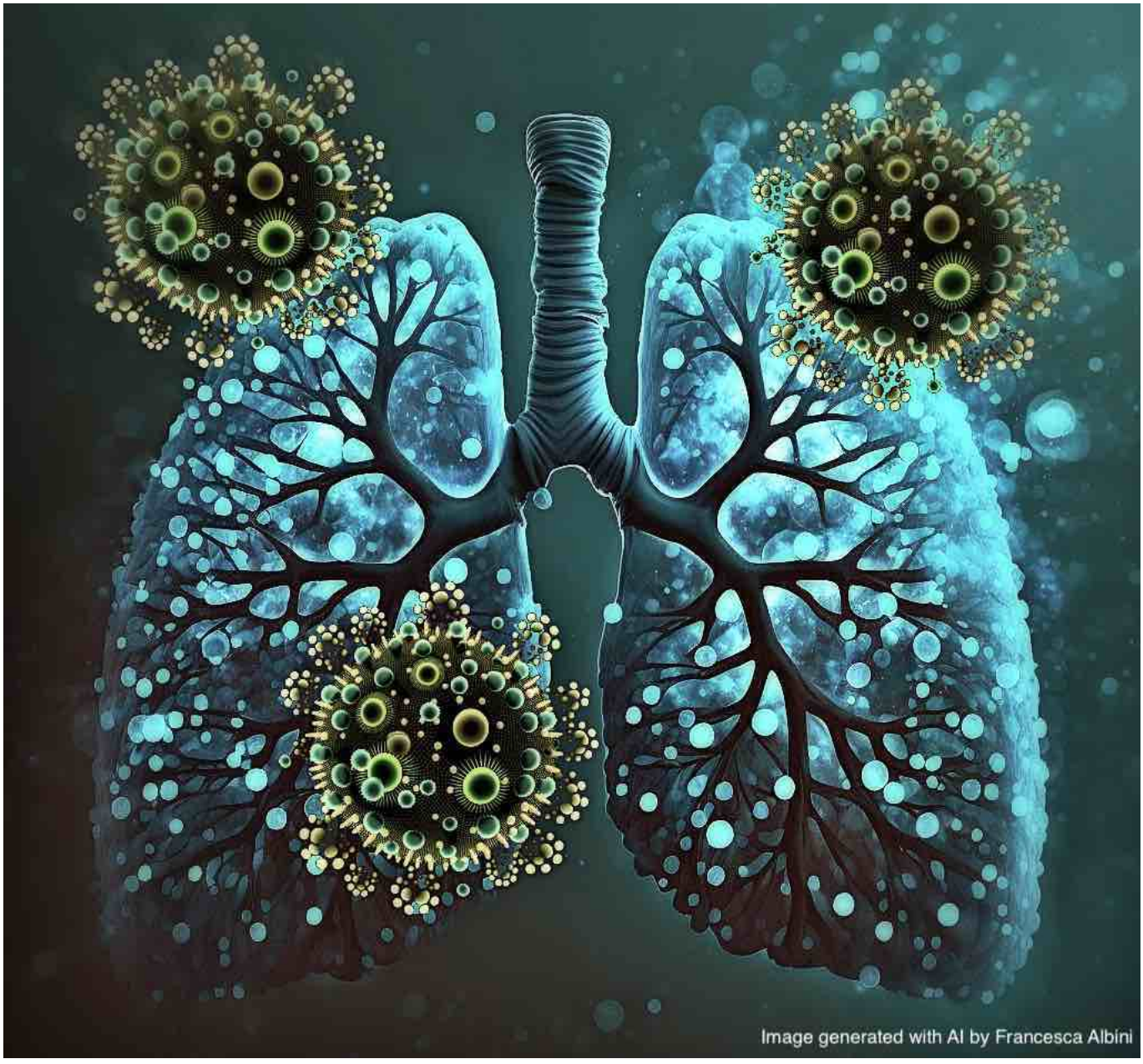
Cancerworld

How did Covid impact healthcare and cancer patients?

Adriana Albini / 12 May 2023



The Covid-19 pandemic has brought unprecedented challenges to the healthcare industry, particularly for cancer patients, who have experienced disruptions to their treatment, delays in diagnosis, and increased stress and anxiety due to the pandemic. This webinar, that took place on

27th March 2023 as part of the SPCC Project “Cancer & Covid”, addressed some of these issues. Two experts alternated two presentations each exploring how Covid-19 has impacted healthcare and cancer patients, and the lessons learned from the pandemic. The webinar was moderated by **Aleksandra Filipovic**, Clinical Research Fellow at Imperial College London, London, United Kingdom.

Impact of Covid on cancer patients on hospital admission resulting from poor follow-up

Antonio Voza is Head of the Emergency Department at the Humanitas Research Teaching Hospital in Milan, Italy. Although the last significant wave of the Covid-19 pandemic was quite a while ago, it remains critical to focus on understanding the disease process in various patient populations for effective risk stratification. This is especially important for cancer patients, due to their peculiarities. First of all, they usually require prolonged hospitalisation and follow-ups which increase the risk of infection with SARS-CoV-2 virus. Additionally, their weakened immune system, resulting from both disease and treatment, further increases their susceptibility to infection. The Humanitas Hospital, where Prof. Voza works, has emerged as a prominent institution for treating infectious diseases during the pandemic. Since February 2020, over 5,000 Covid-19 patients have been admitted to the hospital. In addition to treating Covid-19 patients, the hospital is also recognised as a leading cancer centre. Both from the hospital experience and findings from international literature, it has clearly emerged that oncological patients exhibit a higher prevalence of comorbidities upon discharge. They are also more likely to require intubation and experience a prolonged length of stay during hospitalisation compared to non-cancer Covid-19 patients. However, no significant differences in ICU admissions or development of complications have been observed in cancer patients.

As to the prognosis for oncological patients, it is important to note that both the hospital’s experience and international data indicate that factors such as obesity, smoking, and diabetes can increase the risk of unfavourable outcomes. For cancer patients receiving anti-cancer treatment, mortality rates appear to be influenced more by age, gender, and comorbidities. It should be emphasised, however, that while the Humanitas research data suggests a trend towards better survival rates for non-active cancer patients, the literature does not demonstrate a significant difference in mortality between cancer and non-cancer patients or between active and non-active cancer patient groups. In an article published in the *Lancet* in 2020, Camille Maringe and her group postulated that a considerable increase in the number of avoidable cancer mortality in England is to be expected due to diagnostic delays caused by the Covid-19 pandemic. In another article published at the same time, Deepak Sundriyal and his colleagues demonstrated that by utilising telemedicine and tele-consultation, providing supportive care in or near the patient’s home, and involving a general practitioner early on in their care, while still maintaining the hospital chemotherapy program, it was possible to reduce hospital admissions and improve the outlook for these patients.

If we focus on the prognosis for oncological patients with Covid-19 in the medium to long term, the literature suggests that their outlook is poorer than that of Covid-19 patients without cancer. However, a slightly shorter observation time enabled us to describe characteristics of Covid-19 survivors with cancer. It is important to note that this frail patient population requires tailored management strategies.

In sum, obesity, active smoking, diabetes, and high Quick Sequential Organ Failure Assessment (qSOFA) score led to intensive care unit (ICU) admission and were associated with an increased risk of mortality. There was no significant difference in ICU admission between cancer and non-cancer patients. There was no significant difference in the rate of complication between cancer and non-cancer patients. Cohorts with cancer stayed longer in the hospital compared with non-cancer

patients. No difference was observed in mortality between cancer and non-cancer groups or between active and non-active patients. It is crucial to emphasise the need for tailored management strategies for the frail oncological patient population.

Studies and data already published on the impact of Covid on cancer patients

Christian Rolfo is Professor of Medicine, Haematology and Medical Oncology, and Associate Director for Clinical Research in the Centre for Thoracic Oncology at the Tisch Centre Institute, NY, US. Although we may have grown tired of talking about Covid, there remains much to be done and learned about this pandemic. There are still several side effects that are being discussed, for instance in patients affected by long Covid. The sequelae of Covid-19 are still prevalent, especially among blood cancer patients and patients with lung cancer, the latter being Prof. Rolfo's specialty area. In these populations the risk of complications and death is significantly higher. We know that cancer patients had higher rates of hospitalisation and mortality than Covid-19 patients without cancer. We also know that certain populations and disparity groups required more invasive tests and procedures. Additionally, patients with lung cancer required ICU admission more frequently than those with other types of cancer.

Interesting data were published in the *JCO* in 2020, elucidating how the pandemic impacted the diagnosis and treatment process. The data are limited to American senior patients, of course, but they are generally relevant. Compared to 2019 breast mammograms decreased over the months, and dramatically so in May, June, and July. Colorectal, lung and prostate screenings followed a similar pattern. The consequences of reduced screening efforts are becoming evident now, and we can expect to see their impact in the future as well. Patients may not have received timely diagnoses, which could negatively affect their overall survival. As a result, oncologists may be forced to make decisions based on more advanced stages of cancer rather than catching them at an early stage. Furthermore, the delivery of treatments such as chemotherapy in professional or institutional settings has also been affected. The frequency of biopsies and surgeries was also impacted, especially in cases where they were not considered urgent, although they are necessary for diagnosing cancer. The data shows a significant delay in procedures such as colon, breast, and lung cancer biopsies during the months of May, June, and July.

Additionally, there was a decrease in the number of new patients, established patients, and outpatients seeking medical services due to fear of exposure to contagion. Many individuals were hesitant to visit hospitals because of the high risk of infection and the various restrictions in place in different countries. Some countries even required certification to permit free movement. Furthermore, there were no vaccines available then, making it even more challenging for patients to attend appointments. One positive aspect of the pandemic was the advancement of telehealth or telemedicine technology. A comparison between 2019 and 2020 revealed a decrease in in-person visits but an increase in telehealth consultations. This allowed for the continued monitoring and treatment of cancer patients remotely, despite the lack of physical exams. While it is challenging to provide a complete diagnosis without examining the patient physically, it was a valuable addition to our healthcare system during Covid.

In 2020 Prof. Rolfo and colleagues published a paper in *JCO Global Oncology* with the results of a survey they conducted from April 21 to May 8, involving 356 centres around 54 countries in six continents. These centres serve over 700,000 new patients with cancer a year. The findings indicated that 55% of them implemented reduced services as a pre-emptive strategy. Some of the prevalent reasons included an overwhelmed system. Services were restricted, including bed availability, due to the focus on pandemic-related care. In some parts of the world, the lack of protective equipment also contributed to delays in treatment. Additionally, Covid-related care demands led to personnel shortages, while restricted access to medications, particularly those used to treat Covid symptoms, led to delays in cancer treatment. There were also delays in planned surgery. The interruption of palliative care should be mentioned as well. Many services faced obstacles in providing this critical care, and while some attempted to use telemedicine, we must acknowledge the challenges faced by patients in these situations, particularly regarding the limited contact with their treatment teams.

A study published in JCO Global Oncology in 2020 explored the impact of Covid-19 on expected mortality rates among cancer patients in Latin America through mathematical modelling. This exercise was crucial in providing insight into how healthcare systems in countries with poorer infrastructure would be overwhelmed by the health crisis. There were significant numbers of unaccounted deaths that occurred due to the pandemic's impact on cancer care, and complications

worsened. The recovery of both the healthcare systems and cancer patients will take time, and even after two years since the virus outbreak, some systems are still experiencing the effects of the disruption.

The lessons learned from this health emergency helped redesign the concept of clinical trials. Before, they used to be primarily site-centric, conducted at hospitals or large centres. Now resources are being implemented to conduct them remotely and make them more accessible to patients. This is a significant benefit that has emerged from the pandemic, as it addresses disparities not only related to race or ethnicity, but also to older patients, those with underlying conditions such as immunological diseases, and those with certain types of cancer, for instance haematological and lung cancer.

According to the AACR Report on the Impact of Covid-19 on Cancer Research and Patient Care published in 2022, there was a high level of patient acceptance towards telemedicine, with 43% of users expressing a desire to continue using it in the future. However, it is important to note that there were some negative aspects associated with telemedicine, such as low engagement among certain individuals who may struggle with technology. The pandemic also highlighted the remarkable efforts made by regulatory agencies, scientific groups, researchers, and clinicians to expedite vaccine development and distribution in a timely manner. This has generated a lot of controversy. Some individuals who lack understanding of the drug development process have criticised the speed at which the vaccines were created. However, it was an incredible feat that required tremendous effort. Ultimately, the development around the world of these vaccines with different approaches was a life-saving achievement. It is important to remember the struggles that patients, especially those with cancer, faced during this time. A qualitative study was conducted by Phyllis Butow and colleagues to explore the impact of the pandemic on patients living with cancer, family carers, and oncology health professionals. Participants completed semi-structured interviews and anxiety and depression assessments. The analysis revealed three shared themes: fear and death anxiety, isolation, and uncertainty. Advanced cancer patients and carers with high anxiety/depression scores were more affected by isolation and expressed greater death anxiety.

In conclusion, patients with cancer have a significantly higher risk of Covid-19 infection, severe disease, and death compared to individuals without cancer. Patients with blood and lung cancers, and those on active anticancer treatments, are more vulnerable compared to patients with other types of cancers, or those who are not on active anticancer treatments. Covid-19 vaccines are effective in patients with cancer, with few to no side effects. Certain patients with blood cancers, who are receiving specific types of treatments, respond to the vaccines to a lesser extent because of the nature of their illness and treatment. The Covid-19 pandemic caused the closure of research laboratories and a pause in clinical trials, negatively impacting career development opportunities for science. It also caused burnout among healthcare workers. Patient care was disrupted, resulting in a decline in cancer screening, delays in treatment, and negative effects on the mental and psychosocial health of cancer survivors, as well as widening cancer health disparities. Although some aspects of cancer research and patient care are returning to pre-pandemic levels, the full impact of the disruptions will only become clear in the coming years.

Development of pulmonary fibrosis in post Covid patients

Prof. Voza's second presentation focussed on pulmonary fibrosis in post Covid patients, which has been defined as "the presence of persistent and different fibrotic tomographic changes identified on follow-up, often combined with impairment in pulmonary function tests." It is assumed that Covid-19 continues to spread globally and as a result, the number of individuals experiencing pulmonary fibrosis as a secondary effect of the virus will also increase with time. It is important to note that our understanding of post-Covid pulmonary fibrosis, including its risk factors, histopathological

characterisation, pathophysiology, prevalence, and management, is limited. This may be attributed to the fact that so far there have been few studies addressing this condition.

Individuals with post-Covid-19 pulmonary fibrosis may present with dyspnoea, dry cough, oxygen desaturation, reduced diffusion capacity for CO and restrictive pattern. Those are the most common functional abnormalities that can be found in these patients also in the long run. In a survey and meta-analysis published in 2021, Matsuo So and his colleagues analysed 15 studies, examining radiological and lung functional alterations at follow-up periods ranging from one to six months. On average, the follow-up timing was approximately 90 days after symptom onset or hospital discharge. They found that approximately 55% of patients developed chest CT scan alterations, with ground glass opacity being the most common alteration at around 44%, followed by parenchymal band and fibrous stripe at 34%, and bronchiectasis at approximately 24%. These findings are noteworthy and concerning to pulmonologists when compared to previous viral pandemics. For example, fibrotic sequela relating to the H1N1 pandemic of 2012 involved about 10% of patients admitted. Similarly, fibrosis-related MERS-CoV pandemic in 2016 affected approximately 33% of discharged patients after three months, according to a Korean study. In a 2021 Chinese article published in Lancet Respiratory Medicine, Xiaojun Wu and colleagues measured reduced diffusion capacity for carbon monoxide and restrictive patterns at 3, 6, and 12 months after discharge. After 12 months, they found that lung function alterations were present in approximately 33% of patients for diffusion capacity for carbon monoxide and in 11% of patients for restrictive capacity. The same study also presented different percentages with regard to imaging alterations. Wu's team highlighted the tomographic characteristics of pulmonary fibrosis secondary to Covid-19, which included the presence of reticular opacities, ground-glass opacities, architectural distortion, bronchiolar traction, and mosaic attenuation, ultimately leading to the typical honeycombing image. These alterations were observed in 78% of patients who were discharged after three months; the percentage decreased to 24% in patients discharged after 12 months. It is important to note that the paper did not report any significant improvement at 12 months compared to 9 months.

Patients who are at a higher risk of developing post-Covid pulmonary fibrosis include those with severe disease, as well as older patients, male patients, smokers, and individuals with multiple comorbidities. Also at a higher risk are patients with pulmonary lesions and involvement, high CRP and interleukin-6 levels, high lactic dehydrogenase levels, and oedema without pulmonary emboli. The same applies to patients who have been managed in an intensive care unit or high dependency unit, or those who have had a protracted dependence on high inspired fraction of oxygen, such as patients requiring oxygen support with high flow nasal cannula, CPAP, or bi-level non-invasive ventilation. As to treatment, the strategies to reduce the severity and the progression of this post-Covid condition are unclear. Potential therapeutic modalities include antifibrotic drugs, prolonged use of corticosteroids or other anti-inflammatory and immunosuppressive drugs, or spironolactone. Three pilot studies have explored the use of mesenchymal stem cells in the treatment of post-Covid-19 pulmonary fibrosis, and there are also anecdotal cases of patients undergoing lung transplantation. However, it is important to identify a subgroup of patients with Covid-19 who may benefit from prolonged corticosteroid use. The use of corticosteroids is recommended for a longer duration in patients with tomographic features consistent with organised pneumonia, particularly in the presence of hypoxemia. For these patients, an initial dose of prednisone is suggested at 0.5-1 mg/kg/day, followed by a gradual tapering over a period of four to six weeks. Further research will be needed to assess whether pirfenidone, an antifibrotic medication, could be effective in treating post Covid-19 pulmonary fibrosis. According to the international literature antifibrotic treatment should be considered for patients with progressive interstitial lung disease. However, its use for patients with non-progressive pulmonary lesions should be individualised and not done routinely.

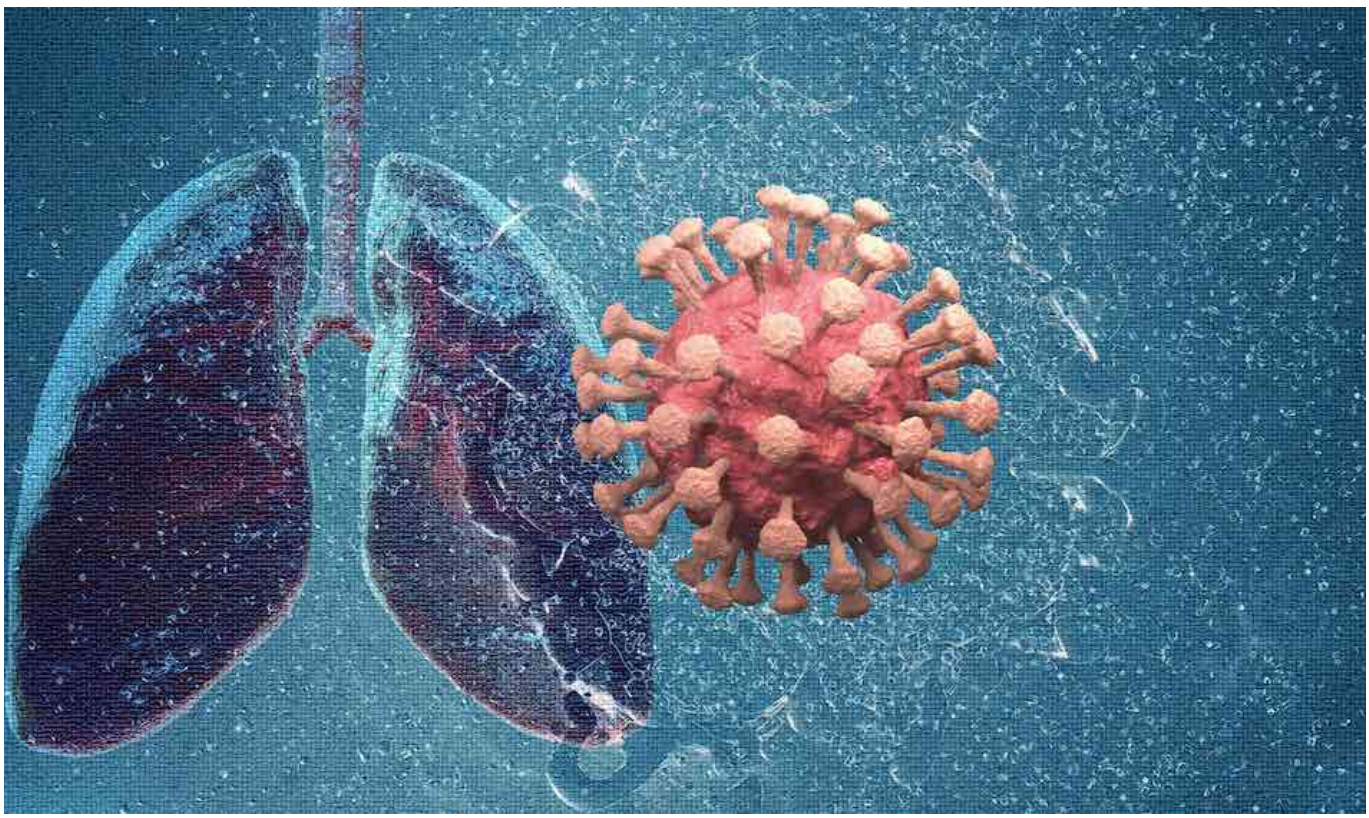
Although the prevalence of post-Covid pulmonary fibrosis will become more apparent over time, the

pre-vaccination era has shown that around 33% of Covid-19 patients developed fibrotic abnormalities after being discharged. It is important to investigate the protective effects of vaccination, the potential progression of fibrotic changes, and the possibility of using new antifibrotic agents. Additionally, the emergence of new variants should not be overlooked. Post-Covid pulmonary sequelae should be considered as a possible cause of pulmonary fibrosis, and screening for this condition should be performed in patients who have had Covid-19 with pulmonary involvement, particularly during the acute phase of the disease.

Update on current research on cancer patients

In his second presentation, **Prof. Rolfo** recalled that his lab, like most institutions, was facing closure during the pandemic. Originally, he and his team were focussing on lung cancer biomarkers in liquid biopsy, but in order to maintain the lab open and utilise their expertise in the field of liquid biopsy, they began to work on Covid-19 research. As a result, they are currently following several of these Covid-19 research projects. Their main focus is on the role of liquid biopsy and analytes such as accessory vesicles in the transportation of spike proteins and biomarkers related to Covid-19 treatments. The team is also studying the characteristics of fibrosis in patients with lung cancer who have pre-existing lung damage to improve research in this area. The closure of labs and decrease in funding caused by the pandemic has significantly affected the development of therapies for other types of tumours as well and the progress of clinical trials. But we are recuperating now, and over the past two years investigators and regulatory agencies have done a terrific job in this regard.

A lot has been learned about the variants of Covid-19 and how to adapt vaccines accordingly. As a result, various vaccines are now available and being used in the general population as well as in cancer patients. Prof. Rolfo and colleagues published an article in Cancer Cell in 2022 discussing the response to vaccines in patients with lung cancer. They observed that certain cancer patients did not have an increase or decrease in titers over time after being administered the vaccine, thus requiring more boosters. Ongoing research in this area is being funded by the U54 and led by Dr. Hirsch and Dr. Garcia-Sastre, who are working to gain a deeper understanding of the impact of vaccinations on cancer patients.



Another important contribution during the pandemic were also the Covid registries. Not only did they help us understand the characteristics of the patients involved and the number of cases, but they also provided invaluable information for future studies. Some of these registries even collected samples, for instance blood, although obtaining respiratory samples like bronchoalveolar lavage or sputum was challenging due to the infectious risk involved. Nonetheless, it was a valuable opportunity to obtain such samples. During the pandemic telehealth allowed for increased access to healthcare for many people. It has been especially beneficial in cases where patients were hesitant to visit hospitals or in areas that were difficult to reach. Additionally, telehealth has facilitated engagement between caregivers, family members, and patients. However, there are also drawbacks. Some patients, particularly those in rural areas without stable internet connections, were unable to benefit from this technology. Older patients or those with disabilities also faced challenges in accessing telehealth. Finally, the rapid changes in policies and reimbursement rules have created issues that must be taken into consideration. In the United States, for instance, the licensing issues are a problem. Patients who wish to continue using telemedicine in the future may need permanent changes to the rules, that were allowed during the pandemic. One example is the ability to provide care to patients outside of their state of residence, which is normally limited by state licensing regulations. Changing these regulations for the future will be crucial, as it could provide more opportunities for patients in remote areas to access centres with high levels of expertise and receive second opinions. However, this will require legislative changes, which may take significant effort. Additionally, implementing telemedicine in some areas may be costly, as certain equipment like cameras, lights, and stable internet connections may be needed. Although these issues may seem trivial, they can have significant impacts. Lastly, ensuring the security of patient data is fundamental and must comply with HIPAA telemedicine rules, making it an important consideration for the future.

As already mentioned, a significant proportion of patients prefer telemedicine, particularly those with cancer who have reported a decrease in travel time and greater satisfaction with access to healthcare. Genetic counselling has also been successfully conducted through telehealth. However, certain subgroups of patients, such as the Hispanic population, have faced challenges in utilising this technology compared to other ethnic groups. Additionally, some patients have encountered difficulties with video-based telemedicine visits, but it is worth noting that teleconsultations by phone have also been implemented, especially for follow-ups or patient inquiries. Overall, telehealth offers a range of options beyond video consultations and has proven to be an important development in healthcare.

Covid has taught us valuable lessons about conducting clinical trials in various locations, including rural areas. In some instances, experimental drugs were administered directly to patients in isolated locations, and remote consent to participate in clinical trials has proven to be very useful. A collaborative effort was initiated with local clinics and labs for blood sample collections and cancer screening. These measures helped to increase engagement with community-based networks, allowing for the establishment of research infrastructure and physicians in areas closer to patients' homes. Ongoing clinical trials across the globe continue to focus on cancer and Covid, particularly in lung cancer and the long-term effects on cancer patients. These trials aim to answer pressing questions surrounding Covid's impact on patients with cancer, specifically lung sequela. It is true that amidst this terrible ordeal, there has been a modernisation of clinical trials and drug development, and funding has increased in some cases to support these endeavours. Federal agencies in the United States, for instance, have made concerted efforts to optimise returns on prior investments in medical research and expand access to drugs for future clinical trials. It is clear that the lessons learned from Covid-19 will lead to numerous future efforts aimed at modernising clinical trials.

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