

Long Covid; terminologies, classifications and real world

WICC Open day
Sydney
October 25, 2023

Marc Jamouille, MD, PhD. Family physician
HEC, Information Science, Université de Liège, Belgium
D2IM, Informatics lab, University of Rouen, France

Johan Van Weyenbergh, PHD, senior immunologist,
University of Leuven (KUL), Rega Institute, Belgium



J.Bosh 1500

What are we discussing today in Long Covid World?

- Classification & terminologies
- Open bibliography on Zotero
- Advances in pathophysiology
- Real world research in family practice

Terminology or Classification	ID	Preferred term	Class, category or Metaterm
MeSH	D000094024	Post-Acute COVID-19 Syndrome	Pathological conditions, signs and symptoms Respiratory tract diseases
ICD10	U09 U09.9	Post COVID-19 condition	Provisional assignment of new diseases of uncertain etiology or emergency use
ICD11	RA02 RA03	Post COVID-19 condition Multisystem inflammatory syndrome associated with COVID-19	International provisional assignment of new diseases of uncertain aetiology and emergency use
ICPC2	A77 R80	viral disease other/nos Coronavirus infection: possible case covid19	-Diagnosis general -Infection others Respiratory system -Diagnosis
ICPC3	RD08	Coronavirus disease 2019 (COVID-19)	RD Diagnoses and diseases of respiratory system
Disease ontology	DOID:0080848	Long COVID	Coronavirus infectious disease
SNOMED_CT	1119304009	Chronic post-COVID-19 syndrome (disorder)	diagnosis infectious disorder
MedDRA LLT	10085504 10085868	Long COVID Long COVID-19	Infections and infestations Respiratory, thoracic and mediastinal disorders
NCIt concept	C189191 C179263	COVID-19 Symptoms and Sequelae Post-Acute Sequelae of COVID-19	-Clinical or Research Assessment Question -COVID Clinical Classification Question -Viral Infection -Coronavirus Infection

using
HeTOP
(<https://www.hetop.eu/hetop/en>)

**condition
disease
disorder
diagnosis
symptom
syndrome
sequelae**

not in
HPO!

Long Covid / Terminology and classification / NICE

OSC ; Ongoing symptomatic COVID-19 (OSC) describes signs and symptoms of COVID-19 that persist for 4–12 weeks

PCS ; Post-COVID-19 condition/ syndrome (PCS) describes signs and symptoms that develop during or after an infection consistent with COVID-19 and continue for more than 12 weeks

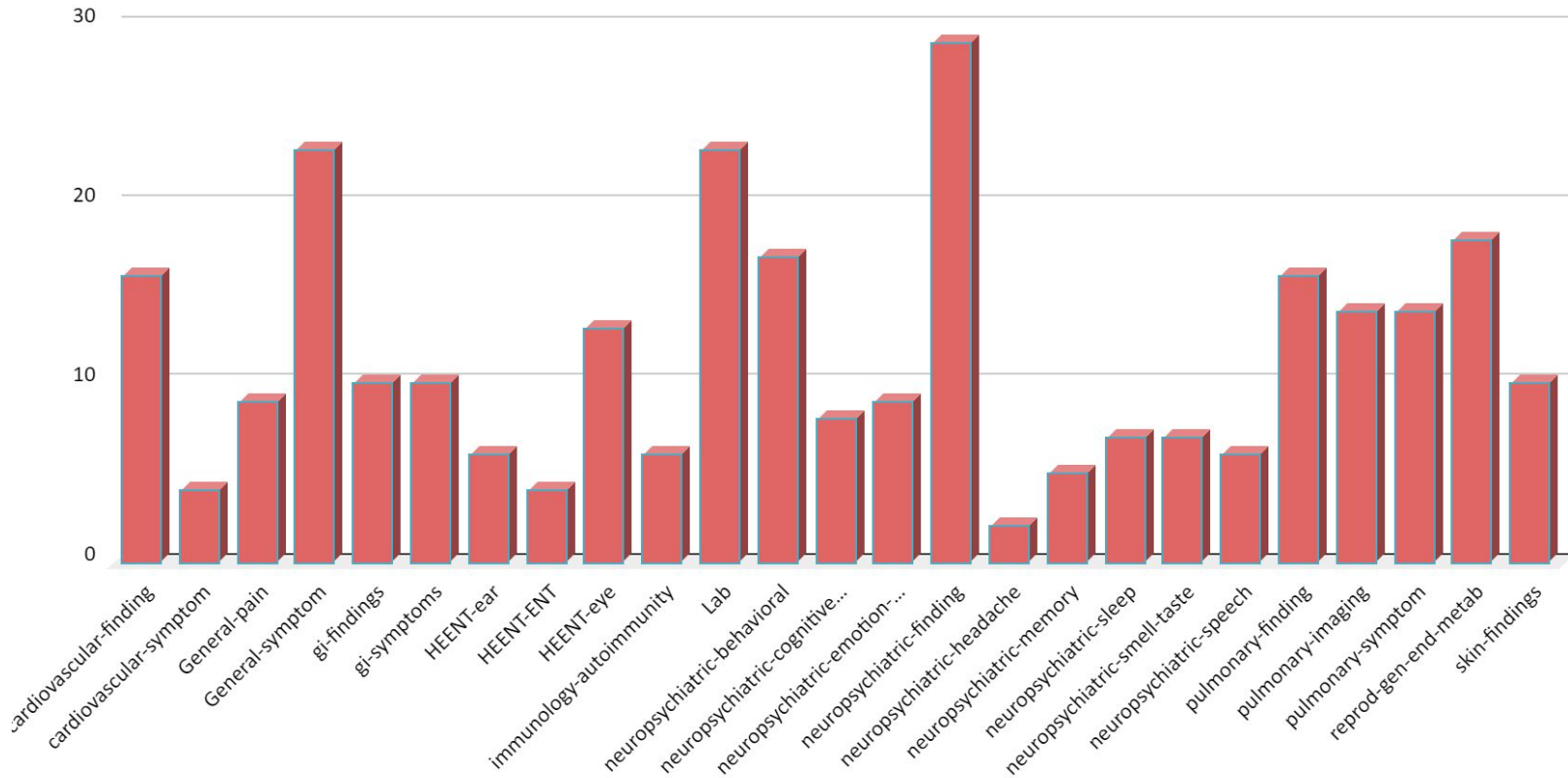
Kamalakkannan A, Sezgin G, McLeod A, et al. Classification of Long COVID from General Practitioner Diagnosis Text. *Stud Health Technol Inform.* 2023;304:124-125. doi:10.3233/SHTI230387

ICPC-3 Respiratory System RD08.00

Post COVID-19 condition occurs in individuals with a history of probable or confirmed SARS CoV-2 infection, usually 3 months from the onset of COVID-19 with symptoms and that last for at least 2 months and cannot be explained by an alternative diagnosis. Common symptoms include fatigue, shortness of breath, cognitive dysfunction but also others and generally have an impact on everyday functioning. Symptoms may be new onset following initial recovery from an acute COVID-19 episode or persist from the initial illness. Symptoms may also fluctuate or relapse over time.

<https://extended.icpc-3.info/>

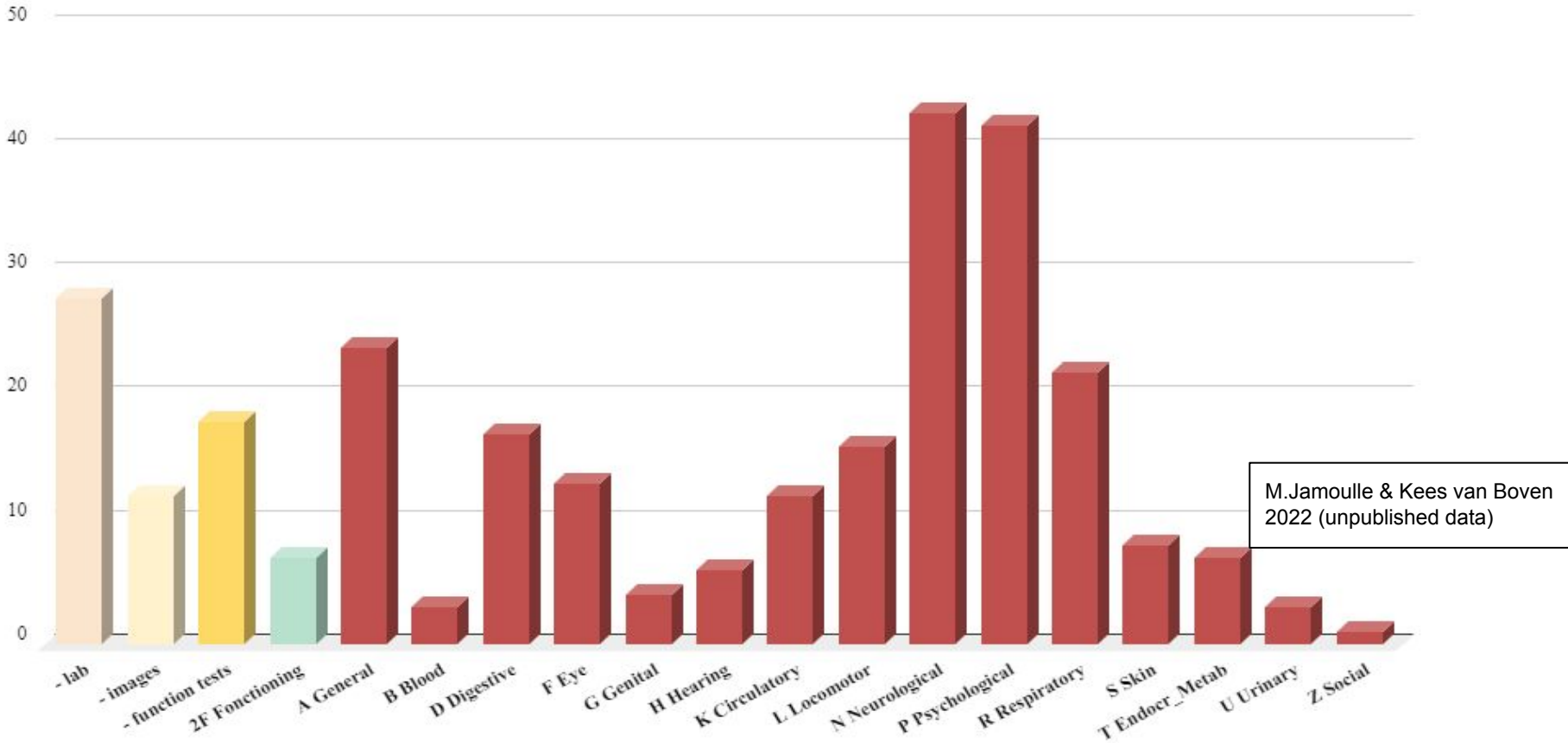
LCPO Ontology ; Distribution according to the headings (classes) of 286 concepts extracted by NLP out of 47 publications on Long Covid published by Deer and all 2021.




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/>

Mapping the Long Covid Phenotype Ontology to ICPC-3

The 286 entries of Deer et al. ontology according to ICPC-3 chapters



▼  Long Covid Open Library

- 📁 Covid-Ontology
- 📁 LC - publications MJ
- 📁 LC-28 (Disability)
- ▶ 📁 LC-33 (immunol.)
- ▶ 📁 LC-41(imaging)
- 📁 LC-44 (vaccine)
- ▶ 📁 LC-50 (therapeutics)
- 📁 LC-51 (Phys.Revalidation)
- 📁 LC-58 (Cogn revalidation)
- 📁 LC-A (gen)
- ▶ 📁 LC-B (bood)
- 📁 LC-D (Dig)
- 📁 LC-F (eye)
- 📁 LC-G (Gender)
- 📁 LC-H (ear)
- ▶ 📁 LC-K (Circul)

- 📁 LC-L(Osteoart)
- 📁 LC-N (neuro)
- 📁 LC-P (Psycho)
- ▶ 📁 LC-QC12(child)
- 📁 LC-QD23 (Health educ.)
- 📁 LC-QD321(MUS)
- 📁 LC-QD34 (genetics)
- 📁 LC-QH1(envirr.)
- 📁 LC-QR 1(epistemo)
- ▶ 📁 LC-QR2(epidemio)
- 📁 LC-QR31 (quali)
- 📁 LC-QR4 (research network)
- ▶ 📁 LC-QR51 (Class.)
- 📁 LC-QR52(scale)
- 📁 LC-QS33 (Coordination)
- 📁 LC-QT32 (guidelines)
- ▶ 📁 LC-R (Respir)
- 📁 LC-S (Skin)

ICPC and Q-Codes

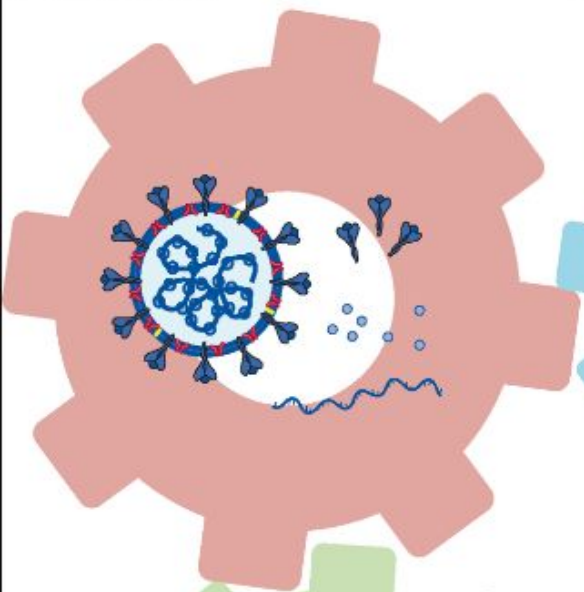
(<https://www.hetop.eu/hetop/3CGP/en>)

based open bibliography on
Zotero

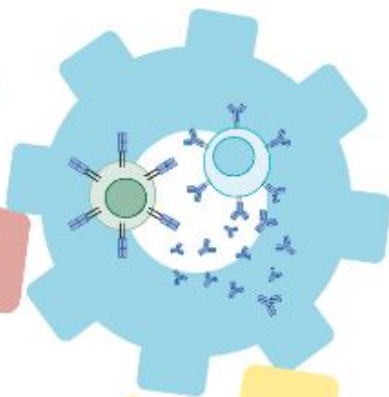
https://www.zotero.org/groups/4929325/long_covid_open_library/library

- 📁 LC-T (metab)
- 📁 LC-W (Pregnancy)
- 📁 LC-Z (Social)
- 📁 Z Publication EJM 2023

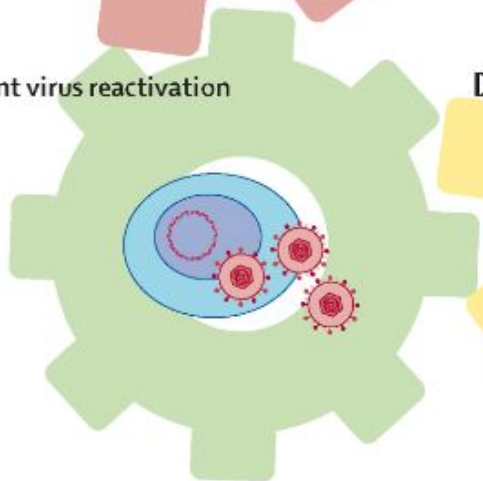
A Viral reservoir



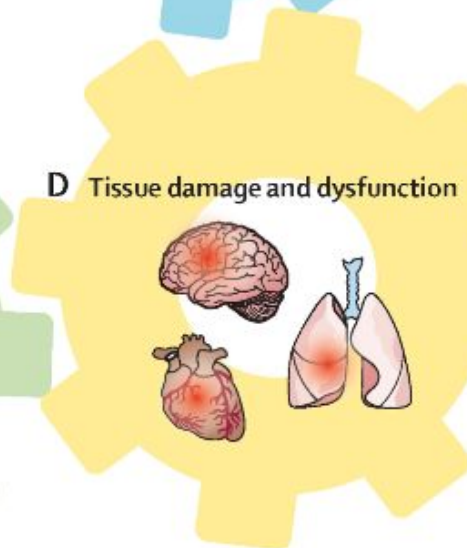
B Autoimmunity



C Latent virus reactivation



D Tissue damage and dysfunction



Pathophysiology Most recent hypothesis

- Vascular damage
 - Microclots
 - Platelet activation
- Hormonal imbalance
- Mitochondrial dysfunction



- Fatigue and post-exertional symptoms
- Dysautonomia and postural orthostatic tachycardia syndrome
- Cognitive impairment and neuropsychiatric symptoms
- Gastrointestinal disturbance and gut dysbiosis
- Impaired gas exchange and shortness of breath
- Structural and functional cardiac pathology
- Mast cell activation syndrome
- Reproductive organ dysfunction

Iwasaki, A., & Putrino, D. (2023). Why we need a deeper understanding of the pathophysiology of long COVID. *The Lancet Infectious Diseases*, 23(4), 393-395.

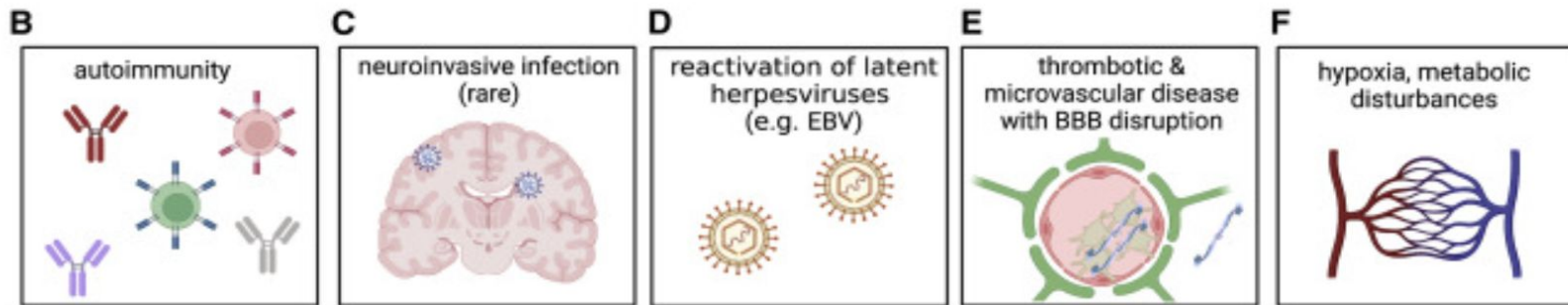
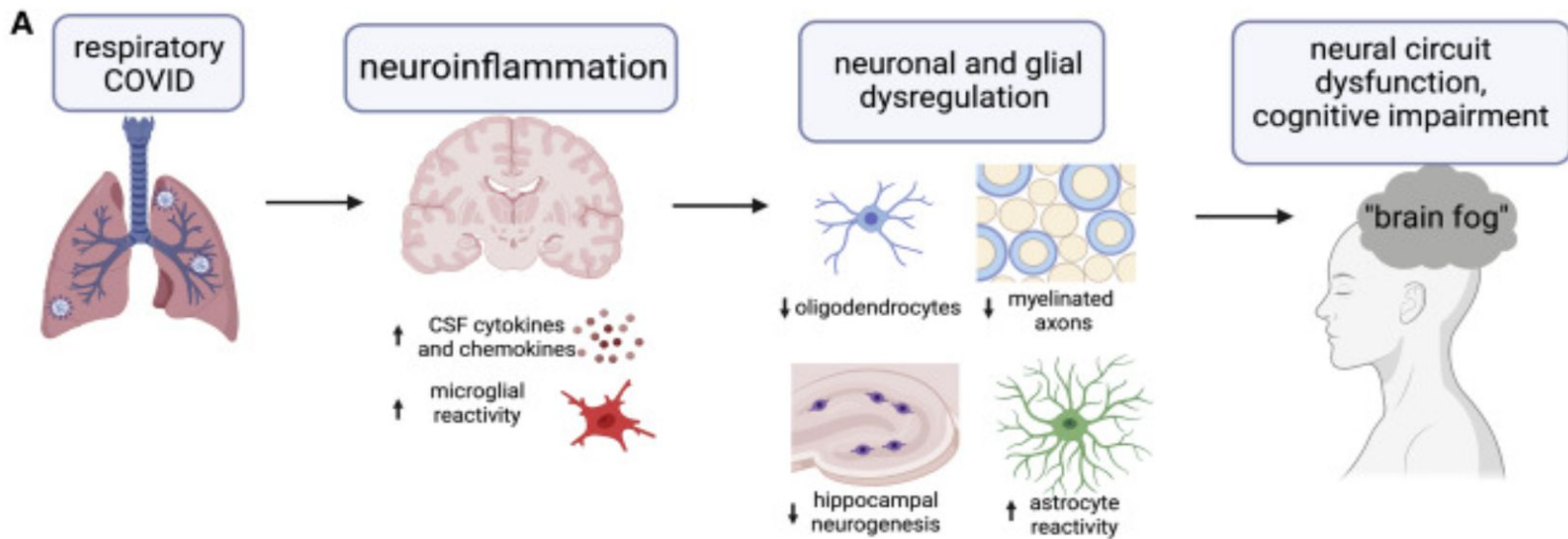


Figure 1 Possible mechanisms contributing to COVID-19-related cognitive impairment

Observational data from patients seen in GP/FM practice in Charleroi, Belgium since July 2021 (104 patients - ongoing)

CRS_master_MGA.all ☆ 📁 ☁

Fichier Édition Affichage Insertion Format Données Outils Extensions Aide

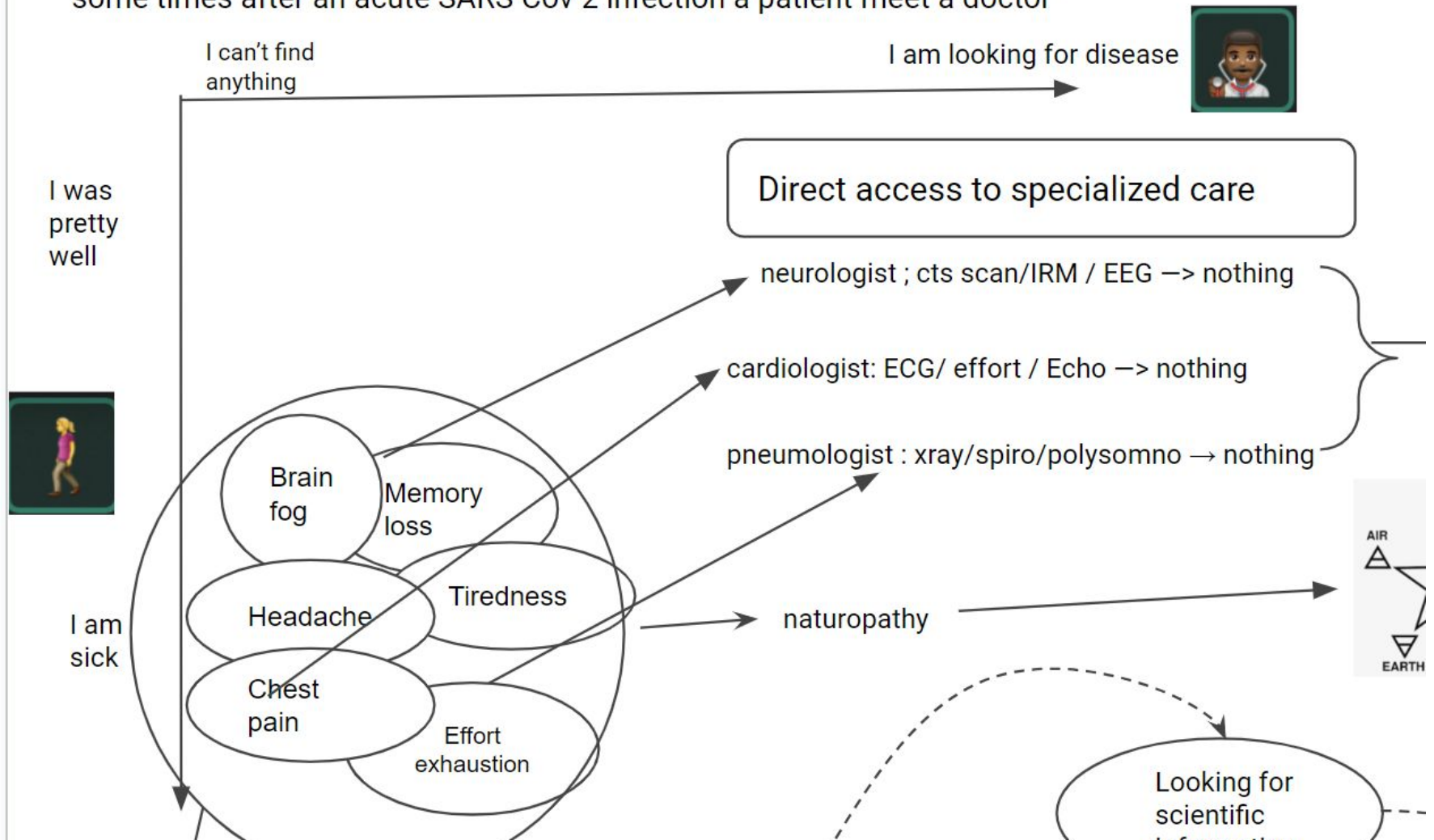
🔍 ↶ ↷ 🖨 📄 100% ▼ | € % .0 ← .00 → 123 | Times ▼ | - 9 + | **B** *I* 🔗 A 🎨 🏠 📏 ⋮ ^

A1 | ✖ Patient_ID

	A	B	C	D	E	F	G	H	I	J	K
1	Patient_ID	Viral Load (RNA)	Lost of view	Pick-up_Date	Genetic relationships	Serial_number	Pat_age	Pat_sex	Pat_occupation	Days_off_work(months)	Comorbidity_before_id
2	MGA_nnn		x if yes	dd/mm/yy	yes = 1, no = 2 same household = 3	1 to n	years	M=1;I=2	terms between semicolon :	months or text	ICPC2 code ;
3	MGA.001	1040,74		6/7/2021	2	1	48	2	housewife	-	R97; R96; U04; N89; X11; P03; R75; L86; B78; Z25
4	MGA.002			03/05/2021	3	2	39	1	civil servant	3	K86; K85; K93; I.03; L74; L80;L86; N89;P S91;
5	MGA.003	9,69		07/10/2021	2						R96; D93; K95; T82
6	MGA.004	49,13		26/10/2021	2						T82;P17

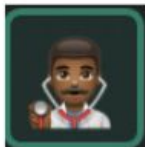
First results on 34 patients ; Jamouille, M., Kazeneza-Mugisha, G., & Zayane, A. (2022). Follow-Up of a Cohort of Patients with Post-Acute COVID-19 Syndrome in a Belgian Family Practice. *Viruses*, 14(9), 2000. <https://doi.org/10.3390/v14092000>

some times after an acute SARS Cov 2 infection a patient meet a doctor



When a patient meets a doctor

I am looking for disease



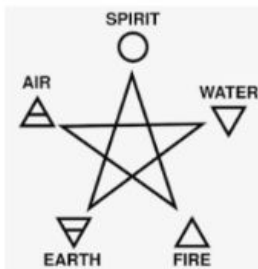
Direct access to specialized care

neurologist ; cts scan/IRM / EEG -> nothing

cardiologist: ECG/ effort / Echo -> nothing

pneumologist : xray/spiro/polysomno -> nothing

naturopathy

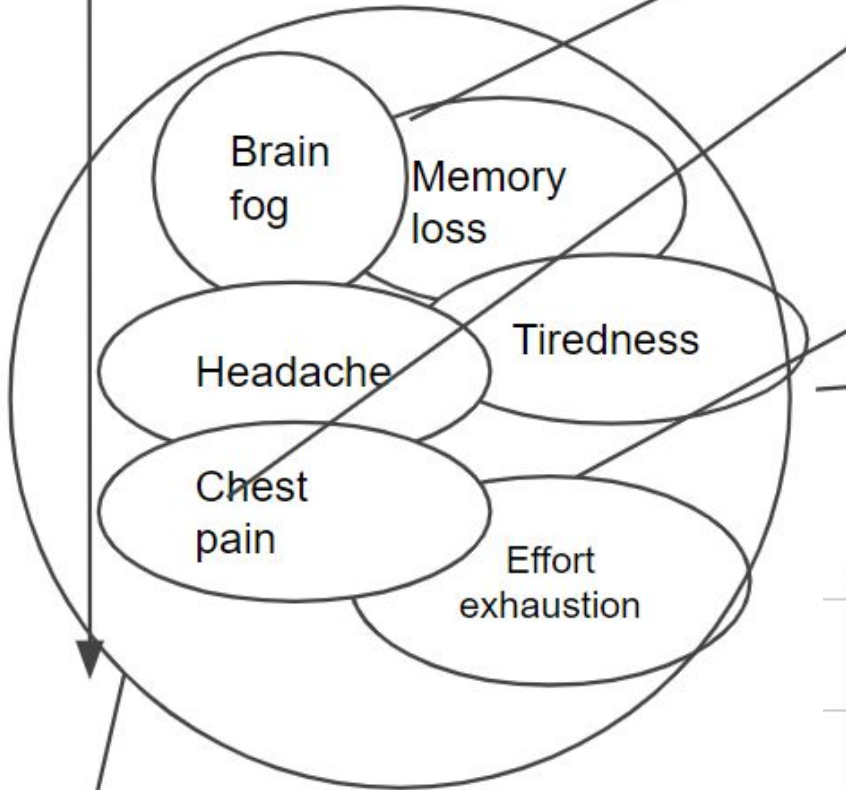


Burnout
Depression
Fibromyalgia
Anxiety

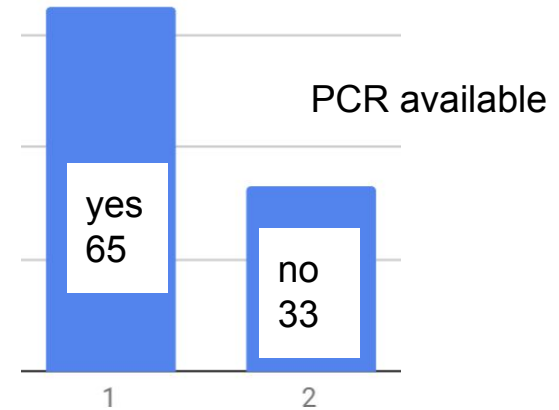
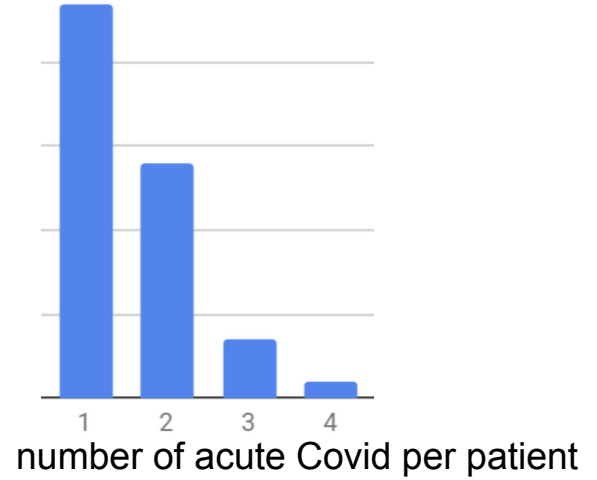


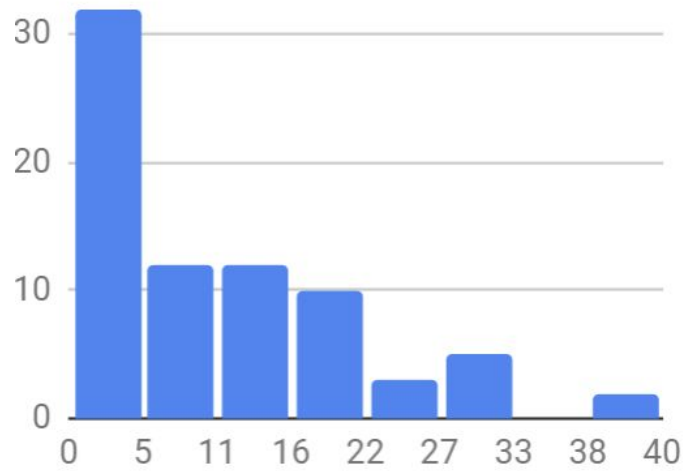


I am sick

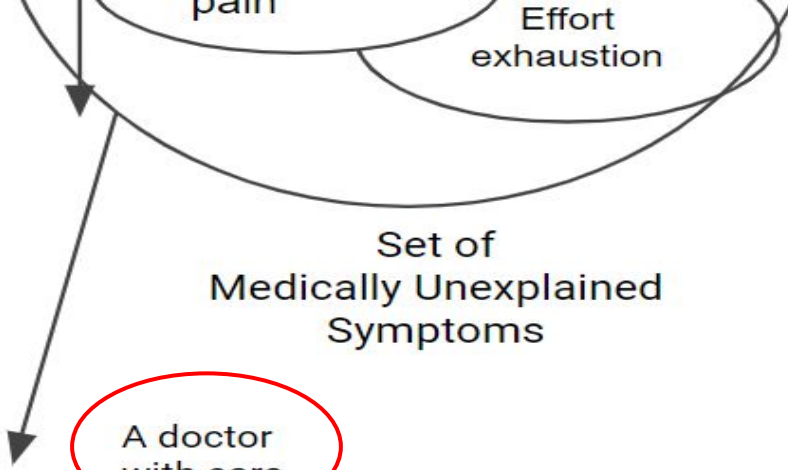


Set of Medically Unexplained Symptoms

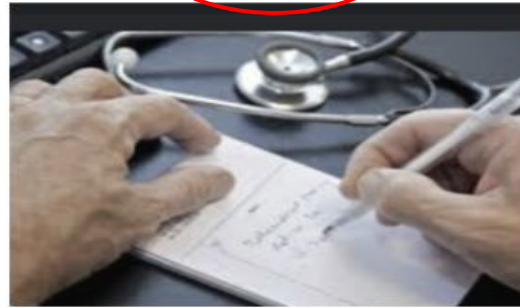




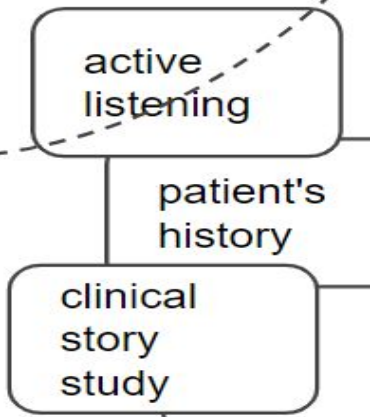
number of months before diagnosis



A doctor with ears



listen, hear, understand, synthesize, evaluate, advocate, , reduce uncertainty



Mainly qualitative data about Medically Unexplained Symptoms

In the weeks that followed, she experienced dizziness, headaches, head pressure and helmet pressure. She was able to return to work part-time, but it was impossible for her to take on any more. Exhausted, she had to stop work completely. It was no longer possible for her to do sport, and she had numerous episodes of abdominal pain. At this point, she was more breathless when she exerted herself.

multitasking woman, executive, mother of two, former athlete, never sick, in her thirties
diagnosed as Burnout

#5 N17 vertige; étourdissement
CIP_D_N17
T_DESC_CISP2_DESCRIPTEUR

#6 Vertige MSH_M_0022633
T_DESC_MESH_CONCEPT

#7 sensation vertigineuse
MSH_D_004244
T_DESC_MESH_DESCRIPTEUR

#8 vertige MSH_D_014717
T_DESC_MESH_DESCRIPTEUR

#9 vertige NCI_CO_C38057
T_DESC_NCIT_CODE

#10 vertige SNO_NO_F-F6000
T_DESC_SNOMED_NOTION

#11 Vertige TSP_DE_012526
T_DESC_TSP_DESCRIPTOR

parus des **vertiges** céphalées, **pression frontale** et en **casque**. Elle a pu reprendre le **travail** à mi-temps mais il lui a été
elle a dû **complètement arrêter le travail**. Il ne lui était plus possible de faire du **sport**, elle a eu de nombreux **épisodes**
omment plus **essouffée à l'effort**.

vertigo

Dyspnea

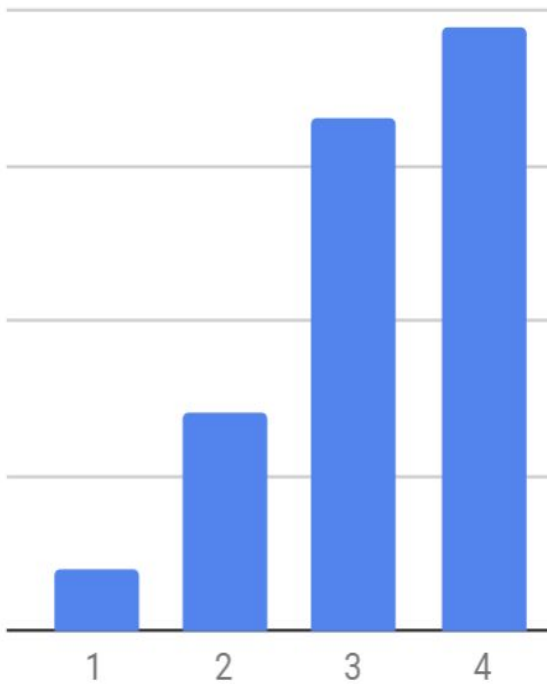
HeTOP
(<https://www.hetop.eu/hetop/en>)
**Automatic concept
extractor**
[https://ecmt.chu-rouen.fr/MTC
Efrontend/](https://ecmt.chu-rouen.fr/MTC
Efrontend/)

#50 R02 souffle court; dyspnée
CIP_D_R02
T_DESC_CISP2_DESCRIPTEUR

#51 R060 dyspnée ICD_SC_R060
T_DESC_ICD10_SUBCATEGORY

#52 dyspnée MSH_D_004417
T_DESC_MESH_DESCRIPTEUR

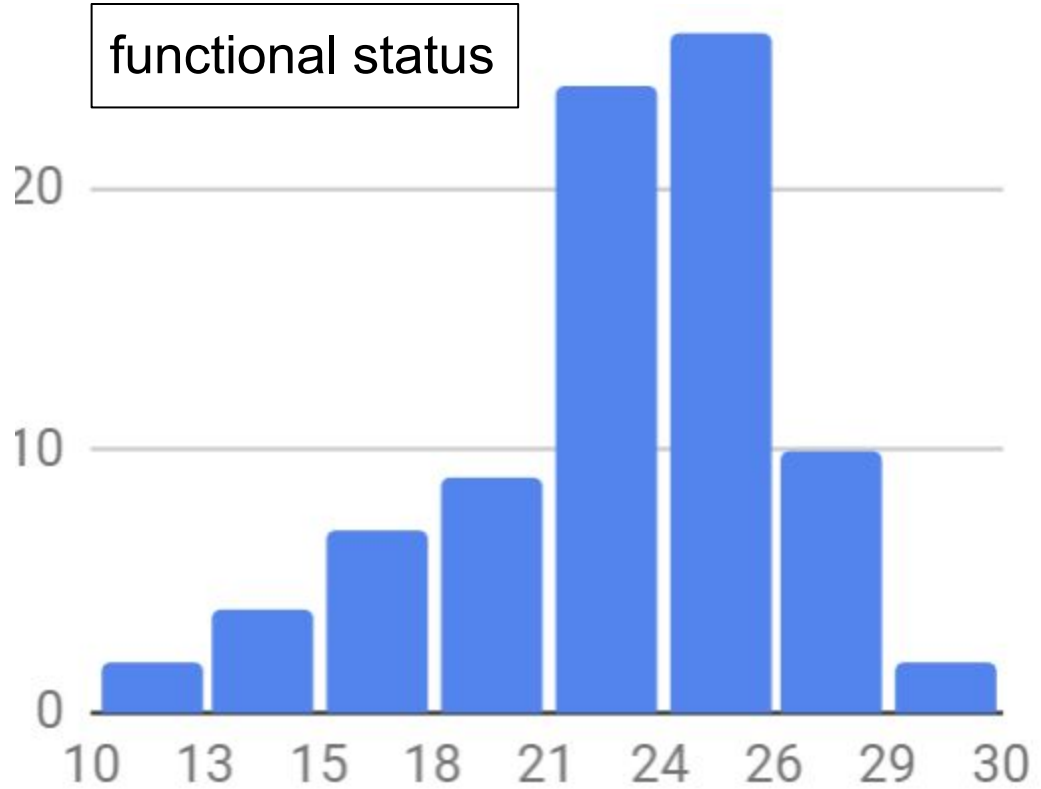
#53 dyspnée SNO_NO_F-20040
T_DESC_SNOMED_NOTION



DUSOI; gravity seen by the doctor (from 0 to 5)

Parkerson, G. R., Broadhead, W. E., & Tse, C. K. (1993). The Duke Severity of Illness Checklist (DUSOI) for measurement of severity and comorbidity. *Journal of Clinical Epidemiology*, 46(4), 379–393.

Van Weel, C. (1993). Functional status in primary care: COOP/WONCA charts. *Disability and Rehabilitation*, 15(2), 96–101.



COOP Charts global (min 6 max 30) Above 20 the patient can hardly work

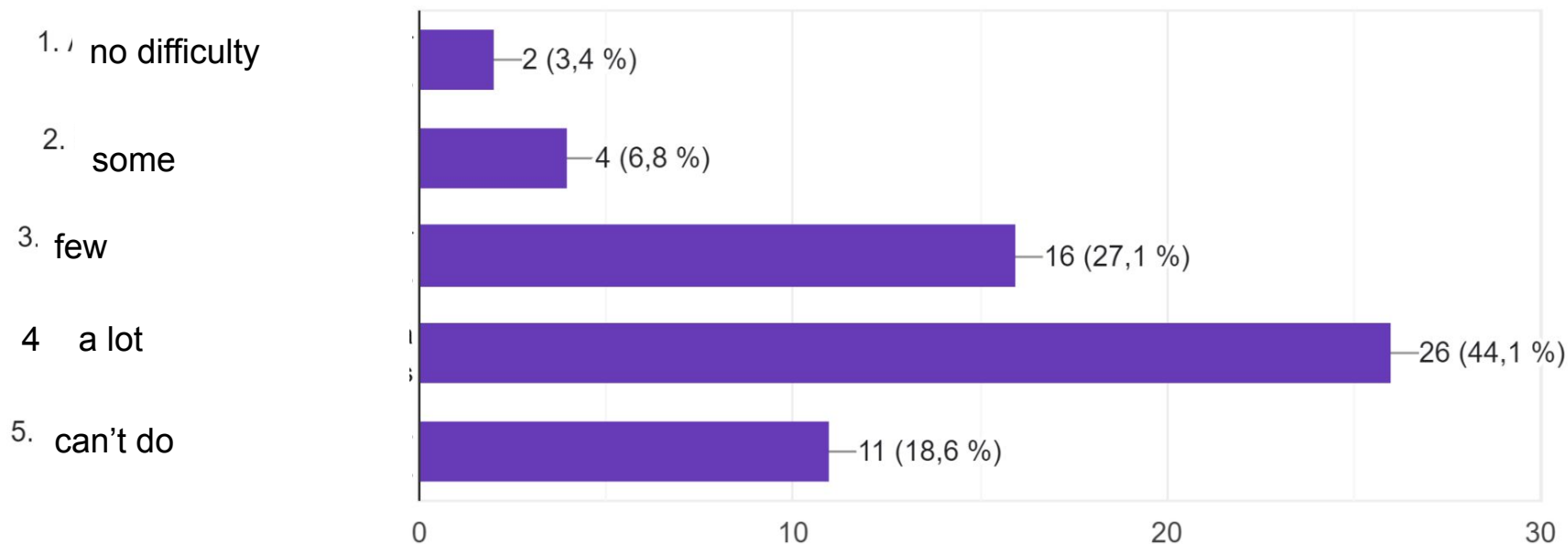
ADL (From COOP Charts)

over the past month

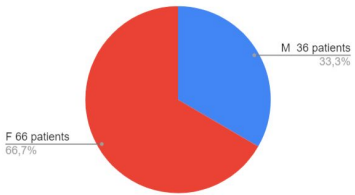
How difficult has it been for you to carry out your usual activities, in and out of the house, given your physical condition and emotional state? Please tick one box only.

59 réponses

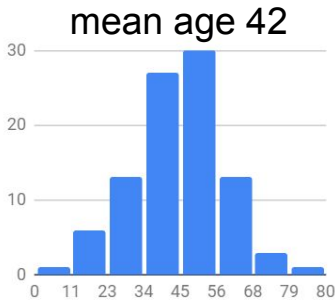
59 answers



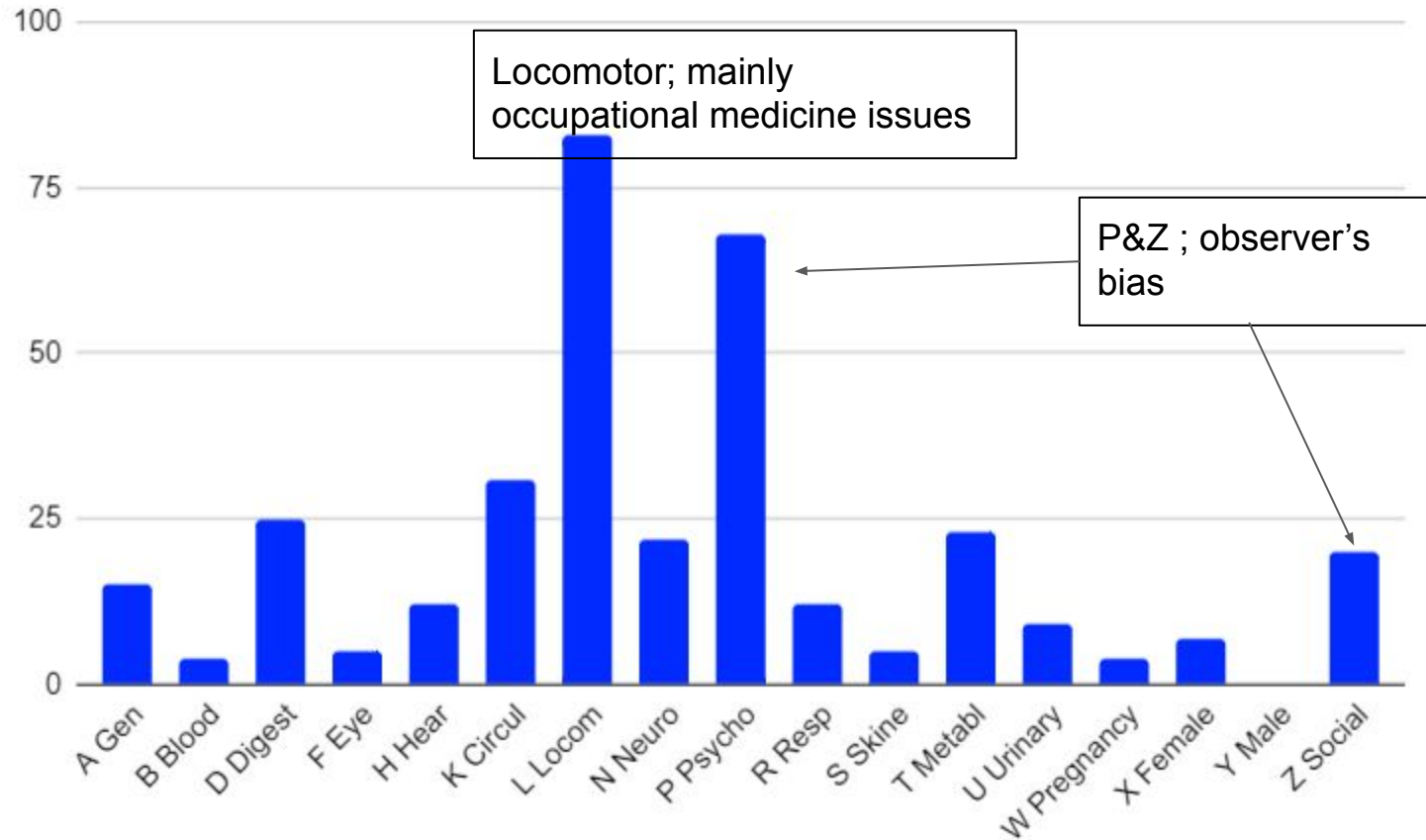
Morbidity of 104 Patients before acute covid; mainly usual



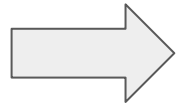
66% women



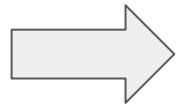
ICPC 2 classified



Considering Long Covid as a set of medically unexplained symptoms, how to reduce uncertainty?



Imaging : 18FDG PET Scan —>>> SPECT-CT



Biology ; thanks to <https://www.covidhge.com/>

- Transcriptomics : KUL Leuven
- Proteomics: Brodin Lab, Stockholm
- Genomics ; Necker, Paris

Imaging

Technetium scintigraphy (SPECT-CT) in Long Covid patients

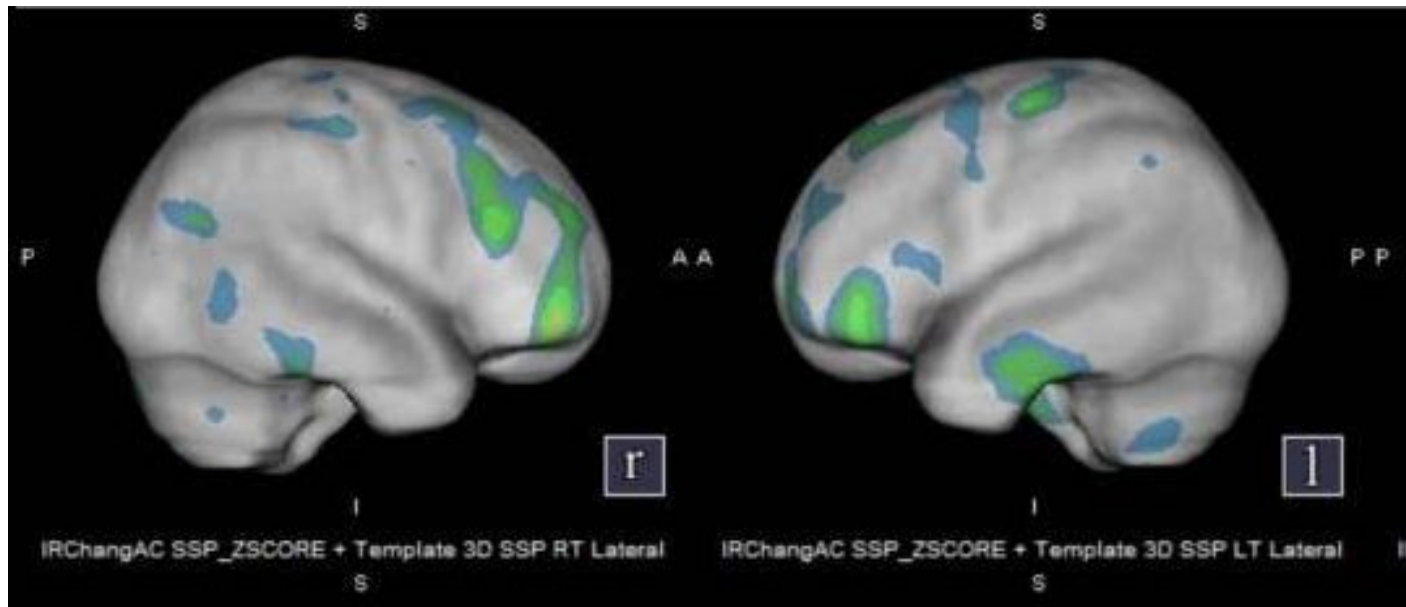
The green & blue areas show a disturbance in blood flow (images obtained by comparing the patient's images with a reference database) Cerebral scintigraphy. Q-Brain technique.

53 SPECT-CT scans requested

45 cerebral flow disorders identified (here in green)

1 confirmed by PET

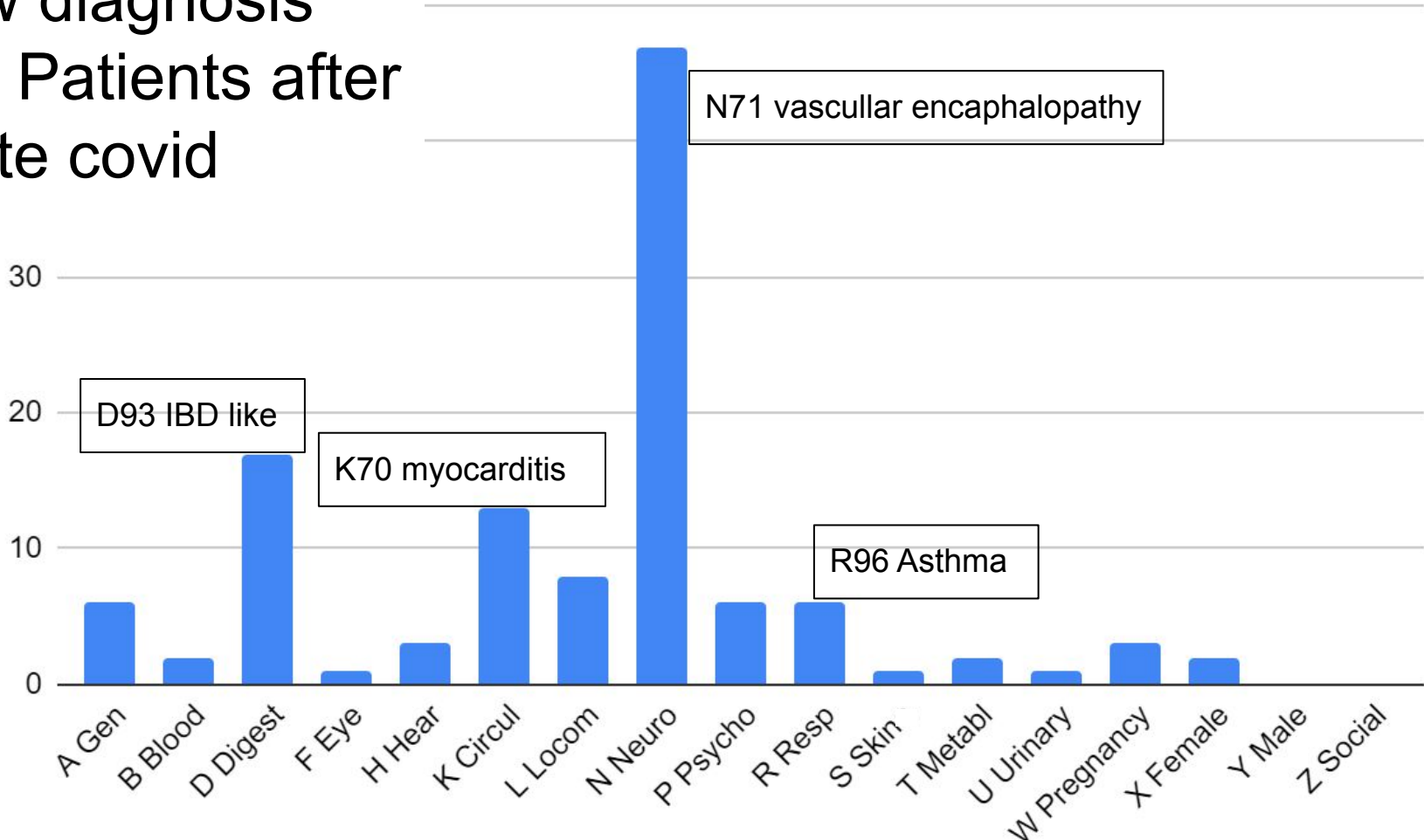
5 PET negative

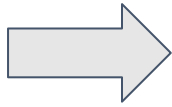


Male, 47 years old Before acute Covid (14/10/2020); D84;D93;K84;L82;P06;T82;T86 (ICPC-2); Post Covid: N71; DUSOI 4; COOP Charts 24; 31 months between acute Covid and diagnosis of long Covid; MRI normal; on 15/09/2023 abnormal fatigue, disturbed sleep, burning sensation in legs, loss of words, loss of immediate memory, nausea, difficulty concentrating, claustrophobia, increase in known pain, shortness of breath, recurrent headaches.

by courtesy; Dr Salima Bouazza, Hôpital Vésale, Charleroi ISPPC

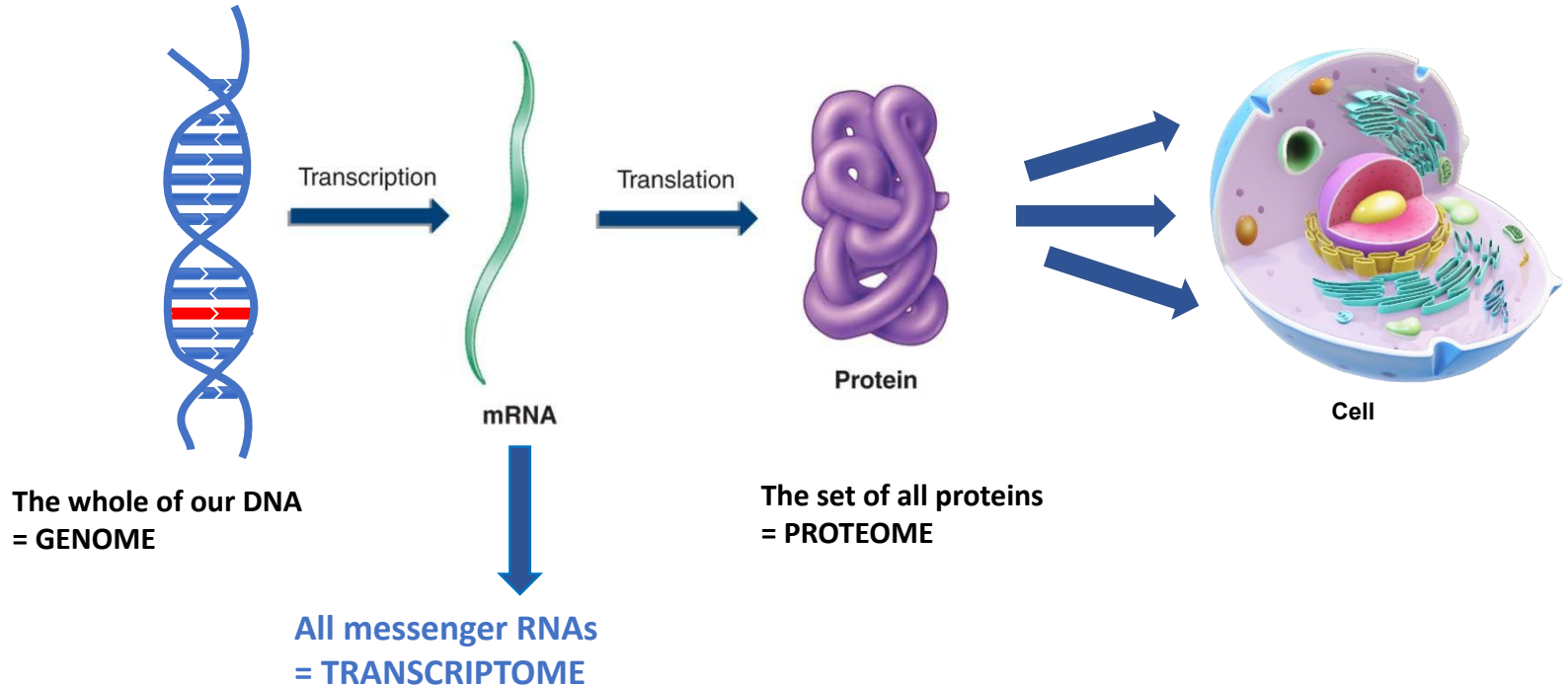
New diagnosis 104 Patients after acute covid



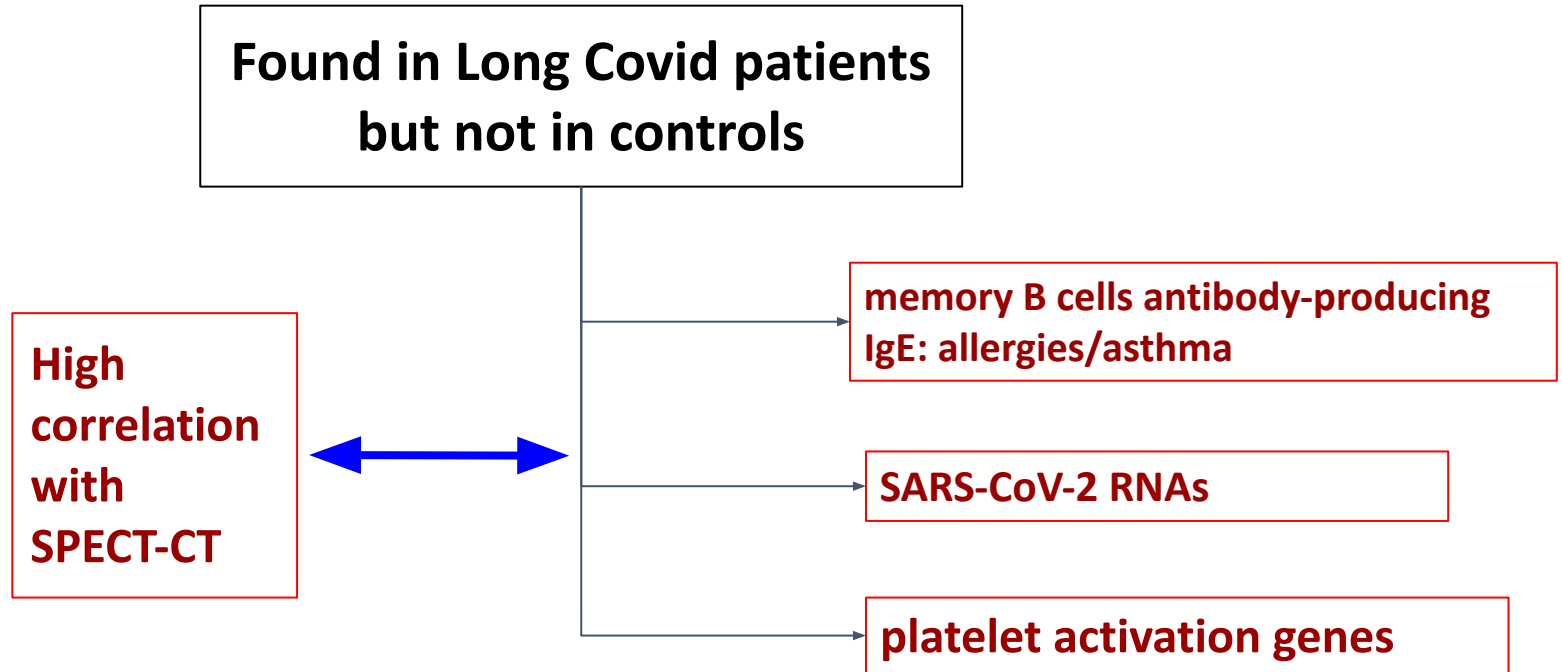


Biology

What is transcriptomics?



Digital transcriptomic results: COVID long (n=48) vs. Controls (n=12)



lessons learned to date

- **Long Covid is an astonishingly complex syndrome that challenges our medical knowledge**
- **teaching doctors to listen to the patients**
- **teaching doctors to read the scientific literature**
- **learning partnership with patients**
- **translational research is possible in GP/FM**
- **We must keep searching**

Coding and new rubrics to be considered in ICPC-3

- **Long Covid implies a new class in ICPC-3**
- **dramatic change in one's live**
- **mourning for oneself**

Keep searching



THANKS TO

- Prof Casanova, Rockefeller institute and the Covid Human Genetic Effort network
- Dr Isabelle Meyts, Rega Institute, KUL, Leuven, Belgium
- King Bauduin Foundation, Belgium
- Pathology and Genetic Institute (IPG) Belgium
- All my colleagues and students supporting this work