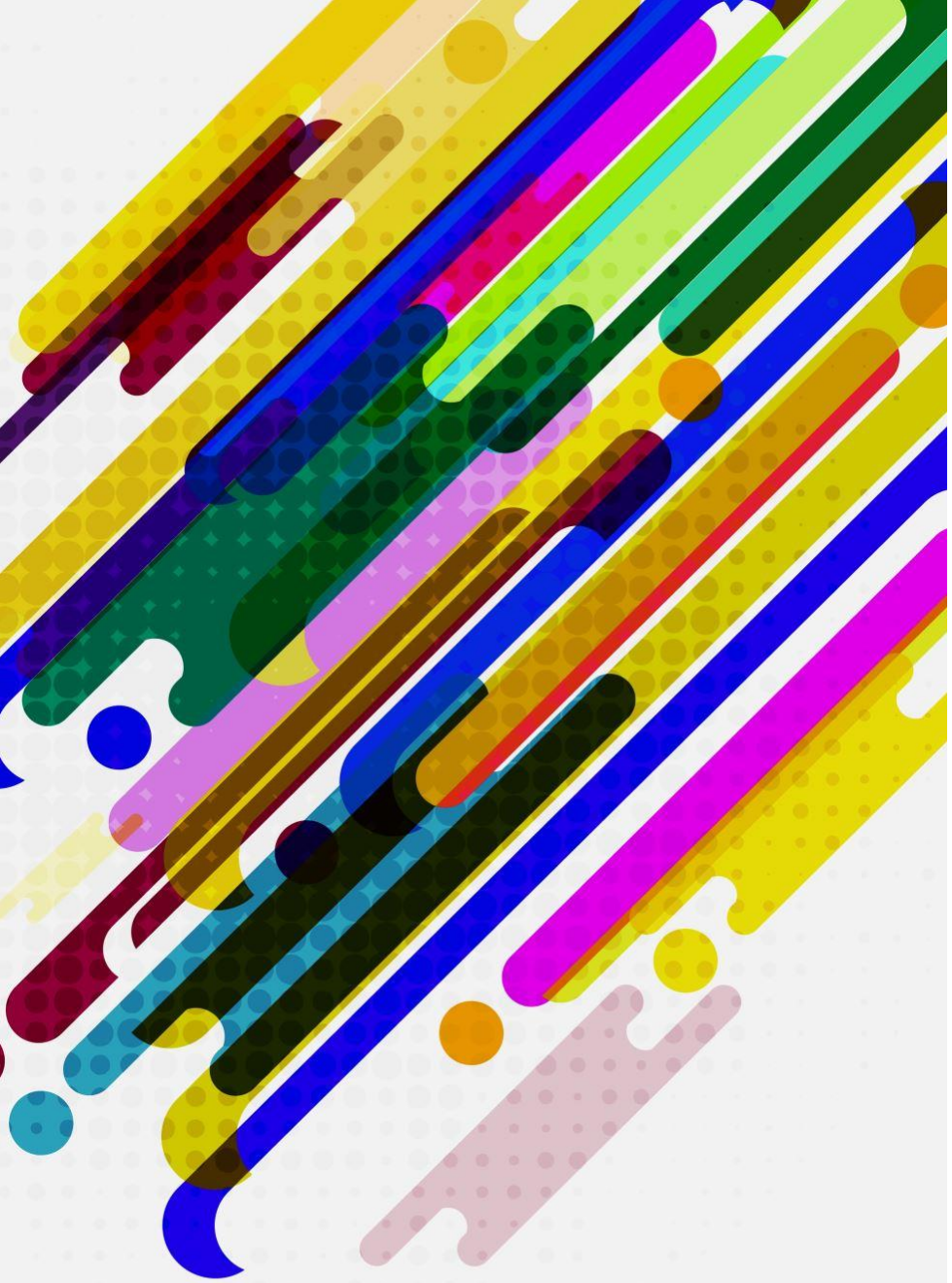


Exploring the Interplay Between Long COVID, Inflammation, chronic diseases and Cancer

- Kashyap Patel, MD, AboiM, BCMAS
- **Recognized by the US congress as an outstanding citizen who set the Gold Standard for decades**
- CEO, Carolina Blood and Cancer Care
- Imm past President, Community Oncology Alliance
- Imm. past Chairman, Clinical Affairs, Association of Community Cancer Centers
- Medical Director, International Oncology Network
- Medical Director, Blue Cross Blue Shields (consultant), SC
- Associate Editor in Chief, AJMC (EBO)
- Member task force, NCCN DEI initiative

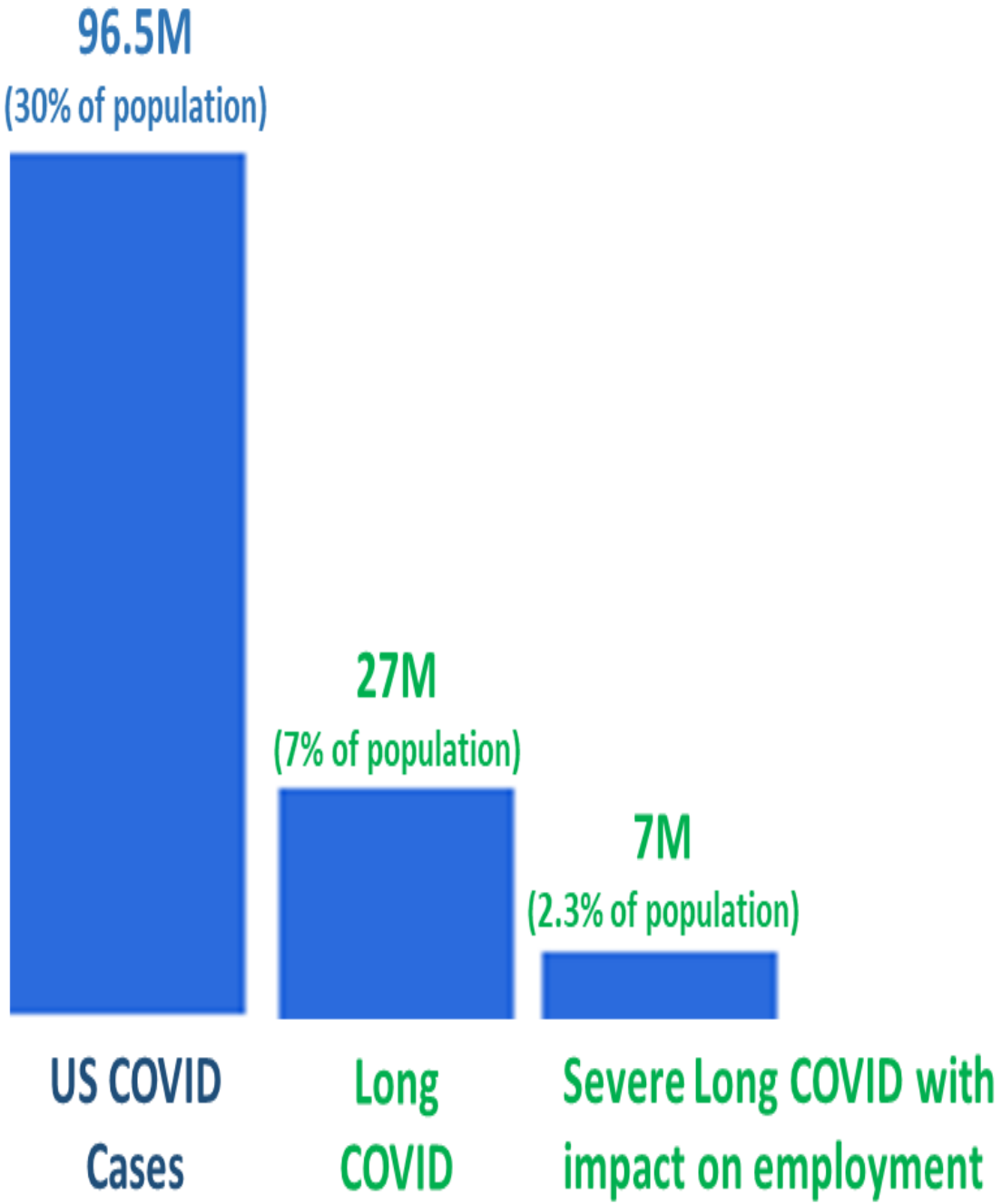
Course Description

Learning Objectives

Nothing to disclose

Disclosures

- Nothing to disclose

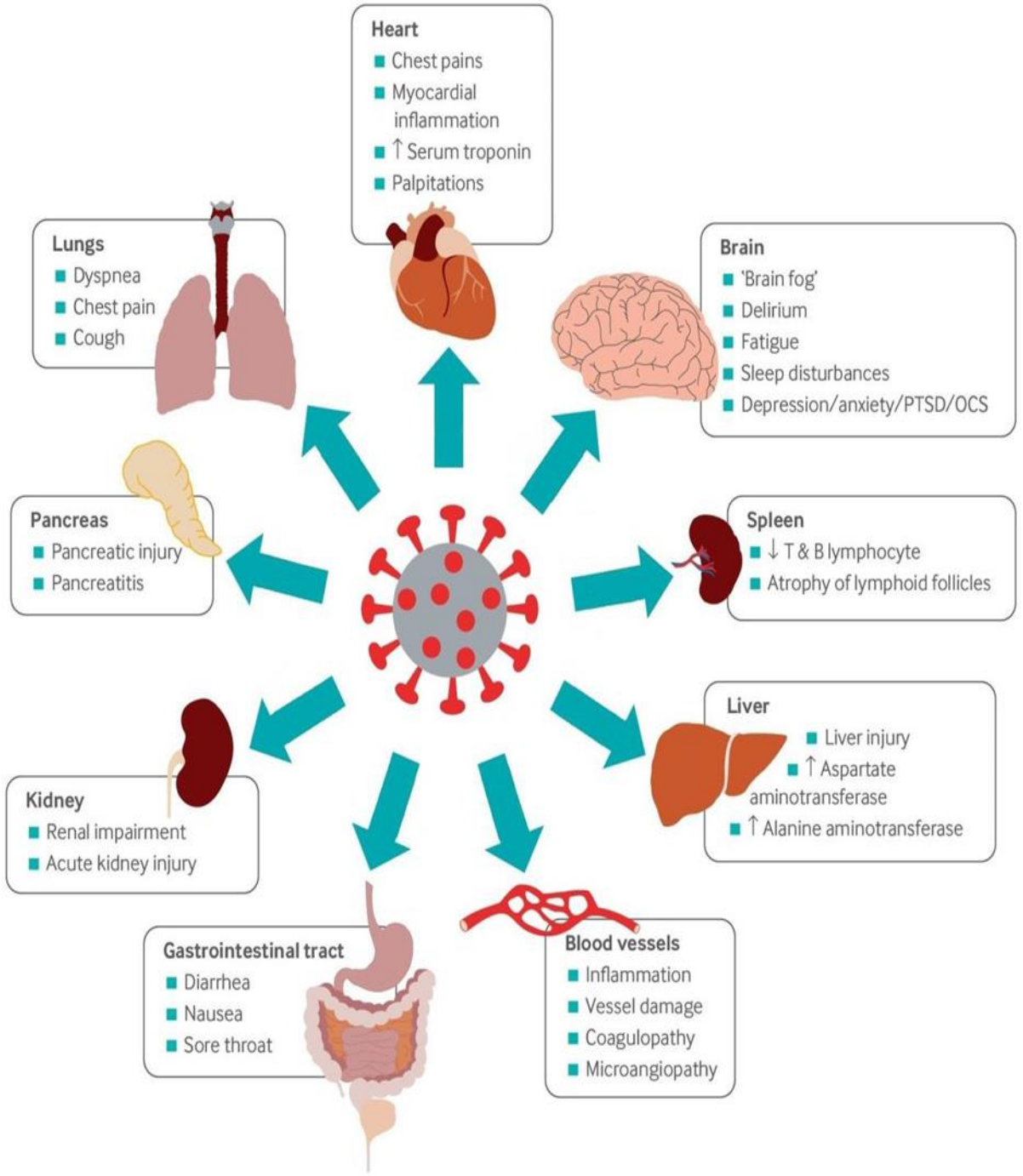


The Problem of Long Covid and Inflammation

Long COVID affects tens of millions of Americans

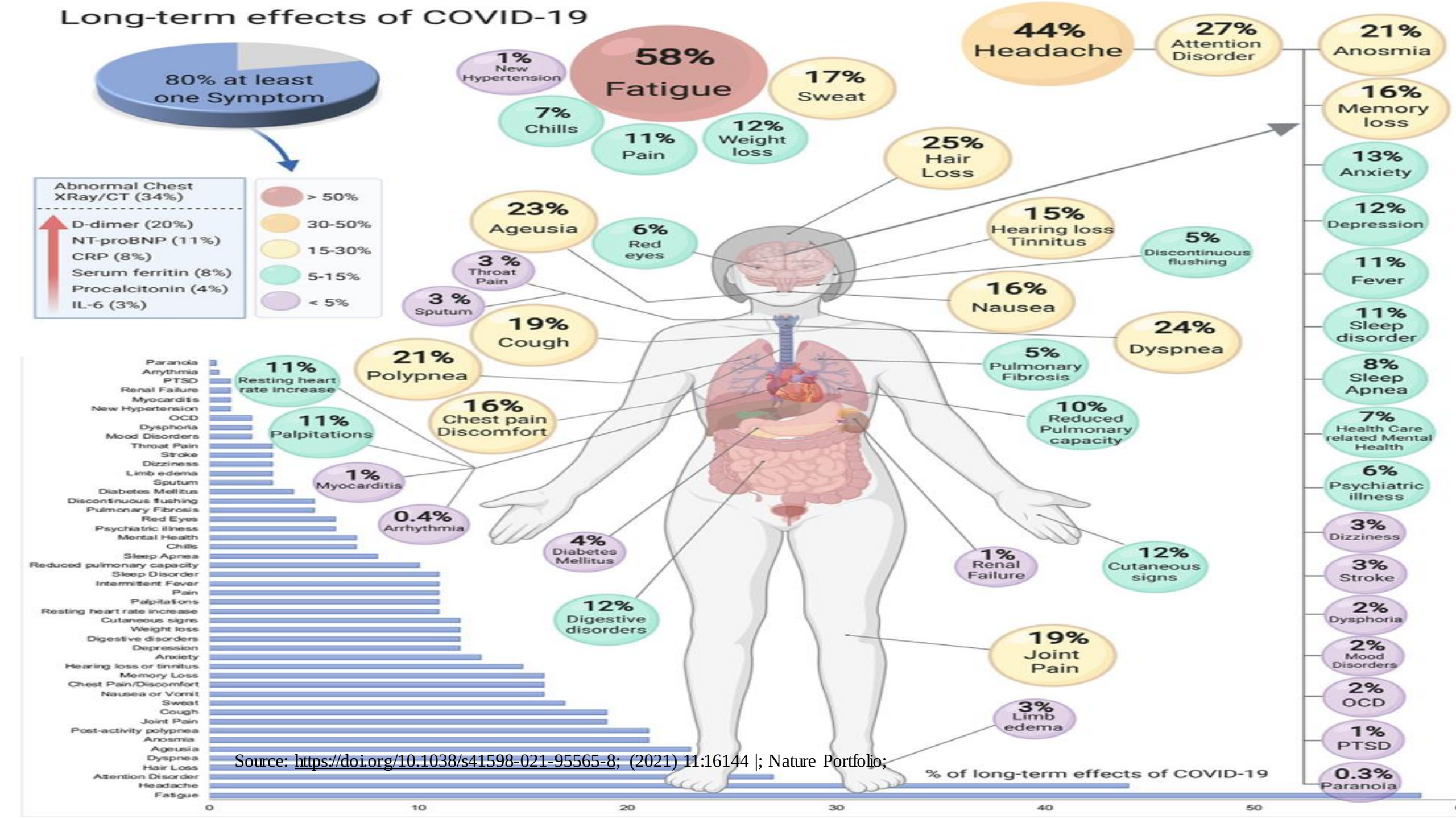
Long Covid is a complex, multi-organ illness that occurs in individuals with a history of SARS-CoV-2 infection, usually 3 months from the onset of COVID-19 with symptoms that last for months or years and cannot be explained by an alternative diagnosis (WHO)

- Over **100 million COVID infections** are expected to occur in the **fall and winter of 2022-23**. It is estimated **15-30% of those infected will develop Long COVID**
- 27 million Americans have been impacted by long COVID, with millions more at risk as COVID persists (Department of Health and Human Services, Dec 2022).
- Long COVID outpaces Diabetes in terms of cost per member for a given health plan (Beckers Payer).
- 4 million Americans currently unable to work because of Long COVID, corresponding to $170B in lost wages



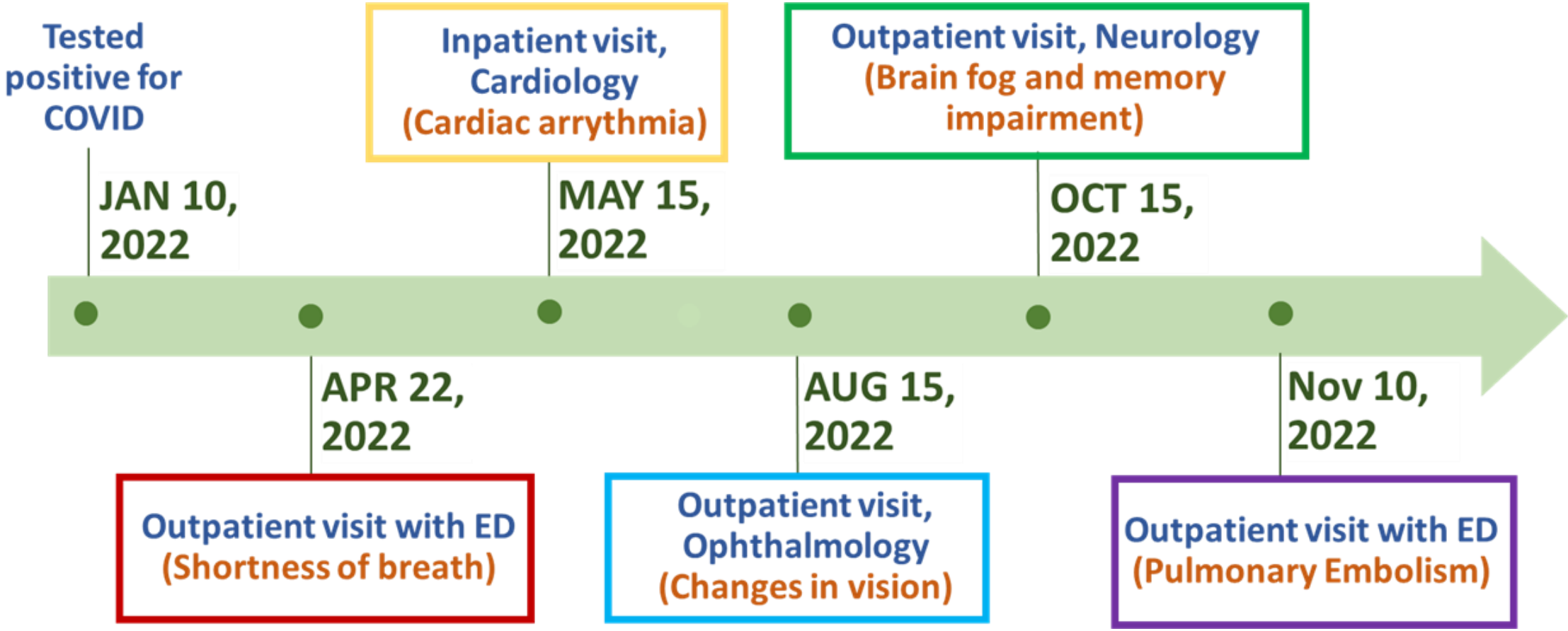
- **Long Covid is a multi-system disease requiring need for multiple specialists**
- **"The early reports suggest that a high percentage of COVID patients will develop some Long COVID symptoms. We're going to have to work hard to set up the right kind of clinical response to that." Andrew Dreyfus, CEO of Blue Cross**

- **Long COVID has a major impact on the healthcare system with an annual financial burden of $386B in the US**
- **Long Covid will be in top 10 medical cost driver at least for the next 5 years**
- **$57K/patient for cost of inpatient**
- **$6.2K/patient for ED visits**
- **50% had > 20 outpatient visits in the first 12 months**
- **46% had to reduce their work hours**



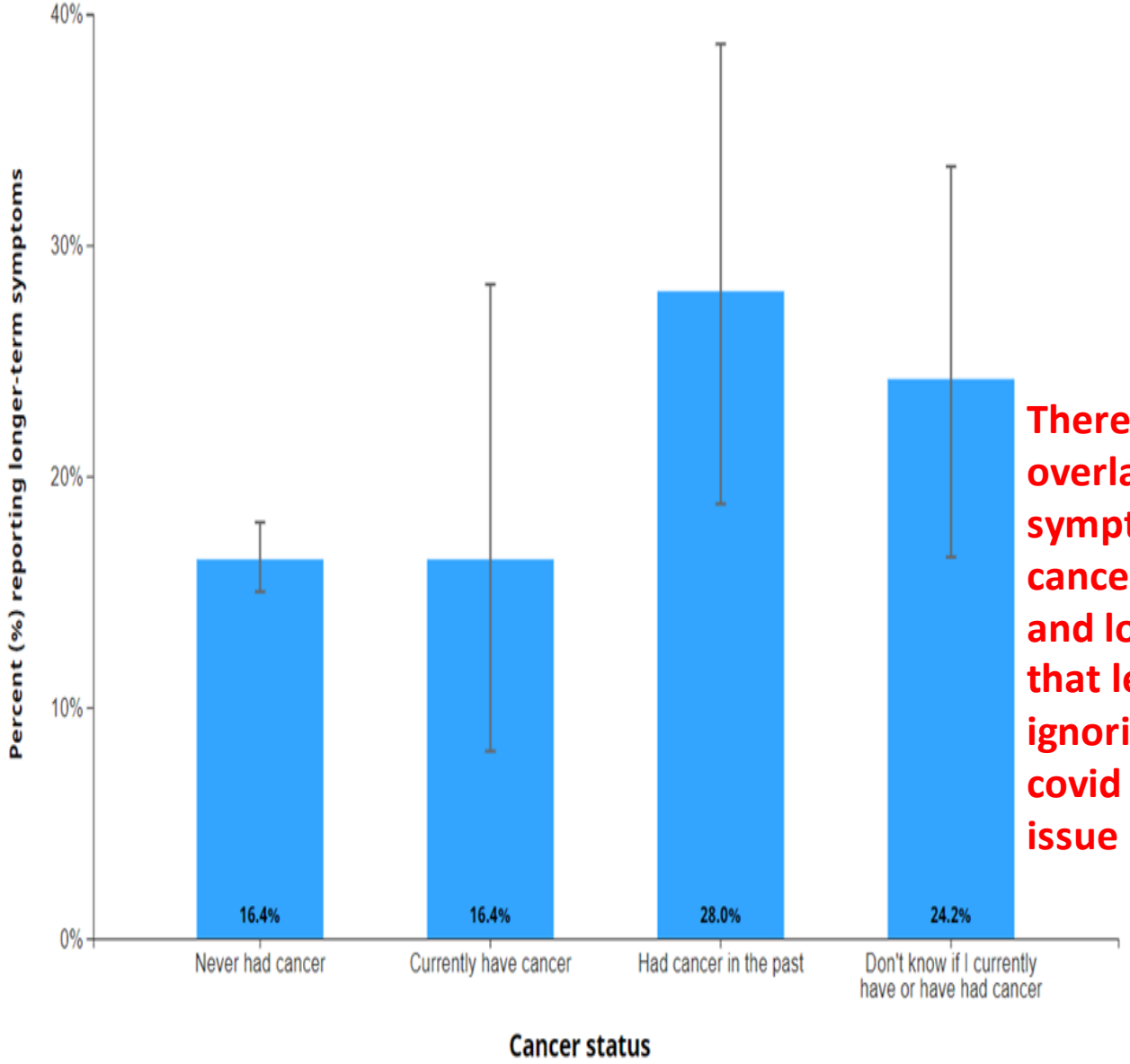
Source: https://doi.org/10.1038/s41598-021-95565-8; (2021) 11:16144 |; Nature Portfolio;

Typical Care Journey for a Long COVID Patient

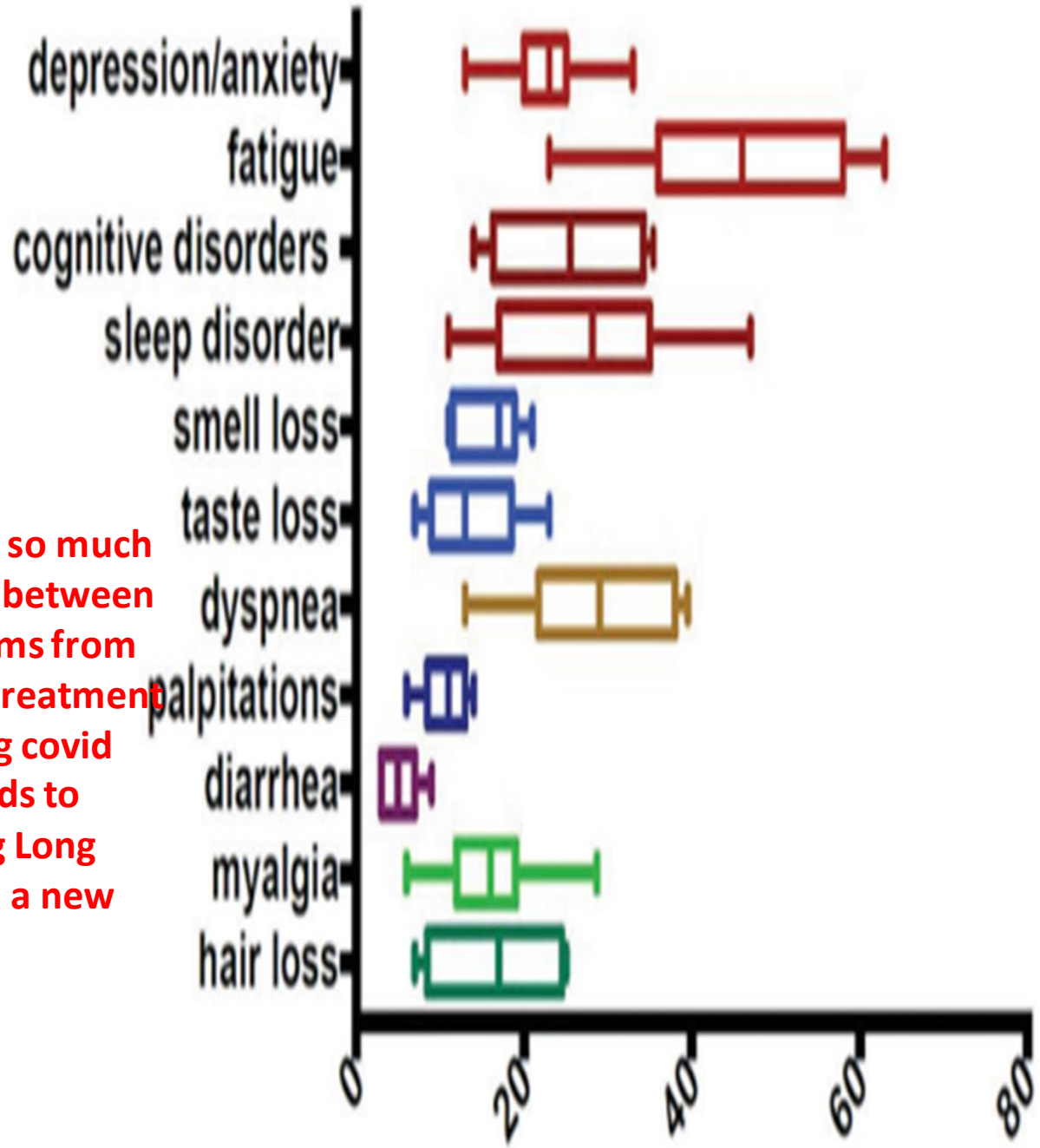


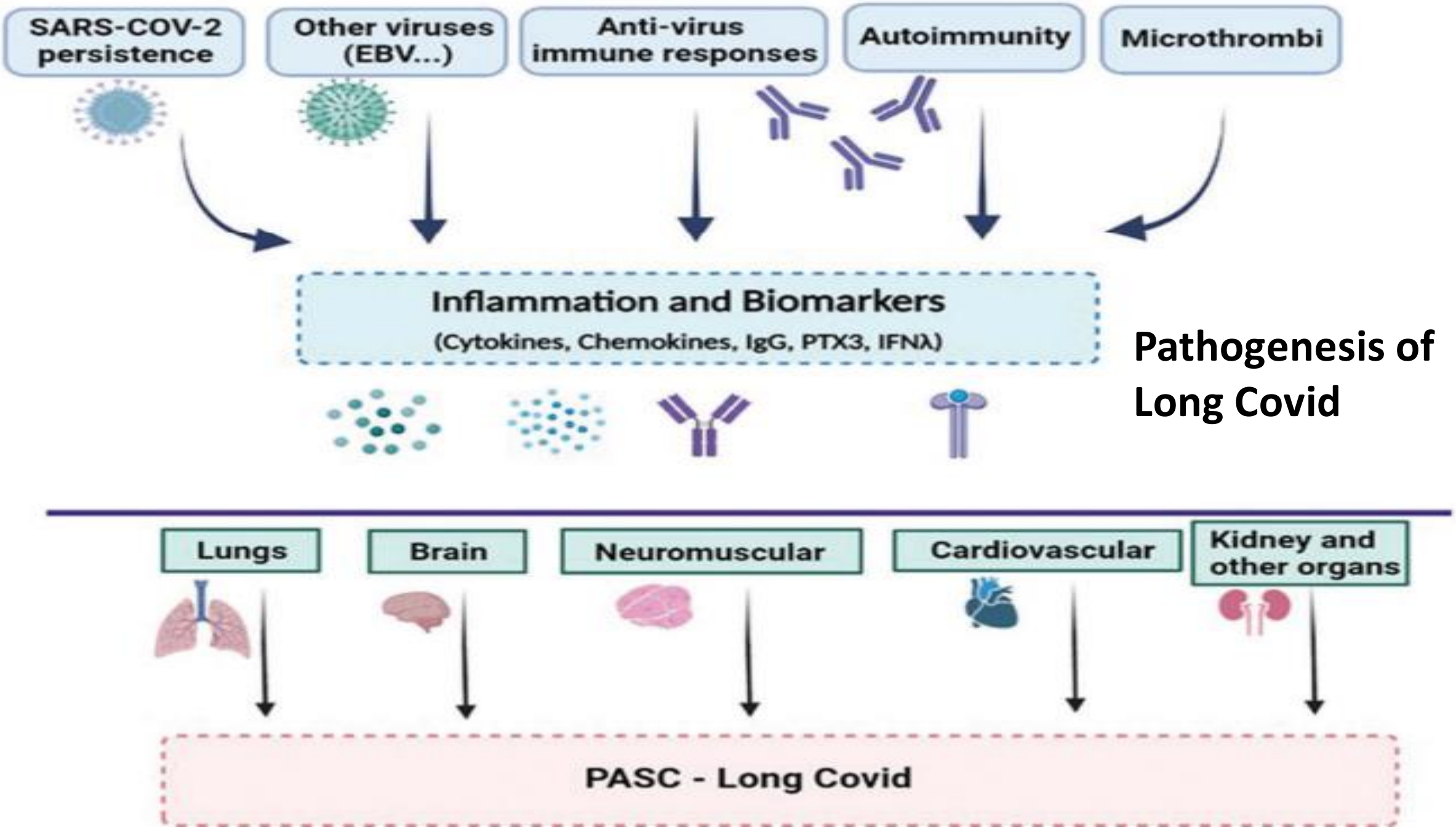
- ICD-10 diagnosis code for Long Covid (U09.9) released in October 2021 and many health systems still not using it
- Only 1 in 10 Long Covid patients have the diagnosis code
- Over 90% of Long COVID patients currently undiagnosed
- For Health Plans, insurers, Pharma and employers understanding the size of the healthcare cost associated with Long COVID in each population and how best to manage it is critical

Figure 5: Percent of adults (aged 18+) self-reporting longer-term symptoms after a positive COVID-19 test or suspected infection by cancer status, Canada, January 2020 to August 2022



There is so much overlap between symptoms from cancer treatment and long covid that leads to ignoring Long covid as a new issue





Pathogenesis of Long Covid

Cardiorespiratory complications with PASC

Persistent dyspnea, frequently associated with fatigue, chest pain, and cough affect ~20% of patients 3 months after the acute SARSCoV-2 infection

The main symptoms still present 1 year after the acute disease included cognitive and mental health disorders, such as depression, anxiety, memory loss, concentration difficulties and insomnia, fatigue, dyspnea, muscle, and joint pain

A higher risk of diabetes has also been observed (8.3/1000)

In EPILOC cohort, (age 18–65), the three most frequent clusters of symptoms were fatigue, neurocognitive, and chest/cardiorespiratory, with at least moderate impairment (>20%) of general health and working capacity in 26% of the subjects

In the general population, an incidence of Covid19-associated myocarditis of ~150 cases per 100,000 was observed

Neurological impairments in PASC

- **Cognitive dysfunction in PASC is affects attention, executive function, problem solving, and decision making.**
- **Memory impairment, affecting up to 73%, inducing both short and long-term memory loss**
- **The probability of experiencing memory symptoms increased over the first few months, with 56% reporting memory symptoms at month 4 and 50% at month**
- **While age is an important factor in cognitive and memory disfunction, young people (16–30 years old) suffer potentially severe symptoms, such as concentration and memory problems, 6 months after infection**
- **The study of the anatomical or functional imaging of brain alterations in PASC shows consistent changes in many brain areas, including the somatosensory cortex, rectal/orbital gyrus (including the olfactory system), temporal lobe (including the amygdala, piriform cortex, and the hippocampus), hypothalamus/thalamus, brainstem, and cerebellum**
- **A pronounced loss of gray matter was also observed in crus II, part of the cognitive, and olfactory-related lobule VII of the cerebellum; there is also an increase in CSF volume and decrease of whole brain volume respect to the controls, suggesting an additional diffuse loss of gray matter**
- **This reinforces neuropsychological data that showed Covid-19 as a risk factor to develop dementia, neurodegenerative diseases and mild cognitive impairments even in 50-year-old adults**

What we know beyond doubt so far

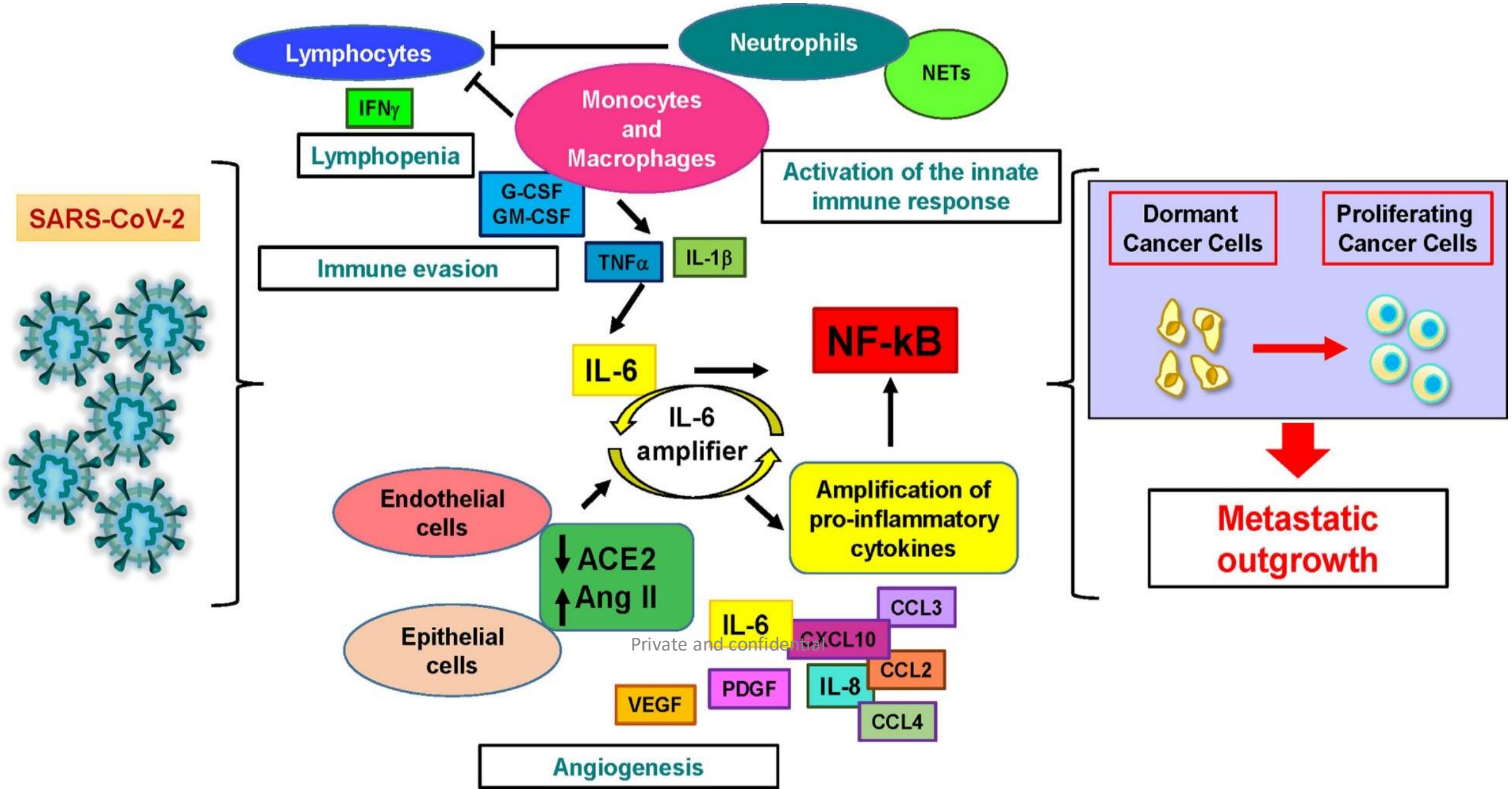
- More than 700 million across the world and 110 million Americans have had covid (actual number much higher due to self-test)
- While more than 6.5 million died across the world and more than 1.1 million died in the USA; the true death toll may be 4.2 times higher(close to 25 million)
- Fatality and impact on minorities is under reported (USA today 1/10)
- Life expectancy in the USA has dropped by 2.7 years in middle of 2022.
- With continued Covid related deaths, decline will continue
- Covid has triggered mental health crisis (triggering excess drug use, violence, and other societal issues)
- Work force shortages impacting healthcare delivery
- PASC (post-acute sequelae of covid) likely to impact 80% infected with covid and can linger on in anywhere between 2.5 to 15%;
- Majority due to inflammation related injury like myocarditis, atrial fibrillation, neuropathy, endocrinopathy, and other tissues
- COVID-19 pandemic triggers 25% increase in prevalence of anxiety and depression worldwide

- **Autophagy: The Potential Link between SARS-CoV-2 and Cancer**
- **In this work, building on the previous investigations demonstrating long-term persistence of the SARS-CoV-2 nucleic acids and antigens in human tissues and also other research studies showing the interaction of the viral particles with the host autophagy machinery, we hypothesize that SARS-CoV-2 could potentially be an oncogenic virus by blocking the autophagic flux, and also leading to immune escape by downregulation of MHC-I. We also propose that the resultant dysregulation in cellular autophagy could affect the response to treatment in cancer cells. Further laboratory-based, clinical, and population-based studies are required to explore this matter.**
- Parham Habibzadeh 1 , Hassan Dastsooz 2,3,4 , Mehdi Eshraghi 5 , Marek J. Łos 6,*, Daniel J. Klionsky 7 and Saeid Ghavami 5,8,9,*). . Cancers 2021, 13, 5721. https://doi.org/10.3390/ cancers1322572

- Given, the disproportionate impact of the disease on the African American community, yet another unanswered question is whether racial disparities are to be expected in COVID-19 sequelae. **Herein, we propose that long COVID-19 may predispose recovered patients to cancer development and accelerate cancer progression. This hypothesis is based on growing evidence of the ability of SARS-CoV-2 to modulate oncogenic pathways, promote chronic low-grade inflammation, and cause tissue damage. Comprehensive studies are urgently required to elucidate the effects of long COVID-19 on cancer susceptibility.**

- This study was supported by a grant from the National Cancer Institutes of Health (R01CA239120) to R.A, https://onlinelibrary.wiley.com/doi/10.1002/bies.202000331
- https://onlinelibrary.wiley.com/authored-by/ContribAuthorRaw/Aneja/Ritu

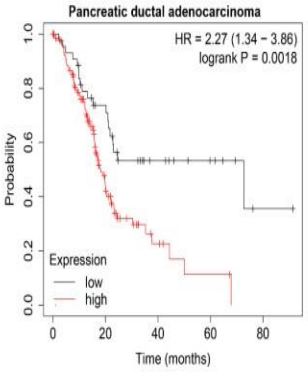
COVID-19–Induced Modifications in the Tumor Microenvironment: Do They Affect Cancer Reawakening and Metastatic Relapse?; Front Oncol. 2020; 10: 592891. : 10.3389/fonc.2020.592891

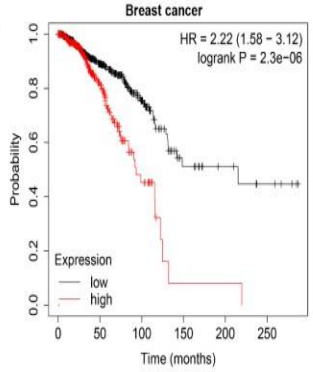


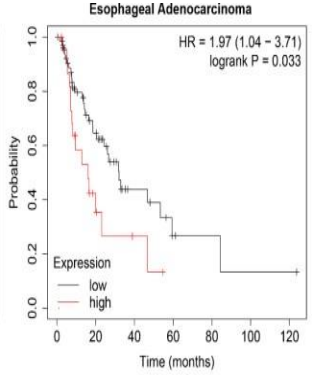
miR-2392 and Cancer Link

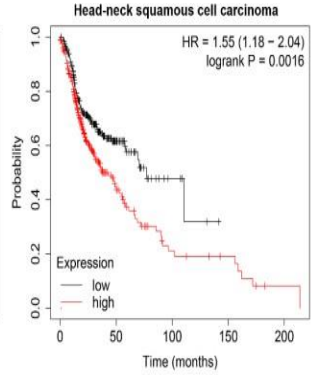
COV-IRT
COVID-19 International Research Team

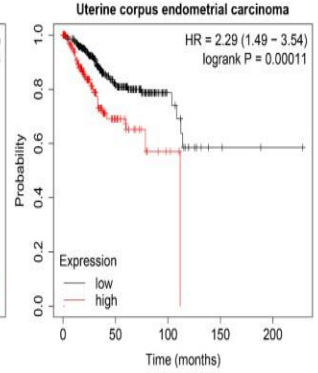
Significant Increase

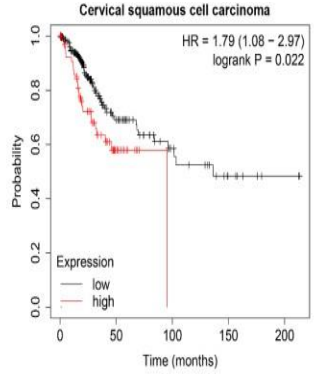


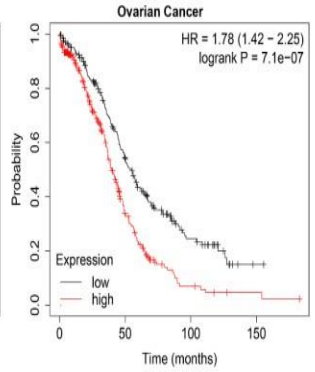




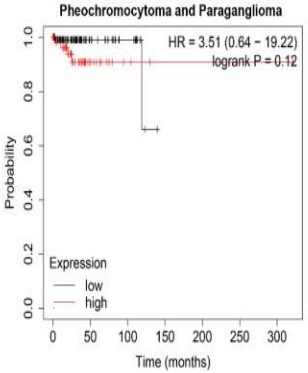


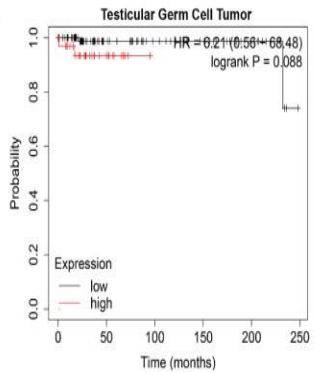


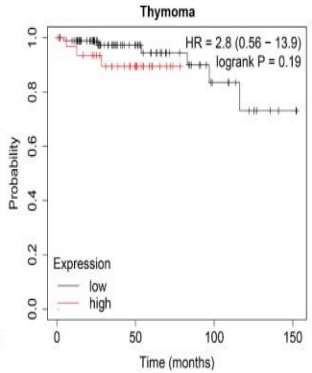


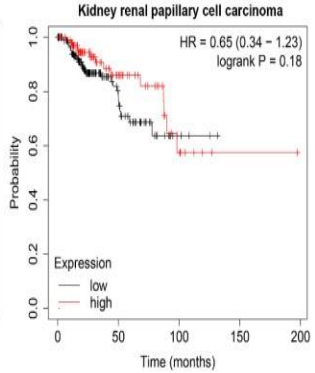


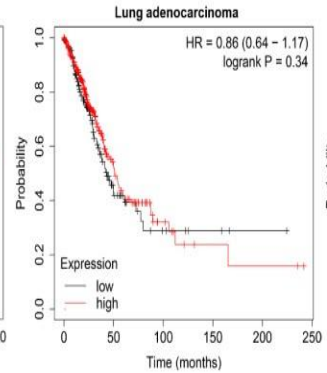
Increase

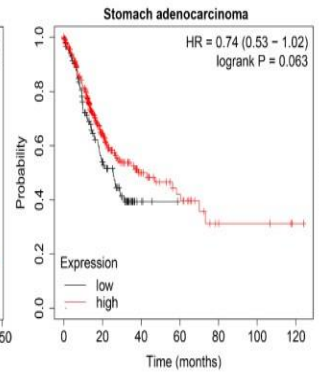


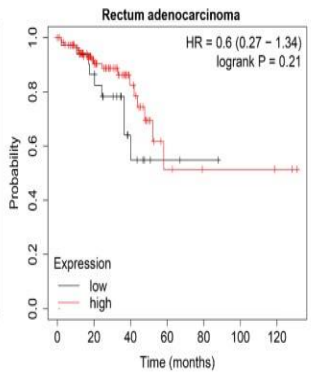


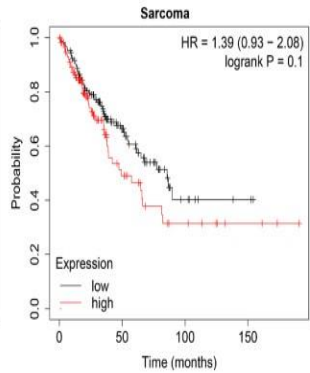




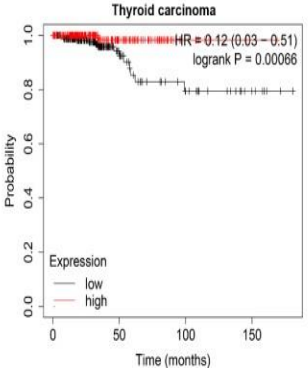


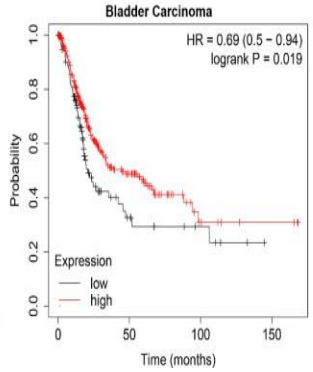


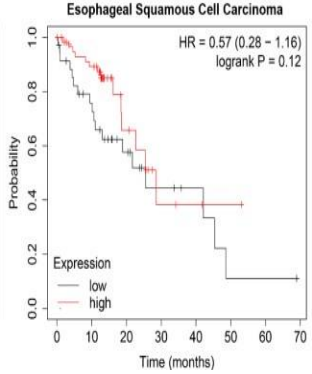


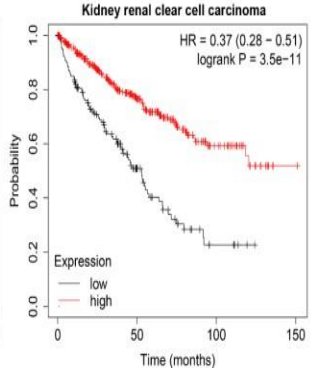


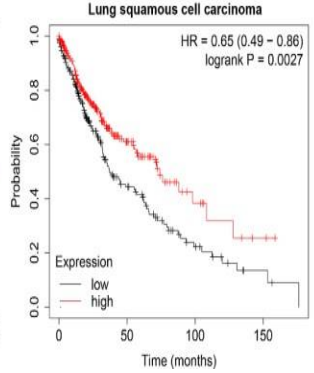
Significant Decrease

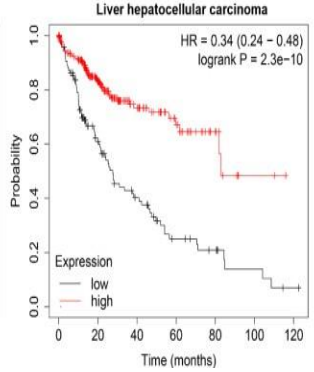












Blood cytokine analysis suggests that SARS-CoV-2 infection results in a sustained tumour promoting environment in cancer patients

https://doi.org/10.3390/cancers13225718

Cytokines, chemokines and (angiogenic) growth factors (CCGs) have been shown to play an intricate role in the progression of both solid and haematological malignancies. Recent studies have shown that SARS-CoV-2 infection leads to worse outcome in cancer patients, especially in haematological malignancy patients. Here, we investigated how SARS-CoV-2 infection impacts the already altered CCG levels in solid or haematological malignancies, specifically whether there is a protective effect or rather a potentially higher risk for major COVID-19 complications in cancer patients due to elevated CCGs linked to cancer progression. Serially analysing immune responses with 55 CCGs in cancer patients under active treatment with or without SARS-CoV-2 infection, we first showed that cancer patients without SARS-CoV-2 infection (n=54) demonstrate elevated levels of 35 CCGs compared to the non-cancer, non-infected control group of health care workers (n=42). Of the 35 CCGs, 19 were common to both solid and haematological malignancy groups and comprised previously described cytokines such as IL-6, TNF-α, IL-1Ra, IL-17A, and VEGF, but also several less well described cytokines/chemokines such as Fractalkine, Tie-2, and T cell chemokine CTACK. Importantly, we show here that 7 CCGs are significantly altered in SARS-CoV-2 exposed cancer patients (n=52). Of these TNF-α, IFN-β, TSLP and sVCAM-1, identified to be elevated in haematological cancers, are also known tumour-promoting factors. Longitudinal analysis conducted over 3 months showed persistence of several tumour-promoting CCGs in SARS-CoV-2 exposed cancer patients. **These data urge for increased vigilance for haematological malignancy patients as a part of long COVID follow-up**.

The systemic pro-inflammatory response: targeting the dangerous liaison between COVID-19 and cancer

G. M. Dettorre1y , M. Patel1y , A. Gennari2 , G. Pentheroudakis3,4 , E. Romano5 , A. Cortellini1,6* & D. J. Pinato1,2*
1 Department of Surgery and Cancer, Imperial College London, Hammersmith Hospital, London, UK; 2 Division of Oncology, Department of Translational Medicine, University of Piemonte Orientale and Maggiore della Carità Hospital, Novara, Italy; 3 Department of Medical Oncology, University of Ioannina, Ioannina, Greece; 4 Chief Medical Officer, European Society for Medical Oncology, Lugano, Switzerland; 5 Department of Medical Oncology, Center for Cancer Immunotherapy, Institut Curie, Paris, France; 6 Department of Biotechnology and Applied Clinical Sciences, University of L'Aquila, L'Aquila, Italy

- **Inflammation is an established driver of severe SARS-CoV-2 infection and a mechanism linked to the increased susceptibility to fatal COVID-19 demonstrated by patients with cancer. As patients with cancer exhibit a higher level of inflammation compared with the general patient population, patients with cancer and COVID-19 may uniquely benefit from strategies targeted at overcoming the unrestrained pro-inflammatory response. Targeted and nontargeted anti-inflammatory therapies may prevent end-organ damage in SARS-CoV-2-infected patients with cancer and decrease mortality. Here, we review the clinical role of selective inhibition of pro-inflammatory interleukins, tyrosine kinase modulation, anti-tumor necrosis factor agents, and other non-targeted approaches including corticosteroids in their roles as disease-modulating agents in patients with COVID-19 and cancer. Investigation of these therapeutics in this highly vulnerable patient group is posited to facilitate the development of tailored therapeutics for this patient population, aiding the transition of systemic inflammation from a prognostic domain to a source of therapeutic targets**
- **The in-hospital COVID-19 case fatality rate was higher in patients with cancer than in those without it — 17.9% and 12.7%, respectively (adjusted odds ratio [aOR], 1.29; 95% CI, 1.27-1.32). It was also higher in men than in women — 14.5% and 11.2%, respectively (aOR, 1.28; 95% CI, 1.27-1.30)**
- **The associations of a concurrent malignant neoplasm with the COVID-19 case fatality were overall more substantial for women than for men," the researchers wrote.**

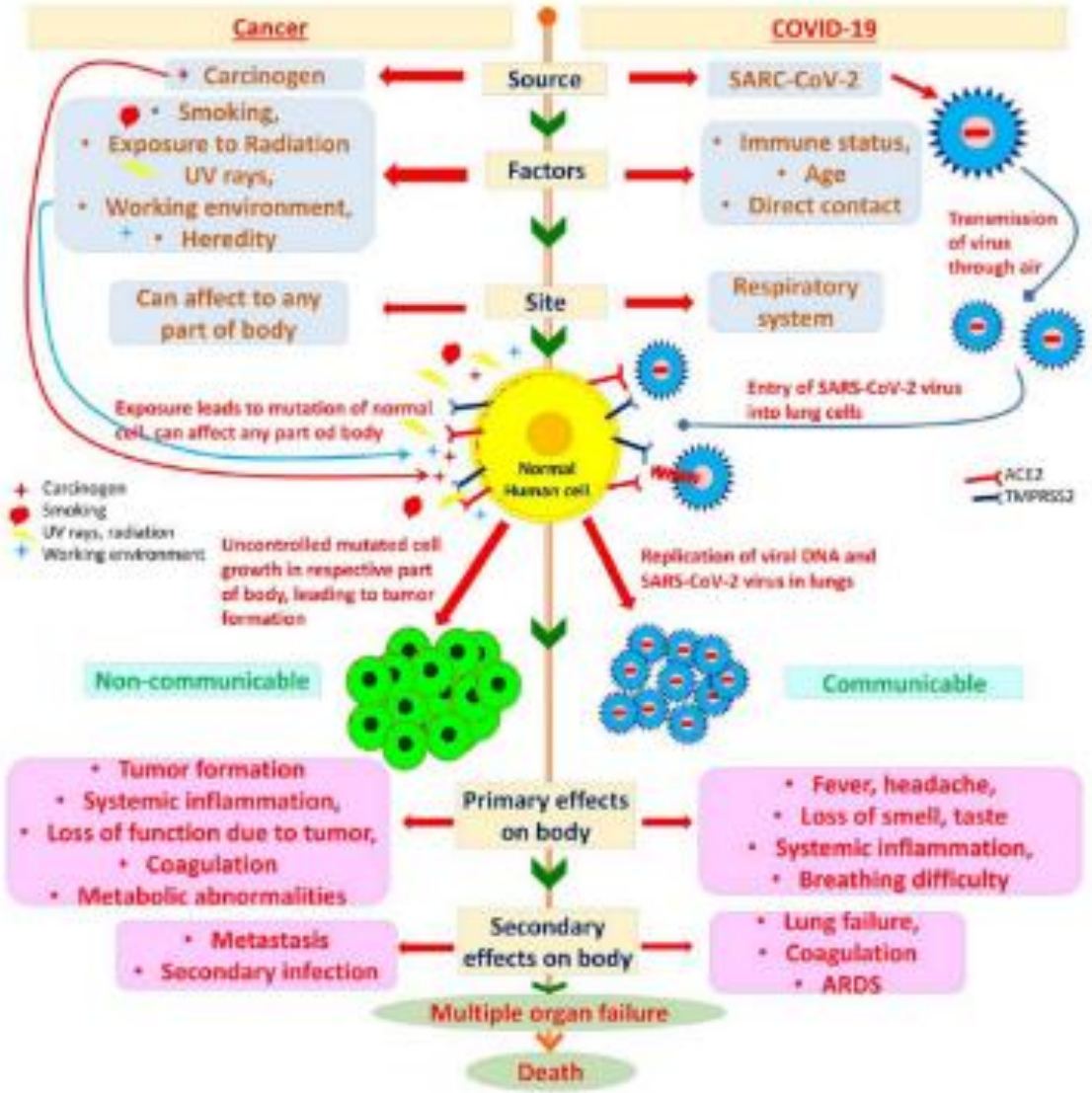
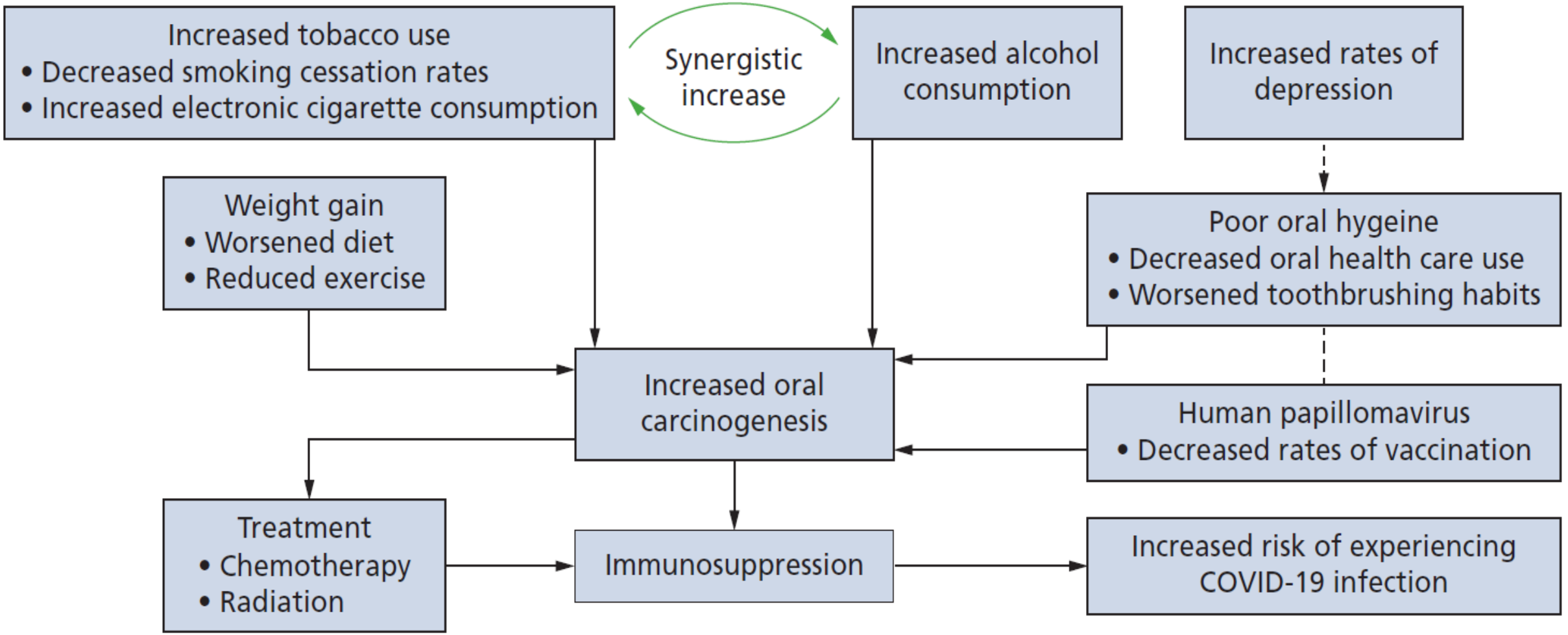


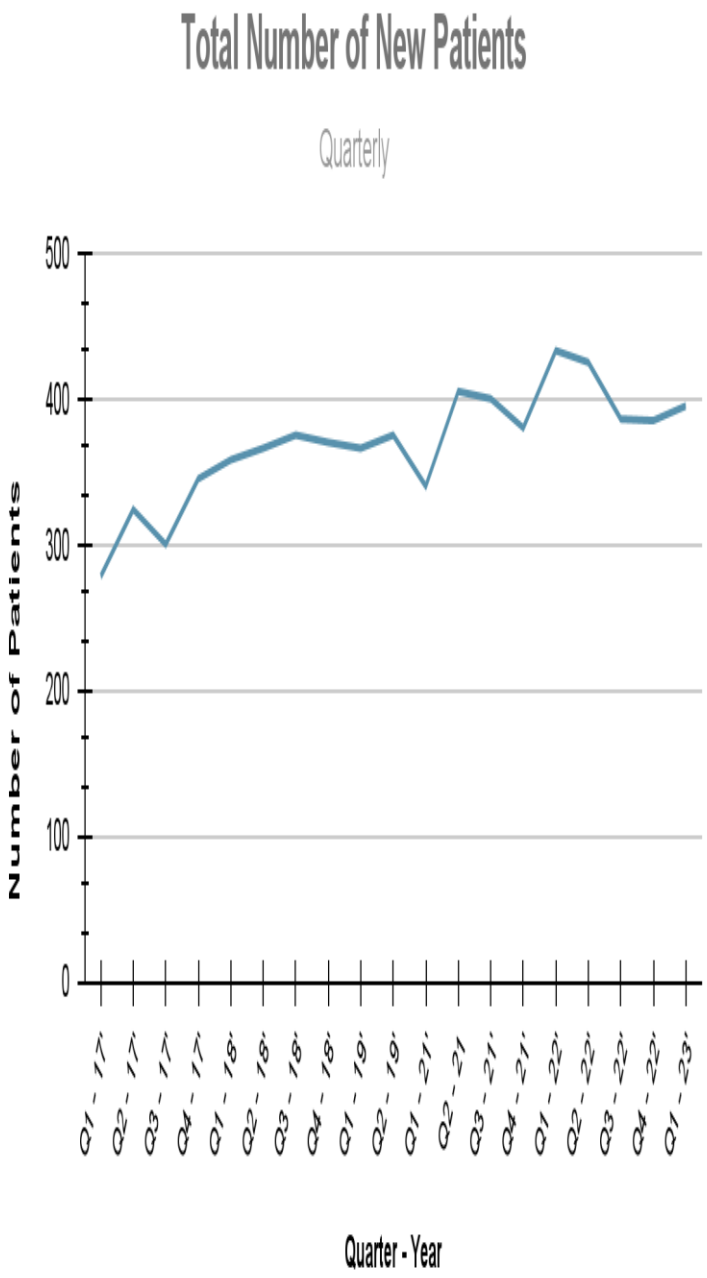
FIGURE 1. Link between cancer and COVID-19. On the left, cancer progression is illustrated. Cancer is a disease caused by exposure to carcinogens, factors such as smoking, exposure to radiation, UV rays, working environment, and heredity can increase the risk of cancer. Any part of the body can be mutated resulting in cancer. After mutation there is uncontrolled growth of the mutated cells leading to the formation of a tumor, the tumor is non-communicable. Systemic inflammation, loss of function of the respective organ or part of body, coagulation, and metabolic abnormalities are the primary effects of cancer. As cancer progresses to advanced stages, metastasis along with increased susceptibility to secondary infections is observed leading to multiple organ failure and ultimately death. On the right, COVID-19 progression is illustrated. The source of COVID-19, a viral infection, is SARS-CoV-2, risk factors include immune status, age, and direct contact with the virus or infected person. The virus enters through the respiratory system into the human body and gets entry into the lung cells, where the replication of the virus occurs. COVID-19 is highly communicable and leads to fever, headache, loss of smell and taste, along with systemic inflammation and difficulty in breathing. Secondary infection to other organs is observed if the infection is chronic leading to lung failure, coagulation, and acute respiratory distress syndrome. Multiple organ failure leading ultimately to death is observed in COVID-19.

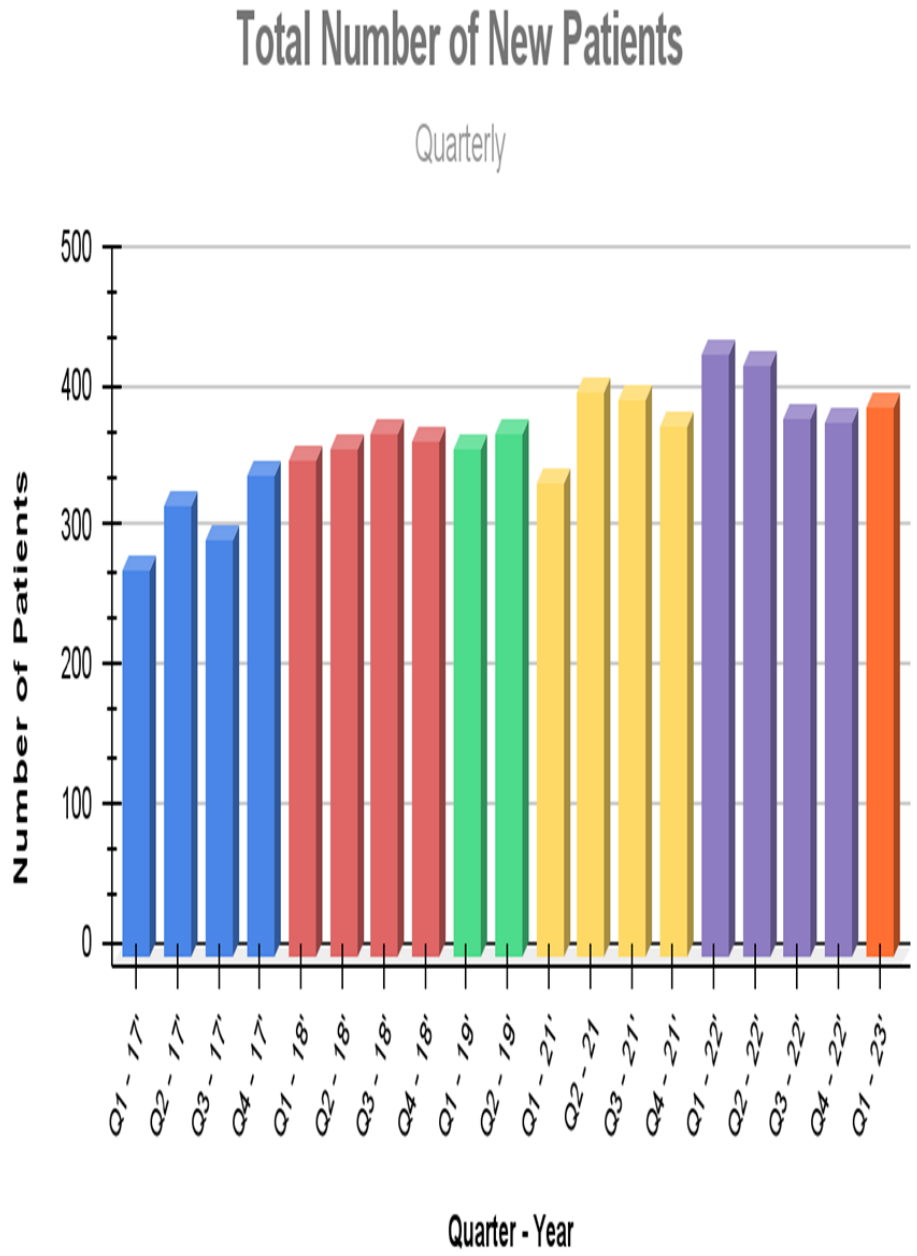
Front. Mol. Biosci., 12 April 2021
Sec. Molecular Diagnostics and Therapeutics; Volume 8 - 2021
| https://doi.org/10.3389/fmolb.2021.643004https://doi.org/10.3389/fmolb.2021.643004



Pathway of rising oral cancer risk factors and incidence in the context of the COVID-19 pandemic. The flowchart depicts how screening tion can disrupt the cycle of immunosuppressant and increased infection rate. Figure created with BioRender.com.

https://linkinghub.elsevier.com/retrieve/pii/S0002817722000253





- At least 30% surge in the total number of new patients despite one new practice within 10 miles radius
- Unusual cancers like Cholangiocarcinoma,sarcomas, Merckel cell cancers
- Multiple patients with multiple cancers after long Covid
- Siblings and spouses developing cancer within months

Cancer patients and Covid

Delayed or drop in cancer screenings [11]

Higher risk of morbidity and mortality[12]

Covid associated cardiac and other tissue complications interfering with cancer treatment[13]

Covid induced systemic inflammatory response and how it may impact cancer recurrence[14,15]

Mental stress and impact of isolation in itself can lead to additional inflammation and perhaps oncogenic drivers[16,17]

Cancer being a chronic disease, full impact may take upto a decade to study concerns of link beween covid and cancer

Study Suggests a Link between Stress and Cancer Coming Back

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January 14, 2021, by NCI Staff

For many cancer survivors, their worst nightmare is finding out that their cancer has come back. Even years after a seemingly successful treatment, cancer can start growing again, and scientists don't know how this happens.

Now, a new study suggests that stress hormones may wake up dormant cancer cells that remain in the body after treatment. In experiments in mice, a stress hormone triggered a chain reaction in immune cells that prompted dormant cancer cells to wake up and form tumors again.

But if you are stressed, that doesn't mean your cancer is going to come back, said the study's lead researcher,

Stress hormones can alter the behavior of some neutrophils,

Long Covid International Research Conclave

Distinguished Speaker Panel

Dr. Kashyap Patel	*Medical Oncologist; CEO Carolina Blood and Cancer Care,President, Community Oncology Alliance (DC); Medical Director (consultant-part time); Blue Cross Blue Shields SC; Trustee and Clinical Affairs Chair, Association of Community Cancer Centers (DC) Medical Director, International Oncology Network.*
Dr. Afshin Beheshti	*Visiting Researcher at Broad Institute; President of COVID-19 International Research Team; Scientific Advisor at Ursa Bio.*
Dr. Douglas C. Wallace, PHD	*Micheal and Charles Barnett Endowed Chair in Pediatric Mitochondrial Medicine and Metabolic Disease; Director, Center for Mitochondrial and Epigenomic Medicine; Professor, Department of Pediatrics, Division of Human Genetics At University of Pennsylvania*
Dr Hariharan Easwaran, PHD	*Associate Professor of Oncology in Sydney Kimmel Cancer center at John Hopkins University.*
Dr. Mohammed Jahanzeb	*Medical Oncologist; Professor of Medical Oncology, University Miami School of Medicine of Medical Oncology, University Miami School of Medicine.*
Dr. Ralph Boccia	*Medical Oncologist; Associate professor of medicine at MedStar Georgetown University Hospital;Medical Director of the International Oncology Network (ION) Clinical Research Program;Chairman of the ION medical Advisory Board.*
Dr. Rahul Nathwani	*Consultant Gastroenterologist at Mediclinic Group of Hospital, Dubai(UAE); Adjunct Clinical Associate Professor of Gastroenterology Sheikh Mohd Bin Rashid University in Dubai (UAE)*
Dr. Rob Schwartz	*Assistant Professor of Medicine at the Sanford I. Weill Medical College of Cornell University;Attending Physician, New York-Presbyterian Hospital Cornell campus.*

Dr. Neal Flomenberg	*Chief Scientific Officer and Global Head of Research and Development at Tevogen Bio.*
Dr Charles Vanderburg	*Senior Research Scientist; Broad Institute of MIT and Harvard.*
Dr. Alistair Nunn	*Professor at University of Westminster, United Kingdom; Director of Science for the Guy Foundation.*
Dr. Fred Divers	*Board Certified Medical Oncologist; Chief Medical Officer at AON*
Dr.Christopher Mason	*Professor of Physiology and Biophysics.Director, WorldQuant Initiative for Quantitative Prediction and WorldQuant Foundation Research Scholar; Professor of Computational Genomics in Computational Biomedicine in the Institute for computational Biomedicine*
Dr. Hala Borno	*Board Certified Medical Oncologist; Founder and CEO of Trail Library*
Dr. Scott Lippman	*Associate Vice Chancellor, Cancer Research and Care Professor of Medicine, UC San Diego Health*

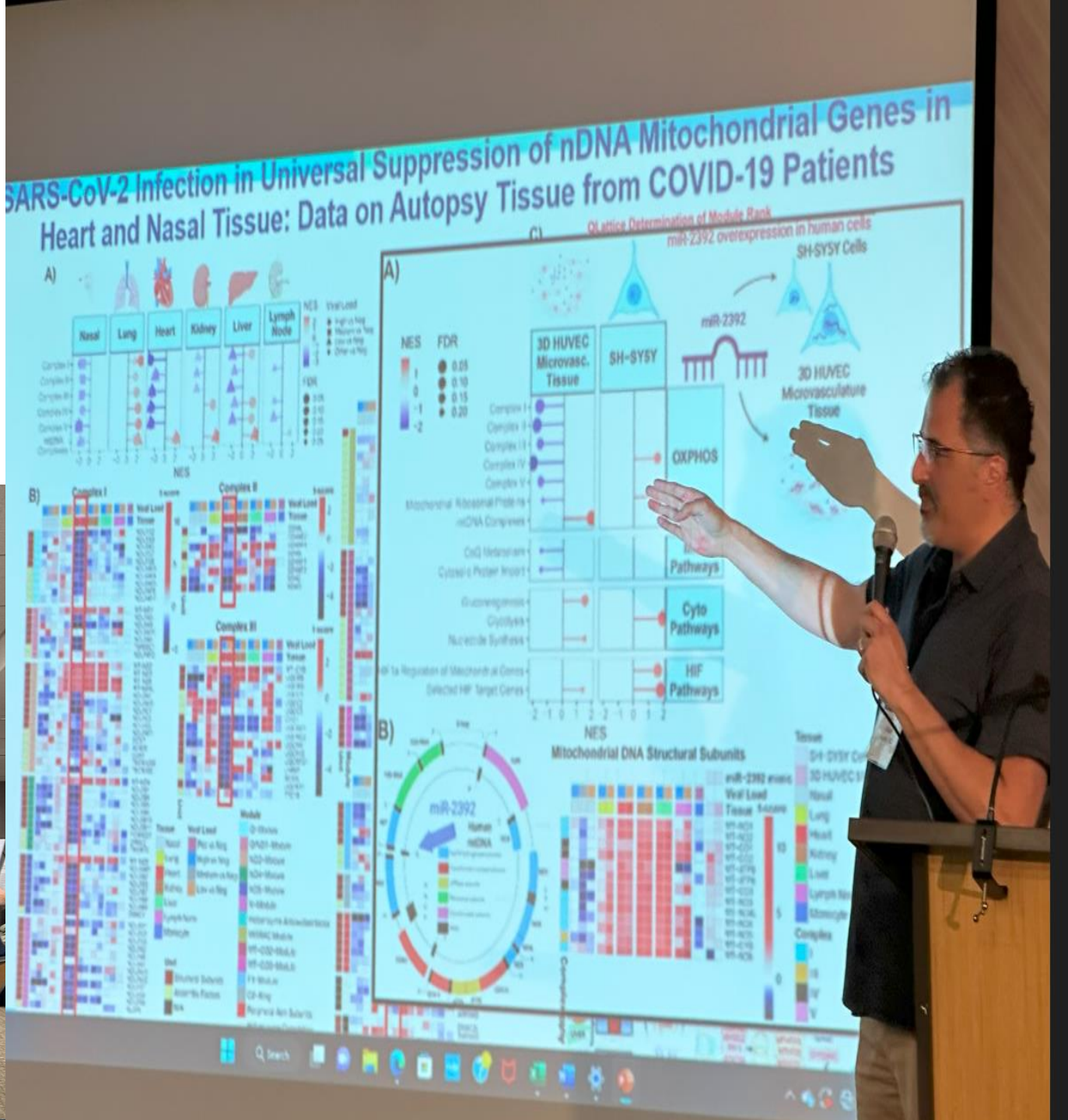
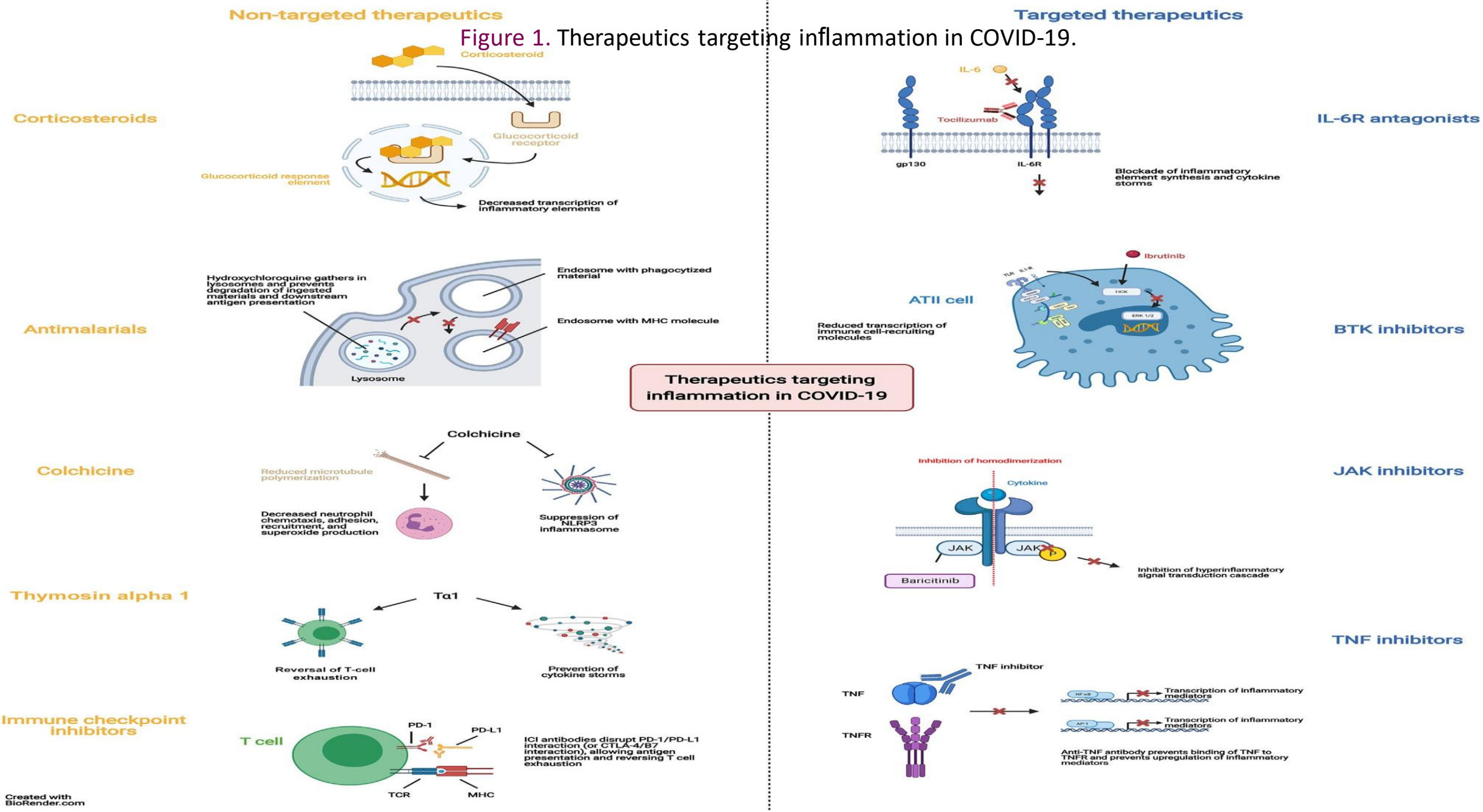


Figure 1. Therapeutics targeting inflammation in COVID-19.



OPEN QUESTIONS

Occurrence, mechanism, and significance of SARS-CoV-2 persistence in different organs

Mechanisms, targets, and significance of autoimmune reactions

Role of other viruses.

Impact of host genetics and microbiome.

Actual impact of vaccination in people who get breakthrough infections and its duration.

Occurrence and severity of PASC after infection with future variants

Impact of severe inflammation on chronic end organ damage including myocarditis, neuropathy

? Links of Covid related inflammation and cancer

Preventive and therapeutic approaches.

Potential retrospective data analytics

- ER visits for cancer patients pre 2000 and 2022 onwards
- Hospitalizations (cardiovascular, syncopal episodes, strokes, chest pain, seizures pre and post)
- New cancers pre and post 2022
- New stroke, MI and other cardiovascular causes requiring ER, hospitalization
- PMPM beneficiary spending pre and post Covid

Some of the key publications and references

- COVID-19–Induced Modifications in the Tumor Microenvironment: Do They Affect Cancer Reawakening and Metastatic Relapse?
- https://www.frontiersin.org/articles/10.3389/fonc.2020.592891/full
- COVID-19: a potential driver of immune mediated breast cancer recurrence?
- https://breast-cancer-research.biomedcentral.com/track/pdf/10.1186/s13058-020-01360-0.pdf
- Cancer as a prospective sequela of long COVID-19
- https://pubmed.ncbi.nlm.nih.gov/33914346/
- Blood Cytokine Analysis Suggests That SARS-CoV-2 Infection Results in a Sustained Tumour Promoting Environment in Cancer Patients
- https://pubmed.ncbi.nlm.nih.gov/34830872/
- The Deadly Duo of COVID-19 and Cancer!
- https://www.frontiersin.org/articles/10.3389/fmolb.2021.643004/full