	0.0052	0.0053	0.0303	0.0107	0.0116	0.0202	0.0052	0.0056	1.9245
		200,50,50	0.0109	0.0085	0.0086	0.0592	0.0206	0.0241	0.0463	0.0113	0.0135	1.9840
		30,30,30	-0.0013	0.0147	0.0147	0.1023	0.0262	0.0367	0.0143	0.0138	0.0140	1.9829
		50,50,50	-0.0014	0.0104	0.0104	0.0665	0.0168	0.0212	0.0173	0.0074	0.0077	1.9500
	Yan	100,100,100	0.0030	0.0050	0.0050	0.0361	0.0098	0.0111	0.0101	0.0043	0.0044	1.9168
		200,200,200	0.0048	0.0029	0.0029	0.0196	0.0052	0.0056	0.0032	0.0026	0.0026	1.8953
		200,50,50	-0.0066	0.0058	0.0058	0.0602	0.0152	0.0189	0.0147	0.0084	0.0086	1.9358
Youden		30,30,30	-0.0004	0.0082	0.0082	0.0351	0.0191	0.0203	-0.0007	0.0083	0.0083	1.9017
		50,50,50	-0.0047	0.0048	0.0048	0.0197	0.0115	0.0119	0.0054	0.0040	0.0040	1.8880
	Normal	100,100,100	0.0001	0.0023	0.0023	0.0107	0.0060	0.0061	0.0006	0.0021	0.0021	1.8790
		200,200,200	0.0010	0.0012	0.0012	0.0046	0.0029	0.0030	-0.0005	0.0011	0.0011	1.8727
		200,50,50	-0.0047	0.0020	0.0020	0.0156	0.0105	0.0107	0.0023	0.0049	0.0049	1.8809
		30,30,30	0.0523	0.0137	0.0165	0.1434	0.0263	0.0469	0.0551	0.0131	0.0162	2.1183
		50,50,50	0.0376	0.0102	0.0117	0.1042	0.0185	0.0293	0.0494	0.0097	0.0122	2.0587
	Stepwise	100,100,100	0.0307	0.0068	0.0077	0.0623	0.0154	0.0193	0.0328	0.0071	0.0081	1.9934
		200,200,200	0.0213	0.0043	0.0047	0.0404	0.0087	0.0104	0.0199	0.0050	0.0054	1.9492
		200,50,50	0.0149	0.0070	0.0072	0.1050	0.0167	0.0266	0.0494	0.0102	0.0126	2.0370

Web -Appendix C (Simulation Results for Scenarios Generated from Lognormal Distributions)

Table C.1

The table provides results for the lognormal scenarios with
$\rho = 0.7I + 0.3J$. The table provides the point estimate and variance for TCR_1, TCR_2, and TCR_3, as well as the $Sum(\widehat{TCRs})$.

| Method	Approach	n_1, n_2, n_3	$Var(\widehat{TCR_1})$	$Var(\widehat{TCR_2})$	$Var(\widehat{TCR_3})$	$\widehat{TCR_1}$	$\widehat{TCR_2}$	$\widehat{TCR_3}$	$Sum(\widehat{TCRs})$
		30,30,30	0.0094	0.0083	0.0124	0.5554	0.4794	0.6813	1.7162
		50,50,50	0.0069	0.0057	0.0084	0.5588	0.4948	0.6728	1.7264
	Logistic	100,100,100	0.0042	0.0033	0.0057	0.5628	0.4995	0.6784	1.7406
		200,200,200	0.0028	0.0023	0.0035	0.5606	0.5065	0.6801	1.7473
		200,50,50	0.0046	0.0049	0.0092	0.5907	0.4723	0.6649	1.7279
		30,30,30	0.0045	0.0031	0.0071	0.5551	0.4777	0.6505	1.6834
		50,50,50	0.0030	0.0018	0.0043	0.5581	0.4906	0.6537	1.7024
	Yan	100,100,100	0.0017	0.0009	0.0023	0.5621	0.5023	0.6626	1.7271
		200,200,200	0.0010	0.0005	0.0012	0.5619	0.5085	0.6682	1.7387
		200,50,50	0.0021	0.0015	0.0042	0.5687	0.4855	0.6551	1.7094
Euclidean									
		30,30,30	0.0022	0.0014	0.0033	0.5728	0.5163	0.6881	1.7772
		50,50,50	0.0013	0.0008	0.0017	0.5739	0.5244	0.6896	1.7880
	Box-Cox	100,100,100	0.0009	0.0006	0.0014	0.5766	0.5286	0.6908	1.7960
		200,200,200	0.0003	0.0002	0.0004	0.5777	0.5312	0.6928	1.8017
		200,50,50	0.0010	0.0007	0.0022	0.5777	0.5251	0.6882	1.7910
		30,30,30	0.0087	0.0084	0.0111	0.5486	0.4463	0.6849	1.6798
		50,50,50	0.0064	0.0056	0.0074	0.5492	0.4666	0.6843	1.7001
	Stepwise	100,100,100	0.0038	0.0031	0.0046	0.5551	0.4825	0.6852	1.7228
		200,200,200	0.0025	0.0021	0.0030	0.5578	0.4927	0.6842	1.7347
		200,50,50	0.0040	0.0046	0.0075	0.5844	0.4464	0.6811	1.7119
		30,30,30	0.0192	0.0236	0.0144	0.5618	0.3606	0.7930	1.7153
		50,50,50	0.0146	0.0198	0.0113	0.5695	0.3745	0.7885	1.7324
	Logistic	100,100,100	0.0095	0.0141	0.0076	0.5827	0.3676	0.8025	1.7529
		200,200,200	0.0071	0.0103	0.0046	0.5885	0.3641	0.8116	1.7641
		200,50,50	0.0090	0.0170	0.0121	0.6231	0.3268	0.7850	1.7350
		30,30,30	0.0155	0.0163	0.0095	0.5750	0.3688	0.7603	1.7041
		50,50,50	0.0113	0.0112	0.0065	0.5839	0.3684	0.7735	1.7259
	Yan	100,100,100	0.0065	0.0070	0.0031	0.5938	0.3679	0.7926	1.7543
		200,200,200	0.0040	0.0040	0.0016	0.5968	0.3669	0.8043	1.7680
		200,50,50	0.0081	0.0073	0.0058	0.5936	0.3708	0.7718	1.7362
Youden									
		30,30,30	0.0060	0.0065	0.0033	0.5910	0.4075	0.7992	1.7976
		50,50,50	0.0036	0.0038	0.0016	0.5928	0.4106	0.8081	1.8115
	Box-Cox	100,100,100	0.0020	0.0023	0.0015	0.6016	0.4057	0.8139	1.8212
		200,200,200	0.0008	0.0010	0.0004	0.6043	0.4052	0.8183	1.8277
		200,50,50	0.0026	0.0030	0.0023	0.5973	0.4100	0.8085	1.8158
		30,30,30	0.0171	0.0179	0.0137	0.5472	0.3630	0.7717	1.6818
		50,50,50	0.0142	0.0154	0.0090	0.5578	0.3630	0.7854	1.7062
	Stepwise	100,100,100	0.0096	0.0123	0.0062	0.5703	0.3658	0.8000	1.7361
		200,200,200	0.0070	0.0082	0.0037	0.5784	0.3666	0.8088	1.7538
		200,50,50	0.0103	0.0133	0.0097	0.5855	0.3537	0.7835	1.7227
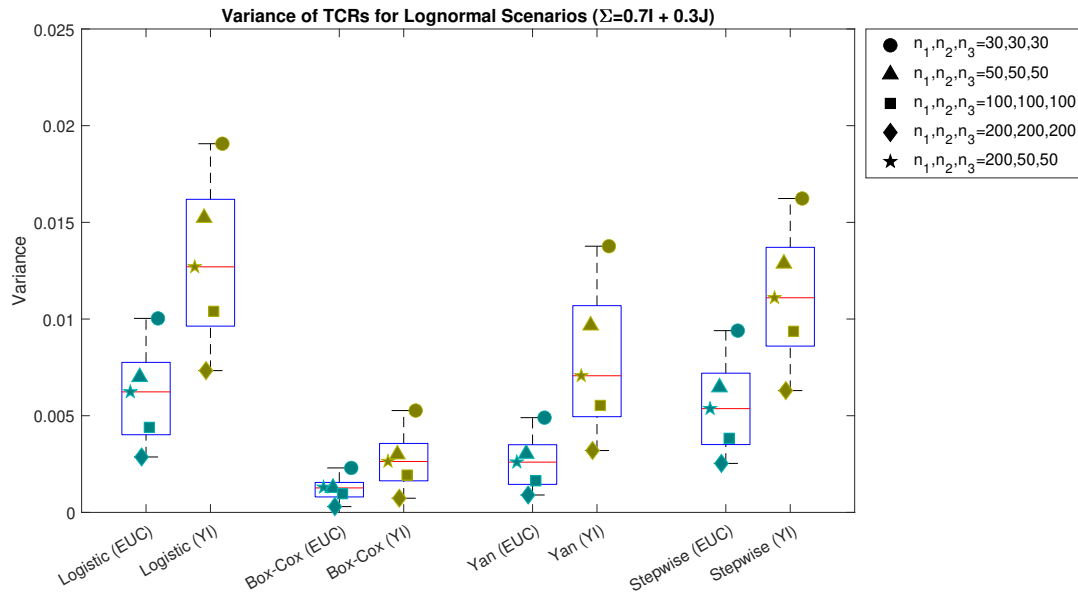
Figure 5: The plot displays the average of the variances of $\widehat{TCR}_1$, $\widehat{TCR}_2$, and $\widehat{TCR}_3$ for each sample size explored. For all explored scenarios, the Euclidean method had smaller variances for the $\widehat{TCRs}$ than the Youden index.
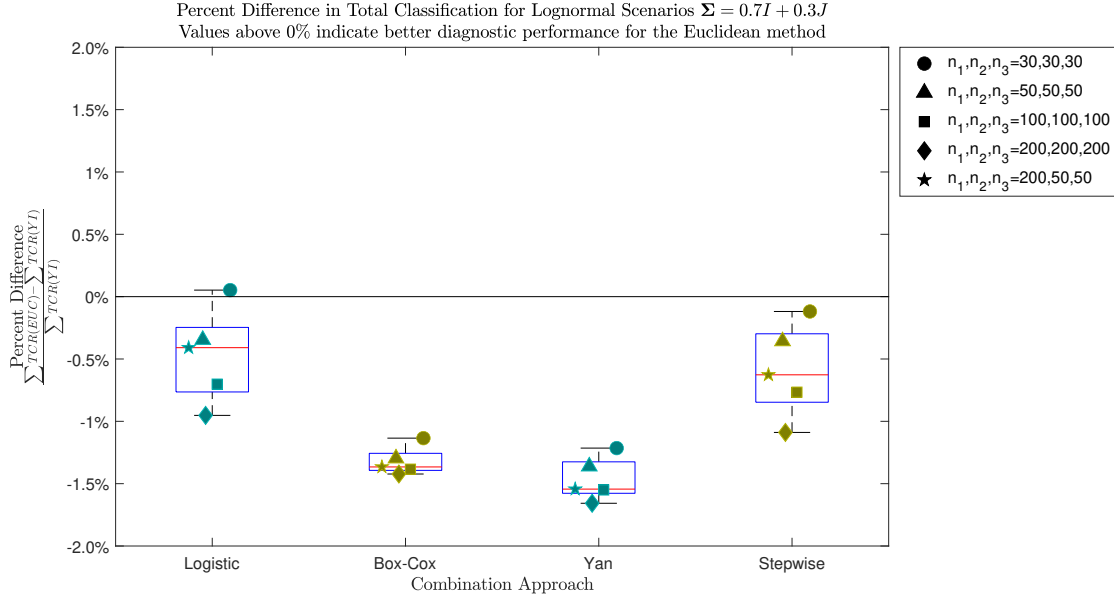
Figure 6: The plot displays the percent difference in $\sum_i \widehat{TCR}_i$, $i = 1, 2, 3$, i.e. total classification, for the Euclidean method (EUC) versus the Youden index (YI) for each of the combination approaches and sample sizes, where the correlation matrix is $\boldsymbol{\Sigma} = 0.7\boldsymbol{I} + 0.3\boldsymbol{J}$. The percent difference is calculated by $\frac{\sum \widehat{TCR}(EUC) - \sum \widehat{TCR}(YI)}{\sum \widehat{TCR}(YI)}$. Values above 0% correspond to a higher total classification for the Euclidean method than the Youden index, indicating better diagnostic performance for the Euclidean method. The Youden index saw higher total classification than the Euclidean method for all scenarios except when the sample size is $(n_1, n_2, n_3) = (30, 30, 30)$, and when using logistic regression to combine the scores. The difference in total classification was less than 2% higher for the Youden index in all scenarios.

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Table C.2

The table provides results for the lognormal scenarios with
$\rho = 0.5I + 0.5J$. The table provides the point estimate and variance for TCR_1, TCR_2, and TCR_3, as well as the $Sum(\widehat{TCRs})$.

| Method	Approach	n_1, n_2, n_3	$Var(\widehat{TCR_1})$	$Var(\widehat{TCR_2})$	$Var(\widehat{TCR_3})$	$\widehat{TCR_1}$	$\widehat{TCR_2}$	$\widehat{TCR_3}$	$Sum(\widehat{TCRs})$
		30,30,30	0.0103	0.0087	0.0131	0.5388	0.4569	0.6679	1.6635
		50,50,50	0.0075	0.0061	0.0090	0.5433	0.4733	0.6584	1.6705
	Logistic	100,100,100	0.0046	0.0037	0.0068	0.5481	0.4782	0.6620	1.6883
		200,200,200	0.0028	0.0024	0.0038	0.5481	0.4849	0.6624	1.6955
		200,50,50	0.0050	0.0052	0.0101	0.5854	0.4479	0.6383	1.6717
		30,30,30	0.0048	0.0028	0.0080	0.5454	0.4635	0.6261	1.6350
		50,50,50	0.0033	0.0016	0.0047	0.5473	0.4737	0.6314	1.6524
	Yan	100,100,100	0.0018	0.0009	0.0027	0.5495	0.4835	0.6415	1.6745
		200,200,200	0.0011	0.0005	0.0015	0.5500	0.4882	0.6476	1.6858
		200,50,50	0.0023	0.0013	0.0047	0.5565	0.4676	0.6342	1.6584
Euclidean									
		30,30,30	0.0026	0.0014	0.0037	0.5495	0.4888	0.6655	1.7038
		50,50,50	0.0018	0.0010	0.0025	0.5500	0.4961	0.6662	1.7124
	Box-Cox	100,100,100	0.0010	0.0006	0.0015	0.5538	0.5004	0.6682	1.7224
		200,200,200	0.0004	0.0002	0.0005	0.5547	0.5030	0.6707	1.7283
		200,50,50	0.0008	0.0004	0.0019	0.5549	0.4977	0.6664	1.7190
		30,30,30	0.0090	0.0081	0.0121	0.5368	0.4339	0.6678	1.6385
		50,50,50	0.0069	0.0063	0.0082	0.5421	0.4471	0.6633	1.6525
	Stepwise	100,100,100	0.0039	0.0035	0.0054	0.5448	0.4639	0.6662	1.6749
		200,200,200	0.0027	0.0023	0.0034	0.5463	0.4749	0.6651	1.6862
		200,50,50	0.0044	0.0047	0.0079	0.5747	0.4283	0.6637	1.6666
		30,30,30	0.0197	0.0237	0.0175	0.5516	0.3318	0.7789	1.6623
		50,50,50	0.0139	0.0200	0.0124	0.5606	0.3443	0.7790	1.6839
	Logistic	100,100,100	0.0098	0.0149	0.0081	0.5726	0.3341	0.7969	1.7035
		200,200,200	0.0067	0.0106	0.0051	0.5818	0.3275	0.8060	1.7152
		200,50,50	0.0091	0.0175	0.0143	0.6242	0.2840	0.7723	1.6804
		30,30,30	0.0206	0.0199	0.0142	0.5605	0.3509	0.7424	1.6538
		50,50,50	0.0140	0.0144	0.0080	0.5732	0.3433	0.7603	1.6768
	Yan	100,100,100	0.0080	0.0093	0.0039	0.5855	0.3348	0.7835	1.7038
		200,200,200	0.0050	0.0053	0.0020	0.5882	0.3327	0.7970	1.7179
		200,50,50	0.0099	0.0096	0.0072	0.5858	0.3406	0.7611	1.6876
Youden									
		30,30,30	0.0096	0.0097	0.0055	0.5643	0.3691	0.7899	1.7233
		50,50,50	0.0057	0.0056	0.0027	0.5680	0.3699	0.7995	1.7373
	Box-Cox	100,100,100	0.0026	0.0029	0.0017	0.5798	0.3633	0.8072	1.7503
		200,200,200	0.0012	0.0014	0.0005	0.5827	0.3623	0.8122	1.7573
		200,50,50	0.0034	0.0038	0.0021	0.5737	0.3705	0.8018	1.7460
		30,30,30	0.0191	0.0195	0.0156	0.5393	0.3354	0.7647	1.6394
		50,50,50	0.0157	0.0164	0.0113	0.5479	0.3466	0.7682	1.6627
	Stepwise	100,100,100	0.0109	0.0126	0.0070	0.5591	0.3409	0.7914	1.6915
		200,200,200	0.0083	0.0094	0.0046	0.5714	0.3346	0.8012	1.7072
		200,50,50	0.0115	0.0139	0.0108	0.5775	0.3249	0.7772	1.6796
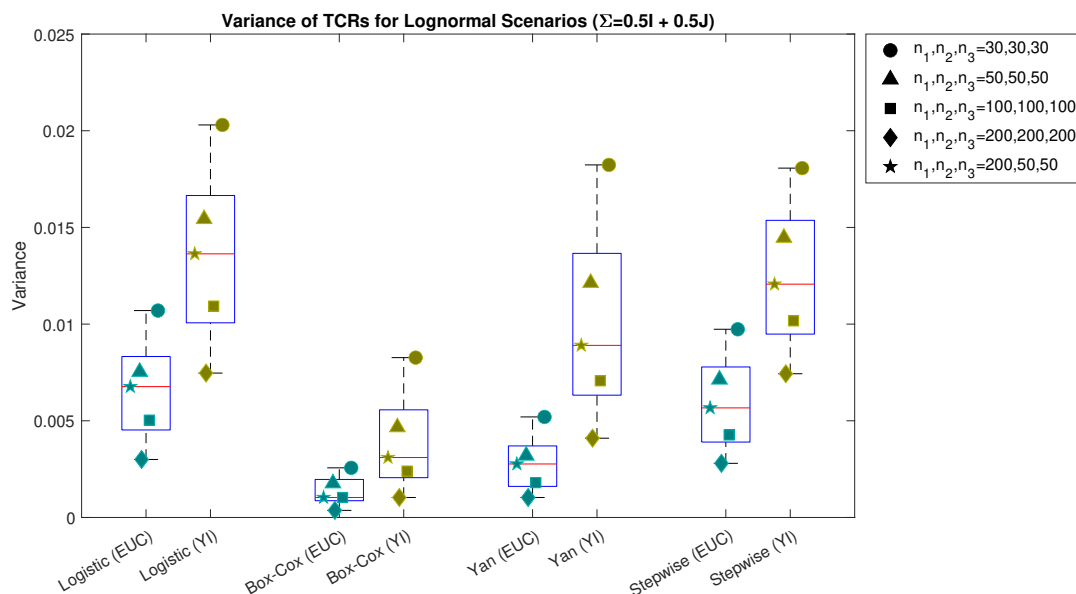
Figure 7: The plot displays the average of the variances of $\widehat{TCR}_1$, $\widehat{TCR}_2$, and $\widehat{TCR}_3$ for each sample size explored. For all explored scenarios, the Euclidean method had smaller variances for the $\widehat{TCR}s$ than the Youden index.
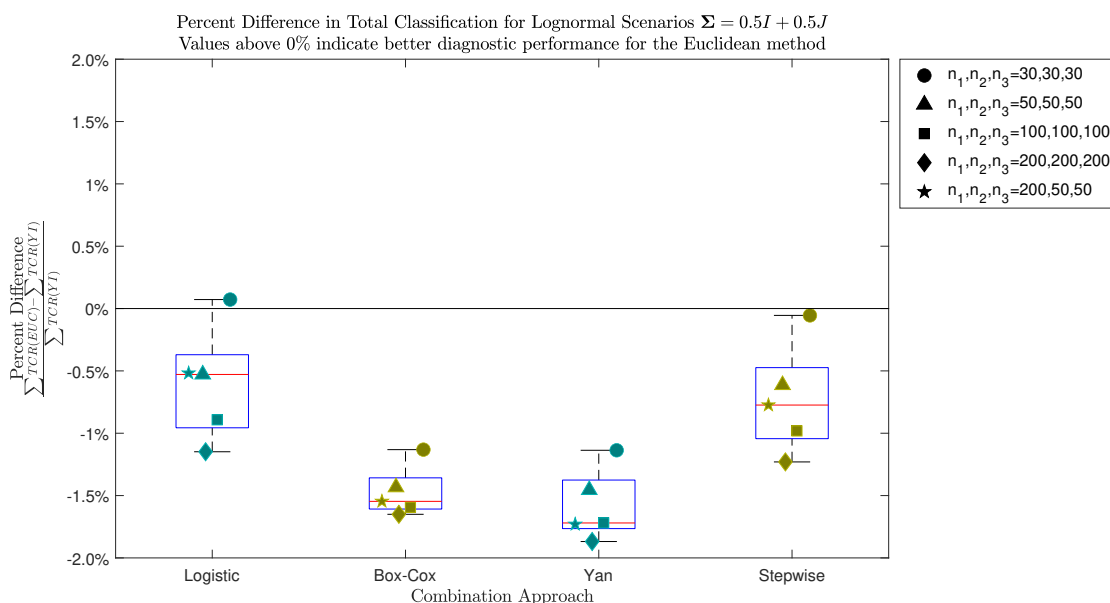

Figure 8: The plot displays the percent difference in $\sum_i TCR_i$, $i = 1, 2, 3$, i.e. total classification, for the Euclidean method (EUC) versus the Youden index (YI) for each of the combination approaches and sample sizes, where $\Sigma = 0.5I + 0.5J$. The percent difference is calculated by $\frac{\Sigma TCR(EUC) - \Sigma TCR(YI)}{\Sigma TCR(YI)}$. Values above 0% correspond to a higher total classification for the Euclidean method than the Youden index, indicating better diagnostic performance for the Euclidean method. The only scenario where the Euclidean method saw higher total classification was when the sample size was 30 for each group and the combination approach used was logistic regression. The difference in total classification was less than 2% for all scenarios.

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Table C.3

The table provides results for the lognormal scenarios with
$\rho = 0.3I + 0.7J$. The table provides the point estimate and variance for TCR_1, TCR_2, and TCR_3, as well as the $Sum(\widehat{TCRs})$.

| Method	Approach	n_1, n_2, n_3	$Var(\widehat{TCR_1})$	$Var(\widehat{TCR_2})$	$Var(\widehat{TCR_3})$	$\widehat{TCR_1}$	$\widehat{TCR_2}$	$\widehat{TCR_3}$	$Sum(\widehat{TCRs})$
		30,30,30	0.0120	0.0084	0.0152	0.5384	0.4463	0.6520	1.6367
		50,50,50	0.0076	0.0062	0.0097	0.5408	0.4653	0.6472	1.6533
	Logistic	100,100,100	0.0047	0.0037	0.0068	0.5481	0.4674	0.6525	1.6681
		200,200,200	0.0030	0.0023	0.0041	0.5461	0.4758	0.6533	1.6752
		200,50,50	0.0092	0.0055	0.0113	0.5921	0.4342	0.6077	1.6340
		30,30,30	0.0057	0.0025	0.0086	0.5462	0.4585	0.6173	1.6220
		50,50,50	0.0038	0.0016	0.0056	0.5494	0.4672	0.6190	1.6357
	Yan	100,100,100	0.0021	0.0008	0.0031	0.5522	0.4749	0.6289	1.6560
		200,200,200	0.0013	0.0005	0.0018	0.5517	0.4790	0.6363	1.6670
		200,50,50	0.0025	0.0012	0.0050	0.5582	0.4623	0.6221	1.6426
Euclidean									
		30,30,30	0.0031	0.0014	0.0044	0.5417	0.4725	0.6529	1.6671
		50,50,50	0.0021	0.0010	0.0029	0.5428	0.4793	0.6530	1.6751
	Box-Cox	100,100,100	0.0014	0.0008	0.0021	0.5456	0.4829	0.6550	1.6834
		200,200,200	0.0004	0.0002	0.0006	0.5470	0.4858	0.6584	1.6912
		200,50,50	0.0009	0.0004	0.0022	0.5469	0.4809	0.6537	1.6816
		30,30,30	0.0101	0.0084	0.0137	0.5389	0.4232	0.6490	1.6111
		50,50,50	0.0073	0.0061	0.0091	0.5407	0.4394	0.6502	1.6303
	Stepwise	100,100,100	0.0048	0.0037	0.0060	0.5485	0.4512	0.6513	1.6510
		200,200,200	0.0031	0.0022	0.0039	0.5496	0.4627	0.6490	1.6612
		200,50,50	0.0051	0.0052	0.0088	0.5714	0.4218	0.6486	1.6417
		30,30,30	0.0209	0.0238	0.0207	0.5535	0.3198	0.7663	1.6396
		50,50,50	0.0146	0.0198	0.0146	0.5632	0.3292	0.7701	1.6626
	Logistic	100,100,100	0.0099	0.0144	0.0090	0.5773	0.3115	0.7956	1.6844
		200,200,200	0.0065	0.0104	0.0055	0.5808	0.3143	0.8024	1.6975
		200,50,50	0.0130	0.0173	0.0177	0.6393	0.2619	0.7455	1.6468
		30,30,30	0.0249	0.0232	0.0197	0.5693	0.3344	0.7347	1.6383
		50,50,50	0.0185	0.0178	0.0103	0.5752	0.3262	0.7618	1.6633
	Yan	100,100,100	0.0097	0.0104	0.0048	0.5908	0.3146	0.7820	1.6874
		200,200,200	0.0059	0.0060	0.0024	0.5928	0.3115	0.7969	1.7013
		200,50,50	0.0107	0.0117	0.0095	0.5937	0.3204	0.7600	1.6741
Youden									
		30,30,30	0.0159	0.0139	0.0079	0.5504	0.3471	0.7878	1.6853
		50,50,50	0.0089	0.0077	0.0040	0.5590	0.3441	0.7980	1.7011
	Box-Cox	100,100,100	0.0040	0.0037	0.0025	0.5724	0.3343	0.8072	1.7139
		200,200,200	0.0016	0.0017	0.0006	0.5771	0.3328	0.8133	1.7231
		200,50,50	0.0054	0.0051	0.0024	0.5641	0.3445	0.8019	1.7105
		30,30,30	0.0232	0.0209	0.0205	0.5375	0.3267	0.7546	1.6187
		50,50,50	0.0184	0.0170	0.0125	0.5472	0.3304	0.7655	1.6432
	Stepwise	100,100,100	0.0137	0.0127	0.0076	0.5548	0.3282	0.7857	1.6687
		200,200,200	0.0103	0.0105	0.0049	0.5665	0.3193	0.7991	1.6850
		200,50,50	0.0145	0.0144	0.0115	0.5741	0.3089	0.7754	1.6584
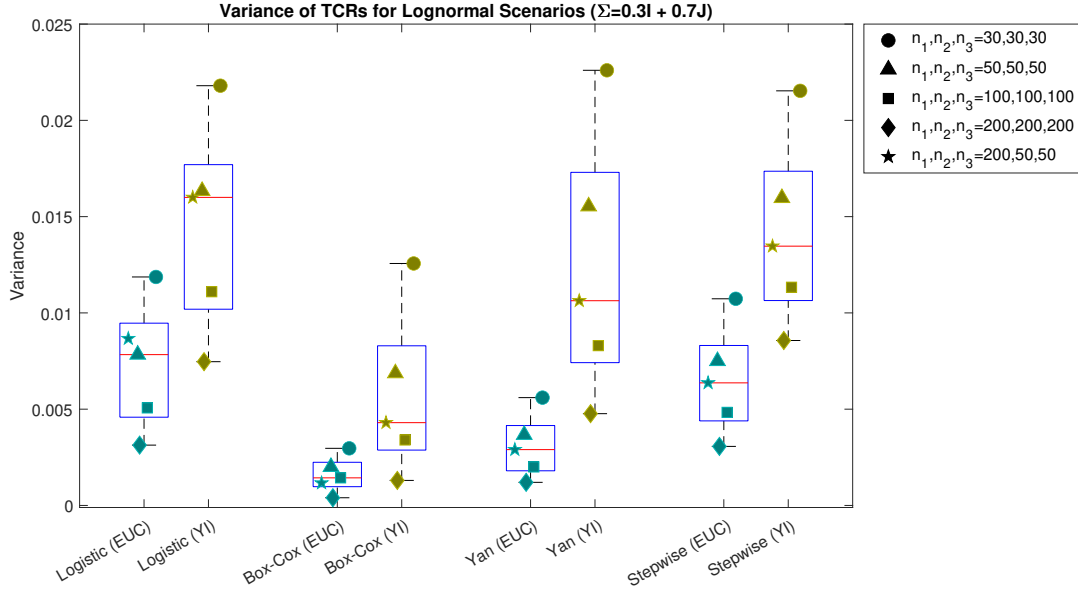
Figure 9: The plot displays the average of the variances of $\widehat{TCR}_1$, $\widehat{TCR}_2$, and $\widehat{TCR}_3$ for each sample size explored. For all explored scenarios, the Euclidean method had smaller variances for the $\widehat{TCR}s$ than the Youden index.
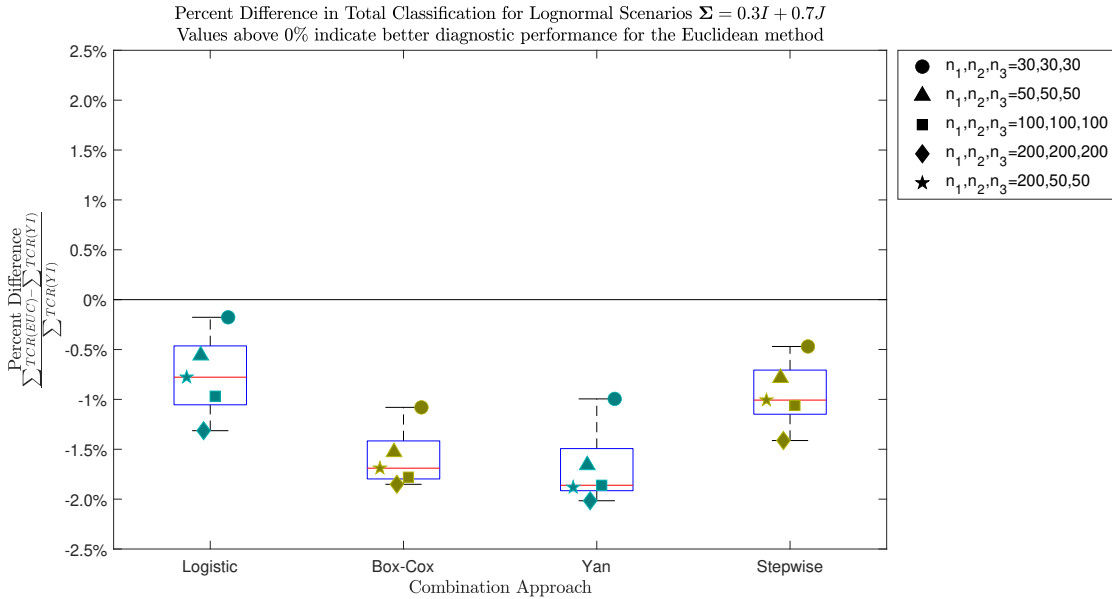

Figure 10: The plot displays the percent difference in $\sum_i TCR_i$, $i = 1, 2, 3$, i.e. total classification, for the Euclidean method (EUC) versus the Youden index (YI) for each of the combination approaches and sample sizes, where $\Sigma = 0.3I + 0.7J$. The percent difference is calculated by $\frac{\Sigma TCR(EUC) - \Sigma TCR(YI)}{\Sigma TCR(YI)}$. Values above 0% correspond to a higher total classification for the Euclidean method than the Youden index, indicating better diagnostic performance for the Euclidean method. The Youden index saw higher total classification for all scenarios, but the difference was an improvement of approximately 2% or less.

Table C.4

The table provides results based on training data for the lognormal scenarios with $\rho = 0.7I + 0.3J$. The table provides the point estimate and variance for TCR_1, TCR_2, and TCR_3, as well as the $Sum(\widehat{TCRs})$.

Method	Approach	n_1, n_2, n_3	$\widehat{TCR_1}$	$\widehat{TCR_2}$	$\widehat{TCR_3}$	$Var(\widehat{TCR_1})$	$Var(\widehat{TCR_2})$	$Var(\widehat{TCR_3})$	$Sum(\widehat{TCRs})$
		30,30,30	0.6258	0.5808	0.7227	0.0103	0.0094	0.0106	1.9294
		50,50,50	0.6060	0.5677	0.7086	0.0075	0.0061	0.0072	1.8823
	Logistic	100,100,100	0.5933	0.5480	0.7011	0.0042	0.0035	0.0047	1.8424
		200,200,200	0.5797	0.5355	0.6944	0.0029	0.0024	0.0031	1.8095
		200,50,50	0.6066	0.5470	0.6988	0.0049	0.0055	0.0079	1.8524
		30,30,30	0.6096	0.5865	0.6815	0.0080	0.0057	0.0070	1.8776
		50,50,50	0.5940	0.5643	0.6799	0.0047	0.0035	0.0044	1.8382
	Yan	100,100,100	0.5841	0.5456	0.6775	0.0022	0.0020	0.0021	1.8072
		200,200,200	0.5772	0.5318	0.6759	0.0013	0.0011	0.0012	1.7849
		200,50,50	0.5801	0.5614	0.6828	0.0023	0.0032	0.0041	1.8243
Euclidean									
		30,30,30	0.5970	0.5482	0.6992	0.0059	0.0074	0.0046	1.8443
		50,50,50	0.5859	0.5422	0.7010	0.0034	0.0049	0.0025	1.8291
	Box-Cox	100,100,100	0.5854	0.5395	0.6966	0.0016	0.0026	0.0013	1.8214
		200,200,200	0.5819	0.5344	0.6942	0.0008	0.0012	0.0006	1.8105
		200,50,50	0.5825	0.5396	0.6999	0.0012	0.0049	0.0025	1.8221
		30,30,30	0.6542	0.6214	0.7541	0.0076	0.0073	0.0077	2.0297
		50,50,50	0.6244	0.5961	0.7375	0.0055	0.0050	0.0055	1.9579
	Stepwise	100,100,100	0.6050	0.5673	0.7206	0.0037	0.0032	0.0036	1.8928
		200,200,200	0.5907	0.5453	0.7062	0.0024	0.0021	0.0026	1.8422
		200,50,50	0.6079	0.5884	0.7367	0.0039	0.0045	0.0055	1.9330
		30,30,30	0.6638	0.4766	0.8451	0.0223	0.0323	0.0121	1.9655
		50,50,50	0.6262	0.4614	0.8287	0.0163	0.0254	0.0097	1.9163
	Logistic	100,100,100	0.6197	0.4260	0.8293	0.0100	0.0172	0.0067	1.8751
		200,200,200	0.6123	0.4020	0.8286	0.0073	0.0118	0.0042	1.8430
		200,50,50	0.6414	0.4190	0.8250	0.0094	0.0226	0.0101	1.8853
		30,30,30	0.6423	0.4747	0.8005	0.0257	0.0372	0.0109	1.9175
		50,50,50	0.6294	0.4440	0.8041	0.0174	0.0239	0.0069	1.8775
	Yan	100,100,100	0.6229	0.4113	0.8107	0.0088	0.0131	0.0032	1.8449
		200,200,200	0.6152	0.3934	0.8131	0.0052	0.0071	0.0017	1.8217
		200,50,50	0.6082	0.4499	0.8040	0.0095	0.0189	0.0065	1.8620
Youden									
		30,30,30	0.6191	0.4401	0.8170	0.0124	0.0194	0.0052	1.8762
		50,50,50	0.6072	0.4290	0.8196	0.0075	0.0120	0.0025	1.8558
	Box-Cox	100,100,100	0.6113	0.4167	0.8212	0.0035	0.0063	0.0011	1.8492
		200,200,200	0.6101	0.4085	0.8212	0.0018	0.0030	0.0006	1.8398
		200,50,50	0.6035	0.4252	0.8213	0.0032	0.0110	0.0024	1.8500
		30,30,30	0.6615	0.5473	0.8500	0.0187	0.0239	0.0105	2.0588
		50,50,50	0.6400	0.5009	0.8469	0.0150	0.0193	0.0073	1.9878
	Stepwise	100,100,100	0.6251	0.4574	0.8401	0.0103	0.0147	0.0050	1.9225
		200,200,200	0.6143	0.4258	0.8338	0.0072	0.0096	0.0034	1.8739
		200,50,50	0.6118	0.5066	0.8461	0.0108	0.0168	0.0074	1.9645

Table C.5

The table provides results based on training data for the lognormal scenarios with $\rho = 0.5I + 0.5J$. The table provides the point estimate and variance for TCR_1, TCR_2, and TCR_3, as well as the $Sum(\widehat{TCRs})$.

Method	Approach	n_1, n_2, n_3	$\widehat{TCR_1}$	$\widehat{TCR_2}$	$\widehat{TCR_3}$	$Var(\widehat{TCR_1})$	$Var(\widehat{TCR_2})$	$Var(\widehat{TCR_3})$	$Sum(\widehat{TCRs})$
		30,30,30	0.6096	0.5616	0.7107	0.0114	0.0093	0.0115	1.8819
		50,50,50	0.5926	0.5469	0.6961	0.0079	0.0066	0.0076	1.8356
	Logistic	100,100,100	0.5803	0.5268	0.6855	0.0046	0.0039	0.0055	1.7926
		200,200,200	0.5667	0.5142	0.6772	0.0029	0.0025	0.0032	1.7582
		200,50,50	0.6020	0.5248	0.6717	0.0052	0.0058	0.0087	1.7985
		30,30,30	0.5983	0.5691	0.6583	0.0084	0.0063	0.0079	1.8258
		50,50,50	0.5825	0.5457	0.6587	0.0053	0.0039	0.0047	1.7869
	Yan	100,100,100	0.5728	0.5266	0.6565	0.0024	0.0021	0.0024	1.7560
		200,200,200	0.5646	0.5120	0.6558	0.0016	0.0012	0.0014	1.7323
		200,50,50	0.5681	0.5450	0.6612	0.0027	0.0034	0.0046	1.7743
Euclidean									
		30,30,30	0.5738	0.5194	0.6778	0.0062	0.0082	0.0050	1.7710
		50,50,50	0.5642	0.5142	0.6800	0.0033	0.0052	0.0027	1.7585
	Box-Cox	100,100,100	0.5616	0.5111	0.6737	0.0017	0.0028	0.0013	1.7464
		200,200,200	0.5591	0.5064	0.6725	0.0009	0.0013	0.0007	1.7380
		200,50,50	0.5601	0.5142	0.6766	0.0013	0.0049	0.0027	1.7508
		30,30,30	0.6387	0.6073	0.7351	0.0083	0.0076	0.0082	1.9811
		50,50,50	0.6178	0.5781	0.7195	0.0063	0.0056	0.0063	1.9154
	Stepwise	100,100,100	0.5935	0.5493	0.7020	0.0036	0.0033	0.0041	1.8447
		200,200,200	0.5788	0.5287	0.6873	0.0026	0.0022	0.0029	1.7948
		200,50,50	0.5977	0.5690	0.7196	0.0043	0.0044	0.0059	1.8863
		30,30,30	0.6336	0.4505	0.8335	0.0230	0.0336	0.0147	1.9176
		50,50,50	0.6181	0.4292	0.8212	0.0150	0.0254	0.0106	1.8686
	Logistic	100,100,100	0.6101	0.3925	0.8247	0.0106	0.0183	0.0069	1.8273
		200,200,200	0.6055	0.3653	0.8227	0.0072	0.0126	0.0046	1.7935
		200,50,50	0.6433	0.3753	0.8152	0.0096	0.0233	0.0124	1.8338
		30,30,30	0.6277	0.4572	0.7856	0.0314	0.0431	0.0153	1.8706
		50,50,50	0.6215	0.4173	0.7930	0.0202	0.0283	0.0082	1.8319
	Yan	100,100,100	0.6160	0.3774	0.8030	0.0104	0.0163	0.0039	1.7963
		200,200,200	0.6087	0.3578	0.8069	0.0065	0.0087	0.0020	1.7735
		200,50,50	0.6011	0.4167	0.7950	0.0116	0.0021	0.0079	1.8127
Youden									
		30,30,30	0.5958	0.4023	0.8107	0.0164	0.0239	0.0072	1.8087
		50,50,50	0.5840	0.3880	0.8138	0.0039	0.0140	0.0027	1.7859
	Box-Cox	100,100,100	0.5898	0.3732	0.8143	0.0040	0.0072	0.0013	1.7773
		200,200,200	0.5884	0.3654	0.8154	0.0021	0.0034	0.0007	1.7692
		200,50,50	0.5794	0.3856	0.8154	0.0043	0.0127	0.0027	1.7805
		30,30,30	0.6507	0.5185	0.8445	0.0219	0.0275	0.0118	2.0137
		50,50,50	0.6292	0.4859	0.8310	0.0170	0.0213	0.0092	1.9462
	Stepwise	100,100,100	0.6133	0.4320	0.8323	0.0116	0.0151	0.0057	1.8776
		200,200,200	0.6081	0.3946	0.8266	0.0088	0.0112	0.0041	1.8294
		200,50,50	0.6035	0.4761	0.8418	0.0121	0.0187	0.0085	1.9214

Table C.6

The table provides results based on training data for the lognormal scenarios with $\rho = 0.3I + 0.7J$. The table provides the point estimate and variance for TCR_1, TCR_2, and TCR_3, as well as the $Sum(\widehat{TCRs})$.

Method	Approach	n_1, n_2, n_3	$\widehat{TCR_1}$	$\widehat{TCR_2}$	$\widehat{TCR_3}$	$Var(\widehat{TCR_1})$	$Var(\widehat{TCR_2})$	$Var(\widehat{TCR_3})$	$Sum(\widehat{TCRs})$
		30,30,30	0.6090	0.5522	0.6976	0.0129	0.0088	0.0135	1.8588
		50,50,50	0.5899	0.5394	0.6861	0.0077	0.0070	0.0079	1.8155
	Logistic	100,100,100	0.5794	0.5154	0.6780	0.0045	0.0043	0.0054	1.7727
		200,200,200	0.5657	0.5049	0.6682	0.0031	0.0025	0.0036	1.7389
		200,50,50	0.6077	0.5130	0.6457	0.0095	0.0062	0.0103	1.7663
		30,30,30	0.5976	0.5580	0.6504	0.0091	0.0066	0.0082	1.8060
		50,50,50	0.5851	0.5359	0.6460	0.0055	0.0043	0.0052	1.7670
	Yan	100,100,100	0.5734	0.5160	0.6444	0.0026	0.0023	0.0026	1.7338
		200,200,200	0.5662	0.5010	0.6441	0.0018	0.0012	0.0016	1.7113
		200,50,50							
Euclidean									
		30,30,30	0.5642	0.5029	0.6660	0.0062	0.0086	0.0053	1.7332
		50,50,50	0.5570	0.4982	0.6679	0.0034	0.0054	0.0029	1.7231
	Box-Cox	100,100,100	0.5539	0.4928	0.6615	0.0017	0.0028	0.0014	1.7082
		200,200,200	0.5512	0.4893	0.6604	0.0009	0.0014	0.0007	1.7010
		200,50,50	0.5519	0.4968	0.6655	0.0013	0.0050	0.0028	1.7141
		30,30,30	0.6379	0.5959	0.7211	0.0093	0.0077	0.0097	1.9549
		50,50,50	0.6158	0.5680	0.7063	0.0065	0.0057	0.0067	1.8901
	Stepwise	100,100,100	0.5957	0.5356	0.6882	0.0044	0.0035	0.0046	1.8196
		200,200,200	0.5814	0.5168	0.6720	0.0030	0.0022	0.0032	1.7702
		200,50,50	0.5940	0.5605	0.7067	0.0047	0.0050	0.0065	1.8613
		30,30,30	0.6337	0.4382	0.8228	0.0241	0.0338	0.0175	1.8947
		50,50,50	0.6210	0.4154	0.8138	0.0153	0.0264	0.0123	1.8502
	Logistic	100,100,100	0.6149	0.3697	0.8240	0.0103	0.0178	0.0077	1.8085
		200,200,200	0.6049	0.3517	0.8196	0.0068	0.0122	0.0050	1.7762
		200,50,50	0.6574	0.3560	0.7903	0.0137	0.0239	0.0155	1.8036
		30,30,30	0.6372	0.4314	0.7788	0.0358	0.0483	0.0199	1.8474
		50,50,50	0.6236	0.3926	0.7949	0.0243	0.0326	0.0098	1.8111
	Yan	100,100,100	0.6217	0.3541	0.8014	0.0123	0.0181	0.0047	1.7771
		200,200,200	0.6128	0.3350	0.8070	0.0072	0.0095	0.0022	1.7547
		200,50,50	0.6096	0.3913	0.7935	0.0121	0.0259	0.0096	1.7945
Youden									
		30,30,30	0.5843	0.3843	0.8099	0.0216	0.0299	0.0092	1.7785
		50,50,50	0.5776	0.3629	0.8141	0.0114	0.0168	0.0039	1.7546
	Box-Cox	100,100,100	0.5825	0.3445	0.8158	0.0049	0.0079	0.0014	1.7428
		200,200,200	0.5826	0.3364	0.8171	0.0025	0.0037	0.0007	1.7361
		200,50,50	0.5704	0.3604	0.8177	0.0062	0.0142	0.0027	1.7485
		30,30,30	0.6459	0.5085	0.8364	0.0267	0.0285	0.0154	1.9908
		50,50,50	0.6275	0.4675	0.8286	0.0193	0.0218	0.0100	1.9236
	Stepwise	100,100,100	0.6077	0.4183	0.8272	0.0143	0.0156	0.0063	1.8532
		200,200,200	0.6036	0.3786	0.8246	0.0109	0.0124	0.0044	1.8068
		200,50,50	0.5995	0.4591	0.8391	0.0151	0.0197	0.0095	1.8976

Table C.7

The table provides results for the gamma scenarios with
$\rho = 0.7I + 0.3J$. The table provides the point estimate and variance for TCR_1, TCR_2, and TCR_3, as well as the $Sum(\widehat{TCRs})$.

| Method	Approach	n_1, n_2, n_3	$Var(\widehat{TCR_1})$	$Var(\widehat{TCR_2})$	$Var(\widehat{TCR_3})$	$\widehat{TCR_1}$	$\widehat{TCR_2}$	$\widehat{TCR_3}$	$Sum(\widehat{TCRs})$
		30,30,30	0.0077	0.0067	0.0046	0.7020	0.6219	0.7643	2.0883
		50,50,50	0.0056	0.0044	0.0032	0.7072	0.6382	0.7570	2.1024
	Logistic	100,100,100	0.0035	0.0026	0.0018	0.7116	0.6431	0.7601	2.1148
		200,200,200	0.0020	0.0015	0.0012	0.7108	0.6536	0.7564	2.1208
		200,50,50	0.0038	0.0037	0.0032	0.7417	0.6325	0.7445	2.1187
		30,30,30	0.0035	0.0033	0.0036	0.7366	0.6319	0.7151	2.0836
		50,50,50	0.0019	0.0019	0.0019	0.7397	0.6484	0.7169	2.1050
	Yan	100,100,100	0.0010	0.0009	0.0011	0.7413	0.6572	0.7226	2.1211
		200,200,200	0.0006	0.0004	0.0006	0.7392	0.6633	0.7262	2.1287
		200,50,50	0.0011	0.0013	0.0020	0.7450	0.6464	0.7194	2.1109
Euclidean									
		30,30,30	0.0025	0.0017	0.0023	0.7064	0.6316	0.7207	2.0588
		50,50,50	0.0015	0.0009	0.0012	0.7091	0.6416	0.7187	2.0694
	Box-Cox	100,100,100	0.0007	0.0004	0.0006	0.7117	0.6469	0.7204	2.0790
		200,200,200	0.0004	0.0002	0.0003	0.7127	0.6494	0.7210	2.0830
		200,50,50	0.0007	0.0006	0.0012	0.7129	0.6421	0.7189	2.0739
		30,30,30	0.0076	0.0071	0.0063	0.7080	0.6057	0.7421	2.0558
		50,50,50	0.0048	0.0040	0.0033	0.7172	0.6291	0.7391	2.0855
	Stepwise	100,100,100	0.0027	0.0025	0.0024	0.7211	0.6442	0.7412	2.1065
		200,200,200	0.0019	0.0014	0.0014	0.7207	0.6567	0.7406	2.1180
		200,50,50	0.0031	0.0040	0.0038	0.7420	0.6157	0.7388	2.0965
		30,30,30	0.0156	0.0176	0.0051	0.7012	0.5618	0.8052	2.0682
		50,50,50	0.0115	0.0129	0.0037	0.7246	0.5698	0.7973	2.0917
	Logistic	100,100,100	0.0065	0.0084	0.0023	0.7374	0.5706	0.8022	2.1103
		200,200,200	0.0044	0.0058	0.0017	0.7441	0.5778	0.7982	2.1202
		200,50,50	0.0065	0.0108	0.0044	0.7711	0.5540	0.7818	2.1068
		30,30,30	0.0053	0.0068	0.0052	0.7891	0.5553	0.7323	2.0767
		50,50,50	0.0034	0.0048	0.0029	0.7963	0.5674	0.7387	2.1024
	Yan	100,100,100	0.0019	0.0026	0.0017	0.7989	0.5746	0.7493	2.1229
		200,200,200	0.0012	0.0015	0.0009	0.7958	0.5830	0.7545	2.1333
		200,50,50	0.0019	0.0029	0.0030	0.8003	0.5674	0.7434	2.1111
Youden									
		30,30,30	0.0033	0.0028	0.0028	0.7442	0.5642	0.7545	2.0630
		50,50,50	0.0018	0.0016	0.0015	0.7514	0.5678	0.7567	2.0759
	Box-Cox	100,100,100	0.0009	0.0008	0.0007	0.7579	0.5691	0.7596	2.0865
		200,200,200	0.0004	0.0004	0.0004	0.7603	0.5701	0.7606	2.0911
		200,50,50	0.0010	0.0010	0.0014	0.7551	0.5692	0.7565	2.0808
		30,30,30	0.0133	0.0164	0.0096	0.7256	0.5479	0.7621	2.0355
		50,50,50	0.0096	0.0111	0.0059	0.7401	0.5681	0.7628	2.0710
	Stepwise	100,100,100	0.0055	0.0076	0.0039	0.7575	0.5712	0.7722	2.1009
		200,200,200	0.0040	0.0051	0.0022	0.7607	0.5835	0.7733	2.1175
		200,50,50	0.0066	0.0096	0.0060	0.7676	0.5483	0.7691	2.0850
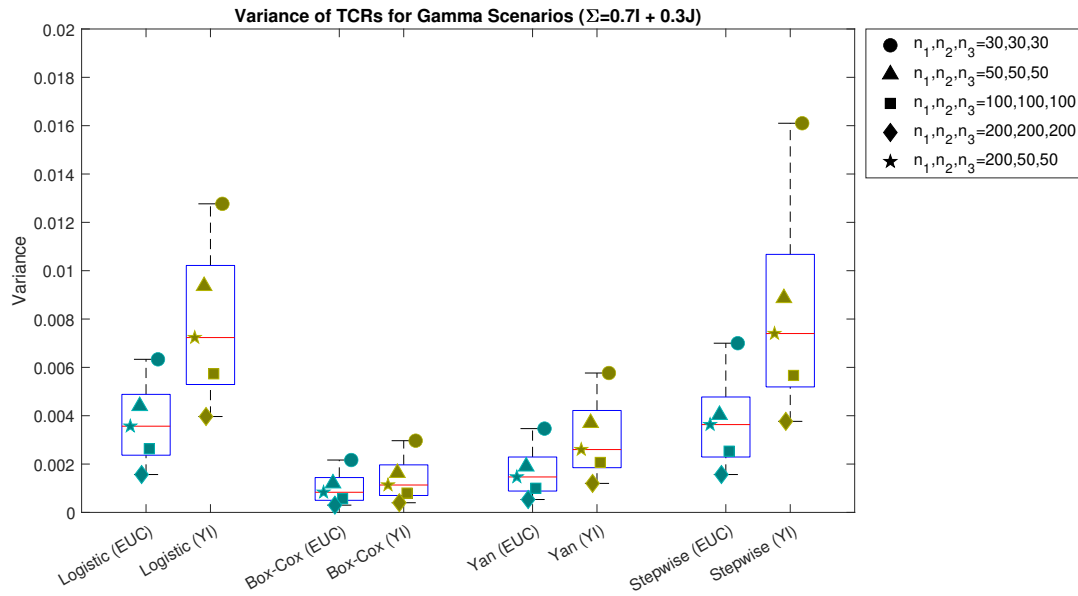
Figure 11: The plot displays the average of the variances of $\widehat{TCR}_1$, $\widehat{TCR}_2$, and $\widehat{TCR}_3$ for each sample size explored. For all explored scenarios, the Euclidean method had smaller variances for the $\widehat{TCR}s$ than the Youden index.
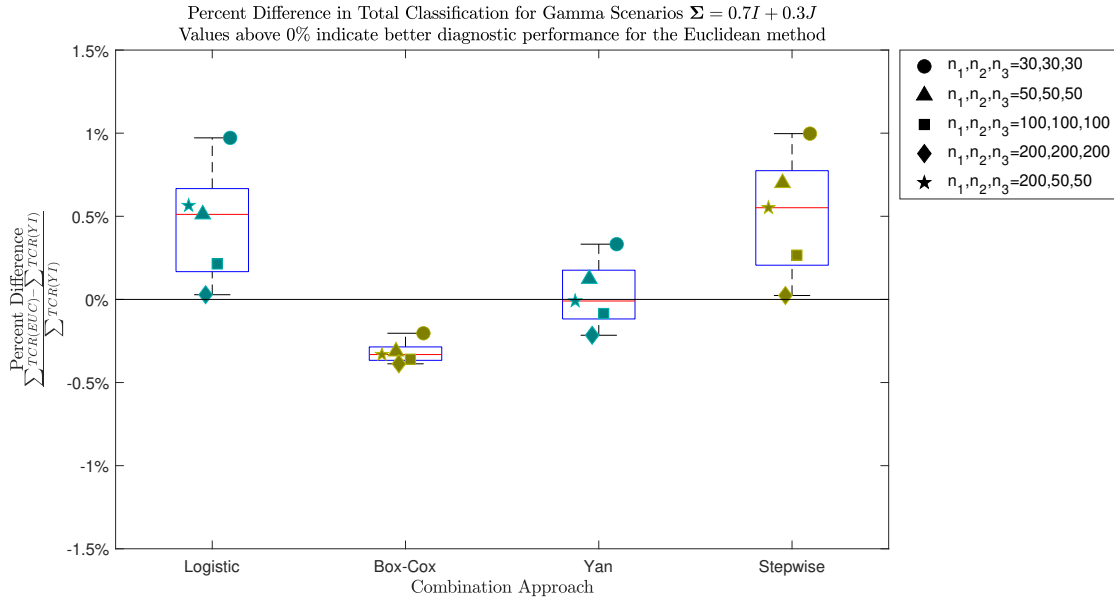
Figure 12: The plot displays the percent difference in $\sum_i TCR_i$, $i = 1, 2, 3$, i.e. total classification, for the Euclidean method (EUC) versus the Youden index (YI) for each of the combination approaches and sample sizes, where $\boldsymbol{\Sigma} = 0.7\boldsymbol{I} + 0.3\boldsymbol{J}$. The percent difference is calculated by $\frac{\sum TCR(EUC) - \sum TCR(YI)}{\sum TCR(YI)}$. Values above 0% correspond to a higher total classification for the Euclidean method than the Youden index, indicating better diagnostic performance for the Euclidean method. Both the logistic regression approach and the stepwise procedure saw higher total classification for the Euclidean method for all scenarios. Yan's method saw higher total classification when the sample size was 30 for each group, and when it was 50 for each group. The Box-Cox approach saw less than a 0.5% difference in total classification between the methods.

Table C.8

The table provides results for the gamma scenarios with
$\rho = 0.5I + 0.5J$. The table provides the point estimate and variance for TCR_1, TCR_2, and TCR_3, as well as the $Sum(\widehat{TCRs})$.

| Method	Approach	n_1, n_2, n_3	$Var(\widehat{TCR_1})$	$Var(\widehat{TCR_2})$	$Var(\widehat{TCR_3})$	$\widehat{TCR_1}$	$\widehat{TCR_2}$	$\widehat{TCR_3}$	$Sum(\widehat{TCRs})$
		30,30,30	0.0093	0.0078	0.0054	0.6667	0.5865	0.7399	1.9932
		50,50,50	0.0068	0.0053	0.0031	0.6733	0.6024	0.7349	2.0106
	Logistic	100,100,100	0.0040	0.0031	0.0024	0.6739	0.6114	0.7337	2.0190
		200,200,200	0.0025	0.0018	0.0015	0.6751	0.6183	0.7330	2.0264
		200,50,50	0.0028	0.0040	0.0031	0.7053	0.6101	0.7202	2.0356
		30,30,30	0.0037	0.0037	0.0043	0.7199	0.5993	0.6781	1.9973
		50,50,50	0.0022	0.0021	0.0022	0.7231	0.6166	0.6788	2.0184
	Yan	100,100,100	0.0011	0.0010	0.0013	0.7235	0.6277	0.6858	2.0369
		200,200,200	0.0006	0.0005	0.0007	0.7201	0.6344	0.6905	2.0450
		200,50,50	0.0011	0.0014	0.0023	0.7273	0.6167	0.6822	2.0262
Euclidean									
		30,30,30	0.0029	0.0016	0.0027	0.6836	0.6032	0.6921	1.9790
		50,50,50	0.0017	0.0009	0.0014	0.6866	0.6136	0.6891	1.9894
	Box-Cox	100,100,100	0.0008	0.0005	0.0007	0.6891	0.6184	0.6908	1.9984
		200,200,200	0.0004	0.0002	0.0004	0.6900	0.6208	0.6916	2.0023
		200,50,50	0.0009	0.0007	0.0013	0.6898	0.6135	0.6898	1.9931
		30,30,30	0.0081	0.0080	0.0076	0.6862	0.5799	0.7106	1.9767
		50,50,50	0.0056	0.0050	0.0043	0.6950	0.6025	0.7060	2.0035
	Stepwise	100,100,100	0.0034	0.0029	0.0029	0.7020	0.6181	0.7065	2.0266
		200,200,200	0.0020	0.0017	0.0017	0.7044	0.6275	0.7056	2.0375
		200,50,50	0.0034	0.0041	0.0046	0.7223	0.5882	0.7041	2.0146
		30,30,30	0.0201	0.0215	0.0060	0.6730	0.5133	0.7876	1.9740
		50,50,50	0.0153	0.0169	0.0039	0.6893	0.5283	0.7808	1.9984
	Logistic	100,100,100	0.0089	0.0110	0.0031	0.7016	0.5301	0.7830	2.0147
		200,200,200	0.0062	0.0079	0.0020	0.7138	0.5322	0.7799	2.0260
		200,50,50	0.0079	0.0126	0.0055	0.7491	0.5239	0.7487	2.0216
		30,30,30	0.0057	0.0086	0.0071	0.7804	0.5171	0.6914	1.9889
		50,50,50	0.0042	0.0060	0.0038	0.7835	0.5302	0.6992	2.0129
	Yan	100,100,100	0.0022	0.0031	0.0023	0.7860	0.5417	0.7078	2.0355
		200,200,200	0.0014	0.0017	0.0013	0.7806	0.5510	0.7156	2.0472
		200,50,50	0.0022	0.0035	0.0040	0.7888	0.5337	0.7012	2.0237
Youden									
		30,30,30	0.0045	0.0040	0.0046	0.7256	0.5291	0.7262	1.9809
		50,50,50	0.0025	0.0024	0.0024	0.7341	0.5325	0.7286	1.9952
	Box-Cox	100,100,100	0.0011	0.0011	0.0011	0.7414	0.5321	0.7324	2.0058
		200,200,200	0.0006	0.0006	0.0006	0.7436	0.5332	0.7337	2.0105
		200,50,50	0.0013	0.0016	0.0021	0.7373	0.5335	0.7289	1.9997
		30,30,30	0.0150	0.0201	0.0124	0.7154	0.5096	0.7326	1.9576
		50,50,50	0.0122	0.0149	0.0080	0.7274	0.5295	0.7336	1.9904
	Stepwise	100,100,100	0.0072	0.0103	0.0056	0.7435	0.5390	0.7358	2.0183
		200,200,200	0.0044	0.0061	0.0031	0.7474	0.5470	0.7417	2.0361
		200,50,50	0.0071	0.0121	0.0074	0.7531	0.5214	0.7312	2.0057
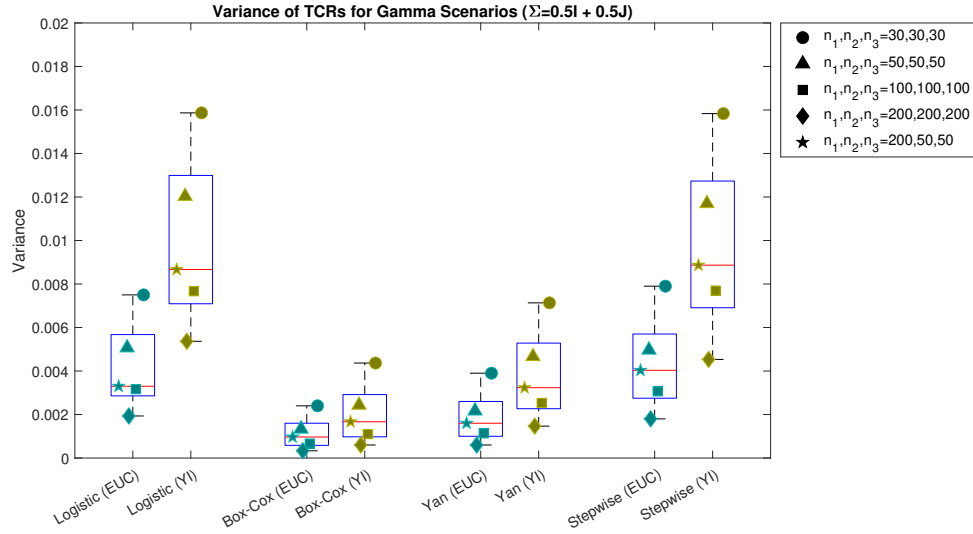
Figure 13: The plot displays the average of the variances of $\widehat{TCR_1}$, $\widehat{TCR_2}$, and $\widehat{TCR_3}$ for each sample size explored. For all explored scenarios, the Euclidean method had smaller variances for the $\widehat{TCRs}$ than the Youden index.
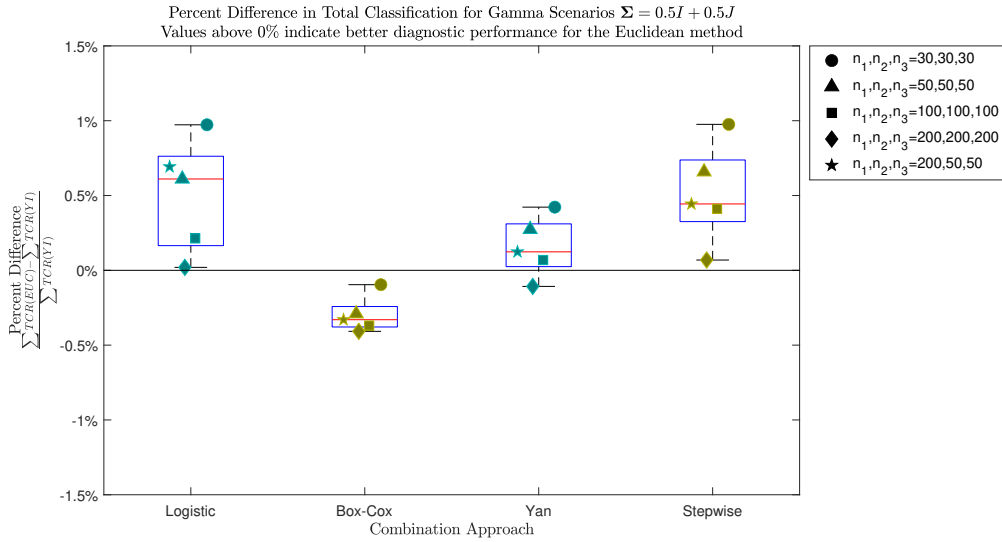

Figure 14: The plot displays the percent difference in $\sum_i TCR_i$, $i = 1, 2, 3$, i.e. total classification, for the Euclidean method (EUC) versus the Youden index (YI) for each of the combination approaches and sample sizes, where $\Sigma = 0.5I + 0.5J$. The percent difference is calculated by $\frac{\Sigma TCR(EUC) - \Sigma TCR(YI)}{\Sigma TCR(YI)}$. Values above 0% correspond to a higher total classification for the Euclidean method than the Youden index, indicating better diagnostic performance for the Euclidean method. For logistic regression and the stepwise procedure, the Euclidean method found higher total classification than the Youden index for all scenarios. For Yan's method, the Youden had lower total classification than the Euclidean method for all sample sizes except when the sample size was 200 for each group. For the Box-Cox approach, the Youden index had higher total classification for all scenarios, but its performance was poor since the data could not be adequately transformed to normality.

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Table C.9

The table provides results for the gamma scenarios with

$\rho = 0.3I + 0.7J$. The table provides the point estimate and variance for TCR_1, TCR_2, and TCR_3, as well as the $Sum(\widehat{TCRs})$.

| Method	Approach	n_1, n_2, n_3	$Var(\widehat{TCR}_1)$	$Var(\widehat{TCR}_2)$	$Var(\widehat{TCR}_3)$	$\widehat{TCR}_1$	$\widehat{TCR}_2$	$\widehat{TCR}_3$	$Sum(\widehat{TCRs})$
		30,30,30	0.0108	0.0092	0.0054	0.6466	0.5629	0.7365	1.9460
		50,50,50	0.0077	0.0059	0.0036	0.6484	0.5822	0.7306	1.9613
	Logistic	100,100,100	0.0044	0.0036	0.0026	0.6530	0.5864	0.7294	1.9687
		200,200,200	0.0032	0.0023	0.0017	0.6498	0.5958	0.7287	1.9744
		200,50,50	0.0048	0.0040	0.0039	0.7063	0.5944	0.7001	2.0009
		30,30,30	0.0036	0.0038	0.0045	0.7210	0.5913	0.6607	1.9730
		50,50,50	0.0021	0.0021	0.0024	0.7225	0.6080	0.6604	1.9909
	Yan	100,100,100	0.0012	0.0010	0.0014	0.7219	0.6193	0.6657	2.0069
		200,200,200	0.0007	0.0005	0.0008	0.7165	0.6267	0.6722	2.0154
		200,50,50	0.0011	0.0015	0.0023	0.7259	0.6084	0.6633	1.9975
Euclidean									
		30,30,30	0.0033	0.0016	0.0031	0.6778	0.5945	0.6825	1.9548
		50,50,50	0.0020	0.0009	0.0017	0.6815	0.6052	0.6786	1.9653
	Box-Cox	100,100,100	0.0009	0.0005	0.0009	0.6835	0.6096	0.6804	1.9735
		200,200,200	0.0005	0.0002	0.0004	0.6842	0.6120	0.6812	1.9775
		200,50,50	0.0010	0.0007	0.0015	0.6838	0.6045	0.6798	1.9681
		30,30,30	0.0089	0.0087	0.0088	0.6819	0.5658	0.6937	1.9414
		50,50,50	0.0057	0.0055	0.0054	0.6896	0.5932	0.6846	1.9673
	Stepwise	100,100,100	0.0037	0.0032	0.0034	0.6970	0.6068	0.6857	1.9895
		200,200,200	0.0022	0.0018	0.0022	0.6974	0.6175	0.6869	2.0019
		200,50,50	0.0034	0.0049	0.0054	0.7172	0.5763	0.6845	1.9779
		30,30,30	0.0233	0.0249	0.0059	0.6565	0.4818	0.7909	1.9292
		50,50,50	0.0176	0.0199	0.0044	0.6678	0.4988	0.7843	1.9509
	Logistic	100,100,100	0.0115	0.0144	0.0032	0.6841	0.4958	0.7857	1.9655
		200,200,200	0.0089	0.0103	0.0020	0.6912	0.5006	0.7838	1.9756
		200,50,50	0.0089	0.0139	0.0061	0.7391	0.5111	0.7377	1.9880
		30,30,30	0.0054	0.0097	0.0094	0.7831	0.5128	0.6645	1.9604
		50,50,50	0.0039	0.0060	0.0049	0.7843	0.5266	0.6731	1.9840
	Yan	100,100,100	0.0023	0.0034	0.0030	0.7858	0.5358	0.6822	2.0038
		200,200,200	0.0015	0.0019	0.0016	0.7760	0.5472	0.6925	2.0157
		200,50,50	0.0020	0.0038	0.0047	0.7873	0.5299	0.6762	1.9934
Youden									
		30,30,30	0.0062	0.0053	0.0072	0.7202	0.5185	0.7164	1.9551
		50,50,50	0.0036	0.0035	0.0040	0.7303	0.5221	0.7173	1.9697
	Box-Cox	100,100,100	0.0013	0.0014	0.0017	0.7375	0.5197	0.7236	1.9808
		200,200,200	0.0007	0.0007	0.0008	0.7391	0.5214	0.7251	1.9856
		200,50,50	0.0016	0.0021	0.0030	0.7327	0.5220	0.7197	1.9744
		30,30,30	0.0175	0.0239	0.0162	0.7112	0.4910	0.7150	1.9171
		50,50,50	0.0131	0.0186	0.0118	0.7246	0.5112	0.7144	1.9502
	Stepwise	100,100,100	0.0081	0.0119	0.0074	0.7354	0.5293	0.7150	1.9797
		200,200,200	0.0051	0.0073	0.0048	0.7377	0.5394	0.7194	1.9965
		200,50,50	0.0079	0.0150	0.0107	0.7480	0.5038	0.7134	1.9652
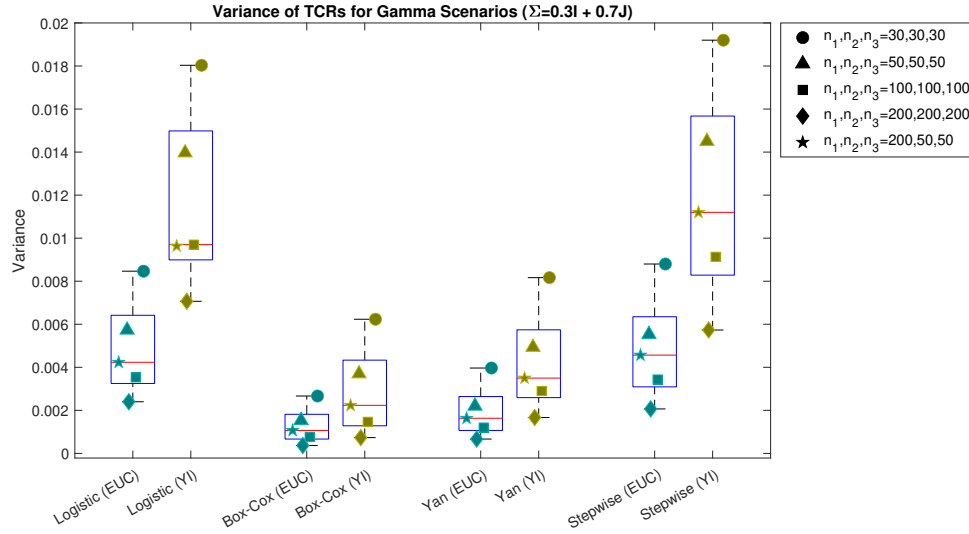
Figure 15: The plot displays the average of the variances of $\widehat{TCR_1}$, $\widehat{TCR_2}$, and $\widehat{TCR_3}$ for each sample size explored. For all explored scenarios, the Euclidean method had smaller variances for the $\widehat{TCRs}$ than the Youden index.
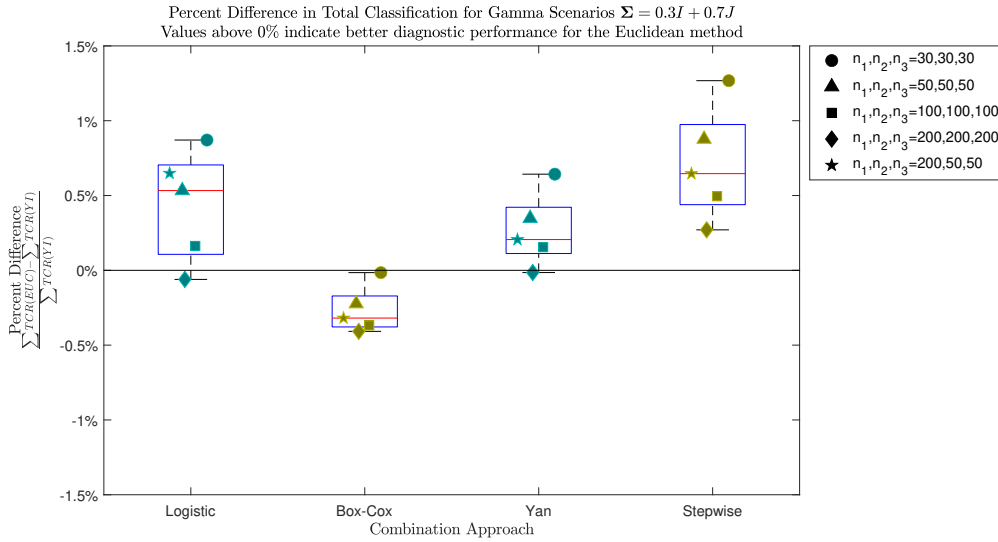

Figure 16: The plot displays the percent difference in $\sum_i TCR_i$, $i = 1, 2, 3$, i.e. total classification, for the Euclidean method (EUC) versus the Youden index (YI) for each of the combination approaches and sample sizes, where $\Sigma = 0.3I + 0.7J$. The percent difference is calculated by $\frac{\Sigma TCR(EUC) - \Sigma TCR(YI)}{\Sigma TCR(YI)}$. Values above 0% correspond to a higher total classification for the Euclidean method than the Youden index, indicating better diagnostic performance for the Euclidean method. For the stepwise procedure, the Euclidean method saw higher total classification than the Youden index for all scenarios. For logistic regression and Yan's method, the Youden index had lower total classification than the Euclidean method for all scenarios except when the sample size was 200 for each group. For the Box-Cox approach, the Youden index saw higher total classification for all scenarios, but its performance was poor since the data could not adequately be transformed to normality.

Table C.10

The table provides results based on training data for the gamma scenarios with $\rho = 0.7I + 0.3J$. The table provides the point estimate and variance for TCR_1, TCR_2, and TCR_3, as well as the $Sum(\widehat{TCRs})$.

Method	Approach	n_1, n_2, n_3	$\widehat{TCR}_1$	$\widehat{TCR}_2$	$\widehat{TCR}_3$	$Var(\widehat{TCR}_1)$	$Var(\widehat{TCR}_2)$	$Var(\widehat{TCR}_3)$	$Sum(\widehat{TCRs})$
		30,30,30	0.7563	0.7167	0.7971	0.0067	0.0059	0.0050	2.2701
		50,50,50	0.7472	0.7036	0.7864	0.0054	0.0043	0.0037	2.2372
	Logistic	100,100,100	0.7376	0.6857	0.7760	0.0030	0.0026	0.0021	2.1993
		200,200,200	0.7279	0.6788	0.7669	0.0019	0.0015	0.0014	2.1736
		200,50,50	0.7554	0.7037	0.7713	0.0034	0.0035	0.0036	2.2304
		30,30,30	0.7782	0.7003	0.7329	0.0030	0.0050	0.0054	2.2113
		50,50,50	0.7684	0.6903	0.7336	0.0019	0.0034	0.0032	2.1923
	Yan	100,100,100	0.7581	0.6800	0.7283	0.0011	0.0017	0.0017	2.1665
		200,200,200	0.7504	0.6754	0.7288	0.0006	0.0008	0.0008	2.1546
		200,50,50	0.7553	0.6892	0.7330	0.0011	0.0028	0.0031	2.1775
Euclidean									
		30,30,30	0.7193	0.6658	0.7312	0.0045	0.0059	0.0041	2.1163
		50,50,50	0.7161	0.6587	0.7298	0.0025	0.0040	0.0023	2.1045
	Box-Cox	100,100,100	0.7164	0.6549	0.7241	0.0013	0.0019	0.0013	2.0953
		200,200,200	0.7164	0.6526	0.7218	0.0006	0.0010	0.0006	2.0907
		200,50,50	0.7168	0.6578	0.7266	0.0010	0.0035	0.0027	2.1012
		30,30,30	0.7855	0.7463	0.7994	0.0048	0.0049	0.0046	2.3312
		50,50,50	0.7731	0.7265	0.7865	0.0034	0.0033	0.0032	2.2861
	Stepwise	100,100,100	0.7575	0.7065	0.7690	0.0022	0.0023	0.0023	2.2330
		200,200,200	0.7459	0.6955	0.7577	0.0015	0.0013	0.0013	2.1990
		200,50,50	0.7613	0.7217	0.7854	0.0026	0.0027	0.0031	2.2684
		30,30,30	0.7703	0.6712	0.8476	0.0142	0.0204	0.0063	2.2891
		50,50,50	0.7729	0.6487	0.8324	0.0109	0.0150	0.0049	2.2541
	Logistic	100,100,100	0.7682	0.6226	0.8225	0.0066	0.0096	0.0028	2.2132
		200,200,200	0.7647	0.6097	0.8120	0.0044	0.0063	0.0021	2.1864
		200,50,50	0.7873	0.6420	0.8147	0.0064	0.0117	0.0056	2.2440
		30,30,30	0.8442	0.6337	0.7511	0.0067	0.0129	0.0086	2.2289
		50,50,50	0.8338	0.6154	0.7567	0.0042	0.0091	0.0051	2.2059
	Yan	100,100,100	0.8227	0.6019	0.7553	0.0024	0.0050	0.0027	2.1798
		200,200,200	0.8095	0.5974	0.7570	0.0015	0.0026	0.0013	2.1638
		200,50,50	0.8136	0.6205	0.7583	0.0021	0.0068	0.0050	2.1925
Youden									
		30,30,30	0.7594	0.5974	0.7671	0.0065	0.0125	0.0062	2.1239
		50,50,50	0.7607	0.5861	0.7704	0.0037	0.0083	0.0032	2.1172
	Box-Cox	100,100,100	0.7635	0.5791	0.7636	0.0016	0.0039	0.0017	2.1062
		200,200,200	0.7643	0.5747	0.7622	0.0009	0.0020	0.0009	2.1012
		200,50,50	0.7595	0.5859	0.7661	0.0014	0.0072	0.0038	2.1115
		30,30,30	0.8097	0.7000	0.8301	0.0111	0.0163	0.0090	2.3398
		50,50,50	0.8032	0.6761	0.8169	0.0087	0.0120	0.0065	2.2963
	Stepwise	100,100,100	0.7975	0.6405	0.8060	0.0052	0.0085	0.0039	2.2439
		200,200,200	0.7884	0.6270	0.7937	0.0037	0.0053	0.0024	2.2091
		200,50,50	0.7880	0.6687	0.8828	0.0062	0.0010	0.0059	2.2796

Table C.11

The table provides results based on training data for the gamma scenarios with $\rho = 0.5I + 0.5J$. The table provides the point estimate and variance for TCR_1, TCR_2, and TCR_3, as well as the $Sum(\widehat{TCRs})$.

Method	Approach	n_1, n_2, n_3	$\widehat{TCR_1}$	$\widehat{TCR_2}$	$\widehat{TCR_3}$	$Var(\widehat{TCR_1})$	$Var(\widehat{TCR_2})$	$Var(\widehat{TCR_3})$	$Sum(\widehat{TCRs})$
		30,30,30	0.7230	0.6828	0.7751	0.0081	0.0071	0.0058	2.1810
		50,50,50	0.7151	0.6691	0.7668	0.0062	0.0050	0.0037	2.1510
	Logistic	100,100,100	0.6999	0.6557	0.7511	0.0036	0.0030	0.0028	2.1068
		200,200,200	0.6925	0.6448	0.7444	0.0025	0.0018	0.0016	2.0817
		200,50,50	0.7180	0.6880	0.7580	0.0021	0.0022	0.0027	2.1640
		30,30,30	0.7632	0.6728	0.6963	0.0034	0.0059	0.0060	2.1323
		50,50,50	0.7549	0.6613	0.6964	0.0023	0.0037	0.0034	2.1125
	Yan	100,100,100	0.7405	0.6510	0.6926	0.0012	0.0019	0.0018	2.0842
		200,200,200	0.7310	0.6465	0.6928	0.0007	0.0009	0.0009	2.0704
		200,50,50	0.7381	0.6607	0.6985	0.0011	0.0031	0.0034	2.0974
Euclidean									
		30,30,30	0.6991	0.6354	0.7020	0.0047	0.0069	0.0046	2.0365
		50,50,50	0.6943	0.6314	0.6999	0.0028	0.0042	0.0027	2.0257
	Box-Cox	100,100,100	0.6943	0.6257	0.6938	0.0014	0.0021	0.0014	2.0138
		200,200,200	0.6939	0.6242	0.6928	0.0007	0.0010	0.0007	2.0108
		200,50,50	0.6933	0.6295	0.7000	0.0011	0.0038	0.0026	2.0228
		30,30,30	0.7638	0.7220	0.7707	0.0059	0.0055	0.0054	2.2565
		50,50,50	0.7517	0.7033	0.7564	0.0041	0.0038	0.0038	2.2114
	Stepwise	100,100,100	0.7387	0.6806	0.7365	0.0027	0.0025	0.0026	2.1558
		200,200,200	0.7291	0.6672	0.7242	0.0017	0.0015	0.0015	2.1205
		200,50,50	0.7418	0.6972	0.7547	0.0032	0.0033	0.0039	2.1936
		30,30,30	0.7428	0.6265	0.8323	0.0181	0.0242	0.0070	2.2015
		50,50,50	0.7408	0.6105	0.8189	0.0141	0.0197	0.0050	2.1702
	Logistic	100,100,100	0.7342	0.5840	0.8048	0.0087	0.0130	0.0035	2.1229
		200,200,200	0.7356	0.5665	0.7947	0.0061	0.0087	0.0023	2.0967
		200,50,50	0.7651	0.6159	0.7851	0.0079	0.0138	0.0064	2.1661
		30,30,30	0.8376	0.6001	0.7124	0.0068	0.0154	0.0105	2.1501
		50,50,50	0.8238	0.5832	0.7186	0.0048	0.0104	0.0061	2.1256
	Yan	100,100,100	0.8105	0.5709	0.7158	0.0026	0.0055	0.0034	2.0972
		200,200,200	0.7959	0.5676	0.7196	0.0016	0.0029	0.0017	2.0831
		200,50,50	0.8032	0.5882	0.7204	0.0024	0.0085	0.0062	2.1118
Youden									
		30,30,30	0.7432	0.5643	0.7400	0.0072	0.0146	0.0078	2.0475
		50,50,50	0.7449	0.5505	0.7541	0.0043	0.0097	0.0041	2.0375
	Box-Cox	100,100,100	0.7475	0.5410	0.7371	0.0019	0.0045	0.0021	2.0256
		200,200,200	0.7481	0.5373	0.7353	0.0010	0.0023	0.0011	2.0207
		200,50,50	0.7415	0.5514	0.7404	0.0017	0.0081	0.0043	2.0333
		30,30,30	0.8004	0.6645	0.8020	0.0127	0.0197	0.0116	2.2670
		50,50,50	0.7907	0.6425	0.7901	0.0106	0.0156	0.0083	2.2233
	Stepwise	100,100,100	0.7849	0.6111	0.7706	0.0070	0.0111	0.0056	2.1667
		200,200,200	0.7750	0.5928	0.7635	0.0042	0.0065	0.0033	2.1312
		200,50,50	0.7740	0.6425	0.7889	0.0068	0.0125	0.0073	2.2054

Table C.12

The table provides results based on training data for the gamma scenarios with $\rho = 0.3I + 0.7J$. The table provides the point estimate and variance for TCR_1, TCR_2, and TCR_3, as well as the $Sum(\widehat{TCRs})$.

Method	Approach	n_1, n_2, n_3	$\widehat{TCR}_1$	$\widehat{TCR}_2$	$\widehat{TCR}_3$	$Var(\widehat{TCR}_1)$	$Var(\widehat{TCR}_2)$	$Var(\widehat{TCR}_3)$	$Sum(\widehat{TCRs})$
		30,30,30	0.7053	0.6613	0.7717	0.0091	0.0088	0.0058	2.1383
		50,50,50	0.6921	0.6517	0.7624	0.0069	0.0062	0.0040	2.1061
	Logistic	100,100,100	0.6811	0.6307	0.7472	0.0041	0.0037	0.0027	2.0590
		200,200,200	0.6684	0.6239	0.7399	0.0029	0.0023	0.0017	2.0321
		200,50,50	0.7205	0.6704	0.7324	0.0047	0.0040	0.0040	2.1233
		30,30,30	0.7637	0.6642	0.6797	0.0033	0.0062	0.0062	2.1076
		50,50,50	0.7524	0.6538	0.6782	0.0023	0.0038	0.0034	2.0844
	Yan	100,100,100	0.7388	0.6418	0.6727	0.0012	0.0020	0.0019	2.0532
		200,200,200	0.7288	0.6398	0.6746	0.0008	0.0010	0.0009	2.0432
		200,50,50	0.7370	0.6534	0.6794	0.0011	0.0033	0.0035	2.0698
Euclidean									
		30,30,30	0.6898	0.6250	0.6927	0.0047	0.0069	0.0047	2.0075
		50,50,50	0.6907	0.6241	0.6917	0.0028	0.0043	0.0027	2.0065
	Box-Cox	100,100,100	0.6885	0.6166	0.6838	0.0014	0.0020	0.0014	1.9888
		200,200,200	0.6882	0.6152	0.6822	0.0007	0.0010	0.0007	1.9856
		200,50,50	0.6872	0.6216	0.6886	0.0011	0.0039	0.0025	1.9974
		30,30,30	0.7596	0.7077	0.7536	0.0058	0.0061	0.0063	2.2209
		50,50,50	0.7448	0.6948	0.7351	0.0042	0.0042	0.0046	2.1748
	Stepwise	100,100,100	0.7338	0.6707	0.7155	0.0030	0.0028	0.0029	2.1200
		200,200,200	0.7225	0.6588	0.7057	0.0019	0.0016	0.0019	2.0870
		200,50,50	0.7360	0.6857	0.7353	0.0032	0.0039	0.0040	2.1570
		30,30,30	0.7382	0.5982	0.8361	0.0203	0.0303	0.0068	2.1625
		50,50,50	0.7221	0.5835	0.8225	0.0162	0.0232	0.0051	2.1281
	Logistic	100,100,100	0.7192	0.5509	0.8082	0.0109	0.0165	0.0038	2.0783
		200,200,200	0.7153	0.5368	0.7978	0.0085	0.0111	0.0022	2.0499
		200,50,50	0.7558	0.6057	0.7766	0.0088	0.0157	0.0073	2.1381
		30,30,30	0.8402	0.5968	0.6882	0.0063	0.0160	0.0126	2.1252
		50,50,50	0.8241	0.5806	0.6928	0.0045	0.0105	0.0068	2.0976
	Yan	100,100,100	0.8110	0.5650	0.6914	0.0027	0.0058	0.0039	2.0675
		200,200,200	0.7926	0.5637	0.6967	0.0018	0.0032	0.0022	2.0530
		200,50,50	0.8019	0.5831	0.6975	0.0022	0.0086	0.0068	2.0825
Youden									
		30,30,30	0.7390	0.5497	0.7325	0.0081	0.0170	0.0097	2.0212
		50,50,50	0.7431	0.5412	0.7333	0.0051	0.0114	0.0056	2.0175
	Box-Cox	100,100,100	0.7442	0.5269	0.7287	0.0022	0.0051	0.0026	1.9998
		200,200,200	0.7436	0.5253	0.7269	0.0011	0.0025	0.0013	1.9958
		200,50,50	0.7374	0.5401	0.7317	0.0018	0.0090	0.0052	2.0092
		30,30,30	0.7967	0.6433	0.7867	0.0140	0.0244	0.0147	2.2267
		50,50,50	0.7895	0.6242	0.7711	0.0111	0.0190	0.0118	2.1848
	Stepwise	100,100,100	0.7771	0.6013	0.7506	0.0074	0.0122	0.0072	2.1290
		200,200,200	0.7661	0.5869	0.7421	0.0047	0.0074	0.0048	2.0951
		200,50,50	0.7695	0.6274	0.7714	0.0076	0.0153	0.0103	2.1684

Table C.13

The table provides results the scenarios generated from: (Group 1, Group2, Group 3): (Lognormal, Gamma, Mixture-normal) distributions. These scenarios were all generated with $n_1, n_2, n_3 = 50, 50, 50$ and $\rho = 0.5I + 0.5J$. The table provides the point estimate and variance for TCR_1, TCR_2, and TCR_3, as well as the $Sum(\widehat{TCRs})$.

Train/Test	Method	Approach	$\widehat{TCR_1}$	$\widehat{TCR_2}$	$\widehat{TCR_3}$	$Var(\widehat{TCR_1})$	$Var(\widehat{TCR_2})$	$Var(\widehat{TCR_3})$	$Sum(\widehat{TCRs})$
	Euclidean	Logistic	0.7127	0.6994	0.8833	0.0048	0.0043	0.0039	2.2954
		Box-Cox	0.6945	0.6860	0.8555	0.0029	0.0036	0.0014	2.2360
		Kernel	0.7163	0.6746	0.8634	0.0027	0.0033	0.0020	2.2543
		Stepwise	0.7371	0.7230	0.8936	0.0035	0.0035	0.0024	2.3536
Train									
	Youden	Logistic	0.7115	0.6506	0.9675	0.0105	0.0123	0.0012	2.3297
		Box-Cox	0.6997	0.6307	0.9555	0.0044	0.0069	0.0006	2.2860
		Kernel	0.7688	0.5987	0.9645	0.0088	0.0147	0.0013	2.3321
		Stepwise	0.7475	0.6660	0.9702	0.0080	0.0096	0.0009	2.3837
	Euclidean	Logistic	0.6723	0.6360	0.8620	0.0042	0.0038	0.0055	2.1703
		Box-Cox	0.6848	0.6696	0.8466	0.0009	0.0008	0.0017	2.2010
		Kernel	0.6810	0.6268	0.8472	0.0015	0.0018	0.0027	2.1549
		Stepwise	0.5585	0.6173	0.8606	0.0036	0.0038	0.0042	2.1465
Test									
	Youden	Logistic	0.6626	0.5780	0.9485	0.0090	0.0093	0.0020	2.1890
		Box-Cox	0.6889	0.6128	0.9497	0.0015	0.0012	0.0005	2.2514
		Kernel	0.7087	0.5131	0.9503	0.0042	0.0060	0.0016	2.1721
		Stepwise	0.6743	0.5488	0.9396	0.0067	0.0080	0.0018	2.1627