ReFlections

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IN THIS ISSUE

FROM THE EDITORS

Happy New Year! We hope all of you had a wonderful and refreshing holiday season.

You might note some changes in *ReFlections*' editorial team: **Dr. Daniel D. Zimmerman** is now RGA's Chief Science Advisor, and *ReFlections* co-editor **Dr. Adela Osman** has assumed Dan's previous position as Head of Global Medical. For more information, please see page 22.

Three familiar *ReFlections* authors are returning to our pages. **Dr. John Lefebre**, FRCPC, Senior Technical Global Medical Director, RGA International, shares his substantial COVID-19 knowledge in his discussion of the sequelae of long COVID and its risk to long-term disability portfolios.

As our knowledge of human genetics expands, so is the range genetic therapies designed to target certain cancers. **Dr. Radhika Counsell**, Consulting Medical Officer, RGA UK Services Limited, weighs in with the newest information about trends in these immunotherapies. **Hilary Henly**, Global Medical Researcher, Strategic Research, RGA, provides a detailed review of cystic fibrosis and encourages insurers to begin contemplating at least limited term cover.

In 2023, the **Longer Life Foundation**, RGA's research collaboration with Washington University School of Medicine in St. Louis, will mark its 25th anniversary. To find out more about the coming year, please see page 21.

We trust you will find this issue both interesting and informative. Please do not hesitate to let us know how we can continue to improve *ReFlections* for you.

Dan and Adela

Daniel Zimmerman Adela Osman

IMMUNOTHERAPY: TRANSFORMING CANCER OUTCOMES

Abstract

The human immune system plays a vital role in protecting the body from infection, harmful substances, and cellular changes such as cancer. Boosting the immune system to treat cancers was first described in the late 19th century,[1] when Dr. William B. Coley discovered that soft tissue and bone sarcomas could be controlled in some patients by injecting them directly with heat-inactivated bacteria. (These later became known as "Coley's toxins."[2])

More recent cancer treatment approaches have utilized immune response mediators such as interleukin and targeted vaccines, but with limited success.

A more effective approach developed during the past 20 years has been to enhance the ability of immune cells, and in particular T-lymphocytes or T-cells, to recognize, target, and eliminate tumor cells. Two main pathways have emerged: immune checkpoint inhibitors, which work by activating T-cells, and CAR T-cell therapy, which modifies and enhances T-cell receptor function.

The immunotherapy path contrasts with chemotherapy and biological or targeted therapies, which work by attacking vital cell functions to kill cancer cells. There is increasing recognition of the importance of the tumor micro-environment for the development and progression of cancer. The side effect profile of immunotherapy is different from that of chemo or targeted therapies, and so may offer a better quality of life to individuals with advanced cancers undergoing such treatments.

This article reviews how modern immunotherapy is transforming cancer outcomes, and the real possibility that it might even cure some highly lethal cancers such as malignant melanoma.

Immune System

The two main components of the immune system are the innate and adaptive systems. Both work together to protect the body against attack from harmful agents.

The innate immune system is composed of dendritic cells and macrophages, i.e., antigen presenting cells. These cells patrol the body and engulf any foreign antigens or proteins associated with pathogens and cancer cells. These are then presented to T-cells (T lymphocytes), which are the main component of the adaptive immune system.

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Dr. Radhika (Radi) Counsell, MBBS, MD, is a Consulting Medical Officer with RGA UK Services Limited. A specialist in gynecological and breast cancers, she provides direct case consultation for annuities, critical illness, terminal illness, and medical insurance claims. She also provides review and input for RGA Global Underwriting Manual's oncology guidelines and for new products under development. Dr. Counsell's managerial role in the National Health Service (from which she recently retired) included the launching of the NHS Trust's Acute Oncology Outreach Service, which provides opinions on cancer patients presenting with acute problems, and leadership of the regional gynecological brachytherapy service, and being Head of Chemotherapy. She has also taught and trained medical students, acute medicine doctors, oncology specialty trainees, and therapy radiographers.

Dr. Counsell's qualifications include obtaining Membership of the Royal College of Physicians (MRCP) of the United Kingdom and Fellowship of the Faculty of the Royal College of Radiologists (FRCR). Her Bachelor of Medicine & Bachelor of Surgery (MBBS) degree, and her medical doctorate (M.D.) for research on magnetic resonance spectroscopy in breast cancer, are from University of London Medical School. She has lectured on oncology at both medical and insurance events.

T-cells are a type of white blood cell. They originate from stem cells in the bone marrow and mature in the thymus into one of three types of cells: helper T-cells, cytotoxic T-cells, and regulatory T-cells. These cells can reside in the peripheral tissues or circulate in the blood or lymphatic system. Based on the nature of the glycoprotein on the cell surface, cytotoxic T-cells are also known as CD8+ cells and helper T-cells as CD4+ cells.[18]

Helper T-cell activation triggers a cascade that allows the immune system to eradicate cells carrying a foreign antigen. They are involved in stimulating cytotoxic T-cells to proliferate and attack and in stimulating B lymphocytes (B-cells) to proliferate and mature into plasma cells which produce antibodies.[19]

Regulatory T cells (also known as TREGs) can suppress the immune response, and thus have a critical role in preventing autoimmunity. Their function is to inhibit T-cell proliferation and production of cytokines.

The adaptive immune system recognizes and remembers specific pathogens to create long-lasting immunity. T-cells carry unique receptors for detecting specific antigens.

Biology-Immune Checkpoint Inhibitors

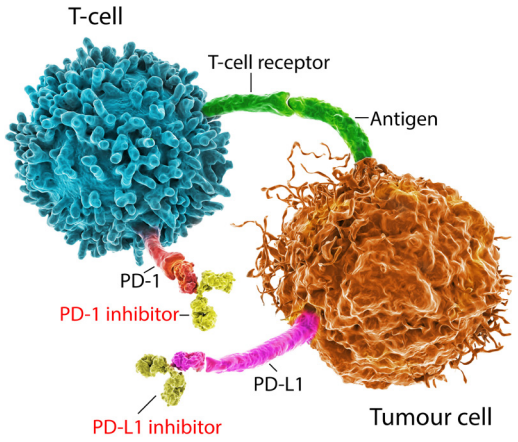
To prevent autoimmunity, i.e., an attack by a person's own immune cells on their autoantigens, the human immune system has several key checkpoints that switch off T-cell responses. In a healthy body, this inhibitory regulation of immune cells can also minimize collateral tissue damage by controlling the duration and extent of an immune response.

Certain cancer cells can survive and continue to proliferate by harnessing immune checkpoint pathways in order to evade detection and destruction by the immune system. Earlier immunotherapy drugs targeted immune checkpoint proteins PD-1 and CTLA-4 on T-cells, and modern approaches to cancer immunotherapy use antibodies that, in essence, blockade specific immune checkpoint molecules.

Figure 1 shows the programmed cell death (PD) pathway. (Programmed cell death, or apoptosis, is a normal physiological process.) The receptor on the surface of the T-cell is called PD-1. The ligand (or protein) that binds to this receptor is called PD-L1 (programmed death ligand 1). PD-L1 may be present on both cancerous and normal cells.

In certain cancers, when a T-cell's PD-1 receptor connects with a cancer cell's PD-L1 ligand, the T-cell is "switched off," which means it will not attack the tumor cell despite being able to detect it. It is as if the cancer cell has become invisible to the T-cell. Immune checkpoint inhibitor therapies work by breaking that immune checkpoint pathway, either by blocking the PD-1 receptor or the PD-L1 ligand , thereby allowing T-cells to become active.

Figure 1: The T-Cell Tumor Blockade



Source: *Adobe Stock*

Immune Checkpoint Inhibitors in Malignant Melanoma

Immune checkpoint inhibitor therapies act as blocks to cancer cell proliferation. They have revolutionized treatment of a range of cancers; in particular malignant melanoma.

Metastatic melanoma, in particular, is a highly lethal cancer with a five-year survival rate of no better than 20% to 30%.[3] Melanomas in visceral sites such as the liver and the brain have the worst outlook, with average life expectancies of less than one year.[4]

Recent trials of certain immune checkpoint inhibitors are yielding interesting results. The CheckMate-067 clinical trial, for example, has been studying the anti PD-1 drug nivolumab and the anti CTLA-4 drug ipilimumab as

potential treatments for advanced malignant melanoma in previously untreated patients. The trial recruited 945 patients with stage III (spread to lymph nodes) and stage IV (spread to distant sites) cancers. Participants were grouped into three arms: one received nivolumab and ipilimumab combination therapy, one received only nivolumab, and one received only ipilimumab. Patients in each of the arms received four courses of treatment followed by maintenance nivolumab until they experienced either disease progression or intolerable adverse events.

As shown in Table 1, nearly two-thirds of the patients receiving nivolumab had ongoing response five years after starting treatment, whether given with ipilimumab or on its own. About a fifth of this patient cohort also experienced complete response (remission), with no sign of cancer on scans after completing treatment.

Many of those receiving combination therapy also experienced long and sustained control of their cancers, with median survival rates of more than five years after starting treatment. These are remarkable results from a well conducted clinical trial and suggest it may be possible to cure some advanced melanomas.

One downside of immune checkpoint inhibitor therapy is that adverse events are common. The reason for this is that by targeting a checkpoint protein, T-cells are switched on and may attack cells throughout the body, including skin, bowel, liver, lung, kidney, and endocrine glands. Although adverse events can be moderate to severe (grade 3 and grade 4), they are rarely life threatening and usually resolve within 12 weeks of starting treatment.

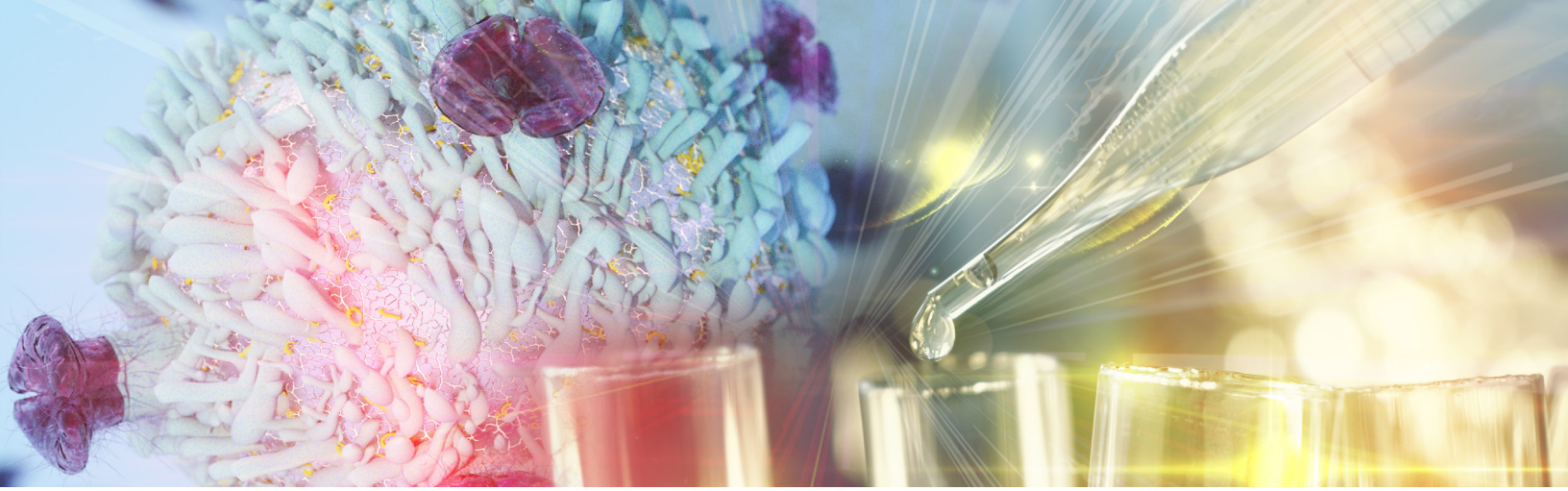
Table 1: Results of CheckMate 067 Trial[20]

	Nivolumab + Ipilimumab	Nivolumab alone	Ipilimumab alone
Ongoing response at five years	62%	61%	40%
Complete Response Rate	22%	19%	6%
Median Survival (months)	>60	36.9	19.9
Adverse Events – Grades 3 (moderate severe) and 4 (severe)	59%	23%	28%

Immune Checkpoint Inhibitors' Efficacy

In the last ten years, immunotherapies have transformed outcomes for many patients with advanced stage cancers. This has not only been for malignant melanomas but also for lung, head and neck, breast, renal, and bladder cancers. In fact, many stage 4 cancer patients who received immunotherapy treatments have achieved durable responses and significantly improved life expectancies.[21]

One drawback of immunotherapy, however, is that many patients do not respond to it. Indeed, only an estimated 12% of all cancer patients will benefit from immune checkpoint inhibitor



treatment.[5] Still, several new immunotherapy drugs are under development and clinical trials are planned for a wide range of cancer types.

Although side effects of checkpoint inhibitor drugs, which can include constipation/diarrhea, fatigue, cough, nausea, muscle/joint pain, and more, are not comfortable, they are better tolerated than those of chemotherapy. Still, there is the potential for the side effects to be severe, resulting in poorer quality of life and even fatality. Considerable effort is currently underway to identify predictive biomarkers that will indicate who may respond well to these treatments and for whom they may have little to no benefit.

Clinical experience also suggests that factors such as tumor mutational burden, mismatch repair deficiency, and PD-L1 expression levels may be able to indicate potential treatment efficacy. At the moment, however, there are no reliable biomarkers for selecting patients for treatment.[6] That being said, obtaining PD-L1 expression levels is recommended in the treatment guidelines for non-small cell lung cancer.

Tumor Mutational Burden

The tumor mutational burden (TMB) is the number of mutations in a DNA of a cancer cell.[22] Cancer is characterized by the continuous proliferation of cells. This generally begins with genetic mutations that occur randomly during the process of DNA replication for cell division. Genetic mutations have the potential to produce abnormal proteins, which may be expressed by cells as cancer antigens. The higher the number of mutations, the higher the likelihood of cells generating antigens which can dysregulate immune checkpoints on the T-cells. This hypothesis has been supported by an analysis of more than 1,600 patients with a range of cancers including malignant melanoma, non-small cell lung cancer, and bladder cancer.

Higher tumor mutational burden has been associated with longer survival and better response rates to Immune checkpoint inhibitor therapies. However, there does not appear to be a common predictive cutoff point for all cancer types, which means the clinical utility of predicting response to therapy is uncertain.[7]

Mismatch Repair Deficiency

The mismatch repair pathway plays a key role in identifying and repairing mismatched bases during DNA replication. The repair process avoids insertions or deletions of abnormal DNA in microsatellites (short repeated sequences of DNA). Defects or deficiencies in this process, known as deficient mismatch repair (dMMR), results in high levels of microsatellite instability (MSI-H) and accumulation of DNA mutations within the cell. Tumors with dMMR are referred to has having high TMB.

Defects of MMR genes may be due to germline mutations, as seen in certain hereditary cancers such as Lynch syndrome, or can occur spontaneously. (Patients with Lynch syndrome are susceptible to developing multiple cancers, especially colon and endometrial cancer.) dMMR occurs in about 15% of sporadic colon cancer.[8]

There are currently numerous clinical trials of pembrolizumab, an immunotherapy drug that targets PD-1 in a range of advanced dMMR cancers which have become resistant to chemotherapy. Overall, about 40% of patients in these trials had some benefit from immunotherapy treatment. The responses lasted more than six months in 78% of patients, with a range from 1.6 to 27 months.[9] These results led to the U.S. FDA approving pembrolizumab for the treatment of inoperable or metastatic dMMR/MSI-H cancers as a second line or subsequent therapy irrespective of the site or type of cancer.

PD-L1 Expression

PD-1/PD-L1 checkpoints have important functions in maintaining immune-tolerance. These checkpoints are also hijacked by cancer cells to avoid detection and destruction by the immune system. In metastatic non-small cell lung cancer, immune checkpoint inhibitors using either a PD-1 or a PD-L1 blockade are now embedded in best practice therapy guidelines, as clinical trials have shown a doubling of median survival rates with this immunotherapy.

The Keynote series of clinical trials focus on pembrolizumab as an immune checkpoint inhibitor and are being conducted for a wide range of cancers, with notable results to date. The Keynote-024 clinical trial, which is testing pembrolizumab in cancers with high expression of PD-L1 (at least 50%), found that the therapy nearly doubled median survival to 26.3 months from 13.4 months for chemotherapy.[10]

In the last ten years, immunotherapies have transformed outcomes for many patients with advanced stage cancers.

The Keynote-189 clinical trial, which focused on cancer patients expressing intermediate levels of PD-L1 (1-49%), showed that adding pembrolizumab to chemotherapy in advanced metastatic non-small-cell lung cancer improved the one-year survival rate from 49% to 69%. Survival at two years also increased, rising from 27% to 46%.[11]

Despite the utility of PD-L1 as a biomarker for guiding selection of treatment for non-small cell lung cancer, a review of studies that supported FDA approval of immune checkpoint inhibitors in a range of cancers highlighted the lack of consistency in methodology, such as type of assay used, type of cell studied (tumor, immune or both), and expression of cutoff values for defining level of expression. The review also reported that positive PD-L1 values predicted improved response to immunotherapy in less than 30% of studies.[12]

CAR T-cell Therapy

CAR T-cells are another type of immunotherapy-based cancer treatment. CAR, or chimeric antigen receptor, is a synthetic protein engineered for T cells that enable them to detect a specific antigen on a cancer cell.

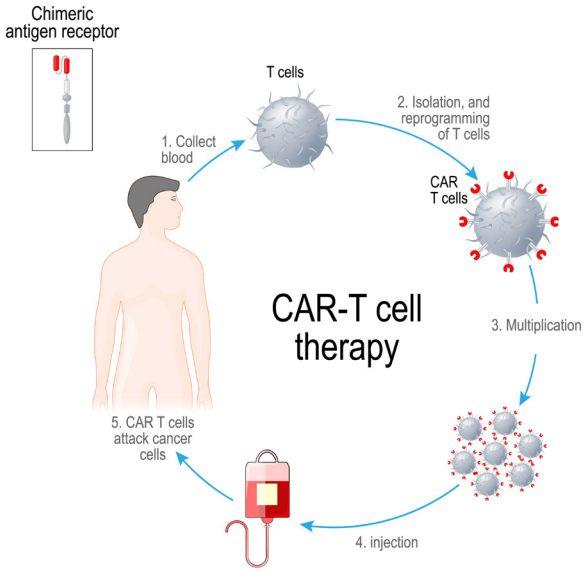
Figure 2 shows the multi-week laboratory and clinical process for providing autologous CAR-T therapy. T-cells from a patient's blood are isolated using apheresis, a process where cells are separated from plasma. The T-cells are then engineered into CAR-T cells by inserting a gene

into them that codes for CAR. After allowing the resulting CAR T-cells to multiply, they are infused back into the patient.

CAR T-cell therapy has been referred to as a "living drug," as these engineered T-cells are stable, continue to multiply in the body, and can detect and eradicate cancer cells if they reappear later in time. It is planned as a one-off treatment with long lasting effects.

The U.S. FDA and the U.K.'s National Institute of Clinical Excellence (NICE) have both given approval for using CAR T-cell therapy for B-cell acute lymphoblastic leukemia (ALL) for those up to the age of 25 years and for adults with three types of blood cancer:-diffuse large B-cell lymphoma; mediastinal B-cell lymphoma; and mantle cell lymphoma. Treatment can be given when the blood cancer is either refractory to first line treatment or has relapsed after at least two lines of therapy.

Figure 2: Process for Autologous CAR-T Therapy



Source: *Adobe Stock*

CAR T-cell therapy was first approved by the FDA for clinical use in 2017. Early clinical reports indicated a complete response rate of greater than 80%,[13] and some patients who have had this treatment achieved sustained remission of more than three years.[14] Longer-term follow up is being undertaken to define more precisely the duration of response and to see whether patients can in fact be cured.

Clinical indications for CAR T-cell therapy are blood cancers, as its use for solid tumors is limited by factors such as the solid tumor microenvironments, which prevent CAR T-cells from reaching target cancer cells, antigen expression by both cancerous and normal cells, and variable expression of antigens within a specific patient, which may even be absent in many cells.[15]

Cost of CAR T-cell Therapy

Despite the dramatic results achieved with CAR-T, it has been criticized for its very high cost. Currently, each patient receives a customized treatment based on the tumor antigen expressed. Cost per treatment can range, depending on the country, from US$0.5 million to as high as US$1 million.

Allogenic, or off-the-shelf CAR, may be a less costly alternative. This involves using T-cells from healthy donors and using gene editing tools rather than a virus to alter the T-cell DNA to make the CAR-T cells.

Immune-Related Adverse Effects

Immune checkpoint inhibitor proteins play a vital role in prevention of autoimmunity. However, therapeutic blockade of inhibitory receptors can also break immune self-tolerance (the ability of an immune system to recognize self-produced antigens as a non-threat), which can lead to undesirable side effects. Treated patients can develop a wide range of autoimmune conditions affecting the gut, the skin, the pituitary and thyroid glands, the pancreas, the lungs, the liver, the joints, the kidneys, and the hematopoietic system.[16] Symptoms, fortunately, are often self-limiting, although certain skin conditions may take a while to resolve, and some patients with endocrine-related side effects may require long term hormone replacement.

With CAR T-cell therapy, following infusion of the modified T-cells, there can be release of large quantities of cytokines, the chemical messengers that orchestrate the immune response.[17] This cytokine release syndrome is associated with high temperatures and drops in blood pressure. Although these symptoms can be severe, they can be successfully managed with steroids and anti-inflammatories.

This syndrome can also cause an inflammatory cascade within the brain, causing severe confusion, seizures, and impaired speech. Varying degrees of immune effector cell-associated neurotoxicity syndrome, which is known to occur in the days and weeks following administration of immune effector cell and T cell engaging therapies, is common, but usually resolves within seven to ten days. Fatality is unusual and when it occurs is due to diffuse cerebral edema.

Current Research

An additional novel approach to cancer-focused immunotherapy is oncolytic virus therapy. Certain viruses are known to have the capacity to infect and destroy cancer cells. How it works: the virus infects or enters a cell and hijacks the cell's DNA to make copies of itself. Currently, a genetically modified version of the herpes simplex virus is the only one approved by the FDA to treat melanoma.[23]

After infection with an oncolytic virus, cancer antigens are released from the dying cancer cells, which then stimulate the immune system to attack and kill any remaining cancer cells nearby and potentially anywhere else within the body. The virus can be engineered so that it is less able to infect healthy cells.

According to the National Institutes of Health's Cancer.gov website, oncolytic viruses are currently being evaluated in clinical trials. Preliminary results are encouraging, but further research with randomized controlled clinical trials will be needed before any expansion in the use of this therapy comes about.

Impact on Insurance Products

These therapies, although relatively new, are already having impacts on our industry.

Advantages

- Delay in terminal illness (TI) claims due to improved life expectancy
- Reduction in TI claims if some advanced cancers are cured
- Life insurance can be underwritten for applicants with certain advanced cancers
- Reduced annual benefits for impaired annuity holders

Disadvantages

- Longer benefit periods for impaired annuities
- Health insurance costs may rise substantially due to the high cost of these treatments

Conclusion

Within the last decade, newly discovered approaches to using immunotherapies to fight cancers have dramatically changed outcomes of treatments for both solid tumors and certain blood cancers. In contrast to chemotherapy and biological therapies, both of which directly kill cancer cells by attacking vital cellular pathways involved in proliferation and growth, immunotherapy is directed at T-cells. Immune checkpoint inhibitors activate T-cells whereas CAR T-cell therapy modifies T-cells to improve their effectiveness as cancer fighters.

Some patients receiving immunotherapy treatments are achieving sustained and long-term remissions, which raises the possibility that it may now be possible to cure some highly lethal cancers. However, it is estimated that only about 12% of cancer patients will benefit from immunotherapy. Although it appears that biomarkers such as high TMB, dMMR/MSI-H, and expression of PD-L1 are associated with efficacy of immunotherapy, they are not consistently reliable across all cancers to be predictive. There is considerable interest, however, in continuing to conduct clinical trials to elucidate the place of immunotherapy in cancer treatment and the use of biomarkers for selection and monitoring of therapy.

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LONG COVID – THE LONG-TERM DISABILITY CLAIMS GAP

Abstract

On March 11, 2020 – just shy of three years ago – the World Health Organization (WHO) declared COVID-19, a multi-organ disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), to be a pandemic. As of January 3, 2023, COVID-19 has infected more than 662 million people worldwide and caused close to 6.7 million deaths.[1]

Fortunately, most infected by COVID-19 do recover. However, an increasing number of survivors are reporting persistent and lingering symptoms after an acute bout, a condition which has come to be known as long COVID.

From a disability insurance standpoint and based on numerous articles in the scientific literature and lay press, insurers might have expected a tsunami of long-term COVID disability claims after the expected six-month waiting period. Thus far, however, this has not been the case. Why, and what could be the possible reasons for this long COVID/long-term disability claims gap?

This article examines medicine's current understanding of long COVID, and some of the potential reasons for this gap.

What is Long COVID?

Long COVID is the most common name in the scientific literature and lay press for a condition in COVID-19 survivors consisting of related symptoms that persist long after the actual illness abates. The World Health Organization (WHO) has given it the name "post COVID-19 condition" and provides the following definitional language: "Post COVID-19 condition (PCC) occurs in individuals with a history of probable or confirmed SARS-CoV-2 infection, usually three months from the onset of COVID-19 symptoms, that last for at least two months and cannot be explained by an alternative diagnosis. Common symptoms include fatigue, shortness of breath, [and] cognitive dysfunction, but also other symptoms which 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."[2]

Long COVID is not a disease *per se*, but a multitude of symptoms that can impact three main health domains. The most common physical domain symptoms reported in long COVID are fatigue and shortness of breath. Common mental health domain symptoms reported are anxiety, depression, and post-traumatic stress disorder (PTSD), and in the cognitive domain, cognitive dysfunction (also referred to as brain fog) is also frequently reported.[3]

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Dr. John J. Lefebre, FRCPC, Vice President, Senior Technical Global Medical Director, is based at RGA International in Toronto, Canada. A member of RGA's Global Medical team, he is responsible for case consultation, product development, internal and external education, client support, and representing RGA to key industry professional organizations. He is a graduate of the University of Alberta, where he earned his Medical Doctor (M.D.) degree, and completed his postgraduate residency with a specialty in Emergency Medicine at the University of Toronto. He also has extensive clinical experience in teaching hospitals in Halifax and Toronto. Dr. Lefebre is a member of the Canadian Life Insurance Medical Officers Association.

There are several proposed etiologies for long COVID conditions, a topic beyond thescope of this article.

Risk Factors for Long COVID – Maybe Less Prevalent in an Insured Working Population?

Risk factors reported for long COVID across a number of studies include increasing age, female gender, overweight and obesity, pre-existing asthma, and overall poor pre-pandemic physical and mental health. The population subsets of healthcare and social workers also report high rates of long COVID, which may be largely explained by this cohort's non-work-related sociodemographic characteristics and their work-related higher risk of initial infection. Individuals sick enough to be hospitalized for COVID-19 infection are also at greater risk of developing long COVID.[4, 5]

Socioeconomic status, as measured by education levels and by the Index of Multiple Deprivation, a widely used geography-based measure of relative deprivation based on factors such as income, environment, employment, and education,[5] has shown inconsistent results about long COVID, with some studies demonstrating a higher risk of long COVID among those living in the most deprived areas.[5]

The inconsistent results may reflect the unmet need of people who live in socioeconomically deprived areas, given that both pre-existing adverse mental and physical health states are associated with greater risk of long COVID and that these conditions are more prevalent in those who are less advantaged.[5]

> **It is possible that the risk factors for serious COVID-19 infections … might be less prevalent in an insured working population.**

One could assume that an actively employed population may be insured, of a younger average age, and have fewer comorbidities, especially comorbidities which could result in significant physical impairment. As such, it is possible that the risk factors for serious COVID-19 infections, especially those requiring hospitalization, and for long COVID, might be less prevalent in an insured working population.

A Disease of the Young, but a Serious Disease Risk for the Old

In general, COVID-19 is today a disease of younger persons. That being said, infections with more serious complications resulting in hospitalizations and deaths tend to occur more frequently in older age groups. It would appear that the majority of the more serious COVID-19 infections are more likely to be confined to persons age 60 and older who are no longer part of the work force.

This trend of "a disease of the young but a serious disease risk for the old" can be seen by examining infection percentages by age, hospitalizations, and mortality rates for COVID-19 in Canada and the U.S.

Table 1: COVID-19 Infection percentages by age of total cases, Canada/U.S.[6, 7, 8]

Population ages	Canada	U.S.
0-29	9%	9%
30-59	27%	31%
60 and older	64%	56%

Note: These numbers have been rounded up or down in order to simplify viewing

Compare the dataset in Table 1 to that in Table 2, which shows hospitalization percentages by age for COVID-19. Hospitalization percentages can be a marker of the more severe infections that would increase the risk of developing long COVID.

Table 2: COVID -19 Hospitalization percentages by age group, Canada/U.S.[7, 9]

Population ages	Canada	U.S.
0-29	9%	9%
30-59	27%	31%
60 and older	64%	56%

The most significant COVID-19 infections would manifest as death. As can be seen in Table 3 of COVID-19 mortality rates in Canada and the U.S., this is primarily confined to older individuals.

Table 3: COVID-19 Mortality percentages of total COVID-19 deaths by age, Canada/U.S.[6, 7, 9]

Population ages	Canada	U.S.
0-29	0.4%	0.7%
30-59	7.0%	16.5%
60 and older	93%	83%

The data in Tables 1, 2, and 3 include the period prior to and after the development of COVID-19 vaccines up until July 2022 and incorporate both vaccinated and unvaccinated individuals. If vaccine uptake is assumed to be more likely in an insured population, less severe COVID-19 infections should be seen in this population and would imply decreased long COVID risk. Indeed, in a recent French study of 28,031,641 fully vaccinated individuals of ages 12 or older, lower hospitalization and mortality rates were found in the vaccinated population. Lower rates of long COVID might therefore be expected in a vaccinated insured population due to less severe infections.[10]

Other Long COVID Risk Factors – Less Likely in an Insured Working Population?

As shown in Tables 1-3, serious COVID-19 infection is a risk factor for long COVID. Age plays a major role in COVID-19's severity, but other risk factors also exist that might increase a patient's likelihood of developing long COVID. These other risk factors can be seen when reviewing the characteristics and outcomes of hospitalized COVID-19 survivors.

To date, there have not been a significant number of long-term total disability claims due to long COVID.

A study of 246 patients treated for COVID-19 in intensive care units (ICUs) who survived one year after their admission had the following characteristics: mean age 61.2 (SD 9.3); 71.5% male; and an elevated mean BMI of 28 with 25% having a BMI of >30. Only 33% had higher vocational or university educations, and 24% had one or more chronic diseases. In the follow-ups conducted one year after their ICU stay, ongoing long COVID symptoms were reported in three main domains: 74% (95% CI, 68.3% to 79.6%) reported ongoing physical issues; 26% (95% CI, 20.8% to 32.2%) reported mental health issues; and 16% (95% CI, 11.8% to 21.5%) reported cognitive issues. In addition, of the survivors who were employed before their ICU admissions, 58% reported ongoing symptoms were still impacting their ability to work one year later, and they were working fewer hours than prior to their hospitalization or were still on sick leave.[11]

These outcomes are probably a combination of post-ICU syndrome and long COVID in a population more likely to be male, older, experiencing pre-existing comorbidities, and were severely ill with COVID-19.

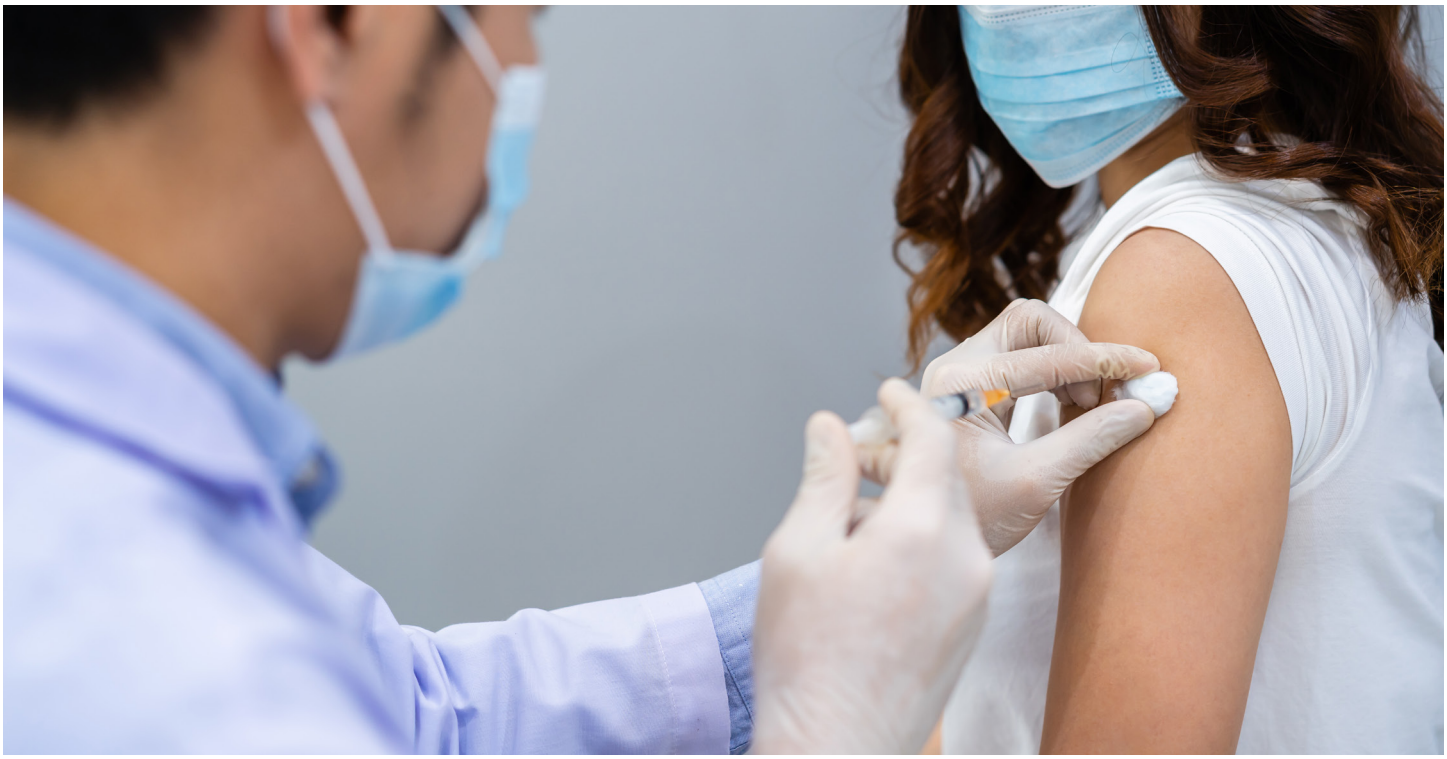
The findings are similar to those for COVID-19 patients who did not have ICU stays. A study of 47,780 patients admitted to hospital for COVID-19, of whom 43,035 (90%) were not ICU patients, found a mean age of 64.5 (SD 19.2) and 55% male. When compared to the general population, persons hospitalized with COVID-19 who were primarily not admitted to an ICU were, aside from more likely to be older than age 50 and male, also more likely to be living in an economically deprived area, a former smoker, and overweight or obese.[12]

The study also found that the incidence of comorbidities in people with COVID-19 was greater than that of a matched control population without COVID-19. This was shown by a higher prevalence of previous hospital admissions and the presence of the following pre-existing medical conditions: hypertension, major adverse cardiovascular events, respiratory disease, and diabetes. During a mean follow-up period of 140 days after hospital discharge, more than 29% of these patients were readmitted (14,060 of 47,780) and slightly more than 12% died (5,875). Readmission and death occurred at rates four and eight times greater, respectively, than those for the matched control group. These outcomes were also substantially

higher for persons hospitalized with COVID-19 when compared with matched controls, even after stratifying for those admitted to the ICU versus those who were not.[12]

As the above two studies consisted only of unvaccinated persons. it might be worthwhile to review these trends in a vaccinated population, as adoption of vaccines may be more likely in an insured population. The previously mentioned French study of 28,031,641 fully vaccinated individuals may provide useful information. Again, it consisted of persons ages 12 or older who were fully vaccinated and followed from the 14th day after complete vaccination for an average of 80 days. The fully vaccinated group of 5,345 persons were hospitalized (87 hospitalizations per 100,000 person-years) for COVID-19 and 996 in-hospital deaths were recorded (16 in-hospital deaths per 100,000 person-years). As seen in previous studies of unvaccinated persons, higher rates of hospitalizations and deaths were observed in fully vaccinated persons of older ages, male gender, and social deprivation. The median age of the entire cohort was 59, 79 for the hospitalized group, and 86 for those who died in the hospital. Again, there was a significant correlation between the presence of pre-existing comorbidities and risk of hospitalization and death from COVID-19: only 9.7% of hospitalized cases and 2% (24/996) of those who died in the hospital had no identified comorbidities. In addition, of the 47 chronic diseases examined in the study, most were positively associated with an increased risk of COVID-19-related hospitalization and a slight excess risk of death.

Based on this study, the more likely uptake of vaccines and boosters by an insured working population means that this group will be less likely to experience significant future COVID-19 infections, may return to work more quickly, and may be less at risk of developing long COVID.[10]



The outcomes of the hospitalized COVID-19 survivors cited above are not particularly surprising given the baseline characteristics and risk factors of persons admitted to the hospital and ICU with moderate or severe COVID-19 infection, especially when they are coupled with the biological insult and physiological stress of such an infection.

Vaccination Reduces Risk of Long COVID

The best way to prevent long COVID is to not contract COVID-19 in the first place. That being said, given that vaccination can to some extent prevent COVID-19, or at least can prevent an infection from becoming severe enough to warrant hospitalization, vaccination should reduce the risk of developing long COVID.

That being said: can vaccination actually reduce the risk of long COVID symptoms after breakthrough infections? The results vary, with studies indicating a reduction of long COVID due to vaccines from 15% to more than 60%.[13]

A study which followed 2,560 healthcare professionals with COVID-19 who did not require hospitalization found that a higher number of vaccine doses was associated with a lower prevalence of long COVID, defined by the study as one symptom with a duration of more than four weeks. Long COVID prevalence for this population was 41.8% (95% CI, 37.0% - 46.7%) in unvaccinated persons, 30.0% (95% CI, 6.7% - 65.2%) for those with one vaccine dose, 17.4% (95% CI, 7.8% - 31.4%) with two doses, and 16.0% (95% CI, 11.8% - 21.0%) with three doses. This study concluded that for COVID-19 infections not requiring hospitalization, two or three vaccine doses, compared with no vaccination, was associated lower long COVID prevalence.[14]

Conclusion

To date, there have not been a significant number of long-term total disability claims due to long COVID recorded in the insured population. While a significant number of claims had been anticipated, given the relatively large number of people who are reported to have demonstrated long COVID symptoms, it is possible that multiple factors in a younger, working-age population may have prevented a multitude of long-term total disability claims.

Time will tell if this pattern will continue to hold.

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CYSTIC FIBROSIS – HOPE FOR A BRIGHTER FUTURE

Abstract

Thirty years ago, applicants with a history of HIV or a cystic fibrosis (CF) diagnosis were uninsurable. Today, while many with HIV are offered life insurance, those diagnosed with CF are generally not. In the past few decades, groundbreaking advances have emerged in early diagnosis, treatment, and management of CF, and those with the condition are now living to age 60 and beyond.[1] Why, then, are life insurance companies not yet offering terms to those living with CF?

This article examines the improvement in CF life expectancy and survival, and why insurers might want to consider offering persons with CF limited term life cover. .

What is CF?

Cystic fibrosis (CF) is an autosomal recessive genetic disorder. Two carriers of a faulty cystic fibrosis transmembrane conductance regulator (CFTR) gene have a 25% chance of having a child with the disorder.[2] Research indicates that about one in 25 people carry a faulty CFTR gene.[3]

The CFTR gene produces the CFTR protein, which is responsible for producing sweat, mucus, saliva, tears, and some digestive enzymes. It also regulates the flow of water and chloride between intracellular and extracellular fluid. When the CFTR protein is not produced or produced in insufficient amounts, it results in the buildup of thick sticky mucus, which impairs the function of the sweat glands, lungs, pancreas, and digestive and reproductive systems.[1]

To date, more than 2,000 mutations have been identified in the CFTR gene, with F508del being the most common. Persons inheriting the same genetic mutation from each parent are said to be homozygous, but someone who inherits two different genetic mutations is said to be heterozygous.[4] Some mutations cause more severe forms of the disease than others.

CF disease is classified into seven different categories based on the patient's level of functional impairment.

- Class I to III: severe phenotype, i.e., little to no CFTR function
- Class IV to VII: less severe phenotype, i.e., residual CFTR function [5]

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Hilary Henly, FCII, is a Global Medical Researcher in RGA's Strategic Research unit. Based in Ireland, she is a Fellow of the Chartered Insurance Institute (FCII) and has more than 25 years of experience in underwriting, claims, and mortality and morbidity research.

Incidence and Prevalence

Approximately 90,000 people worldwide currently live with CF, 30,000 in the U.S. and 50,000 in Europe.[1, 6] Its prevalence is 7.97 and 7.37 per 100,000 population in the U.S. and in E.U. countries, respectively. About one in every 2,000 to 3,000 babies is diagnosed with CF, and incidence rates are around 1,000 new cases each year. Incidence varies significantly around the world, most likely due to genetic drift.[5, 7, 8]

Diagnosis

When CF is suspected in a newborn, a sweat test is carried out between the ages of 2 days and 4 weeks to analyze chloride concentration. Sweat chloride testing is now done in conjunction with newborn screening (NBS) tests, which are usually conducted during the first week of life. The test analyzes dried blood spots for immunoreactive trypsinogen, as elevated levels of this digestive enzyme are indicative of CF.[7, 9]

Sweat chloride concentrations of >60 mmol/L (millimoles per liter) are highly indicative of CF. Those infants with little or no CFTR function generally have very high sweat test results (>90 mmol/L) and are more likely to require pancreatic enzyme replacement therapy.[2, 7] If the result ranges from 30 to 59 mmol/L, the sweat test is usually repeated.

Surprisingly, most babies identified with CF are born to parents with no known family history of the disease.

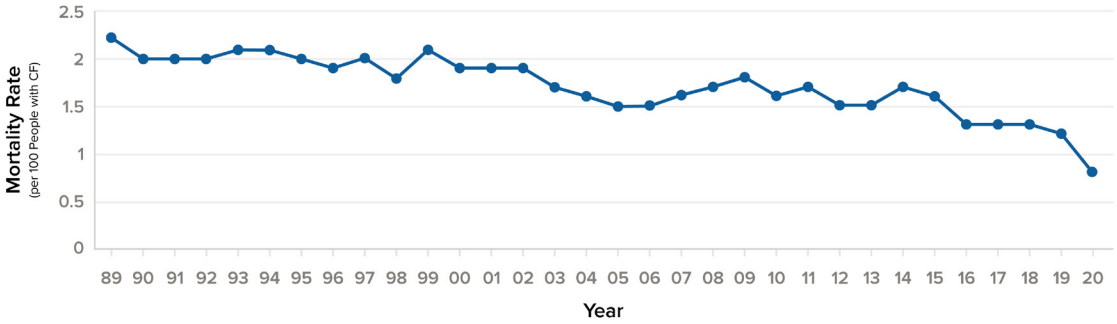
NBS tests can also identify heterozygote carriers of CF or babies with moderately raised sweat chloride levels. Referred to as Cystic Fibrosis Screen Positive, Inconclusive Diagnosis or Cystic Fibrosis Transmembrane Conductance Regulator-Related Metabolic Syndrome (CFSPID/CRMS), individuals with this symptom are at substantial risk of developing full CF, with studies showing that 10% to 44% of those initially identified as CFSPID/CRMS convert to CF.

Prenatal diagnostic testing can also be conducted, using fetal DNA isolated from chorionic villus sampling or from amniotic fluid cells. Ultrasound screening can also be used at 17 to 22 weeks of gestation to identify instances of fetal echogenic bowel. More recently, a CFTR test has been introduced that uses the cell-free fetal DNA (cffDNA) found in maternal blood to assess fetal CFTR variant status.[7]

Life Expectancy, Survival, Mortality

Prior to the 1950s, children with CF rarely lived past age 5. By the 1960s, average life expectancy had increased to age 15, and by the 1980s had risen to age 31.[10] More than half of the babies born in 2018 and half of people living with CF age 30 and older in 2018 will most likely live into their 50s. This compares with a median predicted survival age of approximately 30 years for those born between 1989 and 1993, a massive leap of 20 years.[1, 4] At the same time, annual mortality per 100 persons for CF patients in the U.S. decreased by 50% in just ten years, from 1.6% in 2010 to 0.8% in 2020.

Figure 4: U.S. annual mortality rate (per 100 people with CF), 1990-2020[4]



Source: Cystic Fibrosis Foundation Patient Registry.

U.K. data shows that for those with CF born today, predicted survival is 50.6 years, and that currently more than 145 people in the U.K. who are living with CF are older than age 60.[9] Predicted survival with CF at two, five, and 10 years in the U.K. has been calculated at 87.3%, 84.4%, and 80.5%, respectively.[6] This compares with a U.K. HIV survival rate in one 30-year national study of 85%, 77%, and 67% at two, five, and 10 years, respectively.[11]

A 2018 study by Keogh, et al. of 2011-2015 data from the U.K.'s CF registry showed a reduction in mortality rates in the country of about 2% each year, corresponding to a 10-year decrease of 21%. If this decreasing mortality trend continues, children in the U.K. today born with CF should live to age 65 for males and age 56 for females, corresponding to an increase in median survival age of 20 years for males and 15 for females.[12]

Treatment

Since the discovery of the CFTR gene in 1989, researchers have been working on developing targeted drug therapies to improve the function of abnormal CFTR proteins.[5] In 2014, about 7% of the CF population were eligible for CFTR drug modulator therapy but today, over 80% of patients with CF are eligible for this form of treatment.[4]

In 1993, the U.S. Food and Drug Administration (FDA) approved dornase alfa (Pulmozyme), the first drug modulator for CF, which has. significantly improved patient outcomes in the past 25 years.[8]

In 2012, ivacaftor (Kalydeco) was released. Trials showed that using ivacaftor, the average increase in percent predicted forced expiratory volume in one second (ppFEV1) in spirometry tests was approximately 10%, and that pulmonary exacerbations decreased by about 50%. The FDA then approved ivacaftor in combination with lumacaftor (Orkambi) in 2015, a combination therapy designed for F508del homozygous CF patients. Estimates show that this treatment could increase the median survival age by 6.1 years, but if treatment is started by age six, it could lead to an increase of 17.7 years. A second combination treatment, ivacaftor and tezacaftor (Symdeko), was approved in 2018.[5, 8]

In 2019, the FDA approved the combination treatment ivacaftor, tezacaftor and elexacaftor (Trikafta), and the European Medicines Agency (EMA) subsequently approved it in 2020. Trikafta is designed for use in patients ages six and older who have at least one copy of the F508del

mutation.[13] It has been shown to reduce CF exacerbations as well as everyday symptoms of disease, improve lung function (increased percent predicted forced expiratory volume in one second [ppFEV1]) by 14.3%, and decrease sweat chloride levels with less than six months of treatment.[8] However, approximately 10% of CF patients do not have the F508del mutation and are therefore ineligible to receive this treatment.[1]

Risk Considerations and Non-Pulmonary Complications

Insurers must consider many factors before CF cover can be a viable option. Respiratory conditions such as asthma, bronchiectasis, and chronic lung impairment caused by bacterial infection can play a significant role in CF mortality. An FEV1 of <30% remains a commonly used predictor of two-year survival for these patients.[14] Thanks to new drug therapies, significantly improved FEV1 percentages have been observed in CF patients across all birth cohorts in the U.S., with children ages six to nine in 2020 having a nearly 10% higher median FEV1 percent predicted compared to children ages six to nine who were born between 1991 and 1995. The proportion of people with CF aged 18 years who have an FEV1 >70% predicted more than doubled from 40.1% in 1990 to 87.4% in 2020, and the proportion with an FEV1 <40 percent predicted decreased from 23.6% in 1990 to 1.8% in 2020.[4]

Lung infections can irreversibly reduce lung function, leaving some CF patients needing life-saving lung transplants. Transplants are only considered for patients who are at high risk of death in the coming year, or where predicted survival is less than 30%.[15] The mortality rate for CF lung transplant recipients is nearly double that recorded for all lung transplant recipients, with a five-year survival rate of approximately 50% and a median survival of 6.4 years.[2]

As well as respiratory problems, CF patients commonly suffer from mental health complications such as anxiety and depression. U.S. data shows that 16.4% of CF patients have been diagnosed with anxiety disorder and 18% with depression.[4] Patients are also prone to gastrointestinal problems due to impaired digestion and malnutrition.[1] Approximately 37% of CF patients in the U.S. suffer from gastroesophageal reflux disease (GERD).[4] Other complications include bile duct and intestinal obstructions as well as CF-related diabetes.[2]

Bone density is also often affected in CF patients, with up to 50% of adults experiencing osteopenia. Fertility is yet another impact, with 90% of males with CF experience congenital bilateral absence of the vas deferens, preventing sperm conveyance. Women can also experience fertility challenges due to impaired CFTR function .[5]

Table 5: CF Complications in 2020, U.K. CF Registry[9]

Condition	Overall (N=9922) %	<16 years (N=3910)	> 16 years (N=6012)
Asthma	8.2	4.8	10.4
Raised liver enzymes	10.6	9.6	11.3
Liver disease	15.7	9.2	20.0
GERD*	21.3	6.8	30.7
DIOS**	4.9	2.3	6.5
Osteopenia	11.2	0.4	18.3
Depression	5.0	0.3	8.1

*GERD : Gastroesophageal reflux disease

** DIOS: Distal intestinal obstruction syndrome

As CF patients can now live into their sixth decade and beyond, there is an increased risk of age-related conditions, including bone and joint disease, colon cancer, renal insufficiency, sinus disease and cardiovascular disease. In addition, modulator drugs treatments are generating significant weight gain in younger CF patients, and as more are approved, obesity could become an issue.[5]

Conclusions

The introduction of modulator drugs has led to a substantial increase in the number of adults living with CF into their 40s and 50s. Notably, current survival estimates for CF do not account for ongoing improvements in patient treatment and care, so survival is likely to continue to improve, but may bring new challenges. As people with CF live longer, they will be more likely to experience the comorbidities of aging such as colon cancer, CF-related diabetes, and cardiovascular disease. Given the significant improvements in mortality rates for persons living with CF, there is future potential to offering short-term life insurance policies to some individuals living with CF.

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Longer Life Foundation

An RGA/Washington University Collaboration

The Longer Life Foundation (LLF), a collaboration between RGA and Washington University School of Medicine in St. Louis, is celebrating its 25th year of enhancing longevity and health through research. Please read on for the Foundation's latest news, and to learn more about LLF's activities and events, please visit www.longerlife.org or reach out to Dr. Daniel D. Zimmerman at dzimmerman@rgare.com or Dr. Preeti Dalawari at preeti.dalawari@rgare.com.

In 2023, the Longer Life Foundation will mark its 25th year supporting innovative early-stage research benefiting clinical and insurance medicine. Please click here to explore our newly refreshed and user-friendly website. We also have several activities and events planned for the year. Please read on for the most current information and click here to ask to subscribe to LLF's newsletter, which will also keep you up to date with the Foundation's plans and events.

LONGER LIFE FOUNDATION
CELEBRATING 25 YEARS
1998-2023

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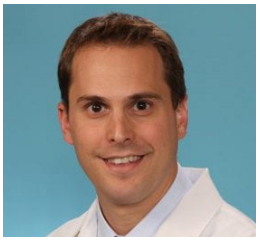

On December 8, 2022, LLF researcher Kory J. Lavine, M.D., Ph.D., presented at Internal Medicine Grand Rounds on "Precision Medicine for Inflammatory Heart Disease," at Washington University School of Medicine in St. Louis. Please click here to view Dr. Lavine's presentation. LLF will be sponsoring two more Grand Rounds in 2023 and we will send out information about presenters and how to access as they are scheduled.

MARK YOUR CALENDARS

The Midwestern Medical Directors Association, a well-known regional industry group for insurance medical directors, will be holding its 2023 annual meeting on May 11 and 12. RGA will be hosting the meeting at its global headquarters in Chesterfield, Missouri. Three alumni LLF investigators – Anjua Java, M.D., Kory J. Lavine, M.D., Ph.D., and Bettina Mittendorfer, Ph.D., will be speaking on relevant topics and presenting their research. Please click here to register.

Midwestern Medical Directors Association
Founded 1954
The Promotion of Medical Knowledge in Insurance

LOOK TO LINKEDIN

Due to Twitter's current challenges, we are pausing LLF's Twitter feed until further notice. You can continue to access LLF's posts on our growing LinkedIn channel. Please click here to follow LLF on LinkedIn.

MEDICAL TEAM UPDATE

RGA is pleased to announce **Dr. Adela Osman**, Chief Medical Research Officer for RGA South Africa, has been promoted to the role of Head of Global Medical. **Dr. Daniel D. Zimmerman**, current Head of Global Medical, has been promoted to the newly created role of Chief Science Advisor. Both will remain editors of *ReFlections*.

RGA THOUGHT LEADERSHIP PUBLICATIONS

RGA's thought leaders publish content on many topics of interest to insurers. Here are links to some articles and white papers published recently on the RGA Knowledge Center.

Predicting – and Preventing – Blood Cancer? An Essential Conversation

Dr. Daniel D. Zimmerman
Chief Science Advisor
RGA

Grant Challen, Ph.D.
Associate Professor, Department of Medicine
Oncology Division and Stem Cell Biology
Washington University School of Medicine
in St. Louis

COVID-19 Pandemic's Impact on Suicide Rates and Risk Factors

Scott Rushing FSA, MAAA
Vice President and Actuary
Head of Risk and Behavioral Science
Global Data and Analytics
RGA

Erin Crump
Vice President
Business Initiatives
RGA International

Nanomedicine – Advances in Medical Technology

Hilary Henly, FCII
Global Medical Researcher
Global Research
RGA

A New Era of Infectious Diseases – What We Should Know About What We Don't Know

Hilary Henly, FCII
Global Medical Researcher
Global Research
RGA

COVID-19 Mortality Surged Among the Young in Third Quarter 2022

Jason McKinley
Actuary, Risk and Behavioral Science
Global Data and Analytics
RGA

Scott Rushing FSA, MAAA
Vice President and Actuary
Head of Risk and Behavioral Science
Global Data and Analytics
RGA

Claims Considerations for Pain Disorders: Common Challenges and Potential Solutions

Belinda Thorpe
Head of Claims
Africa and Middle East
RGA South Africa

Linda Hiemstra
Occupational Therapist
Back2Work
South Africa

Can Polio Be Eradicated?

Dr. Heather M. Lund, MBBCh
Regional Chief Medical Officer
RGA Asia

Innovative Research to Explore the Impact of Lifestyle Factors on Mortality and Morbidity

Kishan Bakrania
Senior Health Data Scientist
Global Data and Analytics
RGA

Kevin Somerville
Medical Director Global Data and Underwriting Research and Manual Development – CWR
Global Research and Data Analytics
RGA

Richard Russell
Lead Health Data Scientist Global
Global Data and Analytics
RGA

Professor Thomas Yates
Professor of Physical Activity
Sedentary Behaviour and Health
University of Leicester

More Than Skin Deep: A Global Overview

Hilary Henly, FCII
Global Medical Researcher
Global Research
RGA

MIcrobiomics: How the Microbiome is Making a Macro Impact

Hilary Henly, FCII
Global Medical Researcher
Global Research
RGA

Platelet-Rich Plasma: A Closer Look (Global Health Brief)

Dr. Avinash Samudre
Health Claims Specialist
RGA Middle East

ReCite

Interesting and relevant articles to the field of insurance medicine recently appearing in the literature...

Long-term Neurologic Outcomes of COVID-19

Xu E, et al. Nature Medicine. 2022 Sept 22.
https://www.nature.com/articles/s41591-022-02001-z

This study, involving 154,068 people who had COVID-19, 5,638,795 contemporary controls and 5,859,621 historical controls, showed that beyond the first 30 days of infection, people with COVID-19 are at increased risk of an array of neurologic disorders. The disorders span several disease categories, including stroke (both ischemic and hemorrhagic), cognition and memory disorders, peripheral nervous system disorders, episodic disorders, extrapyramidal and movement disorders, mental health disorders, musculoskeletal disorders, sensory disorders, and others, including Guillain–Barré syndrome (GBS) and encephalitis/encephalopathy.

The analyses, by age as a continuous variable, revealed that the risks and burdens of the prespecified neurologic outcomes were evident even among those who were not hospitalized during the acute phase of COVID-19 and increased according to the severity of the acute infection from non-hospitalized to hospitalized to those admitted to intensive care. The effect of COVID-19 on risk of memory and cognitive disorders, sensory disorders, and GBS is stronger in younger adults, whereas effects on mental health disorders, musculoskeletal disorders, and episodic disorders are stronger in older adults.

Editor's Note: *The long-term consequences of SARS-CoV-2 infection should be considered in future risk assessment and in developing exit strategies for a post-pandemic era.*

The Coronavirus Disease 2019 Pandemic is Associated With a Substantial Rise in Frequency and Severity of Presentation of Youth-Onset Type 2 Diabetes

Magge SN, et al. The Journal of Pediatrics. 2022 Aug 17
https://www.jpeds.com/article/S0022-3476(22)00719-3/fulltext

A recent study from the Centers for Disease Control and Prevention (CDC) found higher incidence of diabetes in youth ages ≤21 following coronavirus disease 2019 (COVID-19) infection but did not differentiate diabetes type. This study aimed to compare the total number of new cases of youth-onset type 2 diabetes with youth who presented with metabolic decompensation (DKA) and/or hyperosmolar hyperglycemic syndrome (HHS) from March 2020 to February 2021 to levels seen in the prior two years.

The study found that the average number of new diagnoses per year in the two pre-pandemic years (PPY) was 825, compared with 1,463 diagnosed during the first pandemic year, an increase of 77.3%. A concerning finding was that BMI and blood glucose were statistically greater on presentation in the pandemic year measured, and that patients presented with higher HbA1c (median 10.4% vs 9.3% [PPY1] and 9.7% [PPY2], $P < .001$).

Further, 21% of youth presented with metabolic DKA and/or HHS at type 2 diabetes diagnosis during the first year of the pandemic, compared with 9.4% in PPY1 and 9.0% in PPY2. Potential explanations include weight gain due to inactivity, increased psychosocial stress, and the possibility that the COVID-19 may have caused a nonautoimmune destruction of β cells.

Editor's Note: *These findings may have sizable future implications for underwriting and claims, especially if we consider other studies which show rapid β-cell failure and early onset of complications in this group.*

New Evidence that Air Pollution Contributes Substantially to Lung Cancer

Gourd E. The Lancet Oncology. 2022 Oct 1; 23(10): E448
https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(22)00569-1/fulltext

Although smoking remains the biggest risk factor for lung cancer worldwide, an estimated 6,000 people who have never smoked die from lung cancer every year in the U.K., and approximately one in every ten cases of the disease is attributed not to smoking but to air pollution.

Researchers funded by Cancer Research UK, the world's largest independent cancer research organization, studied data from 400,000 people in the U.K. and Asian countries to investigate the association between lung cancer with a mutation in the EGFR gene —a mutation commonly found in people who have never smoked—and atmospheric concentrations of particulate matter less than 2.5 micrometers in diameter ($PM_{2.5}$). The results showed a positive correlation, with higher rates of EGFR-mutation lung cancer and other types of cancer found in areas with higher $PM_{2.5}$ concentrations.

Lung cancer is also not the only cancer implicated in these findings. The analysis showed that growing air pollution levels also increases the risk of mouth and throat cancers. These cancers occur when pollution triggers an alarm response in the upper respiratory tract, causing the inflammation and activation of dormant cells carrying cancer-causing mutations.

The mechanism of cancer identified in this study could ultimately help researchers find better ways to prevent and treat lung cancer in never-smokers and reduce the risk of lung cancer overall.

Editor's Note: *This discovery is of global importance because 99% of the world's population currently live in areas that exceed the World Health Organization's annual limits for $PM_{2.5}$. Not only does this impact the way we understand and assess cancer risk, but it emphasizes that reducing air pollution is paramount to safeguard public health. .*

Association of Ultra-Processed Food Consumption With Colorectal Cancer Risk Among Men and Women: Results From Three Prospective U.S. Cohort Studies

Wang L, et al. BMJ. 2022 August 31
https://www.bmj.com/content/378/bmj-2021-068921

A new study links men who consumed high rates of ultra-processed foods to a 29% higher risk for developing colorectal cancer than men who consumed much smaller amounts. However, the same association was not found for women.

The study analyzed responses from more than 200,000 participants (159,907 women and 46,341 men) across three large prospective studies conducted over more than 25 years which assessed dietary intake. Each participant was provided with a food frequency questionnaire every four years and asked about the frequency of consumption of roughly 130 foods. Participants' intake of ultra-processed foods was then classified into quintiles, ranging in value from the lowest consumption to the highest. Those in the highest quintile were identified as being the most at risk for developing colorectal cancer.

Although ultra-processed foods are often associated with poor diet quality, additional factors might impact the risk of developing colorectal cancer. The potential role of food additives in altering gut microbiota, promoting inflammation, and contaminants formed during food processing or migrated from food packaging may all promote cancer development.

Editor's Note: *It will be important to continue to study the link between cancer and diet, as well as potential interventions to improve outcomes, as this has repercussions for risk assessment and wellness program incentives.*

RECENT WEBCASTS

RGA's most recent webcasts, available for viewing at your convenience, focus on topics of interest to underwriters, claims managers, and insurance medical directors.

New Approaches to Old Problems: Bringing Technology to Treatment in Psychiatry (23:15)

Dr. Newman Harris
Consultant Psychiatrist and Chief Medical Officer
RGA Australia

In recent years, the traditional approaches to treating mental illness, from talk therapies to medication-based treatments, has been augmented by novel technology-based approaches. In this webcast, Dr. Harris discusses the efficacy of many of these novel approaches.
https://www.rgare.com/knowledge-center/media/videos/new-approaches-to-old-problems-bringing-technology-to-treatment-in-psychiatry

Global Perspectives on Suicide: Data, Risk, and Prevention (52:07)

Dennis Barnes, Jr.
Chief Executive Officer, RGAX
Chief Marketing Officer
RGA

Erin Crump
Vice President, Business Initiatives
RGA International

Scott Rushing, FSA, MAAA
Vice President and Actuary
Head of Risk and
Behavioral Science
Global Data and Analytics
RGA

John MacBeth
Chief Executive Officer
TryCycle Data Systems
Ottawa, Canada

Suicide is one of the leading causes of death worldwide. Understanding the metrics surrounding current trends is vital for insurers and reinsurers today. RGA's Dennis Barnes, Jr., moderated this lively panel discussion on trends and analyses currently being explored. A bonus, from TryCycle's John MacBeth, is information about his company's suicide prevention work among indigenous youth in Canada.
https://www.rgare.com/knowledge-center/media/videos/global-perspectives-on-suicide-data-risk-and-prevention

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Dr. Daniel D. Zimmerman
Senior Vice President
Chief Science Advisor
RGA

Can this client be insured, or his/her claim be covered? Case-based teaching is one of the best ways to get a sense of how best to handle challenging cases. Dr. Zimmerman presents here a group of challenging cases from countries around the world.
https://www.rgare.com/knowledge-center/media/videos/a-journey-around-the-world---part-ii-compelling-and-challenging-cases-from-across-the-globe

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