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Interim Guidance on Long-COVID Management Principles

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Interim Guidance on Long-COVID Management Principles. Version of July 1, 2021.

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More than one year into the SARS-CoV-2 pandemic, it has become clear that, for a considerable proportion of individuals affected by COVID-19, significant clinical manifestations may persist after the first weeks of the acute symptomatic phase, with a heterogeneous complex of subacute and chronic symptoms that preclude a full return to the previous state of health. This persistence of symptoms, which may affect patients of any age and with varying degrees of severity of the acute disease, has been recognized as a specific clinical entity, called Long-COVID. Although the breadth of the symptomatology represents a challenge in terms of clinical definition and epidemiology, this condition has a significant clinical impact. The management of Long-COVID requires special measures and funding and dedicated diagnostic and care programs, based on a multidisciplinary approach. This document summarizes the current framework of this new condition and provides general principles for its management, in line with the recommendations issued by the World Health Organization.

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Premise

The SARS-CoV-2 pandemic has affected and continues to affect a very large number of individuals, with a huge burden in terms of disease and mortality (1-2). Although the clinical manifestations of the symptomatic acute phase of the infection are relatively well defined, it has become increasingly evident that the infection, after the end of the acute phase, may determine a heterogeneous complex of subacute and chronic clinical manifestations that preclude a full return to the previous state of health (3-4).

The symptoms attributed to this condition are numerous and heterogeneous, and may arise in subjects of any age and with varying degrees of severity of the acute phase of the disease. The lack of a precise definition of this condition and the breadth of the spectrum of symptoms make the epidemiological evaluation difficult. In fact, to define the epidemiology of the condition a common definition is needed to establish incidence, prevalence and risk factors, as well as socio-demographic and clinical data to identify enabling factors while excluding confounding factors.

However, it is clear that, due to the magnitude of the pandemic and the huge number of people affected by the acute infection, the persistence of significant symptoms, even if only concerning a part of the subjects affected by COVID-19, constitutes a major public health issue in terms of the delivery of care to such large numbers of patients.

This need for assistance and care has been addressed from the standpoint of clinical and instrumental diagnosis and from the management point of view, with the prompt creation in various locations of "post-COVID" clinics and outpatient facilities directly linked to general medicine and hospital medicine. The variety of symptoms and the age range of the population involved have clearly indicated the need for an integrated and multidisciplinary approach.

Alongside clinical management, numerous research questions remain open. The available data have been obtained in different populations, examined in different observation periods and with different symptomatology and instrumental diagnostic approaches. The pathophysiology of such persistent clinical manifestations is not known, and its definition is of great importance both for the treatment of symptoms and for investigating the role of viral infection, inflammation and of the immune response in all the stages of the disease. Besides the severity of the acute form, also the potential role of vaccination in influencing the onset and severity of subacute and chronic forms has not yet been defined.

The aspects that remain to be defined are therefore quite numerous. Given the clinical impact of this condition, it has been deemed necessary to produce, with the support of a multidisciplinary working group, a document that summarizes the current understanding of this new condition and provides general information for its management. The report acknowledges the recommendations on the subject of Long-COVID provided by the World Health Organization and adapts them to the Italian situation.

(<https://apps.who.int/iris/bitstream/handle/10665/339629/Policy-brief-39-1997-8073-eng.pdf>)

1. What is Long-COVID

Long-COVID represents a clinical condition where patients suffering from COVID-19 fail to return to the state of health they had prior to the acute infection.

The mechanisms by which the infection determines the Long-COVID disorder have not yet been fully defined. There is growing evidence that supports the hypothesis of a direct organ damage caused by the virus, but there may also be the involvement of an innate immune response with the release of inflammatory cytokines or the development of a pro-coagulative state.

The reasons why only some patients develop Long-COVID are currently unknown, although advanced age, female sex and hospitalization appear to be associated factors. Sequelae of the COVID-19 disease may be present, albeit rarely, also in children.

Although there is no single symptom or test to diagnose Long-COVID, many patients complain of profound asthenia and a range of clinical symptoms that highlight the possible involvement of most body systems. For the working age population, Long-COVID can make it difficult to return to work, with obvious economic consequences and loss of working days. For elderly people, Long-COVID may have a significant impact on their functional status and reduce their autonomy in performing daily activities.

1.1. Definition

The terminology most frequently used (5) to define the stages following acute disease from SARS-CoV-2 is:

- **Persistent symptomatic COVID-disease**
signs and symptoms attributable to COVID-19 lasting between 4 and 12 weeks after the acute event;
- **Post-COVID-19 syndrome**
signs and symptoms that developed during or after an infection compatible with COVID-19, present for more than 12 weeks after the acute event and that cannot be explained by alternative diagnoses.

Long-COVID includes both the persistent symptomatic form and the post-COVID syndrome. This condition is therefore characterized by signs and symptoms caused by the SARS-CoV-2 infection that continue or develop after 4 weeks from an acute infection. The use of a shared terminology provides a basis for the programming of services to be provided, it facilitates the delivery of care and makes it possible to define a set of clinical data that are necessary for monitoring and research.

1.2. Clinical manifestations

The clinical manifestations of Long-COVID are highly variable and to date there is no consensus on their characteristics. Symptoms and clinical signs varies greatly and can occur both individually and in different combinations (3). They may be transient or intermittent and may change their nature over time, or they may be constant. In general, the more **serious** the acute disease, the greater the **extent** of the symptoms over time. However, it has been observed that Long-COVID may also affect people who have had only mild symptoms such as **fever**, **cough** and **fatigue** in the acute

phase. In recent months, numerous possible manifestations of Long-COVID have been described (reported in Table 1). These can be divided into two categories: general manifestations and organ-specific manifestations. The frequency of presentation of these manifestations has not yet been definitely established.

Table 1. Long-COVID: possible clinical manifestations

Manifestations	Characteristics
General	
	<ul style="list-style-type: none"> ▪ Persistent fatigue/Asthenia ▪ Excessive tiredness ▪ High temperature ▪ Muscle weakness ▪ Diffuse pain ▪ Myalgia ▪ Arthralgia ▪ Worsened perception of health conditions ▪ Anorexia, decreased appetite ▪ Sarcopenia
Organ-specific	
Pulmonary	<ul style="list-style-type: none"> ▪ Dyspnoea/Shortness of breath ▪ Persistent cough
Cardiovascular	<ul style="list-style-type: none"> ▪ Chest tightness ▪ Chest pain ▪ Palpitations ▪ Tachycardia ▪ Arrhythmias ▪ Variations in arterial pressure
Neurological	<p><i>Manifestations of the central nervous system</i></p> <ul style="list-style-type: none"> ▪ Headache (often unresponsive to analgesics) ▪ Cognitive impairment (brain fog) ▪ Difficulties in concentrating and attention ▪ Memory problems ▪ Difficulties in executive functions ▪ Dizziness ▪ Sleep disorders ▪ Dysautonomia (postural hypotension) <p><i>Manifestations of the peripheral nervous system</i></p> <ul style="list-style-type: none"> ▪ Tingling and numbness (peripheral neuropathies) ▪ Loss of taste and smell <p><i>Rare neurological manifestations</i> (complications in the acute phase of the COVID-19 infection which could entail permanent neurological damage)</p> <ul style="list-style-type: none"> ▪ Acute cerebrovascular events (ischemic / haemorrhagic stroke) ▪ Seizures ▪ Meningitis/encephalitis ▪ Myelopathy/myelitis ▪ Guillain-Barré syndrome, Miller Fisher syndrome, cranial polyneuritis, demyelinating disease of the central nervous system
Psychiatric/psychological	<ul style="list-style-type: none"> ▪ Depression ▪ Anxiety ▪ Post-traumatic stress disorder (PTSD) ▪ Obsessive-compulsive symptoms ▪ Delirium (in the elderly) ▪ Psychosis

Manifestations	Characteristics
Gastrointestinal	<ul style="list-style-type: none"> ▪ Abdominal pain ▪ Nausea ▪ Vomiting ▪ Diarrhoea ▪ Dyspepsia ▪ Belching ▪ Gastroesophageal reflux ▪ Abdominal distension
ENT	<ul style="list-style-type: none"> ▪ Tinnitus ▪ Earache ▪ Sore throat (pharyngodynia) ▪ Difficulty in swallowing (dysphagia) ▪ Dysphonia
Dermatological	<ul style="list-style-type: none"> ▪ Erythema pernio ▪ Papulo-squamous disorder ▪ Morbilliform rash ▪ Urticarial eruptions ▪ Alopecia
Haematological	<ul style="list-style-type: none"> ▪ Thromboembolism
Kidney	<ul style="list-style-type: none"> ▪ Haematuria and proteinuria (nephropathy)
Endocrine	<ul style="list-style-type: none"> ▪ New-onset Diabetes mellitus and subacute thyroiditis

1.2.1. General manifestations

The most frequent general manifestations reported by people with Long-COVID include severe and persistent fatigue, anorexia, muscle weakness, relapsing high temperature, widespread pain, myalgia, arthralgia, and deterioration in quality of life. Important and persistent asthenia is the most frequently documented symptom (6, 7, 8-10).

1.2.2. Organ-specific manifestations

To date, a wide range of long-term impairments have been found to affect various organs, including the respiratory, cardiovascular, nervous and gastrointestinal organs, the ear, nose and throat (ENT) system, the skin, kidneys and the haematological and endocrine systems (4-5,7,11-15).

Most patients with Long-COVID continue to have respiratory consequences characterized, in particular, by dyspnoea, with or without the need for chronic oxygen support, persistent cough and decreased capacity to expand the rib cage (4, 7, 10, 16).

Cardiovascular symptoms may vary, ranging from chest tightness and chest pain to tachycardia and palpitations with minimal exertion, arrhythmias and blood pressure changes (6-7).

Headaches are the most frequent neurological manifestation and are characterized by moderately severe bilateral localization, with pulsating or pressing quality in the temporoparietal, frontal or periorbital regions (15, 17-19). The most evident features are a sudden or gradual onset and a poor response to common analgesics (19). The elderly and people with cognitive impairment or those on chronic antihypertensive drug therapy have an increased risk of developing post-COVID encephalopathy (12). Cognitive deterioration, the so-called "brain fog" presents with difficulty in concentration and attention, memory problems, difficulties in executive functions (4, 20-22). The persistent manifestations of the peripheral nervous system after the resolution of other

symptoms include peripheral neuropathies and loss of taste and smell (7,10,16). Furthermore, dysautonomia is a syndrome that has recently emerged as one of the clinical manifestations of Long-COVID (23).

Not restorative and unrefreshing sleep, chronic malaise, depressed mood, anxiety, delirium and psychoses are the psychiatric / psychological manifestations most frequently reported by the survivors of acute infection (7, 24, 25). Compulsory social distancing for COVID-19 is a precipitating factor that contributes to the high incidence of delirium in patients, who feel desperate, isolated and separated from their families (26). Some patients may have symptoms associated with **post-traumatic stress disorder** (27).

The sequelae of COVID-19 described at the gastrointestinal level are **loss of appetite, nausea, vomiting, abdominal pain, diarrhoea, dyspepsia, gastroesophageal reflux, belching, abdominal distension** (13). Several studies are currently evaluating the long-term gastrointestinal consequences of COVID-19 including post-infectious irritable bowel syndrome (4).

A persistent dysfunction of the ENT system long after the acute phase of the COVID-19 infection is accompanied by disturbances of smell, such as hyposmia or parosmia, difficulty swallowing and taste dysfunction, tinnitus, ear pain, sore throat, dysphonia (5).

The most common skin manifestation of Long-COVID is erythema pernio, followed by papulo-squamous eruptions characterized by erythematous-squamous papules and plaques, morbilliform rashes and urticarial allergic eruptions. The most commonly associated form of alopecia is telogen effluvium, more commonly classified as a self-limiting and acute hair loss, lasting less than six months. As for the immune-mediated pathologies with dermatological manifestations, cases of clinically silent forms becoming manifest and exacerbation of psoriasis and alopecia areata have been reported (6, 10, 28).

With regard to haematological manifestations, the literature reports cases of COVID-19 post-acute thromboembolic venous disease (14, 29). Some patients discharged without prophylactic antithrombotic therapy have developed segmental pulmonary embolism, intracardiac thrombi, thrombotic arteriovenous fistulas and ischemic stroke (14).

Kidney damage appears in the form of a reduction in the glomerular filtration rate which occurs over time, even in patients with normal kidney function during the acute phase of the infection (6). The most frequently described endocrine manifestations in this patient group are the sudden appearance of diabetic ketoacidosis (without a previous diagnosis of diabetes mellitus) and subacute thyroiditis with clinically manifest thyrotoxicosis (30).

1.2.3. Clinical picture in children

Although the pathophysiological mechanism is yet to be confirmed (31-33), it is now general knowledge that children, especially those under 11 years of age, who are infected with the virus that causes COVID-19, are less likely to develop a severe disease during the acute phase, as well as in the weeks following diagnosis. However, a limited number of patients, albeit without evident predisposing conditions, may develop a multisystem inflammatory condition (34-35) known as MIS-C (Multisystem Inflammatory Syndrome in Children). This condition requires a timely multidisciplinary approach, aimed at rapidly providing appropriate treatment which, to date, has proved effective in preventing the possible evolution towards multi-organ failure and shock (36). Unlike Long-COVID, MIS-C, which normally occurs between 2 and 6 weeks after acute infection, has well-defined symptoms and classification and seems to recognize well-defined mechanisms (37, 38).

Similar to what is described in adults (24), in children, Long-COVID may cause the onset of late symptoms persisting for several months (39). The symptoms listed below are some of those that characterize the syndrome as described so far by the few studies performed (5, 40-42). These symptoms may appear at different times and combine with each other in different ways:

- high temperature;
- gastro-intestinal disorders;
- nausea;
- persistent fatigue;
- sore throat;
- skin manifestations;
- headache;
- arthromyalgia;
- asthenia;
- changes in mood;
- sleep disturbance;
- difficulty in concentrating;
- dizziness;
- palpitations;
- striving for air;
- cognitive dysfunctions.

It should be underlined that this symptomatology could also be due to the indirect consequences of COVID-19 in the long term, including social isolation and the socio-economic effects of the pandemic on families (43, 44). In fact, children's health may be profoundly affected by changes in living conditions, family income, unemployment, problems with education and access to health services, with the ensuing higher risk of dropping out from school and of domestic violence (45).

1.2.4. Clinical picture in the elderly

Elderly people are more affected by Long-COVID than the younger population. Among elderly people evaluated at two months after the onset of COVID-19, up to 80% report the persistence of at least one symptom, in particular asthenia, dyspnoea, joint pain and cough. This high prevalence may be linked to the reduced functional reserve in the elderly and to the high prevalence of frailty, which results in a reduced ability to recover from stressful situations. COVID-19 may also interact with and determine a worsening of the chronic diseases that often affect elderly people. The consequences of these phenomena are often a worsening of the functional status and the development of disabilities.

The characteristics of Long-COVID in elderly patients are generally comparable to the characteristics of patients in the younger age groups, although often the severity is greater. However, some conditions are particularly important among the elderly. In fact, special attention should be paid to the onset of neurodegenerative, psychiatric and cognitive impairment disorders (46). The data suggest that, compared to other acute clinical events, during the first 90 days after a diagnosis of COVID-19, the likelihood of developing dementia is increased and the risk of dementia is estimated to be around 2% among patients over 65 affected by COVID-19.

Nutritional status is also often altered in elderly patients with Long-COVID. A state of malnutrition has been observed in 26-45% of patients after COVID-19, and the elderly are particularly at risk for this condition and for its associated consequences, such as muscle atrophy, sarcopenia and frailty. Given the multidimensional nature of the issues related to Long-COVID, it is of particular importance to carry out a multidimensional assessment in the elderly in order to obtain a picture not only of the clinical issues, but also of the functional, cognitive and nutritional problems.

1.3. Who is more susceptible

Long-COVID is more frequent in the aftermath of hospitalization, with an apparent correlation with the number of chronic disorders present and with the severity of the interventions required (e.g. hospitalization in intensive care) (6, 47-50). However, an association of Long-COVID with individual diseases that have appeared to predict the severity and mortality of the acute disease (such as diabetes, heart disease, renal failure, cancer, obesity, transplants) has not yet been defined (4).

The risk of persistent symptoms increases with increasing age and body mass index, and appears to be greater, among adults, in females (6, 47, 50). An increasing risk with age has been found in several studies (48, 49, 51). Susceptibility also seems to increase with the number of symptoms in the acute phase (47, 49), but the association with their severity has not yet been clearly defined. Among the various symptoms, previous dyspnoea seems to play a predominant predictive role.

1.4. How frequent it is

An accurate estimate of the prevalence of Long COVID is difficult due to the variability of the methods and definitions used and of the populations studied.

According to a recent summary document of the World Health Organization, a quarter of the patients with COVID-19 show persistent symptoms 4-5 weeks after they have been found to be positive (52). Especially with regard to organ manifestations, the frequency of identification of alterations is strongly influenced by the extent of the tests performed. The variety of symptoms and of the diagnostic approaches have led to very broad prevalence estimates, but the quality of the studies has not always been high, due to limited external validity, lack of control groups, and variability of the methodologies used (53). Finally, despite the spread of the infection, only a few prevalence studies have involved large samples.

The largest of the studies, conducted in the UK by the Office for National Statistics on a sample of over 20,000 people, has shown a prevalence of symptoms of 13% beyond 12 weeks post-infection, with a prevalence eight times higher than that of a control group, a higher risk in women than in men (14.7% vs. 12.7%) and a higher prevalence in the 25-34 age group (18.2%) (41).

In another UK study including over 4,000 subjects (COVID Symptom Study), prevalence was lower: 13% at 4 weeks, 4.5% after 8 weeks and 2.3% after 12 weeks. The patients presented with asthenia, headache, dyspnoea, and anosmia, and the risk increased for patients with a high BMI index and for the female gender (47). In an observational study of patients discharged from 38 US hospitals, the persistence of symptoms at sixty days affected approximately one third of the 488 responders, with dyspnoea being the most frequently reported symptom, followed by cough and altered taste and / or smell (16). Smaller studies in the US, Switzerland, the Netherlands, Belgium,

Canada, France, and the UK have shown a higher prevalence, especially for previously hospitalized patients. In all these studies, dyspnoea and asthenia were the most frequently reported symptoms. A study carried out in Italy on 143 hospitalized patients who were evaluated at 2 months after the first onset of symptoms found that only 13% of patients were completely asymptomatic, while 32% reported 1 or 2 symptoms, and 55% had 3 or more symptoms (7). Also in a study carried out in China including about 1,700 previously hospitalized patients, the prevalence of symptoms at six months was very high (76% of patients with at least one symptom), with residual pulmonary signs being present on imaging techniques in more than half of the cases (6).

Recent data indicate a frequent persistence of symptoms even in children affected by COVID-19, with an important impact on daily activities and on the level of their physical activity (42, 54).

1.5. Diagnosis

The diagnosis of Long-COVID is purely clinical and is based on a history of COVID-19 and the failure to fully recover with the development of some of the symptoms listed in Table 1. Although a positive molecular or antigen swab and a positive antibody test for COVID-19 may be helpful, these are not a prerequisite for diagnosis. This is because the availability of tests was very limited in the early stages of the pandemic (March and April 2020) and because the antibody titre tends to decrease months after the onset of the disease (55). Furthermore, Long-COVID must be distinguished from the Post-Intensive Care Syndrome (PICS), which is characterized by impaired lung function, neuromuscular weakness, long-term psychological disorders and reduced quality of life (56). This condition is common among people with severe acute infections who have spent a long time in intensive care (57) and may coexist with Long-COVID in some cases. Some symptoms of Long-COVID appear to be similar to those of the chronic fatigue syndrome, however, compared to this latter condition, the onset of Long-COVID is accompanied by a broader spectrum of symptoms.

Unfortunately, to date, apart from the definition given in paragraph 1.1, there are no clear, internationally agreed criteria to define Long-COVID. This inevitably creates uncertainty in the diagnosis and wide variability in the identification of this condition.

2. Principles for the Management and Care of Long-COVID

2.1. Identifying patients affected by Long-COVID

Patients affected by Long-COVID can be identified as described in the following:

- proactively, by identifying patients with a history of COVID-19 through health care records or hospital records. Such a patient identification strategy must take account of local care delivery capacity (i.e. identify the patients who can receive care without overloading the local healthcare services), and it needs to focus on the population at high risk of developing Long-COVID, such as for example elderly patients or patients hospitalized and / or admitted to intensive care for COVID-19;
- by the General Practitioner (GP) or the Primary Care Paediatricians during the routine assessments of their patients;
- on the patient's own initiative through their GP, Primary Care Paediatricians or through the local Long-COVID clinics and services.

2.2. Multidimensional evaluation

In view of the wide range of symptoms and conditions that characterize Long-COVID, the evaluation of patients with this condition needs to be multidimensional and include numerous clinical, functional, cognitive, psychological and nutritional aspects.

It is of fundamental importance to obtain:

1. a full medical history including:
 - a. history of acute COVID-19 (suspected or confirmed)
 - b. nature and severity of previous and current symptoms
 - c. timing and duration of symptoms from the onset of acute COVID-19
 - d. history of other health conditions
 - e. current and previous drug treatment;
2. an evaluation of the specific signs and symptoms of Long-COVID (see Table 1);
3. an assessment of how the person's activities, for example work or education, mobility, independence and functional status (activities of daily living), lifestyle have been affected by long-COVID-19 ;
4. an assessment of the psychological impact of COVID-19 and Long-COVID, with particular attention to the onset of symptoms of anxiety, depression and social isolation;
5. an assessment of the impact of COVID-19 and Long-COVID on nutritional aspects, changes in body weight and loss of interest in eating and drinking, particularly in the elderly;
6. an assessment of the presence of new cognitive symptoms or brain fog, using a validated screening tool to assess the patients' cognitive status.

The elements mentioned above represent a minimum set of assessments to be performed in patients who present or report signs or symptoms attributable to COVID-19 that persist for more than 4 weeks from acute infection. This information can be collected by healthcare professionals or through self-completed, self-managed questionnaires by the patient.

For older people or people who may have difficulty reporting signs and symptoms, it is important to involve a family member or caregiver in the assessment (by prior arrangement with the person).

2.3. Multidisciplinary approach

A multidisciplinary approach is to be adopted in the management of patients with Long-COVID in order to be able to respond to the different clinical, functional, cognitive, psychological and nutritional manifestations of the disorder. This approach is to be personalized, modulated and adapted by keeping account of the variety of conditions that may arise in individual patients.

The structuring of the care should be led by a doctor with expertise and experience in COVID-19 (e.g. GP, pneumologist, geriatrician, infectious disease specialist, internist), there should be appropriate specialist support and local programs in which primary and specialist care are integrated, as well as multidisciplinary and hospital rehabilitation services. Based on patient conditions and on local availability, the specific services can be delivered through a one-stop assessment (i.e. concentrating the consultation with the various specialists and the diagnostic tests on a single day, for instance in a Long-COVID day hospital), which is preferable in elderly or frail patients, or staggered over time. The treatment program must also include a follow-up adapted to the characteristics of the patient.

The care envisaged for Long-COVID patients characterized by low clinical complexity can be coordinated and managed by the GP. In more complex patients, treatment can be managed in another context (e.g. hospital), as long as there is always direct contact with the GP who is treating the patient. In order to coordinate the delivery of care in the more complex cases, the family or community nurse can be used; this figure was introduced by decree-law no. 34 of 2020, the so-called “Revitalizing Decree”, converted into Law no. 77/2020, aimed at strengthening the local nursing services.

Some selected patients may be put on multidisciplinary rehabilitation programs that take account the physical, psychological and psychiatric aspects of rehabilitation. These programs must:

- be based on a multidimensional assessment of the person's condition with the development of tailored rehabilitation plans;
- involve a multidisciplinary team which, in addition to the medical doctor, includes an occupational therapist, a physiotherapist and a psychologist;
- provide specific specialist skills in the treatment of fatigue and respiratory symptoms (including dyspnoea).

It is important to define timely and personalized follow-ups tailored to the characteristics and needs of each patient in order to re-evaluate the general conditions and plan new interventions if necessary.

2.4. Primary care

The delivery of primary care for patients with Long-COVID should be structured on at least three levels, as shown below.

2.4.1. Stratification of the groups of patients at risk of developing LONG-COVID

It is very important that patients with a history of COVID-19 be followed up even after a negative swab. In particular, maximum attention must be paid to the more frail, immunosuppressed, elderly patients with multiple comorbidities who have been previously hospitalized for COVID-19 or who have developed significant symptoms during the disease (47, 48, 51). In all these cases, the GP must continue to take care of the patient considering a follow-up (including periodic phone calls), and carry out a multidimensional assessment if a clinical picture compatible with Long-COVID occurs.

2.4.2. Evaluation of patients with Long-COVID-like symptoms

The evaluation should be based on a holistic approach that investigates general, cognitive and psychological symptoms along with an integrated socio-health evaluation (see section 2.2). Blood tests as well as radiological, ultrasound and functional tests, modulated according to the patients' conditions, need to be carried out (5), and functional tests are to be performed to see whether and to what extent the patient's daily life and activities (e.g. work, mobility, degree of autonomy, well-being and social life) are affected by the post-COVID-19 syndrome. This type of assessment is within the mission and task of the GP with the contribution of specialty doctors, including psychologists where necessary.

2.4.3. Planning of care pathways

Once other causes have been excluded, patients could be included in a multidisciplinary program that also involves other specialists and allows for a patient-centred approach (see sections 2.3 and 2.5) (5). Finally, it is important for this purpose to provide advice on self-management to patients with Long-COVID to help them manage their symptoms, providing them with information on the health care services they need to contact in case their symptoms worsen, and make appointments for regular follow-up exams in order to monitor their clinical performance. This can be done also through telemedicine tools such as tele-consultation, tele-visits and other tele-health systems that are useful for monitoring instrumental and non-instrumental data (58).

2.5. Patient involvement and self-management

2.5.1. Patient involvement

Patient involvement is key in shaping awareness about Long-COVID (52, 59), and spontaneous initiatives have appeared in various countries with the establishment of numerous associations dedicated to the advocacy of patients' interests. Some of these associations have an international character (60) and have played a central role in conducting initial research aimed at providing information and raising patient awareness about the issue of Long-COVID (61), and in asking governments for "Recognition, Research and Rehabilitation" as basic needs of patients with Long-COVID (62). This request has been publicly recognized by the World Health Organization (52).

More specifically, in the context of Long-COVID, *recognition* implies taking into account all the aspects of the problem (medical, psychological, social, etc.) and raising the awareness of doctors and of other health professionals (physiotherapists, nurses, etc.); *rehabilitation* involves the development of multidisciplinary programs, coordinated at national level, to assess, test, diagnose and treat patients, including those who were not hospitalized during the acute phase of the infection; and *research* requires coordinated and co-created multidisciplinary studies to understand the clinical consequences and develop treatment plans for Long-COVID.

In Italy, after the first wave of the epidemic (May 2020), a survey was carried out by the Advanced School of Economics and Management of Health Systems (ALTEMS) with gathered evidence about 102 anti-COVID-19 actions implemented by patient associations, the majority of which were “Institutional interventions”, i.e. advocacy actions addressed to institutions or in collaboration with them, in order to communicate the needs of patients and find possible solutions when dealing with an emergency. Other activities include the activation of web conferences and communication activities with and for patients, as well as remote training (63).

2.5.2. Self-management

It is also important to support the self-management of patients suffering from Long-COVID. In this context, the NICE (National Institute for Health and Care Excellence) guidelines offer an overview of Long-COVID self-management (5). The self-management programs provided either formally by patient organizations and support groups online, or provided informally during visits by the GP or other specialists and health professionals should:

- Provide information and training on self-management to patients with Long-COVID, starting with the initial evaluation. This should include:
 - self-management of symptoms, setting realistic goals;
 - indication of people to contact in case of deterioration or need for support;
 - information on possible sources of support, including support groups, social services, online forums, Apps;
 - information on ways of obtaining support from other services including social services, accommodation services and advice on financial support;
 - information about the new and persistent symptoms of COVID-19 that the patient can share with family members, caregivers and friends.
- Provide patient support for interviews with their employer, school or university regarding return to work or teaching activities, for example by providing for a gradual resumption of activities.

2.6. Principles for the management of children

Even though an increasing number of studies offer evidence of the impact of the Long-COVID syndrome, highlighting that children are also affected, the data in the youngest population are probably underestimated, which is why further studies are necessary in order to fully understand its clinical importance. (64). However, it seems clear that if not recognized and adequately treated, Long-COVID can exponentially accentuate physical and mental difficulties in children, damaging their cognitive development and mental health in the medium-long term. In order to properly

manage Long-COVID in children, some indications about information, monitoring and optimization of access appear to be important.

2.6.1. Information

The main objective of providing information is to **enable parents to understand the discomfort and alarming symptoms** they need to recognize in their children, which can lead to real problems if not dealt with promptly. The role of the parents is essential in the early identification of risk signals, in order to allow a targeted intervention by specialists where necessary.

2.6.2. Monitoring

It is important to promote **monitoring programs designed for the paediatric population and their families**, to be activated already during hospitalization with the aim of identifying as early as possible any critical situation in psychic behaviour (43).

2.6.3. Access to care

In order to reduce the impact of Long-COVID in the paediatric population, preferential pathways are to be identified and specific programs are to be promoted that include some key elements:

- **Essential role of Primary Care Paediatricians**

Since they are based in the community, Primary Care Paediatricians are the first interlocutors of the parents and therefore they need to be aware of the multisystemic symptoms that could appear in the aftermath of a COVID-19 infection. To this end, it would be desirable to offer them guidelines as well as training courses (64).

Psychological support

Provide dedicated psychological and neuropsychiatric support programs for children, adolescents and their families. In addition to helping these patients in the acute phase, psychological support could reduce the risk of long-lasting post-traumatic symptoms (65).

- **Creation of call centres and use of remote electronic information technology**

Design telecommunication tools and telephone support for parents of fragile children and of children with pre-existing health conditions for whom access to healthcare facilities is difficult, including children with attention deficit hyperactivity disorder (ADHD) or autism spectrum disorders (ASC) (66), but also children with disabilities and children with special therapeutic or educational needs (67).

- **Design remote monitoring programs**

Implementation of telemedicine programs to support and promote remote clinical care of patients with previous SARS-CoV-2 infection, whether previously hospitalized or not (68, 69).

- **Creation of dedicated outpatient clinics and/or Day Hospitals**

In these outpatient clinics and Day Hospitals children with previous SARS-CoV-2 infection can be assessed in a multidisciplinary manner by specialists adequately trained to recognize the possible late manifestations and complications of the infection (pediatrician, infectious disease specialist, rheumatologist, pneumologist, cardiologist, neurologist, physiatrist), as well as perform haematochemical and instrumental tests deemed necessary (radiographic examinations, respiratory function tests, ECG and echocardiographic evaluation,

electrophysiological tests). Of crucial importance is the presence of the psychologist / psychiatrist who, thanks to the use of standardized screening tools (67, 70-72) and the administration of questionnaires, can assess the state of mental health and measure the frequency of anxiety, depression, phobias, cognitive disorders and other neuropsychiatric disorders that are likely to impair social functioning (73).

- **Rehabilitation**

In addition to providing rehabilitation programs, in the rare cases in which children with a previous SARS-CoV-2 infection present neurological, cardiological or pneumological consequences, it is essential to promptly recognize any signs of psychological distress so as to provide the appropriate specialist care.

3. Examples of Regional Programs

Examples of Long-COVID care pathways set up by the Regions are reported in this section. Common elements of these programs are: the definition of criteria and / or procedures to identify patients with Long-COVID, stratification of patients based on the severity of the condition, application of multidimensional assessment modalities, use of specific tools, and the delivery of multidisciplinary care.

The Emilia-Romagna Region

In July 2020, the Emilia-Romagna Region produced a document with the specific aim of providing indications, upheld by the community of professionals most involved in providing care, useful for guiding the diagnostic-therapeutic follow-up of patients with previous SARS-CoV-2 infection.

The general indications include exemption from co-payment for all the services involved in the follow-up of patients infected by the SARS-CoV-2 virus, the formal establishment, for each provincial or health unit, of a multidisciplinary / multi-professional team of reference; the identification of eligible patients for the various follow-up programs facilitated by sending lists of discharged patients and lists of patients with positive swabs to individual GPs / Primary Care Paediatricians and to the USCA Outpatient Clinics (Units for the Continuity of Special Care).

Three scenarios of reference are envisaged:

1. Patients with a previous positive swab who are currently asymptomatic, regardless of the symptoms they had in the acute phase. A follow-up program for these patients has not been envisaged except in the context of research protocols.
2. Symptomatic patients (Post COVID Pneumonia Syndrome, PCPS) and patients with a clinical history attributable to the SARS-CoV-2 infection with or without confirmation of organ involvement (in any case <30-40% of the lung parenchyma). Regardless of the treatment setting and instrumental or laboratory diagnostics received, the patients described above are expected to be followed-up by the General Practitioner or the USCA. The program foresees that the patient be examined at a general medicine outpatient clinic; where required, the doctor may directly perform or request additional first level examinations, or request a pneumology or internal / geriatric examination, a neurocognitive screening or quality of life assessment to be performed during the medical examination; the GP examines the patient within 3-6 months of hospital discharge or once the acute phase is over and evaluates the priority criteria through triage that may even be done over the telephone; further investigations are managed directly by dedicated specialist clinics.
3. Symptomatic patients (*Post COVID Pneumonia Syndrome*, PCPS) and previous interstitial pneumonia with extensive organ involvement (> 30-40% of the lung parenchyma) and / or patients who have undergone steroid therapy in the acute phase and / or patients discharged who are on oxygen therapy. These patients always have access to the specialist outpatient clinics where the multidisciplinary / multiprofessional teams have been set up in the local healthcare units: the specialist in charge of the patient initiates the diagnostic evaluation involving other professionals identified on the basis of the organ impairment of each patient; access to the specialist outpatient clinic is provided through an appointment made directly

by the specialist at the time of discharge or through a request by the GP; the first follow-up visit at the specialist clinic must take place within 3-6 months after discharge of the patient from the hospital.

The Abruzzi Region

With DGR no. 121 of 04/03/2021, the Abruzzi Region issued the "Guidelines for the follow-up of patients with previous COVID 19 infection" with the specific objectives of providing useful information to define the dedicated diagnostic-therapeutic follow-up programs for patients with previous SARS-CoV-2 infection; and ensure a multidisciplinary and personalized approach in order to identify as early as possible any physical, psychological and neuro-cognitive outcomes acquired during the process of care.

The specific regional program envisages the establishment of the **Long-COVID Outpatient Clinics** - at least one for each ASL - as coordination facilities which, by optimizing the timing of the services and the staff assigned to the services, improve the quality of care and reduce the complications in hospitalized patients discharged from the COVID-19 Operative Units, and in patients followed at home who are clinically recovered and have a double negative nasopharyngeal swab.

The infectious diseases specialist, who coordinates the outpatient clinic, works together with a group of professionals consisting of specialists in various disciplines (pneumologist, cardiologist, neurologist, nephrologist, psychologist / psychiatrist) and with at least one nurse with specific training. In addition, other specialized professional figures may be involved.

In order to classify the patients with sequelae of COVID-19 disease, with particular attention to the respiratory function and to any other problem of specialist interest, the specialist in infectious diseases will use a specific screening questionnaire that can be administered also by telephone, to investigate, in particular, the presence of persistent symptoms that continue for more than 12 weeks after recovery from COVID-19 and that cannot be explained by an alternative diagnosis.

Patients who were treated at home or in long-term health care facilities during the acute phase may be contacted directly by the GPs or by the USCA doctors to begin the follow-up through an interview.

Patients who test positive in the screening questionnaire and comply with specific severity criteria established by the coordinating doctor, have access to the Long-COVID Outpatient Clinic by means of a referral by an NHS prescription issued by the GPs or by the medical specialists. Access is provided via a special agenda that is separate from that of ordinary outpatient services. Following the clinical evaluation and the telephone interview, the infectious disease specialist assigns the patient to a treatment program which may be the Day Hospital Program with diagnostic purposes, the Day Hospital Program with therapeutic purposes (art.43 of DPCM 12.01. 2017), or the Day Service Program with the Complex Outpatient Package, filling in the specific "PAC - POST-ACUTE COVID-19 SYNDROME FORM", to select the specialist services from those that make up the diagnostic PAC. Alternatively, the infectious disease specialist can continue monitoring the patient on an outpatient basis by booking the instrumental clinical examinations and one or more subsequent medical examinations, through the level II Central Reservation Centre (CUP), on dedicated and confidential appointment books.

The Tuscany Region

With DGR no. 744/2020 of 15/06/2020 the Tuscany Region approved the regional guidelines for the delivery of care to all the people who have had a COVID-19-related clinical picture, and for the definition of the operational protocol for the clinical follow-up of COVID-19 patients who are clinically cured.

The protocol establishes a program of continuous clinical care aimed at identifying and treating the outcomes deriving from COVID-19 through a multidisciplinary and personalized approach, in order to identify any early physical, psychological and neurocognitive outcomes that are a consequence of the SARS-CoV-2 infection.

Patients who during the acute phase were hospitalized in a hospital ward in Tuscany for COVID-19, are contacted by the hospital where they were hospitalized, and the GPs are involved for sharing and subsequent management. Patients who were managed at home or in social healthcare facilities during the acute phase are contacted directly by the GPs to start the follow-up activities.

The first step, to be completed within two months from clinical recovery, consists of a clinical questionnaire, from which it is possible to infer whether any problems emerged after recovering, and the performance of the blood tests envisaged in the basic protocol (access to this service is organized by the health local units and the process is explained to the patient at the time of first contact). The questionnaire can be administered by healthcare personnel, doctors or nurses or, depending on the case, delivered to the patient or family by the GP / Primary Care Paediatrician. The information is evaluated and integrated with details from the patient's history by the reference doctor of the follow-up program (hospital specialist, GP / Primary Care Paediatrician, depending on whether the patient is hospitalized or not), preferably through a remote examination.

In relation to the problems that have emerged, the reference doctor for the follow-up may identify the need for an urgent specialist check-up, which can be requested with the exemption code that identifies COVID-19 patients (P01), or activate a personalized day-service program in accordance with the multidisciplinary and multi-organ approach and continuity of the treatment program. The criteria for referring the patient to the various specialists for an evaluation and the associated in-depth diagnostic protocols have been defined in DRG no. 938 / 2020 of 20/07/2020. At the end of the evaluation, a multidisciplinary synthesis is prepared by the specialty doctors who participated in the clinical and instrumental diagnostic phases and a clinical report is prepared and shared with the GP or Primary Care Paediatrician.

A second step is envisaged for patients who have been hospitalized or who are referred to a specialist during the first step. In the second step, the controls, the multidisciplinary and multiprofessional assessments, the blood tests and the instrumental tests are extended up to 12 months after the acute phase of the COVID-19 disease.

Alongside the definition of the post-healing care program, the regional protocol focuses on the importance of carrying out targeted observational studies to better understand the disease and investigate its medium and long-term consequences. In this connection, the data gathered during the first follow-up of patients hospitalized in the first pandemic wave in one of the three University-Hospitals were published recently (74).

The Liguria Region

The Liguria Region is characterized by extremely high aging indices, which makes it the leading aging area in Europe, both for the percentage of people over the age of 65, for the old age index, and for the rate of people who are over a hundred years old. Considering that the pathological picture of Long-COVID does not only affect the "pre-fragile" population aged mainly between 55 and 70, particular attention should be paid to finding solutions to the unmet needs of the population over 70.

Through Act No. 842-2020 of 05/08/2020, the Liguria Region has defined a regional program for the post-recovery care of COVID-19 patients. The program includes:

1. a dedicated healthcare plan for all the patients who were hospitalized for the COVID-19 infection with related pneumonia
2. the conduction of observational studies aimed at better understanding the disease and investigating, in particular, its medium and long-term consequences. The population to be included is represented by the patients hospitalized for COVID-19 with pneumonia.

The general objective of the care pathway is to provide adequate support to individuals who, after the critical phase of the infection, have to face the physical consequences associated with prolonged bed rest, residual respiratory problems and the consequences affecting the cognitive-emotional sphere. The specific objectives are aimed at reducing the physical symptoms related to motor difficulties and muscle pain, at improving respiratory dynamics, at intervening on the psychological and cognitive conditions, at reducing the state of anxiety generated by the prolonged absence of contact with other human beings, and at offering these patients adequate emotional support.

The project of the Liguria Region is based on 2 types of services that complement each other:

- Outpatient service / Day Hospital
- Temporary residential intervention / Short Stay Units

An example of outpatient service is represented by the Day Hospital of the San Martino Hospital in Genoa, shown in section 4. The outpatient service needs to be integrated with the residential area that may on one hand, accommodate people who, for logistical reasons, cannot travel to a day hospital every day and, on the other hand, receive specialist treatment from the outpatient clinic in relation to the psycho-physical areas requiring treatment.

The residential service stems from the positive experience with the "temporary health areas", which are residential socio-healthcare facilities for the elderly where treatment can continue to be provided to frail, not self-sufficient COVID-19 patients. Ensuring the continuity of care in these facilities has made possible to highlight the needs of the patient during and especially after the acute phase of the disease until the recovery confirmed by a double negative swab: in these individuals the disability and limitations to the common activities of daily life require a specific rehabilitation program. Rehabilitation of such patients can be carried out at these facilities, which have specific module requirements.

The program involves initial, intermediate and final evaluations of the physical, psychological and neuropsychological symptoms that are designed to monitor the patient's progress and evaluate the patient from both a qualitative and quantitative point of view.

The **initial evaluation** is important in order to define a care plan that is as specific as possible for each individual patient and include a spirometry test, instrumental examinations, an evaluation

by a physiatrist, the collection of anthropometric data, a 6-minute walk test with SpO2 detection, the dyspnoea assessment scale (MMRC) and the Barthel Scale to measure performance in activities of daily living, an assessment of psychological symptoms (with a focus on anxious and depressive symptoms, post-traumatic symptoms and quality of life), and a neuropsychological assessment.

The **intermediate evaluations** have the purpose of making changes to the plan where necessary.

The **final evaluation** offers the opportunity to quantify the improvements obtained through the execution of physical performance tests, the assessment of the dyspnoea and autonomy achieved in the performance of the activities of daily living and to plan follow-up visits.

4. Examples of local experiences

In the last year there have been various local experiences aimed at evaluating and treating adults and children with Long-COVID. Some examples are presented in this section. These are experiences of day hospitals or outpatient services, and whose main feature is their multidisciplinary approach with the involvement of numerous specialists. These examples are not intended to give an exhaustive picture of all the experiences present at national level, but are only intended to illustrate possible organizational characteristics of outpatient clinics and day hospital facilities intended for the evaluation and care of adults and children with long-COVID. Centres interested in reporting their activities to the ISS for the purposes of future research and / or surveillance activities on long-COVID are free to contact the ISS at the following e-mail address: longcovid@iss.it.

Post-COVID Day Hospital at the Agostino Gemelli IRCCS University Hospital Foundation – Rome

On 21 April 2020, a Day Hospital service dedicated to individuals recovering from COVID-19 was established at the Agostino Gemelli IRCCS University Hospital Foundation. All patients with a previous diagnosis of COVID-19 who met the criteria for ending quarantine were considered eligible (apyrexia for at least 3 consecutive days, improvement in other symptoms, and 2 negative SARS-CoV-2 test results, 24 hours apart). The service initially enrolled people who had received acute phase care at the Agostino Gemelli IRCCS University Hospital Foundation. Later, also patients from the community came to the Day Hospital to be evaluated. The care process is coordinated by a geriatrician who carries out a multidimensional assessment of the patient. Once enrolled, each patient undergoes a series of multidisciplinary evaluations which include: a pulmonary function test, and rheumatological, gastroenterological, ENT, neurological and psychiatric evaluations (75).

Infectious Disease and Pneumology Outpatient Clinic of the University Hospital of Modena

A diagnosis and treatment program (PDTA) for Post-acute COVID Syndrome (PACS) was established in Modena, open to previously hospitalized or symptomatic patients starting from at least 5 weeks after discharge. This is an outpatient service and patients can access using the exemption code P01 (protection of community health). The program includes a multispecialized and multidimensional assessment including the identification of the following clusters of syndromes: respiratory, musculoskeletal, immune-metabolic, neurocognitive and sensory syndromes. The investigations include sampling, spirometry, the 6-minute walk test, the test to evaluate the functionality of the lower limbs (short physical performance battery), the assessment of muscle strength with dynamometer, body composition with DEXA, screening for NAFLD, and neurocognitive screening using the COGSTATE platform. Patients are evaluated by a team including: an occupational therapist, a neuropsychologist, a dietician, a pneumologist, and a specialist of infectious diseases with expertise in immune-metabolic assessments. Before the visit, patients are invited to fill out electronic questionnaires on various patient reported outcomes (PROs), commented in face-to-face meetings through representations in the form of radar charts. In particular, frailty, resilience, quality of life, anxiety, depression, stress, and quality of sleep are

evaluated. The service operators are responders on the online counselling platform www.helpCOVID.it.

Post-COVID Day Hospital at the ASST St. Gerard Hospital of Monza

To deliver care to patients with persistent post-COVID symptoms, the Local Health Unit (ASST) of Monza has set up a day hospital which has been in operation since June 2020 to follow-up on discharged patients. Coordinated by the Infectious Diseases Department, this outpatient clinic has a multidisciplinary character, and comprises various specialists (infectious disease specialists, pneumologists, cardiologists, geriatricians, anesthesiologists and psychologists), in order to identify unresolved clinical problems and the possible presence of permanent sequelae. Depending on the clinical problem detected through the multidisciplinary assessment, a specialist of reference is identified for each patient for further diagnoses, treatment and rehabilitation where necessary.

San Martino Hospital of Genoa

The "Post COVID" day hospital at the San Martino Pneumology Department was opened on June 1, 2020. All patients hospitalized during the first wave were called on the telephone to come in for a follow-up visit. The follow-up visit includes a predefined set of blood tests, HRCT of the chest, respiratory function tests with carbon monoxide diffusing capacity, the 6-minute walk test, an echocardiogram and a blood gas analysis if saturation is less than 95% in ambient air. Patients also undergo a neurological evaluation to assess the presence of central and / or peripheral nervous system disorders. The patients with normal test results and who are clinically asymptomatic, leave the follow-up. Patients with abnormal test results are seen again after 6 months for targeted investigations based on their symptoms and abnormal test results, and, in the case of persistence of alterations coming under the competence of another specialist, the patient is referred to the relevant specialist. The follow-up process involves a multidisciplinary team, managed by the pneumologist, which includes neurologists, psychiatrists, psychologists, dermatologists, radiologists, respiratory pathophysiologists, rheumatologists, nuclear doctors, nephrologists, cardiologists and rehabilitators. Beginning with the second wave, patients are recruited into the follow-up program at the time of discharge.

COVID-19 Follow-up Day Clinic at the ASST Niguarda Metropolitan Hospital in Milan

The day hospital provides care for all patients who have previously been hospitalized for COVID-19 (defined on the basis of a positive swab for SARS-CoV-2 and diagnosis of COVID-19 at discharge). The post-COVID program begins at approximately 30 days after hospital discharge. The first visit is performed by a pneumologist (in the initial months assisted by an infectious disease specialist). During the first visit, all the patients of the first wave were administered a clinical, psychological and rehabilitative questionnaire, and the tests performed included a blood test, electrocardiogram, spirometry and walk tests. Depending on patient outcomes, they would be referred for further specialist visits, for physiotherapy rehabilitation or for psychological assessments. After 3, 6 and 12 months, the patients were re-evaluated on an outpatient basis and blood tests, chest CT scans (if necessary), walking and spirometry tests, echocardiograms and electrocardiograms were performed. The patients hospitalized during the second and third waves

underwent a first visit with subsequent re-evaluation after 3 months. Further follow-up was maintained only for patients with persisting clinical needs.

Bambino Gesù Children's Hospital - Rome

At the Palidoro site of the Bambino Gesù Children's Hospital, identified as the hospital of reference for the Lazio Region for the management and surveillance of paediatric COVID patients, a paediatric clinic providing direct access to patients, open every day from Monday to Friday, as well as a dedicated Day Hospital have been set up. The clinic is open to patients who have presented mild, pauci-symptomatic forms of the infection, who were previously hospitalized or managed at home in fiduciary isolation once they became negative or after the twenty-one days of quarantine required before being allowed to return into the community in accordance with current ministerial indications.

The Day Hospital instead, is reserved for patients who have presented moderate to severe forms of COVID 19, requiring a long follow-up aimed at re-evaluating the problems that appeared during hospitalization or in the weeks following discharge. The Day Hospital is staffed by a team of several specialists including a paediatrician, an infectious disease specialist, a rheumatologist, a bronchopneumologist, a cardiologist, a neurologist, a physiatrist as well as a psychologist / psychiatrist. The team plans the type of intervention and the blood tests and the instrumental tests to be repeated in the weeks following the disease.

San Marco Hospital of Catania: paediatric outpatient clinic

In March 2021 the Pediatric Bronchopneumology Complex Operating Unit of the San Marco Hospital in Catania set up an outpatient clinic dedicated to children (age range 0-16 years) who have recovered from COVID-19 in central-eastern Sicily (provinces of Catania, Syracuse, Ragusa, Messina, Enna, Agrigento, Caltanissetta). Patients can access the service following an email by the primary care paediatrician in which he describes the patient's history. The clinical / instrumental evaluation is multidisciplinary and involves the following professional figures: paediatrician, cardiologist, physiotherapist, psychologist and nurse. The child who enters the Day-Hospital is subjected to the following investigations: patient history, assessment of the persistence of symptoms attributable to COVID-19, physical examination, blood sampling, skin allergy tests, global spirometry, multiple breath washout to measure the lung clearance index, ultrasound of the lungs, echocardiography, quality of life questionnaires, and 6-minute walk test. Based on the outcome of this assessment, a personalized therapeutic program is set up for the patient in relation to the critical issues that emerged.

5. Essential Monitoring Elements

The Sostegni bis decree-law, approved by the Council of Ministers on 21 May 2021, establishes a national monitoring protocol which envisages, at no cost for the patient, specialist services (as per the Essential Levels of Care, LEA), for monitoring, prevention and early diagnosis of any outcomes or complications related to a previous COVID-19 disease. The purpose of this proposal is to ensure uniformity of care across the national territory through a dedicated monitoring program, for people who have had a severe COVID-19-related clinical picture and who might over time present chronic effects of the disease.

Besides the clinical aspects, the monitoring also includes epidemiological elements for an evaluation of the phenomenon so that, on the basis of the evidence acquired by the end of the period provided for by the Sostegni bis decree-law (end of 2022), structural interventions capable of providing an adequate response to the health and social needs that have arisen can be planned and adopted.

The services provided for in the decree include an assessment of blood test parameters, blood gas analysis, tests that evaluate heart function (ECG Holter, Echocardiogram) and lung function (Spirometry, capillary alveolar diffusion of CO, chest CT) and specialist assessments. Particular attention is paid to older patients, for whom a multidisciplinary evaluation is envisaged in consideration of their fragile conditions. Likewise, a psychological interview is provided for patients undergoing intensive / sub-intensive therapy.

The protocol refers specifically to patients who needed hospitalization due to severe forms of the COVID-19 disease (SARS-CoV-2 interstitial pneumonia, with relative cardio-respiratory insufficiency with or without the need for intensive / sub-intensive care), since these individuals, who are often elderly and have multiple disorders, present a greater risk of possible sequelae and complications following the COVID-19 disease.

The Sostegni bis decree-law also indicates the importance of defining **targeted data collection studies for the Long-COVID condition**, since it is particularly important to understand, analyse and study the outcomes of the COVID-19 disease in terms of coordination of responses by the National Health Service. These studies must collect data based on clinical, laboratory and instrumental parameters that are uniform and homogeneous across the national territory.

6. Classification

As part of a continuous effort to update information as the pandemic evolves, the World Health Organization has developed, alongside the international guidelines for the certification and classification (coding) of COVID-19, specific emergency codes for COVID-19 within the framework of the ICD10 classifications, which include a **specific code for the “Post-COVID-19” condition**:

- **U09.9** Post-COVID-19 condition, unspecified
This specific code should not be used if the acute form of the COVID-19 disease is still present

In addition, the World Health Organization has released the following ICD10 codes for the classification of conditions resulting from COVID-19:

- **U08.9** Personal COVID-19 medical history, unspecified
- **U10.9** Multisystem inflammatory syndrome associated with COVID-19, unspecified
 - Multisystem inflammatory syndrome in children (MIS-C) temporally associated with COVID-19
 - Paediatric multisystem inflammatory syndrome (SIMP) (PIMS) temporally associated with COVID-19
 - Kawasaki-like syndrome temporally associated with COVID-19
 - Cytokine storm temporally associated with COVID-19

ICD10 codes are used in Italy mainly for coding causes of death. The ICD-9-CM classification systems, instead, are used for coding of clinical information contained in the hospital discharge form and for the remuneration of hospital services.

With the Decree of 28 October 2020 (Official Gazette no. 26, of 1 February 2021), the Ministry of Health integrated the classification systems (ICD-9-CM) for coding the clinical information contained in the hospital discharge form and for the remuneration of hospital services with specific codes for the SARS-CoV-2 (COVID-19) disease. This document provides a code to identify people with potential risks of disease in relation to their family and personal medical history:

- **V12.04** Personal history of SARS-CoV-2 (COVID-19) disease.

7. Research on Long-COVID

Long-COVID is a condition that has recently been identified and therefore medical knowledge is still largely incomplete and rapidly evolving (5, 52).

From the standpoint of research, there are several aspects to be investigated in the diagnostic, prognostic and therapeutic fields.

The NICE guidelines and some publications on the subject have proposed the main questions to which research on Long-COVID is called upon to answer in the future (5, 76, 77).

Below is a list, taken partly from these publications, of the main research issues.

- **Definition and classification of Long-COVID**
 - Definition of the pathophysiology of the Long-COVID syndrome, with special reference to the correlation between symptoms and organ damage;
 - What are the clinical, laboratory or instrumental factors that can predict the risk of developing Long-COVID, differentiating among the factors present before the COVID disease, those present in the acute phase and those present during the early stages of convalescence;
 - What is the prevalence and incidence of Long-COVID;
 - What are the clinical and functional trajectories of Long-COVID;
 - What are the symptoms that characterize Long-COVID and how do they differ in terms of age groups (in particular in children and in the elderly), sex, severity of the COVID-19 disease (also in terms of previous hospitalization in the COVID ward or in intensive care) and treatment delivered during the acute phase;
 - Which organs are most impaired in patients with Long-COVID;
 - Develop and validate population screening tools for Long-COVID;
 - Develop and validate Long-COVID diagnosis and monitoring tools;
 - Define the main differential diagnoses of Long-COVID and the diagnostic paths / algorithms whereby Long-COVID can be differentiated from the alternative diagnoses;
 - What are the diagnostic investigations to be performed in patients who report symptoms compatible with Long-COVID.

- **The Natural History of Long-COVID**
 - What is the natural history of Long-COVID (longitudinal monitoring of patient cohorts or creation of patient registers);
 - What are the reasons for re-hospitalisation of patients with Long-COVID and what are the clinical outcomes;
 - What is the impact of Long-COVID on the aging process, for example in terms of acceleration of the aging process itself;

- What is the impact of Long-COVID on the treatment course of pre-existing diseases;
 - Identify both clinical and laboratory indicators of Long-COVID;
 - Define the functional and psycho-social consequences of Long-COVID on functional autonomy, quality of life, mental health and participation in work activities or social life.
- **Treatment**
- What are the indicators of effectiveness of the interventions implemented in patients with Long-COVID;
 - What are the therapeutic interventions and management programs which are most effective in patients with Long-COVID;
 - Check if the effectiveness of the interventions varies in relation to age groups, gender, ethnic groups or severity of symptoms;
 - What are the multidisciplinary interventions, including rehabilitation, that are most effective in patients with Long-COVID;
 - What is the effectiveness of physical exercise in patients with the Long-COVID syndrome;
 - What are the most effective forms of physical exercise (e.g. Aerobic, counter resistance, multicomponent) and when is the best time to start physical exercise;
 - Evaluate whether vaccination prevents the appearance of Long-COVID;
 - Develop ways of involving patients in contributing to the management of Long-COVID.

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