

/Predi-COVID/



NEWSLETTER

A word from Dr Guy Fagherazzi

Dear Predi-COVID participants,
Four years after the initial launch of Predi-COVID – which has now evolved into the broader national umbrella programme CoVaLux – we wanted to take a moment to personally update you on the latest developments of the study and express our deepest gratitude for your unwavering support since the very beginning.



In this short newsletter, you will find out more about the tangible results that have stemmed from the Predi-COVID project and that YOU have contributed to generating. Indeed, none of the advancements reported here would have been possible without your participation.

The samples and data collected as part of Predi-COVID have enabled our researchers to carry out and publish several studies exploring in detail the factors that determine the severity of COVID-19 disease, the evolution of the symptoms and the impacts of infection both at the biological level and in terms of quality of life. Moreover, new projects have been launched, aiming to further understand the long-term impact of COVID-19 on various aspects, including on cognition. You will find out more about two innovative digital health projects and get the opportunity to show your support again by participating in one of them, which is currently recruiting, should you be interested to do so.

Once again, on behalf of the entire Predi-COVID team, thank you for your dedication and wish you an enjoyable read.

Yours sincerely,

Guy Fagherazzi
Principal investigator of Predi-COVID

4 years of Predi-COVID: what have we learnt?

The results of the studies stemming from Predi-COVID are illustrated below.

“Long-COVID”: a public health challenge

In a collaborative [study published in August 2022](#), LIH researchers looked at the persisting symptoms of COVID-19, commonly referred to as “long COVID”, exploring the health status of Predi-COVID cohort study participants 12 months after their initial infection. They found that, among the 289 participants who completed the 12-month questionnaire, almost 60% reported at least 1 persisting symptom, with some even experiencing more than 10. These included neurological, cardiovascular and gastrointestinal symptoms, as well as difficulties with sleep, breathing, and feelings of discouragement about their health. Interestingly, participants who initially experienced a more severe form of the illness were more likely to continue facing symptoms compared to those with milder or asymptomatic cases. The research also identified clusters of symptoms that often occurred together. For example, issues like confusion tended to be associated with memory loss, headaches, tired eyes, irritability, anxiety, shortness of breath, and fatigue. *“It is therefore not surprising that, overall, 12.5% of the participants stated they could not envisage coping with their symptoms in the long term, proving that Long-COVID indeed poses a significant burden on their quality of life and that precision health strategies are necessary”*, says Dr Aurélie Fischer, scientist within the Deep Digital Phenotyping (DDP) Research Unit of the LIH Department of Precision Health (DoPH) and first author of the study.

Mental health: a risk factor for COVID-19 recovery

In parallel, a [study led by DDP scientist Dr Gloria Aguayo](#) looked at the possible association between psychological conditions, such as anxiety or mood disorders, prior to SARS-COV-2 infection, indicated by the use of psychotropic medications, and the severity of and recovery from COVID-19. The analysis showed poorer recovery during the first 2 weeks after the infection in individuals with pre-existing psychological conditions, who also had a higher risk of developing the “long-COVID” syndrome. The association between depression and COVID-19 severity could be explained by the shared inflammatory processes between the two conditions, leading to an increase in inflammatory biomarkers. Similarly, the association between pre-existing anxiety and COVID-19 severity could be explained by lower levels of lymphocytes in patients with anxiety, while elevated cortisol levels resulting from psychosocial stress can also be associated with decreased immunity. *“Our findings emphasise the importance of considering mental health factors in the personalised care of people with COVID-19 and underscore the need for a comprehensive understanding of the interplay between mental health and infectious diseases”*, says Dr Aguayo.

Predicting the effectiveness of COVID-19 immunity

[In a collaborative study](#), LIH researchers investigated the immune responses of individuals with different severities of COVID-19, focusing on those with mild symptoms and asymptomatic cases. They observed the early activation of specific immune cells and cytokines in mild COVID cases within three days of diagnosis, suggesting a coordinated and effective immune response. Conversely, hospitalised patients showed impaired responses from key innate immune cells at the beginning of the study. Importantly, the study revealed that early T cell and dendritic cell responses could predict the effectiveness of later antibody responses in mildly symptomatic patients but not in hospitalised ones. *“Overall, we highlighted the importance of considering the full spectrum of immune responses in COVID-19, particularly in mild and asymptomatic cases, suggesting that early immune activation may play a crucial role in determining disease outcomes. These findings could contribute to the development of strategies for predicting and managing COVID-19, including vaccination approaches”*, explains Dr Feng Hefeng of the LIH Department of Infection and Immunity (DII).

COVID-19: How are our gut bacteria affected?

Research Luxembourg scientists investigated how mild-to-moderate COVID-19 impacts the gut microbiome, considering the rising reports of gastrointestinal symptoms in infected individuals. [The study, published in the journal Microbiome](#), revealed that COVID-19 patients exhibit an increased infective capacity in their gut microbiome. Analysing stool samples from COVID-19 patients and healthy controls, researchers found no significant structural differences in the gut microbiome composition between the two groups. However, COVID-19 individuals showed heightened infective potential, indicated by increased virulence factors and antimicrobial resistance genes. Notably, certain bacterial families previously considered beneficial displayed higher prevalence in COVID-19 patients, potentially shifting from protective to harmful roles. Additionally, the study identified increased presence of specific viral genes in COVID-19 patients. This heightened infective capacity of the gut microbiome in COVID-19 patients may predispose them to additional infections. The findings shed light on potential longer-term effects of COVID-19 and may aid future research exploring links between infective competence and disease outcomes.

A novel biomarker of COVID-19 severity and mortality

With the aim of fulfilling the need for reliable and non-invasive indicators to manage COVID-19 patients at risk of severe outcomes, LIH researchers investigated the potential of circulating miRNAs – small non-coding RNA molecules secreted into the circulation that regulate cell function – as biomarkers of disease severity and mortality in a broad spectrum of disease manifestations. By analysing levels of plasma miRNA in a diverse patient cohort, the scientists identified a specific type of miRNAs, namely miR-144-3p, as being significantly altered in response to disease progression. After rigorous validation involving a total of 179 COVID-19 patients and 29 controls across three independent centres, the team brought forward the value of miR-144-3p as a predictor of non-critical or critical disease and of mortality, underscoring its potential of as a non-invasive, adaptable tool for risk assessment and prognosis in COVID-19 patients. [These results were published](#) in the prestigious Nature journal group “Scientific Reports”.

Our work continues!

Despite the remarkable progress made by our scientists, more research is required in order to clarify additional aspects pertaining for instance to the evolution of Long COVID symptoms over longer periods following initial infection, and the persistence of the impacts on the gut microbiome, among others. Below a list of currently ongoing studies:

- **2-Year Trajectories of Long COVID symptomatology and their determinants: results from the Predi-COVID cohort study.** Building on the previous work on Long COVID symptomatology, researchers are currently analysing the symptoms from Predi-COVID participants after 2 years of follow-up, in order to identify different patterns of evolution and the specific factors that determine such developments.
- A study aiming to elucidate the **predictive potential of dysregulated early molecular immune signatures** during the resolving phase of COVID-19 infection for the development and stratification of Long COVID;
- A study aiming to assess the **persistence of altered infective competence in the human microbiome** in relation to Long COVID.

Looking ahead: monitoring Long COVID through the voice

An interview with Dr Aurélie Fischer



In this short interview, Dr Aurélie Fischer, scientist within the Deep Digital Phenotyping (DDP) Research Unit of the LIH Department of Precision Health (DoPH), introduces a satellite project aiming to co-design a digital App that uses voice to monitor persisting symptoms related to Long COVID.

Dr Fischer, why is Long COVID still a public health priority?

A.F.: Although the peak of the COVID-19 pandemic seems to be behind us, the study we performed on Predi-COVID participants on the evolution of Long-COVID symptomatology over a period of 12 months revealed that many participants still experienced symptoms up to 1 year after their initial COVID-19 infection, and that their quality of life is therefore highly impacted. Long COVID is still a poorly known syndrome and people affected by it often feel lonely and sometimes even abandoned by the healthcare system. This makes it a priority in terms of public health policy and, consequently, for us as researchers.

How can digital health solutions help address these issues?

A.F.: Our team at the Deep Digital Phenotyping (DDP) research unit is working on the development of new digital health solutions, and particularly on voice as an innovative tool for the remote monitoring of symptoms related to a variety of different diseases and conditions.

In this context, and given the established burden of Long COVID on public health, I decided to start a PhD project to develop a new digital tool to monitor persisting symptoms related to COVID-19 and to assess to which extent voice could be an added value in this tool. The idea is to be able to develop and share with people affected by Long COVID a companion tool that helps them manage their symptoms on a daily basis and follow their evolution, acting as a support to facilitate communication with healthcare professionals in charge of their care.

Can you tell us more about the approach to the development of the app?

A.F.: The strength of the project’s approach lies in its close collaboration with the final end users. Indeed, we have set up the methodology so as to be able to assess the needs and expectations of people with Long COVID with respect to this type of digital solution, and to co-design the digital solution together with Long COVID patients and their healthcare providers. This will ensure that the app will meet their needs and, therefore, provide a tangible benefit when it comes to managing and living with persisting symptoms.

When can we expect the app to be available?

A.F.: Based on the preliminary results of the study, a first version of the smartphone application is currently under development and should be available for people with Long COVID during the 1st quarter of 2024. Our prime goal is to provide support and help to people living with the debilitating and persisting consequences of COVID-19, and I therefore hope this application will have a concrete positive impact on their daily lives.

Thank you for your inspiring work, Dr Fischer!



We still need you! The DIGICOG project is recruiting

Do not miss the chance to contribute to advancing our knowledge on the cognitive impacts of COVID-19. The DIGICOG project is actively recruiting!

- **WHAT:** The DigiCog project (*Monitoring “long-COVID” impact on cognition via digital neuropsychological assessment*), led by Dr Magali Perquin of the DoPH, aims to investigate persisting symptoms of COVID-19 on cognition, more than 1 year after initial infection.
- **HOW:** The project will combine the results of classical neuropsychological evaluations with a cognitive screening performed through the novel non-invasive “VIEWMIND” digital tool. This digital solution leverages artificial intelligence to deliver accurate results on cognitive performance, related to functioning areas of the brain. The study is mainly conducted on a sub-group of the Predi-COVID cohort and relies on epidemiological and socio-demographic data collected within Predi-COVID project.
- **WHY:** The project aims to test and validate a novel device for the fast evaluation of cognitive functions using eyes movement, in order to study potential cognitive long-term issues arising after COVID-19 infection, and exploring how cognition could be preserved. It will also help bring the tested device to market, enabling the improved diagnosis and monitoring of people with cognitive impairments as a consequence of long COVID.
- **HOW TO PARTICIPATE:** If you are interested in participating in this study, you can contact the Clinical and Epidemiological Investigation Center (CIEC) by email at digicog@lih.lu or at the following phone number : + 352 26 970 400.

Predi-COVID in figures

TOTAL NUMBER OF ADULT PARTICIPANTS



1,136

443 of whom provided biological samples

TOTAL NUMBER OF CHILD PARTICIPANTS



72

44 of whom provided biological samples

TOTAL NUMBER OF HOUSEHOLD MEMBERS INCLUDED:



81

76 adults and 5 children

TOTAL NUMBER OF VISITS PERFORMED BY LIH NURSES



1,175

NUMBER OF BIOLOGICAL SAMPLES COLLECTED



5,045

TOTAL NUMBER OF QUESTIONNAIRES COMPLETED:



14,950

MORE THAN **6,000** VOICE RECORDINGS COLLECTED

Find out more!

Should you wish to find out more about the various projects stemming from Predi-COVID and the related outcomes, please visit the dedicated website:

<https://www.lih.lu/en/predi-covid-scientific-output/>

