Post-acute sequelae of SARS-CoV-2 infection

or Long Covid

Follow-up of a cohort of patients with Long Covid in a family practice

Marc Jamoulle, MD, PhD. Family physician marc.jamoulle@uliege.be
HEC, Information Science, Université de Liège, Belgium
D2IM, Informatics lab, University of Rouen, France

emji2022

1

As seen by doctors

Long Covid

[Disease ontology](#)
ID DOID:0080848

Metadata

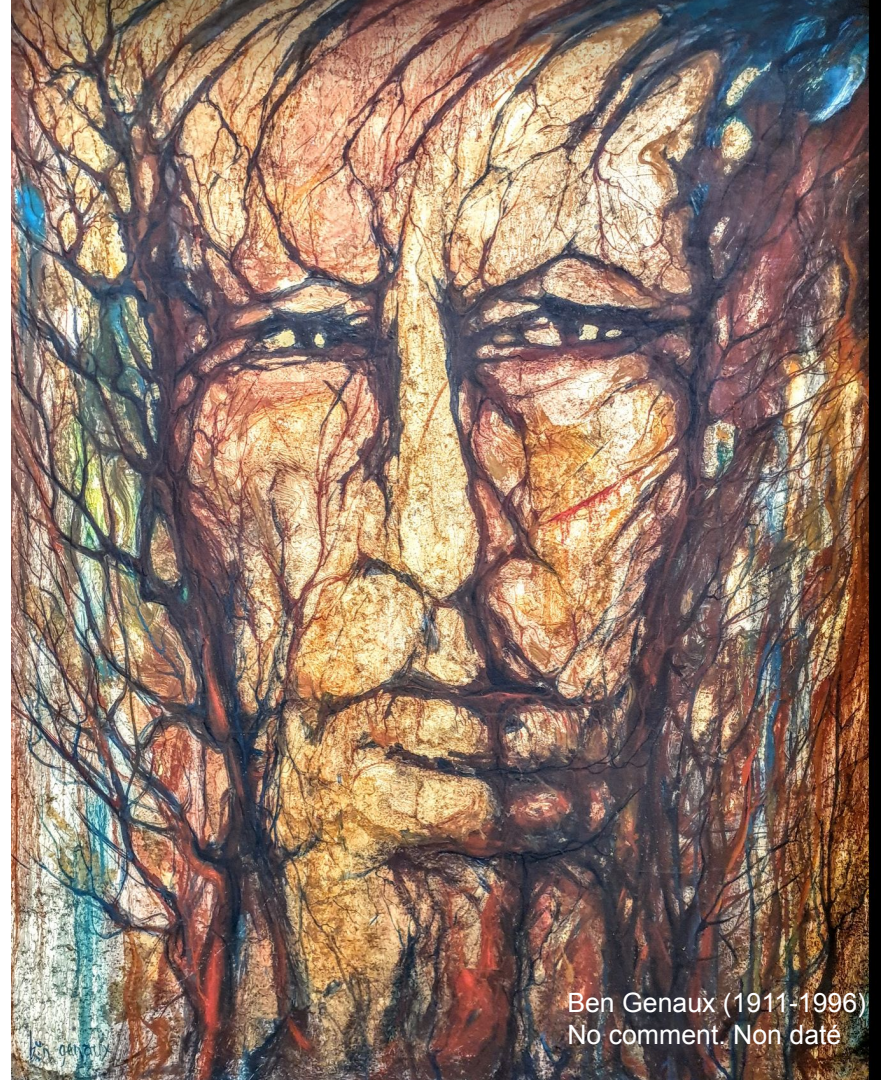|	
ID	DOID:0080848
Name	long COVID
Definition	A Coronavirus infectious disease that is characterized by long-term persistent and fluctuating symptoms, in individuals with COVID-19, persisting beyond three to four weeks, including the loss of the ability to smell and taste, breathlessness, fatigue, difficulty in breathing, difficulty concentrating, memory loss, confusion, headache, heart palpitations, chest pain, pain with deep breaths, dizziness, and tachycardia. https://www.bmj.com/content/371/bmj.m4470, https://www.medrxiv.org/content/10.1101/2020.10.07.20208249v1, https://www.medrxiv.org/content/10.1101/2020.10.07.20208702v1, https://www.medrxiv.org/content/10.1101/2020.10.13.20211854v1, https://www.nature.com/articles/d41586-020-02796-2
Synonyms	chronic COVID-19 [EXACT] PASC [EXACT] post-acute sequelae of SARS-CoV-2 infection [EXACT] post-COVID syndrome [EXACT]
Parent Relationships	is_a Coronavirus infectious disease

Add an item to the term tracker

experienced by the patient

Poly-systemic symptoms dominated by fatigue, cognitive impairment, memory loss, exertional exhaustion, autonomic dysfunction in the weeks/months after even a mild Covid.
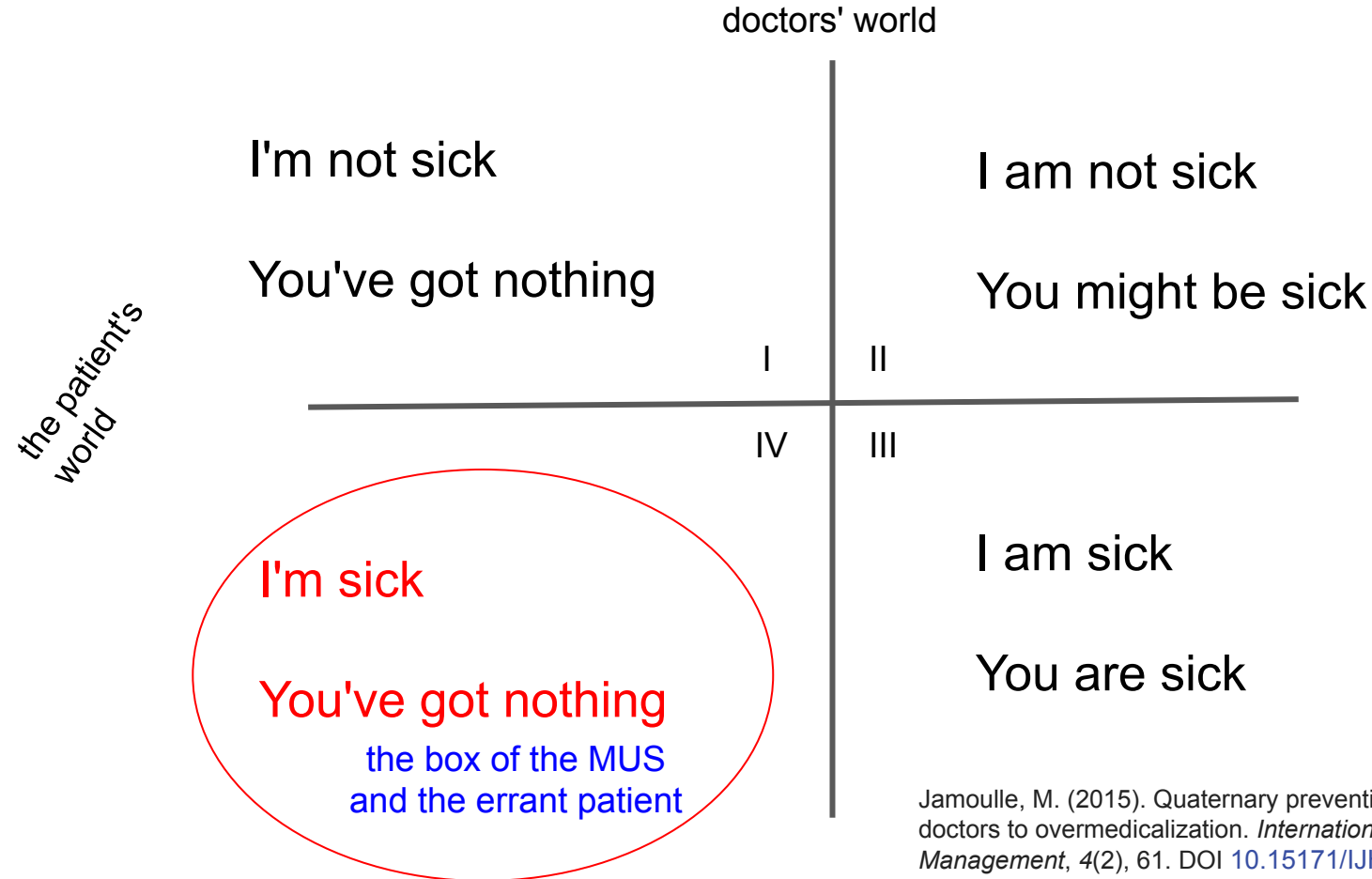
Induces a considerable and abrupt change in life

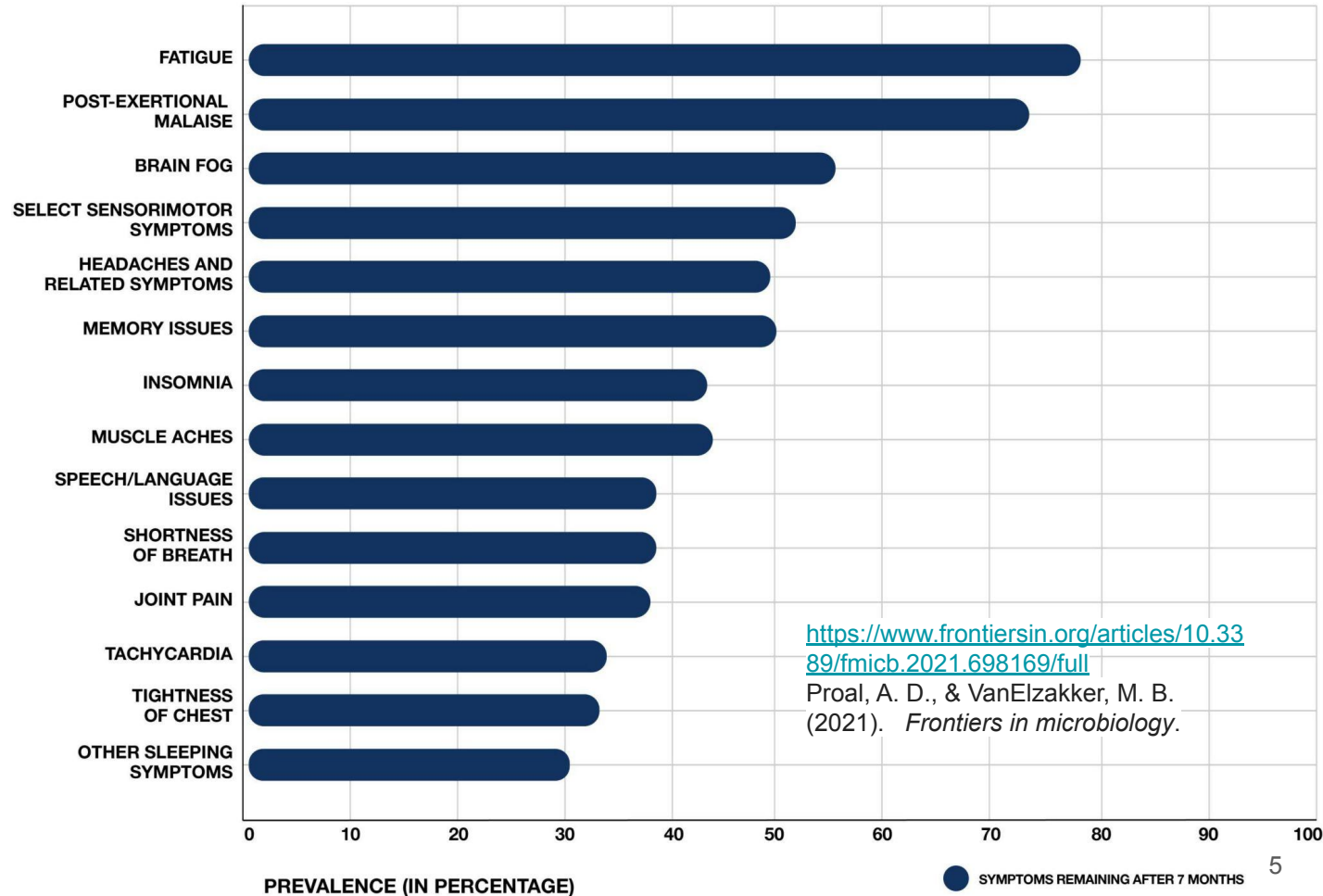Ben Genaux (1911-1996)
No comment. Non daté

3

Long Covid patient is most often in the box four

doctors' world

the patient's world

I'm not sick

You've got nothing

I am not sick

You might be sick

I   II

IV   III

I'm sick

You've got nothing

the box of the MUS
and the errant patient

I am sick

You are sick

Jamoulle, M. (2015). Quaternary prevention, an answer of family doctors to overmedicalization. *International Journal of Health Policy and Management*, *4*(2), 61. DOI 10.15171/IJHPM.2015.24

4

Long Covid multi-systemic disabling condition with no treatment

Six months after a coronavirus infection, at least one in seven people still have some symptoms. KCE Reports 344 (2021)

REMAINING SYMPTOMS AFTER MONTH 7 (PREVALENCE >30%)

PREVALENCE (IN PERCENTAGE)

● SYMPTOMS REMAINING AFTER 7 MONTHS

https://www.frontiersin.org/articles/10.3389/fmicb.2021.698169/full
Proal, A. D., & VanElzakker, M. B. (2021). *Frontiers in microbiology*.

5

Patients express recurrent complaints. We have included here all complaints transcribed in English from the observation records of the first 34 patients seen in the family practice. T

his terminology view, edited in a word cloud (wordclouds.com), gives a conceptual representation of the clinical picture of the PACS recorded by the physicians.

The size of the words gives an idea of their recurrence. One can immediately see that loss and pain are the most important complaints, memory loss but also word loss and then the countless symptoms characteristic of Long Covid

Before Covid

7
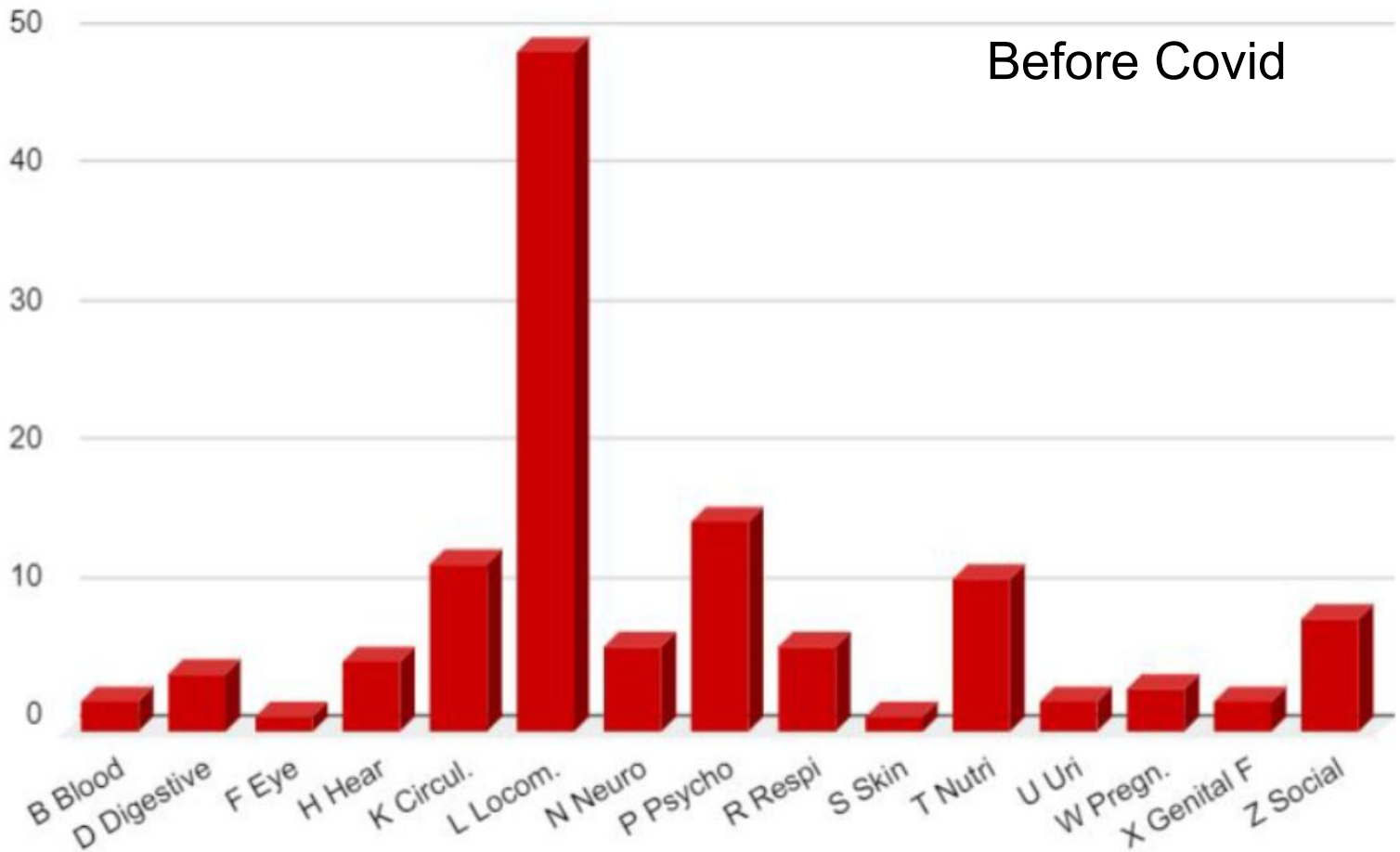
The Long Covid is first and foremost a story of medically unexplained symptoms and medical wandering

Some diagnoses found in the files of the 55 patients

- angina pectoris,
- Alzheimer's disease,
- pulmonary embolism,
- hyperventilation,
- fibromyalgia,
- traumatic shock,
- burnout,
- anxiety attacks,
- post-traumatic stress disorder,
- lazy teenager (a teacher),
- irritable bowel
- functional colopathy

olde Hartman, T. C., Woutersen-Koch, H., & Van der Horst, H. E. (2013). Medically unexplained symptoms: evidence, guidelines, and beyond. *British Journal of General Practice*, *63*(617), 625-626. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3839356/

Neurology and Long Covid

Ke words
'COVID 19' or 'Novel Coronavirus 2019' or 'Coronavirus disease 2019' or '2019-nCOV' or 'SARS-CoV-2' or 'coronavirus-2') and TS = ('neurology'or 'neurological' or 'nervous system' or 'neurodegenerative disease' or 'brain' or 'cerebra' or 'nerve'

5,329 publications from 2020 to 2022

relationship of ICPC-3 with ontologies ; ex Deer Covid ontology

The 286 entries of Deer et all. ontology according to ICPC-3 chapters
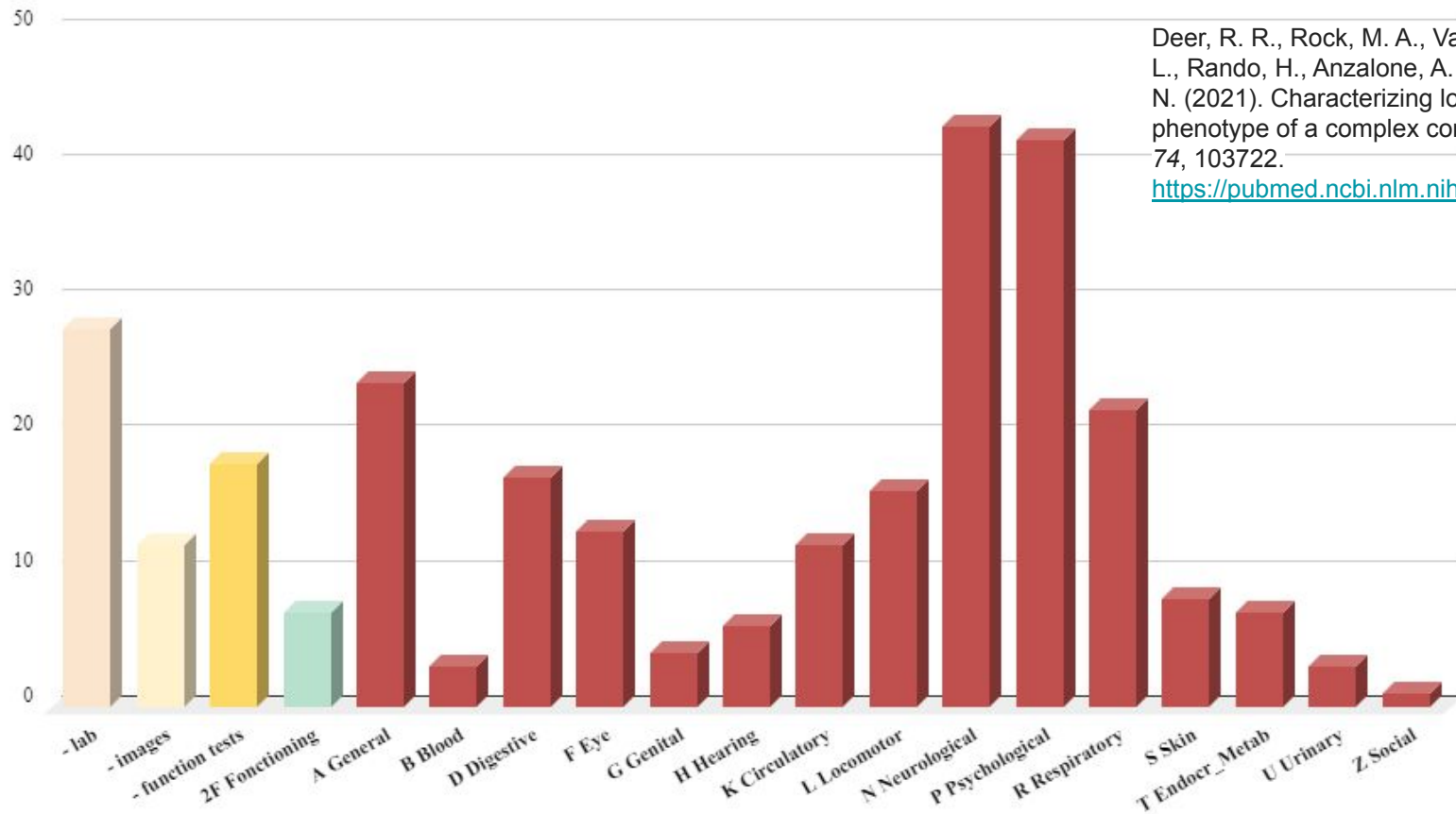
Deer, R. R., Rock, M. A., Vasilevsky, N., Carmody, L., Rando, H., Anzalone, A. J., ... & Robinson, P. N. (2021). Characterizing long COVID: deep phenotype of a complex condition. *EBioMedicine*, *74*, 103722.
https://pubmed.ncbi.nlm.nih.gov/34839263/

Diagnosing LONG Covid in family medicine

- **Validating what the patient says; narrative medicine**

  Greenhalgh T, Hurwitz B. . *BMJ*. 1999;318(7175):48-50.
  https://www.bmj.com/content/318/7175/48.1

- **Search for available information: data collection**

  Electronic Medical Record / RSW / Telephone!

- **Assessing the severity of the situation: DUSOI severity indicator**

  Parkerson 1996 DUSOI WONCA https://tinyurl.com/DUSOIWONCAscore

- **Ask the patient for their assessment: COOP/WONCA functional status indicator**

  Jamoulle, M. (1992). Évaluation de l'état fonctionnel, les cartes COOP/WONCA
  .https://orbi.uliege.be/handle/2268/264661

Diagnosing LONG Covid in family medicine

- **Biology; nothing usual: cortisol ?, monocyte activation syndrome**
- **Imaging; nothing or almost nothing including CT Scan and MRI, PET Scan (Verger et al.)**
- **Cardio; generally nothing. Cardiac MRI (Puntmann et al.)**
- **Pneumo; sometimes diffusion disorder, hyperventilation, O2 extraction defect (Singh et al.)**
- **Clinical neuro / EEG / EMG / PE etc; not much more than history**
- **Hematology; Micro clots (Pretorius)**
- **Dermatology: acrocyanosis like cases (frostbite), vasculitis**

-> No PET scan in MF → Technetium SPECT-CT?

-> Monocyte activation? : → Rega KUL immuno lab
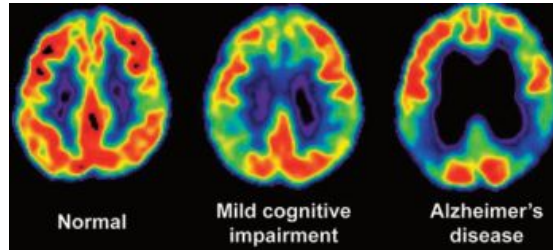
Nuclear medicine resources

SPECT CT

8FDG PET

can be prescribed by the GP

lower sensitivity, similar specificity

less clear images / vascular flow

reimbursed up to 250 euros
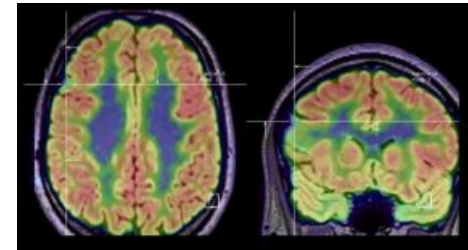
high environmental cost

prescribed by a specialist / not reimbursed in COVID

higher sensitivity, similar specificity

detailed images / glucose metabolism

high cost

very high environmental cost (isotopes produced by cyclotron)

Normal — Mild cognitive impairment — Alzheimer's disease

A SPECT CT was requested in patients with the following three criteria:

➔ Clinical symptoms suggesting a brain disorder in the context of the Covid pandemic

➔ a severity level of 3 or 4 on the DUSOI/WONCA

https://tinyurl.com/DUSOIWONCAscore
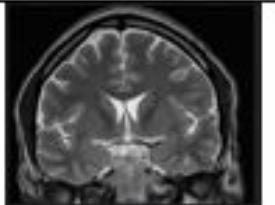
➔ a functional status of more than 20 points on the COOP/WONCA https://tinyurl.com/COOPWONCA
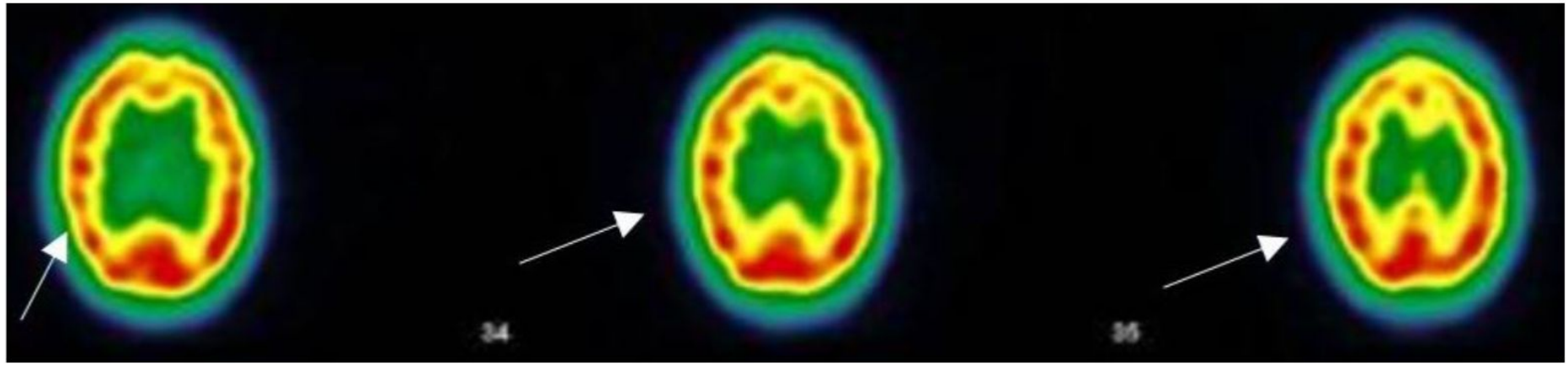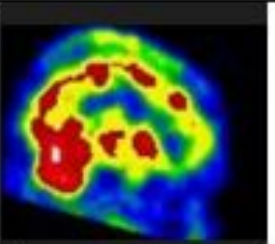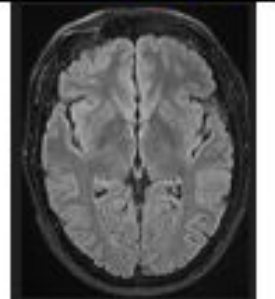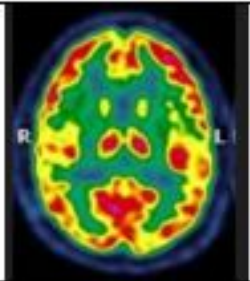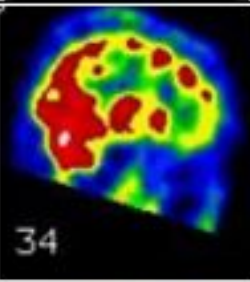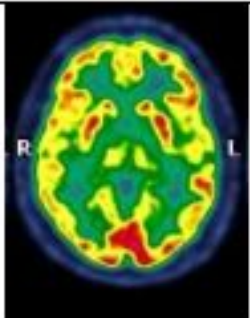
Figure 3. Case MGA010, F, 46, May 2021 ; SPECT-CT examination (ECD Tc-99m): The image shows three brain sections of the same patient.The arrows show the defects of perfusion. The red areas indicate a good tracer fixation and thus a good perfusion. The decrease in flux intensity is highlighted by the color change from red to yellow (see arrows). This indicate hypofixation and thus ischemia. Protocol ;" *Heterogeneous tracer fixation with clearer left frontal, left parietal and right parietal hypofixations. No preservation of the sensory-motor cortices. The fixation in front of the grey nuclei and the cerebellum is correct. Presence of periventricular hypocaptation. Conclusion: Evidence of heterogeneous tracer fixation and periventricular hypocaptation compatible with vascular-type cerebral damage.*" (Images and protocol: Drs Bouazza and Mahy, Vesalius Hospital, ISPPC, Belgium)

Acute symptoms	Long-lasting symptoms	SPECT-CT protocol
MGA001, F, 48		
October 13, 2020 Throat pain, rhinorrhea, bad aches, severe fatigue and headache, but no breathing difficulties, dysgeusia, anosmia. Stays at home, cured after 12 days. Home care only	November 11, 2020 Pain in both eyes, ocular pruritus, rapid ocular fatigue, noise intolerance, memory loss (forgets to pick up her daughter at school), concentration problems, remains isolated in her room, dyspnea at the slightest effort and at speech, almost continuous osteoarticular and muscular pains often with headaches, abnormal dreams, depressive feeling, fatigue, post-exertional malaise (PEM)	July 27, 2021 *"On the images taken, left fronto-parietal, left frontal and left thalamic hypofixation is observed. No preservation of the sensory motor cortices. The fixation in front of the cerebellum is correct. Conclusion: Scintigraphic examination compatible with a cerebral pathology of the vascular type with clearer left fronto-parietal, left frontal and left thalamic vascular disorders"*.

Patient 058   49 ans
Cadre supérieur
en arrêt de travail < 2 ans
Covid en mars 2020
Pas de PCR
Sans diagnostic
depuis 27 mois

SPECT CT 13th month	28/04/2021 Severe disturbance of cerebral vascular perfusion (very heterogeneous fixation throughout the cortex, area of marked hypofixation left fronto-parietal	
Brain MRI 16th month	05/07/2021 Normal caliber of the ventricular system. Trophycity and normal appearance of the hippocampi. No intracranial expansive process; No recent or sequential haemorrhagic lesion. Conclusion: negative examination	
Brain CT-Scan 16th month	06/07/2021 No structural abnormalities. Conclusion: negative examination	

Patient 058
follow

Les autres examens, CT, IRM, PET sont non contributifs

18FDG PET-CT 16th month	29/07/2021 Discrete hypometabolism, not significant compared to a normal database, in the cerebral cortex in the superior parietal ans temporal areas, bilaterally. Conclusion: no formal argument for Alzheimer's dementia	
SPECT CT Control 27th month	23/06/2022 Heterogeneous tracer binding throughout the cerebral cortex, in the basal ganglia and in the thalamus. Normal and symmetrical binding in the cerebellum. Conclusion ; the scintigraphic aspect of the abnormalities rather pleads for a vascular origin	
18FDG PET-CT 29th month	04/08/2022 Compared to the examination of 29/07/2021, persistence of a discrete cortical hypometabolism in the right parieto-temporal brain right cerebral parieto-temporal hypometabolism not significant.	

In this case, the first results from the Rega Institute are known and prove the infection by SARS-Cov-2, with a very weak presence of antibodies, a detectable RNAemia and a very striking monocyte activation

18

Statut	Recovered		Still sick
Grade	1	2	3
Label	mild Long Covid	severe Long Covid	very severe Long Covid
Length	3 à 8 months	6 à 18 months	> 18 months
Number	16 patients (9 f, 7 m)	17 patients (13 f, 4m)	22 patients (18 f, 4 m)
Symptoms	No after-effects	Minor sequelae (e.g. difficult exertion or minor loss of working memory)	Major fatigue, exertional exhaustion, difficulty concentrating, emotional disturbances, paresthesia, persistent memory problems
Capacity	Normal course of life resumed		Unable to resume normal life

Evolution over time of a cohort of patients seen in family medicine with Covid-19 post acute syndrome. (Centre médical Janson, Charleroi, Belgium, 22021-2022)

		Outcome					
		Recovered		Still sick		Test	p
		n	%	n	%		
Sex	Female	22	55	18	45	1.528[#]	0.216
	Male	11	73.3	4	26.7		
First SPECT	No	19	86.4	3	13.6	10.617[#]	**0.001**
	Yes	14	41.9	18	58.1		
Second SPECT	No	28	73.7	10	26.3	12.766[#]	**<0.001**
	Yes	3	20.0	12	80.0		
DUSOI[1]	2	6	100	0	0	13.847[*]	**0.001**
	3	18	78.3	5	21.7		
	4	9	34.6	17	65.4		
		Mean	SD	Mean	SD		
Age (years)		42.9	15.6	42.0	12.9	0.222[##]	0.825
COOP Total score[2]		20.8	3.7	23.4	2.3	2.758[##]	**0.008**
Months after acute COVID		13.3	8.9	18.3	5.9	2.347[**]	**0.019**

[#]Chi-square test, [*]Fisher's exact test, [**]Mann-Whitney U test, [##]Independent samples t-test

Evolution 2021-2022

55 patients, 73% female

23 without PCR

49 vaccinated and 30 systemic reactions to vaccine

30 pathological scans

Clinical picture

+ **Severity**
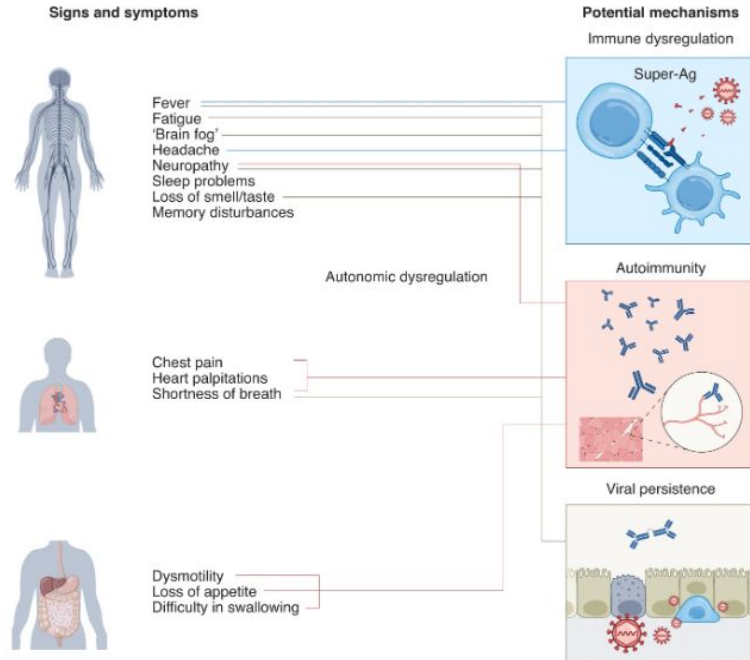+ **Functional status**

→ **SPECT-CT** →

significant statistical relationship with a very severe Long Covid of more than 18 months

Is it COVID? Is it?

→ Thanks to the CHGE network, collaboration with Rega Institute for Medical Research   https://rega.kuleuven.be/cev/mvr

immunology lab: 48 patients / results soon

Fig. 1: Common signs and symptoms and possible causes of long COVID.

From: Studying severe long COVID to understand post-infectious disorders beyond COVID-19

Signs and symptoms

Fever
Fatigue
'Brain fog'
Headache
Neuropathy
Sleep problems
Loss of smell/taste
Memory disturbances

Autonomic dysregulation

Chest pain
Heart palpitations
Shortness of breath

Dysmotility
Loss of appetite
Difficulty in swallowing

Potential mechanisms

Immune dysregulation

Super-Ag

Autoimmunity

Viral persistence

a, Signs and symptoms frequently present or reported in patients with long COVID. b, Hypothetical mechanisms that could explain key signs and symptoms targeted for further investigation. Super-Ag, superantigen. Figure by P.B.

Very active research network

Mainly in genetics and immunology
https://www.covidhge.com/

Brodin, P., ... & Casanova, J. L. (2022). *Nature Medicine*, 1-4. https://www.nature.com/articles/s41591-022-01766-7

22

Covid long therapeutic approach

- **Name the disease, listen to the patient**

- **Neurocognitive revalidation**

- **Physical revalidation**

- **Medications; Nothing from EBM / short corticosteroid therapy / anticoagulant; Aspirin Clopidogrel / Piracetam / Oxygen therapy (hyperbaric) / Cetirizine / Famotidine / Antiviral?**

- **Some social security systems are supporting the LC patients**

therapeutic trial underway at the Vesalius Hospital (Charleroi) hyperbaric chamber

1.000 € to be paid by the patient

Hyperbaric oxygen therapy for the treatment of long COVID: early evaluation of a highly promising intervention

Tim Robbins, Michael Gonevski, Cain Clark, Sudhanshu Baitule, Kavi Sharma, Angel Magar, Kiran Patel, Sailesh Sankar, Ioannis Kyrou, Asad Ali and Harpal S Randeva

⤓ DOWNLOAD PDF   DOI: https://doi.org/10.7861/clinmed.2021-0462
Clin Med November 2021

nature > scientific reports > articles > article

Article | Open Access | Published: 12 July 2022

Hyperbaric oxygen therapy improves neurocognitive functions and symptoms of post-COVID condition: randomized controlled trial

Shani Zilberman-Itskovich, Merav Catalogna, Efrat Sasson, Karin Elman-Shina, Amir Hadanny, Erez Lang, Shachar Finci, Nir Polak, Gregory Fishlev, Calanit Korin, Ran Shorer, Yoav Parag, Marina Sova & Shai Efrati ✉

Scientific Reports **12**, Article number: 11252 (2022) | Cite this article

Current understanding (follow Twitter for more…)

This disease is now considered to be a multisystemic vascular disease with mainly cerebral and cardiac involvement, most likely due to the persistence of the virus in the gut. Virus that is deleterious to coagulation and vascular endothelium in patients with little ability to defend themselves immunologically, as shown by the analysis carried out in KUL Leuven on my patients (Transcriptonomics studies - paper in preparation).

- **PACS has a high prevalence in primary care for those who want to see it.**
- **Clinical skills and narrative medicine are essential to identify and understand patients' experiences. This requires time, openness and empathy.**
- **Cerebral hypo-perfusion demonstrated by SPECT-CT appears to correlate with clinical symptoms in a cohort of PACS patients. This requires further study.**
- **Uncertainty about acute primary infection is an issue. The participation of 48 patients in the European Consortium of Genetic and Immunological Studies on COVID-19 will probably provide answers and further questions.**
- **The impact of PACS is considerable, with many social and economic implications.**

Sources:
Figures and tables are taken from these publications, which have an extensive bibliography:

- ●Jamoulle M. Re: Addressing Post-COVID Symptoms: A Guide for Primary Care. Vascular encephalopathy demonstrated by brain single-photon emission computed tomography (SPECT) in long Covid patients. *J Am Board Fam Med* 2022;35: https://www.jabfm.org/content/35/4/874.full
- ●Jamoulle M. Kazeneza Mugisha G., Zayane A. Follow-up of a cohort of patients with Long Covid in a family practice. Viruses. 2022 *14*(9), hhttps://www.mdpi.com/1999-4915/14/9/2000

For a remarkable overview of Long Covid as a multi-systemic vascular disease on 1/8/2022 see:

Ahamed, J., & Laurence, J. (2022). Long COVID endotheliopathy: hypothesized mechanisms and potential therapeutic approaches. The Journal of Clinical Investigation, 132(15), e161167. https://www.jci.org/articles/view/161167?s=03

Covid-19: WHO calls for action as estimated 17 million Long Covid cases in Europe.

BMJ. 2022 Sep 14;378:o2232. doi: 10.1136/bmj.o2232.

Jerome Bosh, Triptych of the Temptation of Saint Anthony (ca. 1520-1530) MBA Brussels (detail) 27