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**TITLE: Evaluation of MULTIsystemic disease and immunological predisposition in patients with previous COVID19 (MULTICOVID)**

**-Background:** Coronavirus Disease 19 (COVID-19) is a polymorphic disease with variable presentations from asymptomatic cases to extremely serious conditions with a mortality rate up to 5-6% of cases. The lung is the target organ of SARS-Cov-2 infection, but acute or late inflammatory-vasculitis damage can become multisystem, involving organs such as the brain and heart [1]. The pathophysiological process of COVID-19 is not yet fully elucidated, an individual predisposition, an abnormal autoimmune and cytochemical reaction can play an important role in the multiorgan response to infection and therefore contribute to the broad clinical spectrum of the COVID-19 disease [2-5].

**Aims:** The present study involving the G. Monasterio Foundation and the Institute of Clinical Physiology aimed to: 2) identify early signs of morbidity associated with the outcomes of multi-organ disease 3) prevent the development of diseases caused by COVID-19 outcomes (such as heart failure, pulmonary fibrosis) 4) identify both specific variants in the genes involved in the activation of the immune response for the definition of individual susceptibility and circulating biomarkers of the onset and progression of the disease 5) assess the level of psychophysiological stress

**Methods:** 200 patients will be enrolled, aged between 12 and 80 years, with a previous COVID-19 infection symptomatic (history of hospitalization), paucisymptomatic (home care) or asymptomatic (with at least 1 positive test for COVID- 19). The study will last in 24 months: a multimodal screening will be performed including: 1) cardiological evaluation: EKG echocardiogram, cardiac magnetic resonance, laboratory tests 2) neurological evaluation: physical examination, Magnetic Resonance; 3) Lung evaluation: spirometry test, thoracic ultrasound, blood gas analysis; 4) assessment of individual predisposition with quantification of genetic and biomarkers associated with the systemic inflammatory state or the development of interstitial tissue fibrosis, hypertension, endothelial activation, and increased vascular permeability 5) survey questionnaire of the level of psychophysiological stress (PSS; Scale for Perceived Stress). In the event of abnormalities being found at the initial evaluation, the indication for complementary examinations such as pulmonary or coronary CT, MRI under stress, cardio-pulmonary tests will be evaluated.

A personalized clinical-instrumental follow-up will follow after 6-11 months. This innovative diagnostic approach provides for the early diagnosis of any residual disease after clinical and biological recovery from COVID-19 disease and could contribute to a greater pathophysiological understanding of the disease with possible implications in the field of prevention and therapy.

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Hypothesis: It is expected to identify a percentage of the enrolled patients, apparently recovered from

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COVID-19 infection but still with residual defects. In particular, it is expected to identify signs of COVID-19 myocarditis, which could remain evident even months after the acute event, as in others viral myocarditis which could lead to long-term cardiovascular disease and eventually to be the anatomical substrate of threatening ventricular arrhythmic. It is hypothesized, also, that some patients with previous pulmonary involvement, even in the case of pauci or asymptomatic presentation, may present residual lung function disorders. Similarly, brain lesions could, also, lead to morbidity at the follow-up of affected patients. Furthermore, it is hypothesized that patients who have developed the disease may have greater changes in the biomarkers associated with inflammation and fibrosis, compared to those who have remained asymptomatic. In this sense, the research for genetic predisposition factors associated to the immune response could provide important information to understand the mechanisms that lead in some patients to the development of severe manifestations and in others to have few symptoms or even to be completely asymptomatic. -----  
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