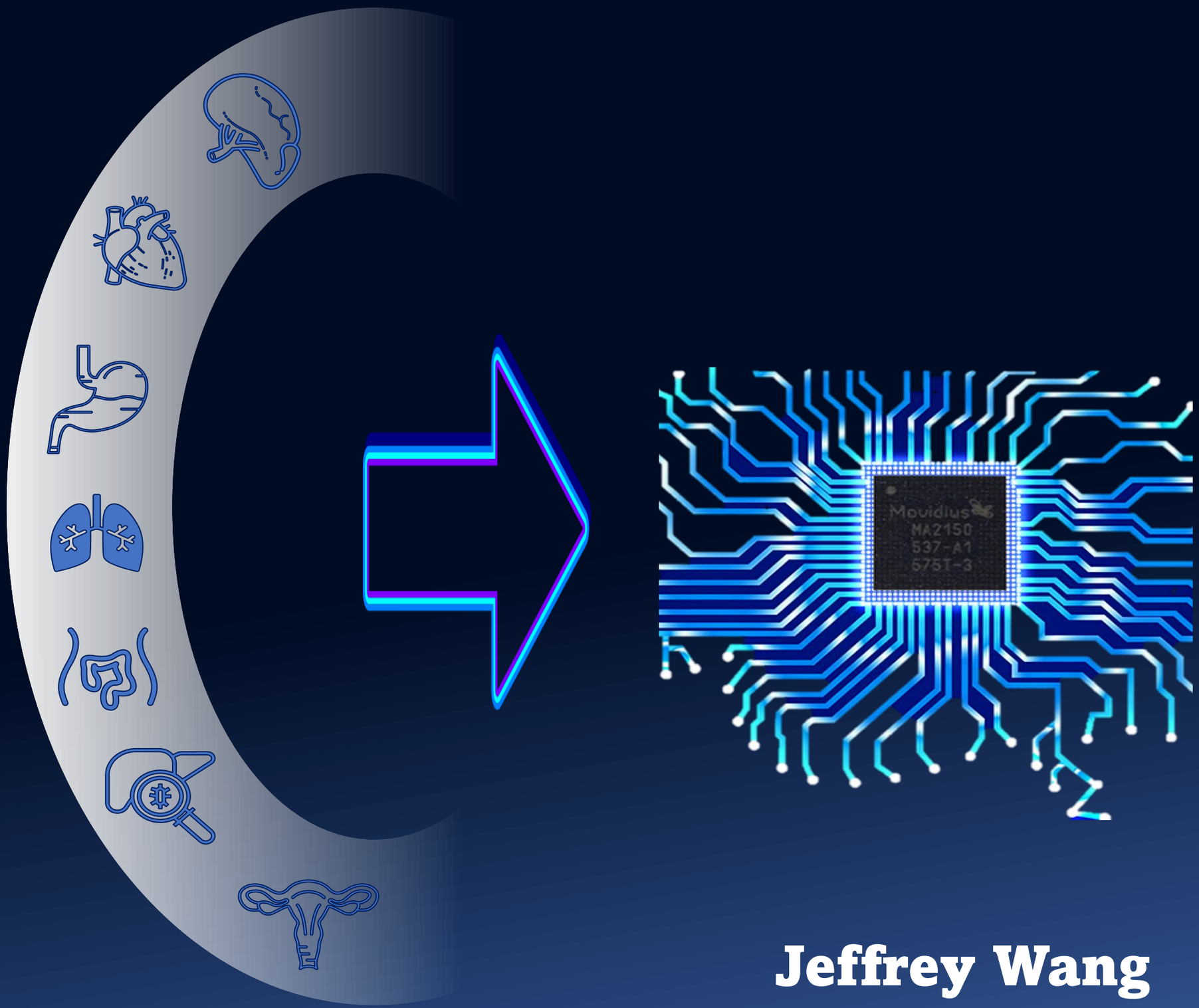
Development of a Deep Neural Network Model for Lupus Anticoagulant Interpretation



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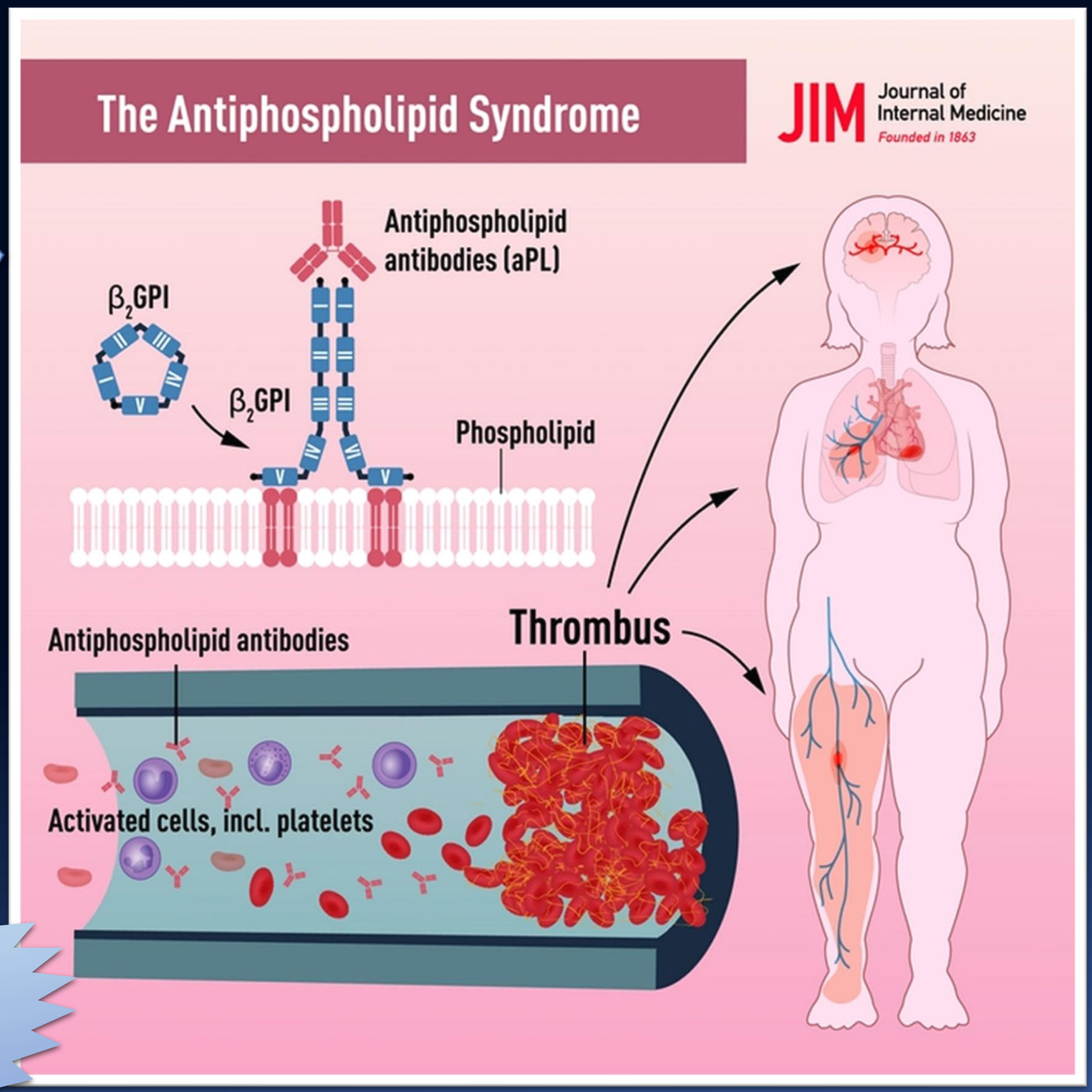
Antiphospholipid antibody syndrome

Antiphospholipid antibody syndrome (APS) is a major cause of unprovoked venous and arterial thromboembolic events as well as pregnancy complications



50/100k population

Svenungsson E, et al.*J Intern Med.*2020.287: 349-372

Lupus Anticoagulant (LAC)

- Antiphospholipid syndrome is an autoimmune disorder where the body’s immune system produces self-attacking antibodies called lupus anticoagulants that can cause the development of a thrombus.
- Laboratory Identification of Lupus Anticoagulant:
  - ✓ Prolongation of a phospholipid-dependent screening test, usually a LAC-responsive dilute Russell’s viper venom time (DRVVT) or activated partial thromboplastin time (APTT)
  - ✓ Inhibition on mixing with pooled normal plasma based on the guideline
  - ✓ Confirmation of phospholipid-dependent inhibition by repeating the prolonged test with excess phospholipid.

Difficulties in Diagnosing LAC

- Diagnosis of a LAC remains challenging due to the heterogeneity of antiphospholipid antibodies, the marked variations in reagents, inconsistencies in post-analytic processes, and the multitude of interferences that may mimic a LAC.
- Anticoagulant drugs, such as heparin, warfarin and direct-acting oral anticoagulants may cause false-negative and false-positive lupus anticoagulant test results, depending on the test methodology and drug concentration.
- Exclusion of anticoagulant drug effects is therefore a critical step when evaluating lupus anticoagulant test results.

Deep Neural Networks

- Deep neural networks (DNNs) have become increasingly prevalent in many different fields involving laboratory medicine, being capable of processing and analyzing sizable clinical and laboratory data sets to support clinical decisions.
- DNNs use a series of hidden layers connected by numerous neurons to learn patterns in large, complex, nonlinear, and multidimensional input data without the need to manually extract features.
- Through deep learning of large amounts of data and analyzing relationships between selected test results, clinical events, and results of diagnosis and treatments, DNNs can establish a predictive model for accurate disease diagnosis, risk stratification, and prognosis that is easy to use.
- Implementation of DNNs in clinic practice serves to significantly reduce the level of human error in the analysis process and save a substantial amount of time.

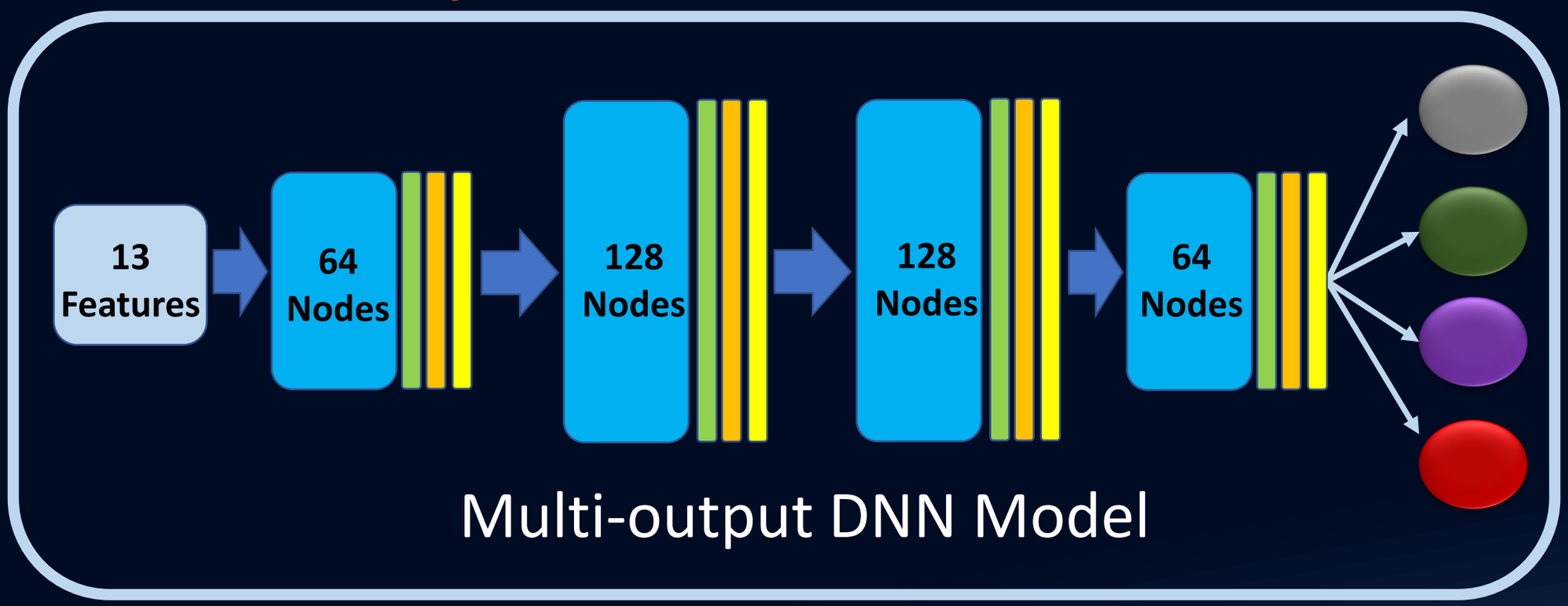
Research Objectives

- Developing a deep neural network model for classification of the presence of a lupus anticoagulant by the DRVVT and APTT methodologies and the presence of anticoagulant drug effects
- Training and validating DNNs to achieve high diagnostic accuracy
- Evaluating the performance of the DNN model in the testing cohort by comparing diagnostic accuracy between DNNs and an expert rater

Design & Methods

Training Cohort
N=4608

Training



Validation

Validation Cohort
N=1153

- Diagnostic Accuracy
- Area Under the Curve (AUC)
- Precision recall curve (PRC)

Testing

Testing Cohort
N=1441

Model performance

- Sensitivity
- Specificity
- Accuracy
- F1 Score
- Index of balanced accuracy

Results: Lab Testing Raw Data and Output labels in Training, Validation and Testing Cohort

Lab Test Raw Data (Mean +/- Standard Deviation)					
	Reference Intervals	Training data	Validation data	Testing data	P Value
APMSC	25-37 seconds	43.61 +/- 22.44	44.08 +/- 20.49	43.02 +/- 24.66	0.77
APTSC	25-37 seconds	42.15 +/- 31.10	41.47 +/- 29.54	41.38 +/- 30.31	0.63
INRSC	0.9-1.1 seconds	1.28 +/- 0.70	1.24 +/- 0.48	1.26 +/- 0.63	0.13
PNPPL	NA	50.23 +/- 13.08	48.66 +/- 11.65	47.78 +/- 10.25	0.11
PNPSA	NA	63.93 +/- 17.56	62.74 +/-13.69	63.24 +/- 15.36	0.80
PNPDEL	<6 seconds	13.70 +/- 4.48	14.08 +/- 2.04	15.46 +/- 5.11	0.30
PTMSC	9.4-12.5 seconds	13.21 +/- 1.47	13.21 +/- 1.40	13.12 +/- 1.23	0.55
RTSC	14.0-23.9 seconds	22.89 +/- 24.17	22.23 +/- 22.71	22.35 +/- 20.44	0.93
RVCR3	<1.20	1.16 +/- 0.43	1.15 +/- 0.43	1.18 +/- 0.47	0.45
RVMR2	<1.20	1.46 +/- 0.47	1.41 +/- 0.38	1.46 +/- 0.47	0.07
RVR1	<1.20	1.25 +/- 0.60	1.22 +/- 0.47	1.26 +/- 0.64	0.22
STBUF	N/A	48.32 +/- 9.80	48.55 +/- 11.15	49.12 +/- 11.13	0.50
STDEL	<= 8 seconds	7.44 +/- 7.09	7.86 +/- 7.19	8.27 +/-8.82	0.23
TTSC	15.8-24.9 seconds	49.78 +/- 80.52	49.57 +/- 81.30	44.35 +/- 72.20	0.17

Output Labels				
	Training data	Validation data	Testing data	P Value
LAC-DRVVT	550/4608 (12%)	148/1153 (13%)	193/1441 (13%)	0.30
LAC-APTT	302/4608 (7%)	73/1153 (6%)	121/1441 (8%)	0.04
HEP	475/4608 (10%)	115/1153 (10%)	137/1441 (10%)	0.20
WAR	628/4608 (14%)	138/1153 (12%)	182/1441 (13%)	0.02

Results: Diagnostic Accuracy of the Multi-Output DNN model in the Validation Cohort

Labels	Accuracy	AUC	PRC
LAC-DRVVT	0.9636	0.997	0.990
LAC-APTT	0.9695	0.994	0.995
HEP	0.9624	0.976	0.992
WAR	1.0000	0.994	0.994

The multi-output DNN model achieved maximum average weighted accuracy at epoch 332

LAC-DRVVT: lupus anticoagulant dilute Russell's viper venom time

LAC-APTT: lupus anticoagulant activated partial thromboplastin time

HEP: heparin

WAR: warfarin

Results: Model Performance in the Testing Cohort

Labels	TP	TN	FP	FN	Accuracy	Sensitivity	Specificity	PPV	NPV	F1	IBA
LAC-DRVVT	180	1235	13	13	0.982	0.933	0.990	0.933	0.990	0.933	0.961
LAC-APTT	112	1314	6	9	0.990	0.926	0.995	0.949	0.993	0.937	0.961
HEP	122	1293	11	15	0.982	0.891	0.992	0.917	0.989	0.904	0.941
WAR	177	1252	7	5	0.992	0.973	0.994	0.962	0.996	0.967	0.983

TP: true positive; TN: true negative; FP: false positive; FN: false negative; PPV: positive predictive value; NPV: negative predictive value; IBA: index of balanced accuracy

LAC-DRVVT: lupus anticoagulant dilute Russell's viper venom time

LAC-APTT: lupus anticoagulant activated partial thromboplastin time

HEP: heparin

WAR: warfarin

Conclusion

- DNNs can accurately classify LAC profiles and common anticoagulant drug effects without the need to extracting features manually.
- Model predictions can be used in downstream processing to append textual comments to cases for review by laboratory specialists prior to releasing results.
- Automated AI/ML-based approach has the added benefit of standardizing classification of LAC profiles across different human raters.

Thank You !