Collaboration between a human group and artificial intelligence can improve prediction of multiple sclerosis course: a proof-of-principle study [version 1; referees: awaiting peer review]

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Abstract

**Background:** Multiple sclerosis has an extremely variable natural course. In most patients, disease starts with a relapsing-remitting (RR) phase, which proceeds to a secondary progressive (SP) form. The duration of the RR phase is hard to predict, and to date predictions on the rate of disease progression remain suboptimal. This limits the opportunity to tailor therapy on an individual patient's prognosis, in spite of the choice of several therapeutic options.

**Methods:** Medical students and a machine learning algorithm predicted the course of disease on the basis of randomly chosen clinical records of patients that attended at the Multiple Sclerosis service of Sant'Andrea hospital in Rome.

**Results:** A significant improvement of predictive ability was obtained when predictions were combined with a weight that depends on the consistence of human (or algorithm) forecasts on a given clinical record.

**Conclusions:** In this work we present proof-of-principle that human-machine hybrid predictions yield better prognoses than machine learning algorithms or groups of humans alone. To strengthen this preliminary result, we propose a crowdsourcing initiative to collect prognoses by physicians on an expanded set of patients.
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**Introduction**

The natural course of multiple sclerosis (MS) is extremely variable, ranging from extremely mild to very aggressive forms. Most patients experience an initial relapsing-remitting (RR) phase, in which symptoms appear and fade. Eventually, remissions fail and the disease proceeds to a secondary progressive (SP) form, leading to incremental disability. The palette of disease-modifying treatments is becoming relatively large, in principle opening the possibility to tailor the therapy to meet the specific needs of each patient. Unfortunately, the accuracy of parameters to predict the rate of disease progression remains suboptimal.

Being all the above therapies preventive, in the absence of exact prognostic indicators we have to accept that a proportion of patients is either under- or over-treated. This is a serious concern as the disease can be severely disabling, and some of the available therapies can lead to adverse events that can be worse than the disease itself. Thus, the possibility to formulate a prognosis as exact as possible is becoming increasingly appealing.

In the clinics, as in any other fields of human knowledge, innovative approaches based on machine learning and collective reasoning methods are used in an attempt to succeed where traditional methods of forecasting failed. Machine learning algorithms catch complex relations among existing data to an extent beyond standard regression models. Good performances have been obtained for the diagnosis of Parkinson’s disease and the prognosis of disease progression in amyotrophic lateral sclerosis (Dinov et al., 2016; Küffner et al., 2015). For MS, machine learning algorithms can correctly classify disease course in about 70% of cases of both clinically definite MS and of clinically isolated syndrome (Fiorini et al., 2015; Wotschel et al., 2014; Zhao et al., 2017), a good result that still requires improvement to become of clinical value. Through collective reasoning, or collective intelligence, groups of lay people may perform as well as experts. In principle, the larger the group, the higher the prediction accuracy (see for review Ponsonby & Mattingly, 2015), which led to the development of several crowdsourcing initiatives for diagnostic purposes (for instance, Candido dos Reis et al., 2015; Lau et al., 2016). However, when expert people are involved, even small groups can outperform the best among them, at least when a yes/no answer to well-defined diagnostic questions is requested based on radiographic/histological images, (Kurvers et al., 2016; Sonabend et al., 2017; Wolf et al., 2015). Studies with medical students show that working in pairs ameliorates diagnostic ability, with further improvements when group size increases (Hautz et al., 2015; Kämmer et al., 2017), in line with the core idea of Collective intelligence.

Combination of human and machine predictions into hybrid forecasts exploits human intuitive reasoning and computer classification capabilities, potentially boosting both. Indeed, at least in the case of predicting the course of actions in American football games within the frame of prediction markets, hybrid groups performed better than either humans or computers. (Nagar & Malone, 2011). In this paper, we report the promising results of a preliminary study on the combination of predictions made by humans with those of a machine learning algorithm on the progression of multiple sclerosis in a set of patients. Machine learning and collective intelligence performed almost equally well, but their combination yielded a small, yet statistically significant, improvement in the reliability of the forecasts on disease evolution over different time periods.

These results indicate that it is worth deepening the study of human and machine clinical predictions, as well as the potentiality of hybrid predictions, for which we propose a crowdsourcing approach on a platform specifically designed for this analysis (DiagnoShare).

**Methods and results**

**Dataset structure**

Our dataset is composed by clinical records gathered during 527 visits of 84 outpatients followed at the Multiple Sclerosis service of Sant’Andrea hospital in Rome. Parameters evaluated during each visit are listed in Supplementary Table 1. All patients had clinically definite MS and the RR stage at the time of the visit(s) included in the database. Data potentially revealing the identity of the patients was removed from the shared database. For each visit, we noted if the patient was in RR or SP stage after 180, 360 and 720 days, so that predictions could be compared with the true progression of disease in each patient (Supplementary File: TrueOutcomes.xlsx).

**Ethics**

Use of database for research purposes was authorized by the Ethical committee of Sapienza University (Authorization n. 4254_2016, dated November 2, 2016).

**Classification with machine learning**

Having a correctly labelled dataset, in which each entry is associated to the outcome, we used the Random forest supervised approach to classification (Breiman, 2001; Liaw & Weiner, 2002), using the Scikit-learn toolbox version 0.16.1.

To benchmark the performance of the trained models, we used a modified *k*-folding strategy. Since data was limited (a set of 527 records), and not independent, as it had been obtained from 84 patients, with a simple random *k*-folding the training set would be composed of many correlated same-patient data. Even worse, some of the data from patients present in the training set would be used to validate the model in the benchmarking stage. As a consequence, the model would overfit the training data, misleadingly showing very good performance. Being presented with many data from the same patient, the model optimizes its ability in recognizing patients themselves, through their highly correlated clinical variables.

To avoid these problems, we developed an alternative approach, training the algorithm with the following rules:

1. We excluded all visits from one patient from the dataset
2. We built 50 training sets, each composed by 83 records, one (randomly chosen) for every remaining patient
3. We trained 50 Random Forest models, one for each training set.
4. We computed the probability of the transition from RR to SP by averaging the predictions of the 50 models on all the visits of the excluded patient. Predictions consisted in scores from 0 (Extremely unlikely) to 1 (Highly probable).

We repeated the procedure for the 84 patients, obtaining an estimation of the probability of the RR to SP transition for each of the 527 clinical records. Three different prediction delays were considered, namely 180, 360 and 720 days. Results obtained are presented in Supplementary File: RF_Predictions.xlsx. The performance of the model was estimated by the Area Under the “Receiver Operating Characteristic” (ROC) Curve (AUC) computed on all the 527 examples. The AUC values obtained are shown in Table 1.

### Human predictions

Forty-two medical students in the final two years of their course (Sapienza University, Rome Italy, based within Sant’Andrea hospital), volunteered to participate in the task. All were familiar with clinical records in general, and were instructed on the meaning of each entry present in the medical records of MS patients. This part of the study was approved by the Ethical Committee of the Department of Physiology and Pharmacology, Sapienza University on July 13, 2017.

For adequate comparison with computer predictions, students evaluated 50 medical records, collected in a questionnaire, randomly extracted from the same dataset used for machine learning and estimated the probability that the patient would progress to the SP phase within 180, 360 and 720 days. Scores were from 0 (Extremely unlikely) to 5 (Highly probable). Predictions (see Supplementary file Student_Predictions.xlsx) were analysed, using the AUC.

On average, each clinical record was evaluated by 4 of the 42 students.

Predictions were less accurate than those proposed by machine learning (Table 1). Standard deviation was larger for the 180 day time point, indicating that opinions on the long-term evolution of the disease are more widely shared, although they are not more precise. To evaluate the impact of collective intelligence, we measured the performance of Pairs, considering all visits evaluated by at least two individual students, randomly selecting only 2 scores when more were available. The prognoses were averaged before computing the AUC, which showed a marked increase (Table 1). Aggregation of all singles (Group) yielded a further small increase in the performance of the forecasting (Table 1), which almost equalled that of random forest algorithm.

### Hybrid predictions

We next integrated human and computer predictions into a hybrid prediction, which combines human clinical reasoning with the classification approach of machine learning algorithms. These different “ways of reasoning” possibly lead to quite divergent predictions on individual cases, a complementarity that should be exploited taking the difference into account when creating hybrid predictions.

To compare the two sets on equal grounds, predictions on each clinical record were ranked in order of consistence, for the two agents separately, that is agreement between students or decision trees in the random forest. Then, a normalized ranking was assigned, ranging from 1 for the most consistent predictions to 0 for the most scattered. The hybrid prediction score for each clinical record was then obtained by summing the two squared rankings, to emphasize the contribution of the most consistent agent.

Note that a linear combination of rankings would result in a worse performance of hybrid predictions, as the information about the most consistent prediction between the two agents would be lost. A similarly degraded performance is observed when predictions are not ranked.

Since our dataset is relatively small, as is the number of students that evaluated the clinical records, we used a bootstrap procedure to evaluate the statistical significance of the improvement. The bootstrap (Efron & Tibshirani, 1994; Felsenstein, 1985) consists in random sampling of the dataset that allows the estimation of confidence intervals.

As shown in Table 1 and Figure 1, hybrid predictions yielded a small but statistically significant (P<0.001) improvement in the prediction of disease course in time. Significance was evaluated from confidence limits using standard methods (Altman & Bland, 2011).

### Table 1. Predictions on disease course by different agents.

<table>
<thead>
<tr>
<th>Agent</th>
<th>180 days</th>
<th>360 days</th>
<th>720 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random Forest</td>
<td>0.710</td>
<td>0.670</td>
<td>0.679</td>
</tr>
<tr>
<td>Singles (n=42)</td>
<td>0.57 ± 0.15</td>
<td>0.57 ± 0.11</td>
<td>0.57 ± 0.10</td>
</tr>
<tr>
<td>Pairs</td>
<td>0.68</td>
<td>0.65</td>
<td>0.65</td>
</tr>
<tr>
<td>Group</td>
<td>0.703</td>
<td>0.667</td>
<td>0.666</td>
</tr>
<tr>
<td>Hybrid predictions</td>
<td>0.725*</td>
<td>0.694*</td>
<td>0.696*</td>
</tr>
</tbody>
</table>

For each clinical record, the indicated agents evaluated the probability that disease evolved from the RR to the SP phase after 180, 360 or 720 days. Data represent the AUC values obtained for each method. *: P<0.001 when compared to Group or Random Forest values at the same time points.
Dataset 1. True outcome of patients, indexed as clinical records
http://dx.doi.org/10.5256/f1000research.13114.d188355

More than one clinical record is pertinent to each patient. T_180, T_360, T_720: clinical conditions of the patient 180, 360 and 720 days after the visit in which clinical record was obtained. 0: still in RR phase; 1: transitioned to SP phase.

Dataset 2. Predictions on individual clinical records made by medical students
http://dx.doi.org/10.5256/f1000research.13114.d188356

Each student worked on a questionnaire (lines labelled "questionnaire", column B.) listing 50 clinical reports (lines labelled "Clinical report N", columns B to AY) and made a prediction on the probability of RR –to–SP transition within 180, 360 and 720 days (lines labelled Prediction @ 180, 360, 720, columns B to AY)
The numbering of Clinical reports is the same used in Dataset 1.

Dataset 3. Predictions on individual clinical records made by a Random Forest algorithm
http://dx.doi.org/10.5256/f1000research.13114.d188357

Score_180, Score_360, Score_720: Probability that the patient will transition to SP phase within 180, 360 and 720 days after the visit in which clinical record was obtained. The numbering of Clinical reports is the same used in Dataset 1.

Discussion
A number of studies have investigated the possibility to increase the appropriateness of clinical decisions through collective intelligence of human groups (for instance, Kurvers et al., 2016; Sonabend et al., 2017; Wolf et al., 2015) or machine learning algorithms. The latter approach has been used in a great variety of tasks, and its value in the medical realm is possibly overstated (Chen & Asch, 2017). However, machine learning methods performed well for prognostic predictions (Küffner et al., 2015; Zhao et al., 2017). In particular, the Random forest approach provided good predictions on ALS course (Küffner et al., 2015).

In this work we present proof-of-principle that human-machine hybrid predictions attain prognostic ability above that of machine learning algorithms and groups of humans alone.

The duration of the RR phase before its shift into progression has always been difficult to predict, and possibly the random occurrence of relapses (Bordi et al., 2013) contributes to the lack of univocal indicators. No approach, no matter how good, can yield certainty when cause-effect relations are unknown. Thus, our aim has been to obtain predictions on the probability that MS patients in the RR phase will convert to a SP form within a certain time frame. Predictions on the course of real patients were provided by medical students and a random forest algorithm. A significant improvement of predictive ability was obtained when predictions were combined in a non-linear manner, with a weight that depends on the consistence of human (or algorithm) forecasts on a given clinical record.

This result can be considered in agreement with several studies on different medical issues showing that predictor’s confidence correlates very well with the correctness of the prediction (Detsky et al., 2017; Hautz et al., 2015; Kämmer et al., 2017; Kurvers et al., 2016). Indeed, the concordance of different members of a given group (students or runs of the random forest model) can be taken as indicating that the agent is “sure” of the forecast.

In spite of the relatively basic machine learning technique used, the small number of students involved and their limited clinical knowledge, this work suggests that hybrid predictions can be useful to improve the prognosis of MS course. A deeper study is therefore of interest. To recruit more and more skilled humans, we propose a crowdsourcing initiative called DiagnoShare that is being advertised among physicians.

Figure 1. Hybrid Students – Machine Learning predictions outperform both human group and computer alone. The box plot shows the distribution of the AUC obtained from the bootstrap. In particular, the colored boxes correspond to quartiles, while the lines show the full range of the generated AUCs.
A reliable tool to predict MS progression can be of aid to clinicians to tailor therapy to each patient, but also in clinical trials, to evaluate whether drugs modify the estimated outcome of each enrolled patient, as proposed for ALS (Küstner et al., 2015).

In the long run, it is possible that further developments in our ability to combine collective reasoning and machine predictions will have a profound impact also on the organization and management of medical care, particularly in hospital settings.

Data availability
Dataset 1: True outcome of patients, indexed as clinical records. More than one clinical record is pertinent to each patient. T_180, T_360, T_720: clinical conditions of the patient 180, 360 and 720 days after the visit in which clinical record was obtained. 0: still in RR phase; 1: transitioned to SP phase. DOI: 10.5256/f1000research.13114.d188355 (Tacchella et al., 2017a)

Dataset 2: Predictions on individual clinical records made by medical students. Each student worked on a questionnaire (lines labelled “questionnaire”, column B.) listing 50 clinical reports (lines labelled “Clinical report N”, columns B to AY) and made a prediction on the probability of RR—to–SP transition within 180, 360 and 720 days (lines labelled Prediction @ 180, 360, 720, columns B to AY)

Dataset 3: Predictions on individual clinical records made by a Random Forest algorithm. Score_180, Score_360, Score_720: Probability that the patient will transition to SP phase within 180, 360 and 720 days after the visit in which clinical record was obtained. The numbering of Clinical reports is the same used in Dataset 1. DOI: 10.5256/f1000research.13114.d188357 (Tacchella et al., 2017c)

Competing interests
No competing interests were disclosed.

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All funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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Supplementary material
Supplementary Table 1: Parameters evaluated for each patient and included in clinical records.

Click here to access the data.

References
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