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A machine learning algorithm based on a 15-autoantibody profile by a novel fully automated multiplexed microarray immunoassay for the diagnosis of autoimmune connective tissue diseases (CTD)

Gerber Gomez[1], Yipeng Cheng[2], Kristiana Nita[2], Michael Hausmann[3], Christian Fischer[1], Yasemin Ataman-Önal[3]

1. Medical & Scientific Affairs, AliveDx, Eysins, Switzerland. **2.** Research & Development, AliveDx, Edinburgh, UK. **3.** Research & Development, AliveDx, Eysins, Switzerland.

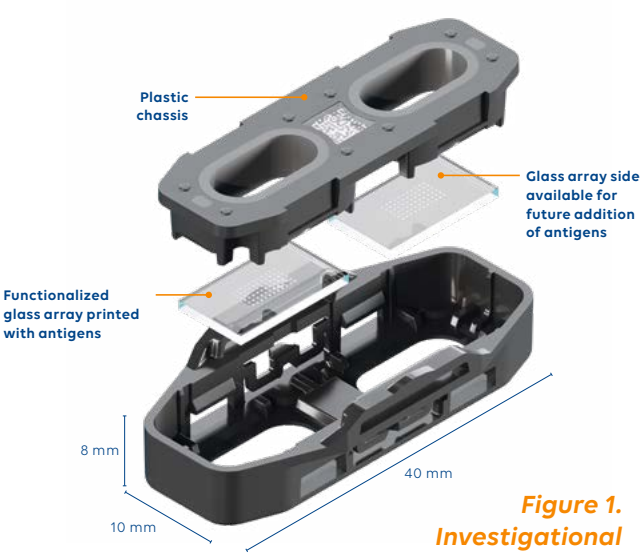


Figure 1. Investigational multiplexed microarray

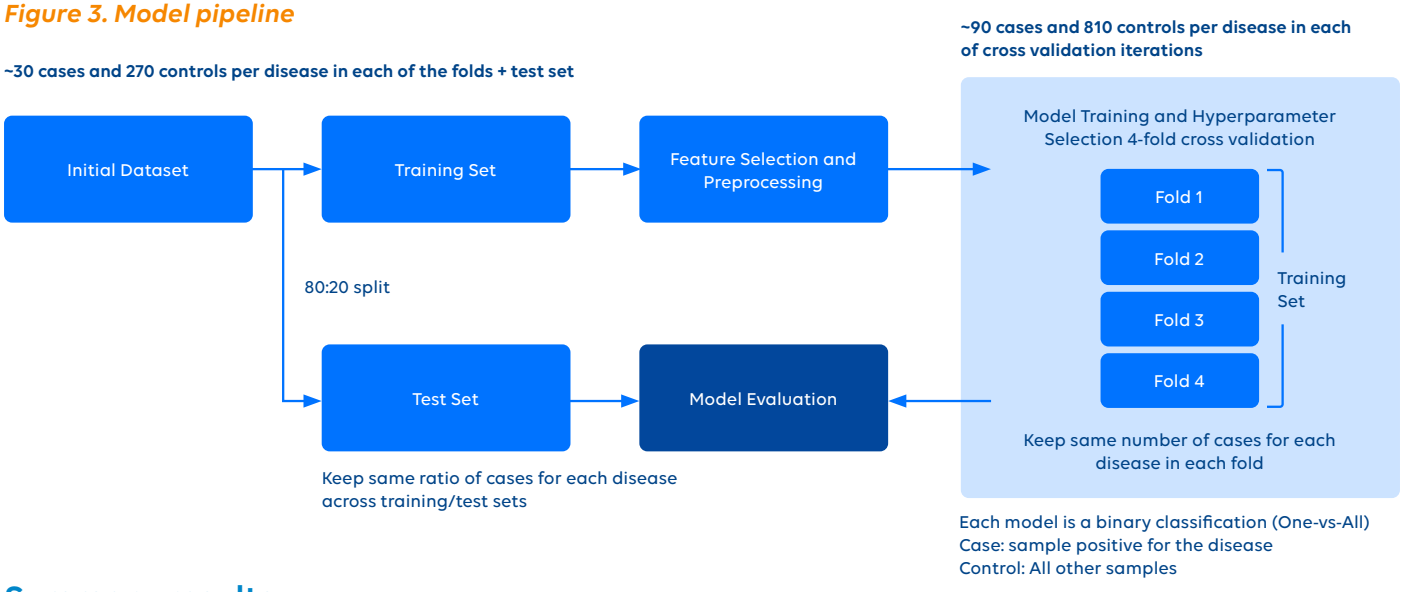
Background-aim

Detection of relevant autoantibodies is key in the identification of autoimmune CTD. The evaluation of multiple autoantibodies for extended serological profiling may improve the diagnosis of these conditions. We evaluated the diagnostic utility, in patients with CTD and controls, of machine learning classifiers based on the 15-autoantibody profile performed by a novel, single-use, multiplexed microarray immunoassay (MosaiQ AiPlex® CTDplus microarray, AliveDx, Switzerland) (***Figure 1***), used with its fully automated high-throughput proprietary system (***Figure 2***) for the detection of IgG autoantibodies directed to dsDNA, SS-A 60, TRIM21 (SS-A 52), SS-B, Sm, Sm/RNP, U1RNP, Jo-1, Scl-70, Centromere B, Chromatin, Ribosomal P, DFS70, RNAP III and CCP2.

Methods

Banked, de-identified sera from 475 patients diagnosed with CTD in accordance with current guidelines [127 patients with systemic lupus erythematosus (SLE), 74 with systemic sclerosis, 76 with Sjögren's syndrome (SjS), 71 with idiopathic inflammatory myopathies, 54 with mixed CTD, 73 with rheumatoid arthritis] and 652 disease controls were tested with MosaQ AiPlex CTDplus. Classification models were developed using all 15 autoantibodies or a selected subset, employing Random Forest, Logistic Regression with Regularization and XGBoost algorithms (see ***Figure 3*** for model pipeline). Each model type was trained using all fifteen autoantibodies and autoantibodies currently considered for each disease: (9-plex for SLE, 3-plex for SjS). Diagnostic performance was evaluated by receiver operating characteristic (ROC) curve analysis.

Figure 3. Model pipeline



Summary results

A Random Forest classifier with all 15 autoantibodies outperformed individual markers or groups of markers in predicting autoimmune CTD.

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Detailed results

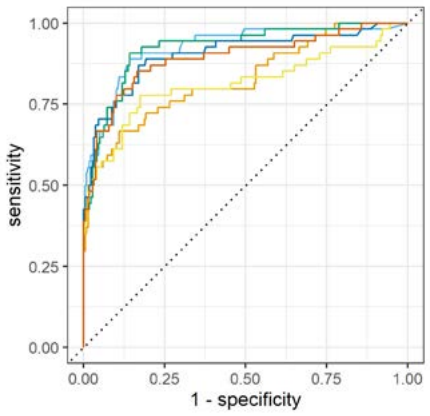
A Random Forest classifier with all 15 autoantibodies showed robust performance in predicting SLE, achieving an area under the curve (AUC) of 0.92 (***Figure 4***), versus individual SLE-specific markers dsDNA (0.68) and Sm (0.60). For SjS, the 15-plex Random Forest classifier achieved an AUC of 0.83 (***Figure 5***), outperforming a 3-plex Random Forest classifier based on SS-A 60, TRIM21 and SS-B autoantibodies (0.62). For other CTD, 15-plex classifiers consistently outperformed the individual disease-specific markers (data not shown).

*Figure 4. ROC Curves and AUCs - SLE. All 15 analytes vs. 9 Outcome-related analytes**

AUC of the 15-plex Random Forest classifier for **SLE**: **0.92**

AUC of dsDNA for **SLE**: **0.68**

AUC of Sm for **SLE**: **0.60**



Model	Analyte Set	AUC
XGBoost	All Analytes	0.924
Random Forest	All Analytes	0.923
Random Forest	Outcome Related	0.903
XGBoost	Outcome Related	0.892
Logistic L1 L2	All Analytes	0.827
Logistic L1 L2	Outcome Related	0.814

SLE: systemic lupus erythematosus

*Antibodies directed to dsDNA, Sm, Chromatin, Ribosomal P, Sm/RNP, U1RNP, SS-A 60, TRIM21, SS-B. ROC: receiver operating characteristic. AUC: area under the curve.

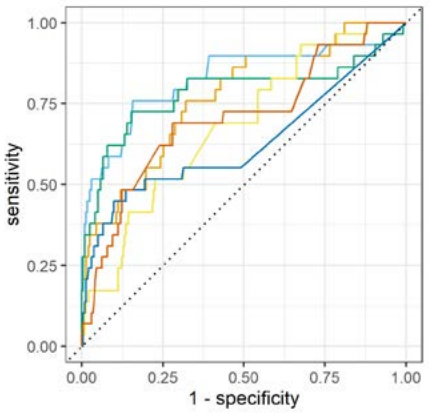
*Figure 5. ROC Curves and AUCs - SjS. All 15 analytes vs. 3 Outcome-related analytes**

AUC of the 15-plex Random Forest classifier for **SjS**: **0.83**

AUC of SS-A 60 for **SjS**: **0.63**

AUC of TRIM 21 (SS-A 52) for **SjS**: **0.59**

AUC of SS-B for **SjS**: **0.58**



Model	Analyte Set	AUC
Random Forest	All Analytes	0.827
XGBoost	All Analytes	0.785
Logistic L1 L2	All Analytes	0.769
XGBoost	Outcome Related	0.704
Logistic L1 L2	Outcome Related	0.68
Random Forest	Outcome Related	0.629

SjS: Sjögren's syndrome

*Antibodies directed to SS-A 60, TRIM21 and SS-B. ROC: receiver operating characteristic. AUC: area under the curve.

Conclusions

Multiplex autoantibody testing combined with machine learning algorithms has the potential to improve the diagnosis of autoimmune CTD.

Figure 2. MosaiQ® instrument

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