doi:10.36849/JDD.2020.5006





BRIEF COMMUNICATION Journal of Drugs in Dermatology

# Predicting Secukinumab Fast-Responder Profile in Psoriatic Patients: Advanced Application of Artificial-Neural-Networks (ANNs)

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## ABSTRACT

**Background:** Drug resistance to biologics in psoriasis therapy can occur – it may be acquired during a treatment or else present itself from the beginning. To date, no biomarkers are known that may reliably guide clinicians in predicting responsiveness to biologics. Biologics may pose a substantial economic burden. Secukinumab efficiently targets IL-17 in the treatment of psoriasis.

**Objective:** To assess the "fast responder" patient profile, predicting it from the preliminary complete blood count (CBC) and clinical examination.

**Materials and Methods:** From November 2016 to May 2017 we performed a multicenter prospective open label pilot study in three Italian reference centers enrolling bio-naive plaque psoriasis patients, undergoing the initiation phase secukinumab treatment (300mg subcutaneous at week 0,1,2,3,4). We define fast responders as patients having achieved at least PASI 75 at the end of secukinumab induction phase. Clinical and CBC data at week 0 and at week 4 were analyzed with linear statistics, principal component analysis, and artificial neural networks (ANNs), also known as deep learning. Two different ANNs were employed: Auto Contractive Map (Auto-CM), an unsupervised ANNs, to study how this variables cluster and a supervised ANNs, Training with Input Selection and Testing (TWIST), to build the predictive model.

**Results:** We enrolled 23 plaque psoriasis patients: 19 patients were responders and 4 were non-responders. 30 attributes were examined by Auto-CM, creating a semantic map for three main profiles: responders, non-responders and an intermediate profile. The algorithm yielded 5 of the 30 attributes to describe the 3 profiles. This allowed us to set up the predictive model. It displayed after training testing protocol an overall accuracy of 91.88% (90% for responders and 93,75% for non-responders).

**Conclusions:** The present study is possibly the first approach employing ANNs to predict drug efficacy in dermatology; a wider use of ANNs may be conducive to useful both theoretical and clinical insight.

*J Drugs Dermatol.* 2020;19(12):1241-1246. doi:10.36849/JDD.2020.5006

## INTRODUCTION

The anti –IL 17 biologic secukinumab has been recently shown to be fast and effective not only in clearing psoriasis skin lesions and preventing the associated cardiovascular damage but also for improving quality of life.[1-4]

Despite the large amount of data from randomized control trials (RCTs) now available on secukinumab, "real-life data" remain scarce, yet play a key role in clinicians' daily practice.[5,6] In fact, switching therapies due to lack of efficacy at 16 weeks[7,8] or because of patients experiencing exacerbated side effects

represents not only a substantial financial burden, but is also likely to decrease a patient's adherence and compliance.[9] The identification of patient response profiles is therefore very relevant; however, currently, physician's therapeutic choices regarding biologics are based only on prior experience and a few random case reports described in literature.[10] Both real-life studies and RCTs suggest that several patterns of response are possible.

In this study, we aimed to assess the characteristics of those patients, whose skin symptoms rapidly improved (so called fast-responders) and who achieved at least Psoriasis Area Severity Index (PASI) >75 in the first 4 weeks of treatment. The profiles so far hypothesized had been based on the hypothesis that the variability of the biological data and the treatments that influenced that outcome were related in a linear manner.[11]

Furthermore, psoriasis remains a systemic disease characterized by an intricate network of relationships between genetic[12] and non-genetic factors[13-15]; the relationship is not fully described by linear statistics, the latter having the limit to verify only postulated hypotheses.

An alternative approach to the problem of profiling these patients is now offered by the use of Artificial Neural Networks (ANNs), which allow defining a set of computerized algorithms capable of recreating and mimicking the processes of analysis and learning typical of the human brain. This approach has recently been demonstrated to be more suitable to evaluate complex non-linear phenomena, such as biological systems.[9] We applied this innovative technique to psoriasis patients treated with secukinumab aiming to predict the various patterns of response at 4 weeks of treatment. Our experience taught us that it is important for understanding of our innovative methodology to stress from the beginning that this approach is neither jeopardized by a small sample size nor by outliers.[9] It makes it possible to generalize results yielded from a small population.

## MATERIALS AND METHODS

### Study Design

Patients with moderate-to-severe plaque psoriasis (Psoriasis Area Severity Index (PASI) >10) treated with secukinumab 300 mg were enrolled in a multicenter 1) Galeazzi Hospital, 2) San Donato Hospital and 3) Policlinico in Milan, Italy) prospective open label pilot study between November 2016 and May 2017 (n=23). Other enrollment criteria were age 18–65 years, negative γ□immune-assay (Quantiferon®), and negative serology for hepatitis B (HBV), hepatitis C (HCV) and human immunodeficiency virus (HIV). Exclusion criteria were pregnancy, present or past erythroderma, concurrent autoimmune disease, immunodeficiency, or presence of psoriatic arthritis.

At baseline, patients underwent dermatologic assessment by two board-certified dermatologists who collected medical and pharmacological history, Body Surface Area (BSA) %, Investigator's Global Assessment (IGA), PASI, Dermatological quality of life (DLQI), CIASsification criteria for Psoriatic ARthritis (CASPAR), and joints sonography to exclude psoriatic arthritis or enthesitis. Blood sample were collected, to provide complete blood count (CBC), transaminases, and detection of anti-nuclear antibodies. Specifically, CBC encompasses red blood cells (RBC), white blood cells (WBC), Neutrophils (N), Lymphocytes (L), Platelets (P), Aspartate Aminotransaminase (AST), Alanine Aminotransferase (ALT), P/L, N/L, AST/ALT, ALT/AST. A second evaluation was performed 4 weeks later. To the purpose of this study, patients were categorized as "fast-responders" if they reached PASI 75, and "non-responders" if they failed to reach PASI 75. All side effects were recorded and provided to AIFA (Drug Italian Agency).

Data are expressed as the median [interquartile range (IQR)] or as a percentage. Descriptive linear statistics were used to describe the dataset. Artificial neural networks analysis (ANN) was then applied to the data.

### Artificial Neural Networks Analysis

*Data mining with auto-contractive map*

An Auto Contractive Map (Auto-CM) was used to construct complex mathematical networks and determine the order of variables within the dataset. The Auto-CM is an unsupervised ANN that applies a learning algorithm that assigns similarities or "weights" among the input variables of a unique dataset, thus creating a square matrix of similarity. The Auto-CM Neural Network always starts with the same value, resulting in a perfectly reproducible graphical representation regardless of the number of iterations. The Auto-CM algorithm works by a) transferring signals from the Input and Hidden layers; b) assigning values between the Input layer and the Hidden layer; c) transferring signals into the Output layer from the Hidden layer; d) adjusting connections between the Hidden and the Output layers.

Once the weights are assigned, the Minimum Spanning Tree algorithm (MST) is utilized to graphically represent the shortest combination to connect the variables.[11,16-19] Any connections which generate a cycle are removed to simplify the graphical representation, because all biological systems exist in a state of minimal energy and the graph represents only the fundamental biologic information. This model ultimately aims to reveal hidden trends and associations between variables by creating connections which preserve non-linear associations and visually represents them.

Simply put, the Auto-CM assigns spacing or 'spatializes' variables based on the correlation distance or 'closeness'

between variables, and MST is then used to construct a cohesive graphical representation using only the relevant associations, which can then be used to construct a more complex global picture representing the entire pattern of variation.

We doubled the preselected clinical variables by reshaping the range of values typical of the variable from 0 to 1 and dichotomized the values in two classes, High (H) and Low (L). To do this we used a particular complement transformation, by scaling original variable values from 0 to 1, and creating a complement variable by subtracting the scaled value from 1. See Gironi et al, 2013 for further details.[20]

In this way the system establishes the mutual relationships among variables as defined by the disease. This is a key issue: in non-linear systems, the position of any given values (High or Low) is not necessarily symmetric.

In this manner the value of the original variables represents the "high" values whereas the complementary transformed values make up the "low" values, which are accordingly demarcated in the generated map. This scaling dynamic makes a proportional comparison possible among all the variables and allows for understanding of the connections between each variable.

*Application of supervised neural networks*

In order to assess the predictive value of the subset of variables most closely correlated to a target diagnosis (ie, response to secukinumab) we assembled a data set with seven variables as input and two variables (fast-responder vs non-responder) as output. The evolutionary algorithm called Training with Input Selection and Testing, or TWIST, was employed to select the most representative variables based on the transformation into Low and High.

TWIST works by taking the global dataset, using it to generate the maximal distribution and processing the data into two balanced subsets, each containing a minimal amount of input data allowing for optimal pattern recognition. The TWIST algorithm approach was first described in 2013, and several promising examples of its use have been published.[21-23] In most cases, the TWIST algorithm is comprised of a population of Multilayer Perceptrons.[21-23]

Each ANN is "taught" a subset of the larger global dataset and then tested in a blinded fashion using with another subset. Here, we re-programmed the TWIST fitness function and exchanged the population of Multilayer Perceptrons with a population of simple K Nearest Neighbor (KNN) values, using Euclidean metrics. This alteration accelerates TWIST and makes it more "focused" on discovering f explicit similarities between input attributes. Indeed, TWIST selects the most appropriate attributes from the original attributes and generates a global dataset of attributes, identifying two optimal subsets for training and testing. By applying the training testing protocol to the global data set, we can verify that the attributes selected by TWIST provide good discrimination between fast-responders and non-responders to secukinumab.

Supervised ANNs with four hidden units equipped with a back-propagation algorithm were trained and tested on this data set employing the Leave One Out protocol (LOOP, or rotational estimation), which is a comprehensive method for cross-validation and can predict all cases in a blinded manner. In this protocol, the training model includes all cases except 1, the latter being used as a rotating test case. This is also called "Leave-p-out cross-validation", where a "p" number of observations are kept for validation while the other observations are used in the training set. Every possible combination of "p" observations and other observations are created for cross-validation.

As mentioned in the introduction, having used ANNs in combination with LOOP, the small dimension of the sample size was counterpartyed. A calculation of sample power is not applicable due to the study nature (pilot study) and the non-linear statistics (ANNs).

## RESULTS

### Demographics

We enrolled 23 bio-naïve plaque psoriasis patients, respectively 6 females and 17 males, with a mean age of 39 [34.3–47.3] years, and a mean body mass index (BMI) of 26.7 [23.5–28.6] kg/m$^2$. No statistical differences in BMI were detected. Scalp was involved in 20 of the patients and nail involvement was present in 11 patients. Among the participants, there were 5 ex-smokers (no

**FIGURE 1.** Semantic connectivity map with profiles of fast responders, non-responders and intermediate profiles.

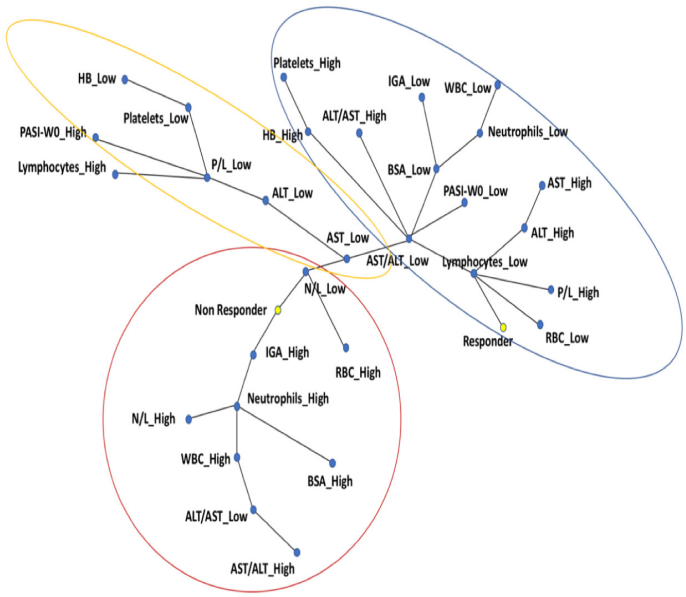

**TABLE 1.**

| Clinical Variables during Week 0 and Week 4, Separated for Fast Responders and Non-responders | | | | |
|---|---|---|---|---|
| Variables | Week 0 (ALL) | Week 0 (fast-responders) | Week 0 (non-responders) | Week 4 (All) |
| Body Surface Area (BSA) (median [IQR]) | 24,45 [17,68-36,60] | 20,85 [16,13-30,93] | 24,85 [18,75-36,60] | 6 [3-8] |
| Investigator's Global Assessment (IGA) (median [IQR], N) | 3 [3-4] | 3 [3-3,25] | 3 [3-4] | 1 [1-2] |
| Psoriasis Area Severity Index (PASI) (median [IQR], N) | 18 [14,4-22,25] | 17 [13,75-20,25] | 18 [14,85-24,00] | 6 [3-8] |
| White Blood Cells (WBC) (median [IQR], U/µL) | 6990 [5770-8190] | 8570 [8372,50-9287,5] | 6320,00 [5470-7725] | 7090 [5770-9090] |
| Red Blood Cells (RBC) (median [IQR], millions/mm3) | 4,9 [4,77-5,28] | 5,05 [3,95-6,11] | 4,91 [4,80-5,21] | 4,9 [4,77-5,3] |
| Hemoglobin (HB) (median [IQR], g/dL) | 15 [13,7-16,05] | 14,7 [13,08-15,98] | 15 [13,85-16,05] | 13 [12,5-13,5] |
| Platelets (P) (median [IQR], Thousands/µL) | 210 [195,5-260] | 235 [182,75-293,25] | 210 [198-241,5] | 214 [195,5-262,5] |
| Neutrophils (N) (median [IQR], N/mm3) | 4229,02 [3332,7-5005] | 5251,15 [4887,15-5602,92] | 4010,56 [3283,35-4777,17] | 4057,44 [3086-5126,7] |
| Lymphocytes (L) (median [IQR], N/mm3) | 1887,6 [1365,49-2219,93] | 2317,88 [1408,68-3441,91] | 1887,6 [1365,49-2156,54] | 2024,4 [1736,34-2621,23] |
| N/L (median [IQR]N) | 1,98 [1,47-2,87] | 2,60 [1,46-4,13] | 1,98 [1,47-2,72] | 1,6 [1,39-2,35] |
| P/L (median [IQR], N) | 0,14 [0,10-0,15] | 0,10 [0,08-0,16] | 0,14 [0,10-0,15] | 0,11 [0,09-0,13] |
| AST (median [IQR], mU/mL) | 20 [16-30,5] | 19 [13,25-34,25] | 20 [17-30,50] | 20 [16-31] |
| ALT (median [IQR], mU/mL) | 19 [16-32] | 16,50 [14,25-30,00] | 21 [16,50-32,00] | 21 [ 16,5-36] |
| AST/ALT (median [IQR], N) | 0,89 [0,75-1,21] | 1,08 [0,92-1,21] | 0,88 [0,75-1,19] | 0,93 [0,78-1,28] |
| ALT/AST (median [IQR], N) | 1,13 [0,83-1,33] | 0,94 [0,83-1,10] | 1,13 [0,84-1,33] | 1,07 [0,78-1,29] |

**TABLE 2.**

| Low and High Transformation of the Variables | |
|---|---|
| BSA_high | BSA_low |
| IGA_high | IGA_low |
| RBC_high | RBC_low |
| HB_high | HB_low |
| WBC_high | WBC_low |
| Platelets_high | Platelets_low |
| AST_high | AST_low |
| ALT_high | ALT_low |
| Neutrophil_high | Neutrophil_low |
| Lymphocyte_high | Lymphocyte_low |
| N/L_high | N/L_low |
| P/L_high | P/L_low |
| AST/ALT_high | AST/ALT_low |
| ALT/AST_high | ALT/AST_low |
| PASI week 0_high | PASI week 0_low |
| Non-responder | Fast-Responder |

**TABLE 3.**

| Variables Selected by TWIST for Prediction |
|---|
| ALT_high |
| IGA_low |
| HB_low |
| WBC_low |
| Neutrophils_low |
| PASI_week_0_low |
| IGA_high |

smoking >5 years), 3 never-smokers, and 15 smokers with 32 [12–219.5] pack/year index. None of the enrolled patients had positive ANA. DLQI at week 0 was 16.[14-18] At week 4, 6 patients achieved PASI > 90 and an additional 13 patients achieved PASI >75. Thus 19 patients were fast-responders and 4 patients' non-responders.

**TABLE 4.**

| Predictive Accuracy With Back Propagation ANNs | | | | | | |
|---|---|---|---|---|---|---|
| ANNs | Training/ Testing sequence | Number of records in testing | Accuracy of responders prediction (%) | Accuracy of non-responders prediction (%) | Overall accuracy (%) | ROC AUC |
| Back propagation 12 hidden units | ab | 13 | 87.5 | 100 | 93.75 | 0.875 |
| Back propagation 12 hidden units | ba | 10 | 100 | 80 | 90 | 0.92 |
| Mean | -- | -- | 93.75 | 90 | 91.88 | 0.88 |

*Artificial Neural Networks Analysis (ANNs)*

We transformed the pre-selected clinical variables (Table 1), using the 15 continuous input variables into 30 input variables constructed for each of the variable two classes: high (H) and Low (L) (Table 2).

The semantic map delineates three main profiles, which were marked with three different colors in Figure 1: fast responders in blue, non-responders in yellow and an intermediate profile in red.

Fast-Responders presented at week 0: Lymphocytes_low, P/L_high, RBC_low, HB_high, WBC_low, Neutrophils_low, Platelets high, AST_high, ALT-high, AST/ALT-high, and clinically PASI_low, BSA_low, IGA_low.

Non-responders presented at week 0: Neutrophils_high, WBC_high, RBC_high, ALT/AST_low, AST/ALT_high and clinically BSA_highand IGA_high. Interestingly, non-responders were related to both low and high N/L, therefore in the next step N/L was discarded by TWIST and depicted as a non-representative variable.

TWIST selected 7 of the 30 attributes (Table 2), namely IGA_low, ALT_high, HB_low, WBC_low, Neutrophils_low, PASI_week_0_low, IGA_high (Table 3).

Table 4 shows the predictive accuracy obtained with a back propagation artificial neural networks equipped with 12 hidden units in forecasting the response or non-response to secukinumab according to baseline variables.

## DISCUSSION

Using for the first time an ANNs based approach on serological (CBC) and clinical data, we outlined precise response profiles of psoriasis patient fast-responders to the drug secukinumab at 4 weeks. Data available at 4 weeks of treatment in real-life are still scanty and have, to date, not been used to obtain a profiling of responders; also, to date, no biomarkers allowing to predict secukinumab efficacy in long and short periods have been identified.[24]

Remarkably, in literature CBC data such as neutrophil/lymphocytes ratio (N/L), mean platelet volume (MPV) or even red blood cell distribution width (RDW) were singularly evaluated in order to predict cardiovascular risk or monitor therapeutic response in psoriatic patients but never as predictors of drug response.[25,26]

In a multicenter, retrospective real-life study of 107 patients treated with secukinumab, Galluzzo et al reported that after four weeks of treatment 41.2% of patients not naïve to biologics and 60% of patients naive to biologics had achieved PASI >75. A univariate logistic regression analysis suggested that the outcome PASI >75 at 4 weeks could be related to age and prior therapies, which would imply that young naïve patients have a higher potential to achieve PASI >75.[5] Remarkably, the presently available literature suggests that the average time to achieve a clinical result could be a significant parameter to predict patients' compliance and adherence in chronic disorders, particularly in psoriasis.[27] In a systematic review, Murage et al concluded that disease severity, reduction of comorbidities, lower out-of-pocket costs, awareness of drug effectiveness, safety, and tolerability were the main determinants for patients' adherence and drug survival.[27]

Hence, one can say that identifying real-life responders to secukinumab has so far represented an unmet need. Linear statistics, based on the generalized linear model, proved to be of limited value in predicting the response to a priori drug treatment.[28] Likewise, multiple regression demonstrated unsatisfactory results not exceeding 80% of the total variance.[29] In contrast, ANNs-based approaches provide a statistical-mathematical method able to determine the existence of a correlation between a series of data and a particular outcome, and when adequately trained, can predict the result against the insertion of data.[10] This characteristic makes ANNs ideal for recognizing patterns and solving complex biologic and therapeutic problems.[30]

Thus, our study used ANNs to depict profiles of fast-responding patients who at week 4 achieved at least PASI >75 using routine blood samples.

The limitation of this study is the small sample size; however, this is a pilot study aimed at investigating the possibility that CBC data may be used to predict patients that would be fast responders to secukinumab at week 4.

This result represents profiling drug response using ANNs. Although the study is a preliminary pilot one, results are encouraging, and the technique should be further pursued. Clinical practice would benefit substantially from profiling data methods applied to biological therapy in psoriasis by decreasing drop out from therapies due to side effects, low adherence, and by increasing the patients' overall quality of life.

## DISCLOSURES

The authors declare no conflict of interest.

*Funding:* This research received no external funding. G.D. is supported by the P50 AR 070590 01A1 grant by the National Institute of Arthritis and Musculoskeletal and Skin Diseases.

## REFERENCES

1. Hawkes JE, Chan TC, Krueger JG. Psoriasis pathogenesis and the development of novel targeted immune therapies. *J Allergy Clin Immunol.* 2017; 140: 645-653.
2. Damiani G, Radaeli A, Olivini A, Calzavara-Pinton P, Malerba M. Increased airway inflammation in patients with psoriasis. *Br J Dermatol.* 2016; 175: 797-799.
3. Fiore M, Leone S, Maraolo AE, Berti E, Damiani G. Liver illness and psoriatic patients. *BioMed Res Int.* 2018; 2018: 3140983.
4. Puig L, Augustin M, Blauvelt A, et al. Effect of secukinumab on quality of life and psoriasis-related symptoms: A comparative analysis versus ustekinumab from the CLEAR 52-week study. *J Am Acad Dermatol.* 2018; 78: 741-748.
5. Galluzzo M, Talamonti M, De Simone C, et al. Secukinumab in moderate-to-severe plaque psoriasis: a multi-center, retrospective, real-life study up to 52 weeks observation. *Expert Opin Biol Ther.* 2018; 18: 727-735.
6. Guerriero F, Orlando V, Monetti VM, Russo V, Menditto E. Biological therapy utilization, switching, and cost among patients with psoriasis: retrospective analysis of administrative databases in Southern Italy. *Clinicoecon Outcomes Res.* 2017; 9: 741-748.
7. Georgakopoulos JR, Ighani A, Phung M, Yeung J. Drug survival of secukinumab in real-world plaque psoriasis patients: A 52-week, multicenter, retrospective study. *J Am Acad of Dermatol.* 2018; 78(5):1019–1020.
8. Damiani G, Conic RRZ, de Vita V, et al. When IL-17 inhibitors fail: Real-life evidence to switch from secukinumab to adalimumab or ustekinumab. *Dermatol Ther.* 2019;32(2):e12793
9. Nast A, Amelunxen L, Augustin M, et al. S3 Guideline for the treatment of psoriasis vulgaris, update - Short version part 2 - Special patient populations and treatment situations. *J Dtsch Dermatol Ges.* 2018; 16: 806-813.
10. Grossi E. Artificial adaptive systems and predictive medicine: a revolutionary paradigm shift. *Immun Ageing.* 2010; 7 (Suppl 1): S3.
11. Buscema M, Grossi E, Snowdon D, Antuono P. Auto-contractive maps: an artificial adaptive system for data mining. An application to Alzheimer disease. *Curr Alzheimer Res.* 2008; 5: 481-498.
12. Hawkes JE, Chan TC, Krueger JG. Psoriasis pathogenesis and the development of novel targeted immune therapies. *J Allergy Clin Immunol.* 2017;140(3):645-653.
13. Thrastardottir T, Love TJ. Infections and the risk of psoriatic arthritis among psoriasis patients: a systematic review. *Rheumatol Int.* 2018;38(8):1385-1397.
14. Adawi M, Damiani G, Bragazzi NL, et al. The impact of intermittent fasting (Ramadan fasting) on psoriatic arthritis disease activity, enthesitis, and dactylitis: a multicentre study. *Nutrients.* 2019;11(3).
15. Damiani G, Watad A, Bridgewood C, et al. The impact of Ramadan fasting on the reduction of PASI Score, in moderate-to-severe psoriatic patients: a real-life multicenter study. *Nutrients.* 2019;11(2).
16. Buscema M, Grossi E. The semantic connectivity map: an adapting self-organising knowledge discovery method in data bases. Experience in gastro-oesophageal reflux disease. *Int J Data Min Bioinform.* 2008; 2: 362-404.
17. Buscema M, Sacco PL. Auto-contractive Maps, the H Function, and the Maximally Regular Graph (MRG): A New Methodology for Data Mining. In: Capecchi V; Buscema M; Contucci P; D'Amore B; editors. Applications of Mathematics in Models, Artificial Neural Networks and Arts: Mathematics and Society. Dordrecht: Springer Netherlands; 2010: 227-75.
18. Kruskal JB. On the shortest spanning subtree of a graph and the traveling salesman problem. *Proc Am Math Soc.* 1956; 7: 48-50.
19. Fredman ML, Willard DE. Trans-dichotomous algorithms for minimum spanning trees and shortest paths. *J Comp Syst Sci.* 1994; 48: 533-551.
20. Gironi M, Saresella M, Rovaris M, et al. A novel data mining system points out hidden relationships between immunological markers in multiple sclerosis. *Immun Ageing.* 2013; 10: 1.
21. Buscema M, Breda M, Lodwick W. Training with input selection and testing (TWIST) algorithm: a significant advance in pattern recognition. *J Intel Learn Syst App.* 2013; 5: 29-38.
22. Buscema M, Grossi E, Capriotti M, Babiloni C, Rossini PM. The I.F.A.S.T. model allows the prediction of conversion to Alzheimer disease in patients with mild cognitive impairment with high degree of accuracy. *Curr Alzheimer Res.* 2010; 7: 173-187.
23. Rotondano G, Cipolletta L, Grossi E, et al. Artificial neural networks accurately predict mortality in patients with non-variceal upper GI bleeding. *Gastrointest Endosc.* 2011; 73: 218-226.
24. Costanzo A, Bianchi L, Flori ML, et al. Secukinumab shows high efficacy irrespective of HLA-Cw6 status in patients with moderate-to-severe plaque-type psoriasis: SUPREME study. *Br J Dermatol.* 2018; 179: 1072-1080.
25. Asahina A, Kubo N, Umezawa Y, Honda H, Yanaba K, Nakagawa H. Neutrophil-lymphocyte ratio, platelet-lymphocyte ratio and mean platelet volume in Japanese patients with psoriasis and psoriatic arthritis: Response to therapy with biologics. *J Dermatol.* 2017;44(10):1112-1121.
26. Yurtdaş M, Yaylali YT, Kaya Y, Ozdemir M, Ozkan I, Aladaş N. Neutrophil-to-lymphocyte ratio may predict subclinical atherosclerosis in patients with psoriasis. *Echocardiography.* 2014;31(9):1095-104.
27. Murage MJ, Tongbram V, Feldman SR, et al. Medication adherence and persistence in patients with rheumatoid arthritis, psoriasis, and psoriatic arthritis: a systematic literature review. *Patient Pref Adheren.* 2018; 12: 1483-1503.
28. Baskin II, Winkler D, Tetko IV. A renaissance of neural networks in drug discovery. *Expert Opin Drug Discov.* 2016; 11: 785-795.
29. Mecocci P, Grossi E, Buscema M, et al. Use of artificial networks in clinical trials: a pilot study to predict responsiveness to donepezil in Alzheimer's disease. *J Am Geriatr Soc.* 2002; 50: 1857-1860.
30. Baldini C, Ferro F, Luciano N, Bombardieri S, Grossi E. Artificial neural networks help to identify disease subsets and to predict lymphoma in primary Sjögren's syndrome. *Clin Exp Rheumatol.* 2018; 36 (Suppl 112): 137-144.

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