Supplemental file

Use of Steroid Profiling Combined With Machine Learning for the Diagnosis of Autonomous Cortisol Secretion

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This supplemental file is derived from the main data set to provide background to the associated concepts and methods of machine learning.

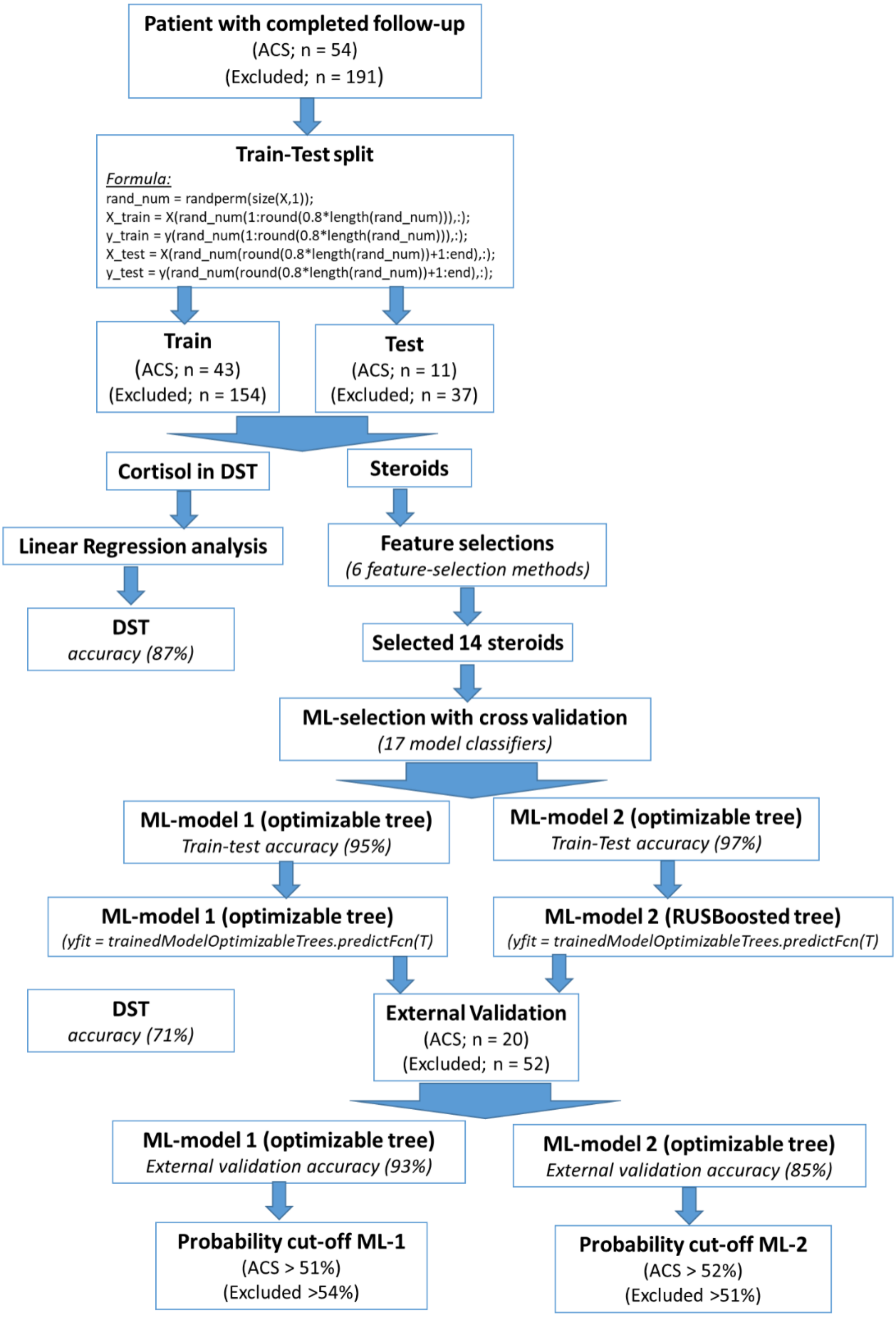
<u>**Generation of machine learning models**</u>

A supervised learning was performed to select the best machine learning (ML)-models by categorizing individual instances in the train data set to established categories through the following steps:

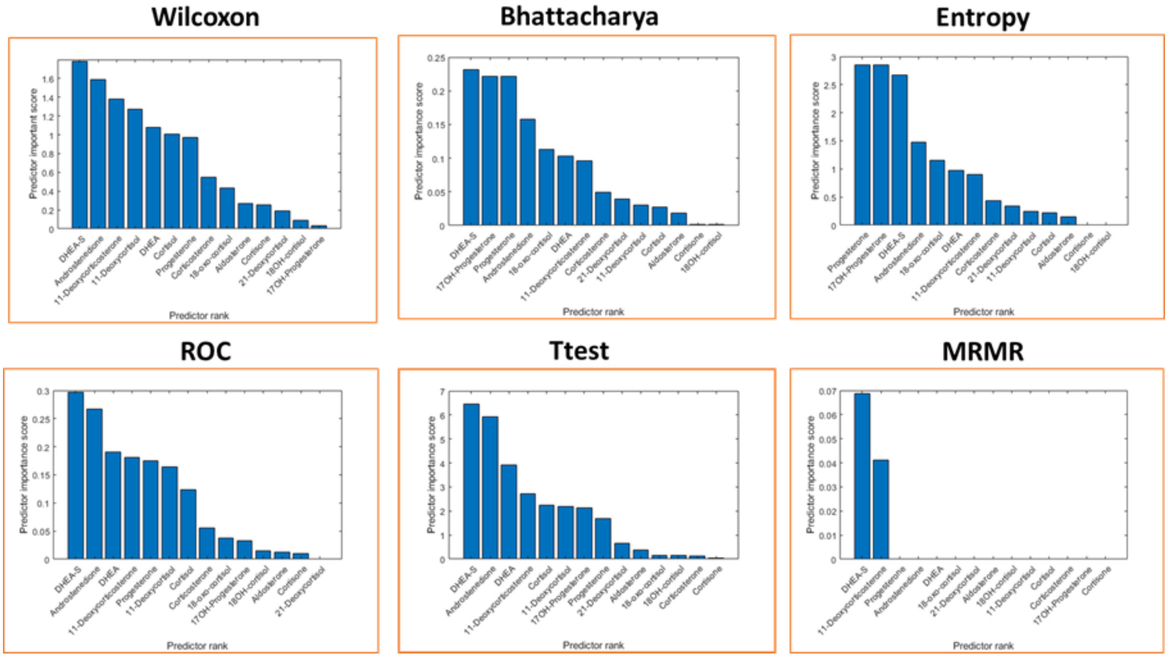
1.) Acquisition of dataset and split into separate training and internal validation.

In total, 54 patients with MACS and 191 patients with non-functional adenomas completed a standardized 3-year follow-up to conclude the final diagnosis. Datasets were split into training and internal validation to estimate the perfomance of machine learning (ML) algorithms. 70% of data points were assigned to train the model and the remaining 30% were utilized to apply the trained model as internal test set. Randperm command in MatLab software was used to assure random splitting *(supplementary figure 1 and supplementary table 2).* Linear regression analysis was performed to determine the accuracy of dexamethason suppression test (DST). In parallel, feature selection was performed to reduces the dimensionality of the streoid data by selecting only a subset of measured steroids that provide the best predictive power in modeling the data set. The steroid profile data was tested using six feature selection methods supported by MatLab software *(supplementary figure 2).* Wilcoxon signed-rank test was eventually applied to select the 14 most useful steroids in this study

Supplementary Figure 1. Flowchart of data generation and the machine learning algorithm used for the prediction of MACS.



Supplementary figure 2. Results of feature selection of six different methods to determine a panel of 14 steroid profile with optimal performance on MACS patient discrimination from Excluded group.



2.Use of the training and validation datasets to inform a model of the relationship between features and target.

17 ML predictive models were generated using either cross-validation or resubstitution validation techniques *(supplementary table 1).* Due to small sample sizes of our study cohort, resubstitution validation was included in the process to minimize variability in the outcome. Two ML prediction models with the most optimal classification performance, the optimizable random tree and random undersampling (RUS) boosted tree were selected to generate the model prediction codes. Both models principally are designed to handle class imbalance problem in data with discrete class labels by using a combination of random sampling and boosting procedure. In each iteration, the perfomance of the algorithm in the training data is compared with the performance on the validation dataset *(supplementary table 2, supplementary figure 3,supplementary figure 4).* Significant differences on sensitivity, specificity and area under roc curve between dexamethasone suppression test and ML models in this phase were determined by p-values *(supplementary table 4 and supplementary figure 3).*

Supplementary table 1. Seventeen predictive models were used to generate ML-agorithms for prediction of MACS. Models are ranked and selected according to their accuracies.

Predictive model	TP	FN	FP	TN	Sens	Spec	PPV	NPV	AUC	Accuracy
RUS Boosted Tree	54	0	8	183	100%	96%	87%	100%	0.98	97%
Optimizable Tree	52	2	11	180	96%	94%	83%	99%	0.99	95%
Quadratic SVM	37	1	17	190	97%	92%	69%	99%	0.96	93%
Kernel Naive Bayes	41	8	13	183	84%	93%	76%	96%	0.95	91%
Coarse Tree	39	11	15	180	78%	92%	72%	94%	0.90	89%
SVM Kernel	25	0	29	191	100%	87%	46%	100%	0.98	88%
Medium Gaussian SVM	22	2	32	189	92%	86%	41%	99%	0.93	86%
Cosine KNN	22	6	32	185	79%	85%	41%	97%	0.88	84%
Linear discriminant	20	6	34	185	77%	84%	37%	97%	0.86	84%
Logistic regression	23	9	31	182	72%	85%	43%	95%	0.86	84%
Linear SVM	15	3	39	188	83%	83%	28%	98%	0.86	83%
Medium KKN	20	8	34	183	71%	84%	37%	96%	0.87	83%
Cubic KNN	14	6	40	185	70%	82%	26%	97%	0.86	81%
Logistic Regression Kernel	5	0	49	191	100%	80%	9%	100%	0.96	80%
Subspace Discriminant	9	5	45	186	64%	81%	17%	97%	0.84	80%
Quadratic discriminant	46	66	8	125	41%	94%	85%	65%	0.86	70%
Gaussian Naive Bayes	45	98	9	93	31%	91%	83%	49%	0.78	56%

Supplementary table 2. Data of 245 patients (54 with MACS and 191 without MACS) were used to generate ML-algorithms. Training-test split was performed als described elswhere

Sample	***Diagnosis***	***1mg-DST***	***OptiTree***	***BoostedTree***	***Data Type***
Patient 1	ACS	ACS	ACS	ACS	Training
Patient 2	ACS	ACS	ACS	ACS	Training
Patient 3	ACS	ACS	ACS	ACS	Training
Patient 4	ACS	ACS	ACS	ACS	Training
Patient 5	ACS	ACS	ACS	ACS	Training
Patient 6	ACS	ACS	ACS	ACS	Training
Patient 7	ACS	ACS	ACS	ACS	Training
Patient 8	ACS	ACS	ACS	ACS	Training
Patient 9	ACS	ACS	ACS	ACS	Training
Patient 10	ACS	ACS	ACS	ACS	Training
Patient 11	ACS	ACS	ACS	ACS	Training
Patient 12	ACS	ACS	ACS	ACS	Training
Patient 13	ACS	ACS	ACS	ACS	Training
Patient 14	ACS	ACS	ACS	ACS	Training
Patient 15	ACS	ACS	Excluded	ACS	Training
Patient 16	ACS	ACS	ACS	ACS	Training
Patient 17	ACS	ACS	ACS	ACS	Training
Patient 18	ACS	ACS	ACS	ACS	Training
Patient 19	ACS	ACS	ACS	ACS	Training
Patient 20	ACS	ACS	ACS	ACS	Training
Patient 21	ACS	ACS	ACS	ACS	Training

Patient 22	ACS	ACS	ACS	ACS	Training
Patient 23	ACS	ACS	ACS	ACS	Training
Patient 24	ACS	ACS	ACS	ACS	Training
Patient 25	ACS	ACS	ACS	ACS	Training
Patient 26	ACS	ACS	ACS	ACS	Training
Patient 27	ACS	ACS	ACS	ACS	Training
Patient 28	ACS	ACS	ACS	ACS	Training
Patient 29	ACS	ACS	ACS	ACS	Training
Patient 30	ACS	ACS	ACS	ACS	Training
Patient 31	ACS	ACS	ACS	ACS	Training
Patient 32	ACS	ACS	ACS	ACS	Training
Patient 33	ACS	ACS	ACS	ACS	Training
Patient 34	ACS	ACS	ACS	ACS	Training
Patient 35	ACS	ACS	ACS	ACS	Training
Patient 36	ACS	ACS	ACS	ACS	Training
Patient 37	ACS	ACS	ACS	ACS	Training
Patient 38	ACS	ACS	ACS	ACS	Training
Patient 39	ACS	ACS	ACS	ACS	Training
Patient 40	ACS	ACS	ACS	ACS	Training
Patient 41	ACS	ACS	ACS	ACS	Training
Patient 42	ACS	ACS	ACS	ACS	Training
Patient 43	ACS	ACS	ACS	ACS	Training
Patient 198	ACS	ACS	ACS	ACS	Internal validation
Patient 201	ACS	ACS	ACS	ACS	Internal validation
Patient 202	ACS	ACS	ACS	ACS	Internal validation
Patient 203	ACS	ACS	ACS	ACS	Internal validation
Patient 204	ACS	ACS	ACS	ACS	Internal validation
Patient 205	ACS	ACS	ACS	ACS	Internal validation
Patient 206	ACS	ACS	ACS	ACS	Internal validation
Patient 207	ACS	ACS	ACS	ACS	Internal validation
Patient 208	ACS	ACS	ACS	ACS	Internal validation
Patient 209	ACS	ACS	Excluded	ACS	Internal validation
Patient 241	ACS	ACS	ACS	ACS	Internal validation
Patient 44	Excluded	Excluded	Excluded	Excluded	Training
Patient 45	Excluded	Excluded	Excluded	Excluded	Training
Patient 46	Excluded	Excluded	Excluded	Excluded	Training
Patient 47	Excluded	Excluded	Excluded	Excluded	Training
Patient 48	Excluded	Excluded	Excluded	Excluded	Training
Patient 49	Excluded	Excluded	Excluded	Excluded	Training
Patient 50	Excluded	Excluded	Excluded	ACS	Training
Patient 51	Excluded	Excluded	Excluded	Excluded	Training
Patient 52	Excluded	Excluded	Excluded	Excluded	Training
Patient 53	Excluded	Excluded	Excluded	Excluded	Training
Patient 54	Excluded	Excluded	Excluded	Excluded	Training
Patient 55	Excluded	Excluded	Excluded	Excluded	Training
Patient 56	Excluded	Excluded	Excluded	Excluded	Training
Patient 57	Excluded	Excluded	Excluded	Excluded	Training

Patient 58	Excluded	Excluded	Excluded	Excluded	Training
Patient 59	Excluded	Excluded	Excluded	Excluded	Training
Patient 60	Excluded	Excluded	Excluded	Excluded	Training
Patient 61	Excluded	Excluded	Excluded	Excluded	Training
Patient 62	Excluded	Excluded	Excluded	Excluded	Training
Patient 63	Excluded	Excluded	Excluded	Excluded	Training
Patient 64	Excluded	Excluded	Excluded	Excluded	Training
Patient 65	Excluded	Excluded	Excluded	Excluded	Training
Patient 66	Excluded	Excluded	Excluded	Excluded	Training
Patient 67	Excluded	Excluded	Excluded	ACS	Training
Patient 68	Excluded	Excluded	Excluded	Excluded	Training
Patient 69	Excluded	Excluded	Excluded	Excluded	Training
Patient 70	Excluded	Excluded	Excluded	Excluded	Training
Patient 71	Excluded	Excluded	Excluded	Excluded	Training
Patient 72	Excluded	Excluded	Excluded	Excluded	Training
Patient 73	Excluded	Excluded	Excluded	Excluded	Training
Patient 74	Excluded	Excluded	Excluded	Excluded	Training
Patient 75	Excluded	Excluded	Excluded	Excluded	Training
Patient 76	Excluded	Excluded	Excluded	Excluded	Training
Patient 77	Excluded	Excluded	Excluded	Excluded	Training
Patient 78	Excluded	Excluded	Excluded	Excluded	Training
Patient 79	Excluded	Excluded	Excluded	Excluded	Training
Patient 80	Excluded	Excluded	Excluded	Excluded	Training
Patient 81	Excluded	Excluded	Excluded	Excluded	Training
Patient 82	Excluded	Excluded	Excluded	Excluded	Training
Patient 83	Excluded	Excluded	Excluded	Excluded	Training
Patient 84	Excluded	Excluded	Excluded	Excluded	Training
Patient 85	Excluded	Excluded	Excluded	Excluded	Training
Patient 86	Excluded	Excluded	Excluded	Excluded	Training
Patient 87	Excluded	Excluded	Excluded	Excluded	Training
Patient 88	Excluded	Excluded	Excluded	Excluded	Training
Patient 89	Excluded	Excluded	Excluded	Excluded	Training
Patient 90	Excluded	Excluded	Excluded	Excluded	Training
Patient 91	Excluded	Excluded	Excluded	ACS	Training
Patient 92	Excluded	Excluded	Excluded	Excluded	Training
Patient 93	Excluded	Excluded	Excluded	Excluded	Training
Patient 94	Excluded	Excluded	Excluded	Excluded	Training
Patient 95	Excluded	Excluded	Excluded	Excluded	Training
Patient 96	Excluded	Excluded	Excluded	Excluded	Training
Patient 97	Excluded	Excluded	Excluded	Excluded	Training
Patient 98	Excluded	Excluded	Excluded	Excluded	Training
Patient 99	Excluded	Excluded	ACS	Excluded	Training
Patient 100	Excluded	Excluded	Excluded	Excluded	Training
Patient 101	Excluded	Excluded	Excluded	Excluded	Training
Patient 102	Excluded	Excluded	Excluded	Excluded	Training
Patient 103	Excluded	Excluded	Excluded	Excluded	Training
Patient 104	Excluded	Excluded	Excluded	Excluded	Training

Patient 105	Excluded	Excluded	Excluded	Excluded	Training
Patient 106	Excluded	Excluded	Excluded	Excluded	Training
Patient 107	Excluded	Excluded	Excluded	Excluded	Training
Patient 108	Excluded	Excluded	Excluded	Excluded	Training
Patient 109	Excluded	Excluded	Excluded	Excluded	Training
Patient 110	Excluded	Excluded	Excluded	Excluded	Training
Patient 111	Excluded	Excluded	Excluded	Excluded	Training
Patient 112	Excluded	Excluded	ACS	ACS	Training
Patient 113	Excluded	Excluded	Excluded	Excluded	Training
Patient 114	Excluded	Excluded	Excluded	Excluded	Training
Patient 115	Excluded	Excluded	Excluded	Excluded	Training
Patient 116	Excluded	Excluded	Excluded	Excluded	Training
Patient 117	Excluded	Excluded	Excluded	Excluded	Training
Patient 118	Excluded	Excluded	Excluded	Excluded	Training
Patient 119	Excluded	Excluded	Excluded	Excluded	Training
Patient 120	Excluded	Excluded	Excluded	Excluded	Training
Patient 121	Excluded	Excluded	Excluded	Excluded	Training
Patient 122	Excluded	Excluded	Excluded	Excluded	Training
Patient 123	Excluded	Excluded	Excluded	Excluded	Training
Patient 124	Excluded	Excluded	Excluded	Excluded	Training
Patient 125	Excluded	Excluded	Excluded	Excluded	Training
Patient 126	Excluded	Excluded	Excluded	Excluded	Training
Patient 127	Excluded	Excluded	ACS	Excluded	Training
Patient 128	Excluded	Excluded	Excluded	Excluded	Training
Patient 129	Excluded	Excluded	Excluded	Excluded	Training
Patient 130	Excluded	Excluded	Excluded	Excluded	Training
Patient 131	Excluded	Excluded	Excluded	Excluded	Training
Patient 132	Excluded	Excluded	Excluded	Excluded	Training
Patient 133	Excluded	Excluded	Excluded	Excluded	Training
Patient 134	Excluded	Excluded	Excluded	Excluded	Training
Patient 135	Excluded	Excluded	Excluded	Excluded	Training
Patient 136	Excluded	Excluded	Excluded	Excluded	Training
Patient 137	Excluded	Excluded	Excluded	Excluded	Training
Patient 138	Excluded	Excluded	Excluded	Excluded	Training
Patient 139	Excluded	Excluded	ACS	Excluded	Training
Patient 140	Excluded	Excluded	Excluded	Excluded	Training
Patient 141	Excluded	Excluded	Excluded	Excluded	Training
Patient 142	Excluded	Excluded	Excluded	Excluded	Training
Patient 143	Excluded	Excluded	Excluded	Excluded	Training
Patient 144	Excluded	Excluded	Excluded	Excluded	Training
Patient 145	Excluded	Excluded	Excluded	Excluded	Training
Patient 146	Excluded	Excluded	Excluded	Excluded	Training
Patient 147	Excluded	Excluded	Excluded	Excluded	Training
Patient 148	Excluded	Excluded	Excluded	Excluded	Training
Patient 149	Excluded	Excluded	Excluded	Excluded	Training
Patient 150	Excluded	Excluded	ACS	Excluded	Training
Patient 151	Excluded	Excluded	Excluded	Excluded	Training

Patient 152	Excluded	Excluded	Excluded	ACS	Training
Patient 153	Excluded	Excluded	Excluded	Excluded	Training
Patient 154	Excluded	Excluded	Excluded	Excluded	Training
Patient 155	Excluded	Excluded	Excluded	Excluded	Training
Patient 156	Excluded	Excluded	Excluded	Excluded	Training
Patient 157	Excluded	Excluded	ACS	Excluded	Training
Patient 158	Excluded	Excluded	Excluded	Excluded	Training
Patient 159	Excluded	Excluded	Excluded	Excluded	Training
Patient 160	Excluded	Excluded	Excluded	Excluded	Training
Patient 161	Excluded	Excluded	Excluded	Excluded	Training
Patient 162	Excluded	Excluded	Excluded	Excluded	Training
Patient 163	Excluded	Excluded	Excluded	Excluded	Training
Patient 164	Excluded	Excluded	Excluded	Excluded	Training
Patient 165	Excluded	Excluded	Excluded	Excluded	Training
Patient 166	Excluded	Excluded	Excluded	Excluded	Training
Patient 167	Excluded	Excluded	Excluded	Excluded	Training
Patient 168	Excluded	Excluded	Excluded	Excluded	Training
Patient 169	Excluded	Excluded	Excluded	Excluded	Training
Patient 170	Excluded	Excluded	Excluded	Excluded	Training
Patient 171	Excluded	Excluded	Excluded	Excluded	Training
Patient 172	Excluded	Excluded	Excluded	Excluded	Training
Patient 173	Excluded	Excluded	ACS	Excluded	Training
Patient 174	Excluded	Excluded	Excluded	Excluded	Training
Patient 175	Excluded	Excluded	Excluded	Excluded	Training
Patient 176	Excluded	Excluded	Excluded	Excluded	Training
Patient 177	Excluded	Excluded	Excluded	Excluded	Training
Patient 178	Excluded	Excluded	Excluded	Excluded	Training
Patient 179	Excluded	Excluded	Excluded	Excluded	Training
Patient 180	Excluded	Excluded	Excluded	Excluded	Training
Patient 181	Excluded	Excluded	ACS	Excluded	Training
Patient 182	Excluded	Excluded	Excluded	Excluded	Training
Patient 183	Excluded	Excluded	Excluded	Excluded	Training
Patient 184	Excluded	Excluded	Excluded	Excluded	Training
Patient 185	Excluded	Excluded	Excluded	Excluded	Training
Patient 186	Excluded	Excluded	ACS	Excluded	Training
Patient 187	Excluded	Excluded	Excluded	Excluded	Training
Patient 188	Excluded	Excluded	Excluded	Excluded	Training
Patient 189	Excluded	Excluded	Excluded	Excluded	Training
Patient 190	Excluded	Excluded	Excluded	Excluded	Training
Patient 191	Excluded	Excluded	Excluded	Excluded	Training
Patient 192	Excluded	Excluded	Excluded	Excluded	Training
Patient 193	Excluded	Excluded	Excluded	Excluded	Training
Patient 194	Excluded	Excluded	Excluded	Excluded	Training
Patient 195	Excluded	Excluded	Excluded	Excluded	Training
Patient 196	Excluded	Excluded	Excluded	Excluded	Training
Patient 197	Excluded	Excluded	Excluded	Excluded	Training
Patient 199	Excluded	Excluded	ACS	Excluded	Internal validation

Patient 200	Excluded	Excluded	ACS	Excluded	Internal validation
Patient 210	Excluded	ACS	Excluded	Excluded	Internal validation
Patient 211	Excluded	ACS	Excluded	Excluded	Internal validation
Patient 212	Excluded	ACS	Excluded	Excluded	Internal validation
Patient 213	Excluded	ACS	Excluded	Excluded	Internal validation
Patient 214	Excluded	ACS	Excluded	Excluded	Internal validation
Patient 215	Excluded	ACS	Excluded	ACS	Internal validation
Patient 216	Excluded	ACS	Excluded	Excluded	Internal validation
Patient 217	Excluded	ACS	Excluded	Excluded	Internal validation
Patient 218	Excluded	ACS	Excluded	Excluded	Internal validation
Patient 219	Excluded	ACS	Excluded	Excluded	Internal validation
Patient 220	Excluded	ACS	Excluded	Excluded	Internal validation
Patient 221	Excluded	ACS	Excluded	Excluded	Internal validation
Patient 222	Excluded	ACS	Excluded	Excluded	Internal validation
Patient 223	Excluded	ACS	Excluded	Excluded	Internal validation
Patient 224	Excluded	ACS	Excluded	Excluded	Internal validation
Patient 225	Excluded	ACS	Excluded	Excluded	Internal validation
Patient 226	Excluded	ACS	Excluded	ACS	Internal validation
Patient 227	Excluded	ACS	Excluded	Excluded	Internal validation
Patient 228	Excluded	ACS	Excluded	Excluded	Internal validation
Patient 229	Excluded	Excluded	Excluded	Excluded	Internal validation
Patient 230	Excluded	ACS	Excluded	Excluded	Internal validation
Patient 231	Excluded	ACS	Excluded	ACS	Internal validation
Patient 232	Excluded	ACS	Excluded	Excluded	Internal validation
Patient 233	Excluded	ACS	Excluded	Excluded	Internal validation
Patient 234	Excluded	ACS	Excluded	Excluded	Internal validation
Patient 235	Excluded	ACS	Excluded	Excluded	Internal validation
Patient 236	Excluded	Excluded	Excluded	Excluded	Internal validation
Patient 237	Excluded	ACS	Excluded	Excluded	Internal validation
Patient 238	Excluded	ACS	Excluded	Excluded	Internal validation
Patient 239	Excluded	ACS	Excluded	Excluded	Internal validation
Patient 240	Excluded	Excluded	Excluded	Excluded	Internal validation
Patient 242	Excluded	ACS	Excluded	Excluded	Internal validation
Patient 243	Excluded	ACS	Excluded	Excluded	Internal validation
Patient 244	Excluded	ACS	Excluded	Excluded	Internal validation
Patient 245	Excluded	ACS	Excluded	Excluded	Internal validation

3.Evaluation of the model via the external validation dataset to determine its prediction abilty for unseen instances.

A new set of data, containing 20 patients with MACS and 52 patients in whom the disease was excluded, was evaluated utilizing the established model prediction codes. Each individual prediction outcomes was compared to actual diagnosis to determine external validation model accuracy. Cut-off value of the prediction models were calculated using the mean rate of probablity values of each instances *(supplementary table 3, supplementary figure 3,supplementary figure 4).* P-values were calculated to denote significant differences on sensitivity, specificity and area under roc curve between dexamethasone suppression test and ML models *(supplementary table 4 and supplementary figure 3).*

Supplementary table 3. 72 patients (20 patients with MACS and 52 patients without MACS) were used to validate the models in external validation. Probability cut-off for each models were determined as mean value of each models.

	Diagnosis	*Prob. [ACS]*	*Prob. [Excluded]*	*ML-2*	*Prob. [ACS]*	*Prob. [Excluded]*	*ML-1*
Patient 1	ACS	55%	45%	ACS	39%	61%	Excluded
Patient 2	ACS	100%	0%	ACS	100%	0%	ACS
Patient 3	ACS	100%	0%	ACS	33%	67%	Excluded
Patient 4	ACS	95%	5%	ACS	87%	13%	ACS
Patient 5	ACS	77%	23%	ACS	73%	27%	ACS
Patient 6	ACS	48%	52%	Excluded	68%	32%	ACS
Patient 7	ACS	72%	28%	ACS	69%	31%	ACS
Patient 8	ACS	95%	5%	ACS	60%	40%	ACS
Patient 9	ACS	74%	26%	ACS	70%	30%	ACS
Patient 10	ACS	41%	59%	Excluded	46%	54%	Excluded
Patient 11	ACS	99%	1%	ACS	74%	26%	ACS
Patient 12	ACS	0%	100%	Excluded	99%	1%	ACS
Patient 13	ACS	100%	0%	ACS	100%	0%	ACS
Patient 14	ACS	91%	9%	ACS	1%	99%	Excluded
Patient 15	ACS	98%	2%	ACS	95%	5%	ACS
Patient 16	ACS	95%	5%	ACS	57%	43%	ACS
Patient 17	ACS	85%	15%	ACS	32%	68%	Excluded
Patient 18	ACS	49%	51%	Excluded	23%	77%	Excluded
Patient 19	ACS	84%	16%	ACS	72%	28%	ACS
Patient 20	ACS	12%	88%	Excluded	79%	21%	ACS
Patient 21	Excluded	58%	42%	ACS	21%	79%	Excluded
Patient 22	Excluded	95%	5%	ACS	51%	49%	ACS
Patient 23	Excluded	1%	99%	Excluded	0%	100%	Excluded
Patient 24	Excluded	99%	1%	ACS	39%	61%	Excluded
Patient 25	Excluded	40%	60%	Excluded	38%	62%	Excluded
Patient 26	Excluded	0%	100%	Excluded	0%	100%	Excluded
Patient 27	Excluded	0%	100%	Excluded	0%	100%	Excluded
Patient 28	Excluded	0%	100%	Excluded	0%	100%	Excluded
Patient 29	Excluded	11%	89%	Excluded	6%	94%	Excluded
Patient 30	Excluded	0%	100%	Excluded	0%	100%	Excluded
Patient 31	Excluded	86%	14%	ACS	70%	30%	ACS
Patient 32	Excluded	48%	52%	Excluded	27%	73%	Excluded
Patient 33	Excluded	6%	94%	Excluded	23%	77%	Excluded
Patient 34	Excluded	11%	89%	Excluded	0%	100%	Excluded
Patient 35	Excluded	30%	70%	Excluded	40%	60%	Excluded
Patient 36	Excluded	73%	27%	ACS	39%	61%	Excluded
Patient 37	Excluded	0%	100%	Excluded	0%	100%	Excluded
Patient 38	Excluded	46%	54%	Excluded	13%	87%	Excluded

Patient 39	Excluded	15%	85%	Excluded	0%	100%	Excluded
Patient 40	Excluded	18%	82%	Excluded	2%	98%	Excluded
Patient 41	Excluded	24%	76%	Excluded	23%	77%	Excluded
Patient 42	Excluded	3%	97%	Excluded	7%	93%	Excluded
Patient 43	Excluded	97%	3%	ACS	75%	25%	ACS
Patient 44	Excluded	8%	92%	Excluded	7%	93%	Excluded
Patient 45	Excluded	15%	85%	Excluded	17%	83%	Excluded
Patient 46	Excluded	52%	48%	ACS	14%	86%	Excluded
Patient 47	Excluded	29%	71%	Excluded	44%	56%	Excluded
Patient 48	Excluded	38%	62%	Excluded	1%	99%	Excluded
Patient 49	Excluded	0%	100%	Excluded	0%	100%	Excluded
Patient 50	Excluded	52%	48%	ACS	1%	99%	Excluded
Patient 51	Excluded	4%	96%	Excluded	1%	99%	Excluded
Patient 52	Excluded	0%	100%	Excluded	0%	100%	Excluded
Patient 53	Excluded	0%	100%	Excluded	0%	100%	Excluded
Patient 54	Excluded	6%	94%	Excluded	9%	91%	Excluded
Patient 55	Excluded	0%	100%	Excluded	1%	99%	Excluded
Patient 56	Excluded	0%	100%	Excluded	0%	100%	Excluded
Patient 57	Excluded	0%	100%	Excluded	0%	100%	Excluded
Patient 58	Excluded	9%	91%	Excluded	5%	95%	Excluded
Patient 59	Excluded	85%	15%	ACS	31%	69%	Excluded
Patient 60	Excluded	0%	100%	Excluded	0%	100%	Excluded
Patient 61	Excluded	92%	8%	ACS	74%	26%	ACS
Patient 62	Excluded	3%	97%	Excluded	2%	98%	Excluded
Patient 63	Excluded	0%	100%	Excluded	1%	99%	Excluded
Patient 64	Excluded	0%	100%	Excluded	0%	100%	Excluded
Patient 65	Excluded	0%	100%	Excluded	0%	100%	Excluded
Patient 66	Excluded	0%	100%	Excluded	0%	100%	Excluded
Patient 67	Excluded	0%	100%	Excluded	2%	98%	Excluded
Patient 68	Excluded	2%	98%	Excluded	0%	100%	Excluded
Patient 69	Excluded	37%	63%	Excluded	72%	28%	ACS
Patient 70	Excluded	31%	69%	Excluded	44%	56%	Excluded
Patient 71	Excluded	1%	99%	Excluded	1%	99%	Excluded
Patient 72	Excluded	5%	95%	Excluded	27%	73%	Excluded

Supplementary table 4. Comparison of sensitivities and specificities of dexamethason suppression test (DST) and machine learning models (ML-1 and ML-2) in training and validation steps.

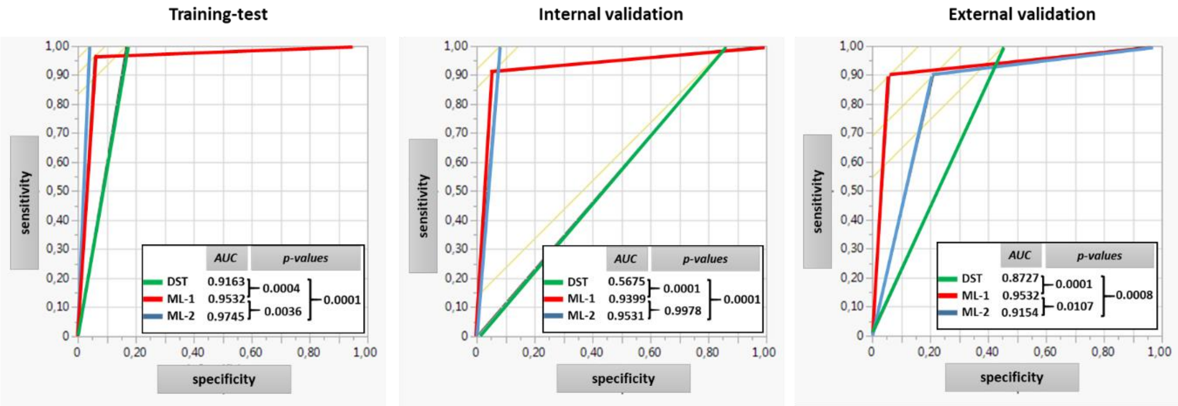
Optimizable tree (ML-1)

		Sensitivity (%)			*Specificity (%)*		
	n	DST	ML-1	p-value	DST	ML-1	p-value
Train-Test	245	100	96	0.0561	83	94	0.0081
Internal validation	48	100	91	0,0341	16	95	<0,0001
External validation	72	100	90	0.0307	53	94	<0,0001

RUS Boosted tree (ML-2)

		Sensitivity (%)			*Specificity (%)*		
	n	DST	ML-2	p-value	DST	ML-2	p-value
Train-Test	245	100	100	0.9987	83	96	0.0072
Internal validation	48	100	100	0.9992	16	92	<0,0001
External validation	72	100	90	0.0237	53	82	<0,0001

Supplementary figure 3. Comparison of area under curve (AUC) of dexamethason suppression test (DST) and steroid profile (SP) with machine learnings (ML-1 and ML-2) in training and validation steps.



Supplementary figure 4. Comparison of area under curve (AUC) of dexamethason suppression test (DST) and steroid profile (SP) with discriminant analisis in training and validation steps