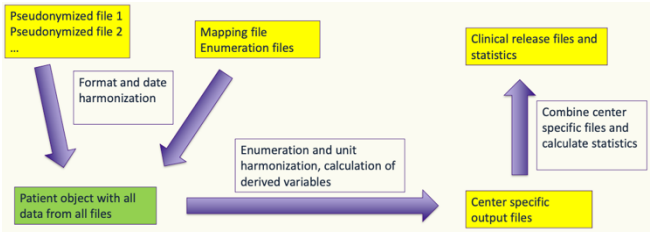
MultipleMS newsletter March 2022

In this newsletter we provide a general update on our work progress, after some difficult years in which many institutions around the world faced a very different working environment, including pressure on clinical duties for many of our central partners.

We present a progress report per work package, with a short introduction of the work in each package, followed by a short overview of the current status and remaining work.



WP2 – Data infrastructure

Complete status: 80 %

Goal: To construct a data infrastructure enabling multidimensional data integration of omics, clinical and lifestyle data resulting in the largest and most comprehensive data set of MS patients. The major objectives of the WP2 are to i) establish a bioinformatics portal for secure and efficient data sharing between partners and to ii) build the largest today, harmonized, multi-dimensional data repository for Multiple Sclerosis. WP2 has also created a data dictionary for the consortium and developed novel methods for data harmonization.

Milestones reached: WP2 with significant input from the analysis teams has reached the majority of its milestones including 1) providing an accessible data resource for storing, managing and sharing data of the existing and prospective MS cohorts; 2) the clinical data from retrospective MS cohorts have been collected and harmonized and is available for sharing; 3) a data portal for relevant public datasets is available at EBI; 4) QC:d and imputed genomic data is available for sharing; 5) most of the MRI data is collected, harmonized and available for sharing.

Biggest challenges: the delays in finalizing the DTAs caused by the new GDPR requirements, getting the original datasets from the cohorts, and building a comprehensive data dictionary for very heterogeneous and occasionally sparse datasets.

Upcoming work: We look forward to finalizing and sharing the lifestyle data of the retrospective cohorts with the analysis teams and adding new omics data modalities to the data resource. We also hope to be able to complete some of the data modalities still lacking data from individual cohorts. As soon as the prospective cohort reaches the 3 year follow-up, we will combine the clinical, omics (genomics, epigenomics and transcriptomics), immunophenotyping, and MRI data as well as the lifestyle data into the research data resource for sharing with the analysis teams.

WP3 – Mechanistic heterogeneity

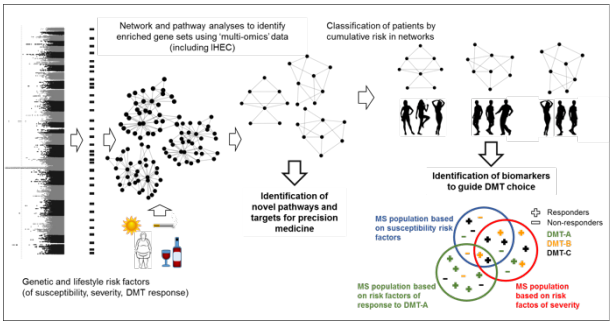
Complete status: 70 %

Goal: We have been looking for genetic factors that can explain different outcomes in MS. This will, we think, help us identify groups of MS patients that will have similar disease courses, and help us predict responses to treatment and outcomes. We also hope to find the specific cellular causes of these differences.

Milestones reached: We have centralized genetic, clinical, and lifestyle data across our participating centers. We have harmonized the genetic data, ran genetic analyses across all samples, and are now looking for specific biological pathways that explain differences between patients.

Biggest challenges: Our goal has been to centralize genetic and clinical data from our participating centers across multiple EU countries in one place, so we can analyze them together. The changes to EU privacy laws (the GDPR) that came into force just as the project was starting meant that legal teams from each institution had to interpret these laws, negotiate their interpretations, and eventually arrive at a data-sharing framework that was acceptable to all. Amendments and clarifications to the GDPR over the interval made this process even longer. Once this was complete, we then had to harmonize data (detailed in the WP2 report) across centers. Now this is done, we are finally able to analyze these data.

Upcoming work: We finally have access to project data across centers and are starting to look for subgroups of MS patients with different outcomes that can be explained by genetic factors.



WP4 – Outcome heterogeneity

Complete status: 70 %

Goal: To use factors associated with MS severity/outcome to identify stratified patient populations that we believe will benefit from different treatments. This involves first identifying factors associated with MS severity/outcome.

Milestones reached: We have identified genetic variants associated with different measures of severity. The most mature analysis is that of MS severity measured using ARMSS derived from EDSS. This analysis has been carried out together with IMSGC and is the result of many different research groups and clinics working together. Other analyses are not quite as mature and also do not have data from quite so many research groups and clinics. These include longitudinal EDSS measurements, response to treatment as well as MS biomarkers.

Biggest challenges: There have been three big challenges; 1) sharing of data was slow mainly due to problems with getting data sharing agreements in place that are in agreement with GDPR. 2) harmonization of outcome variable has taken quite some time (this is work that has been carried out in WP2, with input from WP4). 3) It has taken a while to get good quality imputed genotypes in place for the datasets that we are using. This is work that has been carried out by WP3, but without which analyses in WP4 could not be done.

Upcoming work: We need to finalize the analyses which identify risk factors associated with MS severity/outcome. Then we need to use that data to try to cluster patients into what we think will be biologically meaningful groups. We then need to test if these groups have

responded differently to existing treatments and attempt to identify biomarker(s) that can identify such patient clusters.

WP5 – Clinical applications

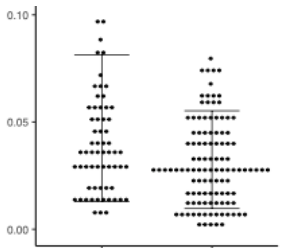
Complete status: 75 %

Goal: WP5 focuses on the validation of algorithms to predict the future course in recently diagnosed treatment-naive patients with multiple sclerosis and clinically isolated syndrome. We have recruited more than 500 patients and performed extensive clinical, paraclinical, and multi-Omic phenotyping. Patients have been followed over a period of up to 3 years to detect clinical and subclinical disease activity.

Milestones reached: 509 patients were recruited. So far 347 patients reach the two-year endpoint. Biosampling was performed in all patients. Genotyping and Immune cell phenotyping was performed. Additional multi-Omic analyses are in progress. MRI data were uploaded and are ready for analysis.

Biggest challenges: We are still missing an algorithm to be validated in the prospective cohort (primary and secondary endpoints).

Upcoming work: Completion of all 24 and most 36 months visits. Completion of clinical data in the database. Shipment of biosamples for further phenotyping.



WP6 - Tools

Complete status: 60 %

Goal: The main goal of WP6 is building models for predicting diagnosis, severity, progression, and response to DMT and packaging these models a) as R-packages for Biostatisticians and bioinformaticians, with programming skills, and b) as user-friendly commercial package for patient stratification. The team from Barcelona is applying advanced network analysis to link the different scales of biology and clinical phenotype for improving our understanding of the pathogenesis of the disease and to develop biomarkers for monitoring the course of MS.

Milestones reached: Models have been developed and are in process of validation. The first version of User interface has been designed. For the Barcelona team, the analysis is still on-going, pending on data availability.

Biggest challenges: Developing robust models ready for validation. The consortium has refined and harmonized the datasets making them available for analysis

Upcoming work: We will focus on preparing the R package and software. Furthermore, we expect to complete our analysis by April 2022 and provide a multi-layer network model of MS

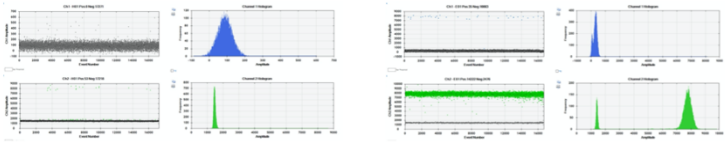
WP7 - Guidelines

Complete status: 60 %

Goal: To formulate final MS guidelines on biomarker-guided therapy, tailored to individual MS patients and the individual European Member States, and a roadmap for their implementation.

Milestones reached: Review of currently used MS guidelines and use of biomarkers in clinical practice across Europe; Development of guidelines for reporting biomarker results and their classification into different levels of evidence.

Biggest challenges: To identify clinically relevant body-fluid biomarkers originated from the project which could be introduced into clinical management of patients
Upcoming work: To identify and classify clinically relevant biomarkers originated from the project which could be introduced into clinical management of patients. To validate and formulate MS guidelines on the implementation of biomarkers, and mostly body-fluid biomarkers, in clinical practice.



WP8 – Dissemination and exploitation

Complete status: 85 %
Goal*:* WP8 is responsible for the clinical translation, dissemination, and exploitation. The goal is to communicate the progress and findings of the project to stakeholders and the general population. Furthermore, we will be responsible for a portfolio of intellectual properties that may result from the project and will create a business plan for the consortium to ensure continued existence beyond the funded period.
Milestones reached: We have created and maintained a website, social media presence, newsletters, and internal and external mailing lists. A stakeholder database is in place and is being expanded with newly identified stakeholders routinely and we completed two workshops for which key stakeholders were invited. The business plan and intellectual property rights portfolio are in draft and will be completed closer to the end of the funding period.
Biggest challenges: The implementation of the GDPR delayed the startup of the activities in the project considerably, in combination with difficulties in completing the projected activities and physical meetings this resulted in an overall delay of results. Since much of the intellectual property was expected to be filed based on the projects' results this portfolio is also delayed.
Upcoming work: During the final phase a business plan will be completed that will ensure that MultipleMS can continue to be productive in scientific terms after the project funding period ends in December 2022. Similarly, the portfolio of intellectual property will be completed as soon as a complete overview is available. The newsletters and website updates will be issued as soon as there is breaking news or relevant updates from the project.