ReFlections

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IN THIS ISSUE

FROM THE EDITORS

Welcome to the September 2022 issue of *ReFlections!* As we transition to new and emerging stages of the pandemic, we continue to wish everyone well.

As always, this issue's articles cover several timely topics. Toronto-based medical underwriting consultant **Dr. James Kim**, DAAPM, CAPM, CFACI, has written, in his first article for *ReFlections*, a thought-provoking piece on the new understanding of pain physiology and evolving treatment frameworks. Interest in mental health continues to increase significantly, and **Erin Crump**, Vice President, Business Initiatives, another first-time *ReFlections* author, shares her expertise on mental health issues impacting insurers today. Finally, **Dr. Paul Davis,** MBBS, FRACP, Chief Medical Officer, RGA Australia, and frequent *ReFlections* contributor, offers an in-depth review of colon polyps and colorectal cancers, the third most common cancer-related mortality worldwide.

The Longer Life Foundation, RGA's research collaboration with Washington University School of Medicine in St. Louis, is pleased to announce its latest grant recipients. The seven 2022-2023 grantees – three renewals and four new investigators – represent an excellent portfolio of innovative and relevant research that will benefit both clinical and insurance medicine.

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

Dan and Adela

Daniel Zimmerman Adela Osman

GLIAL CELLS AND TREATMENT OF CHRONIC PAIN

Abstract

In the May 2022 issue of ReFlections*, Dr. Newman Harris laid out an elegant and compelling discussion on the current state of research into the role of glial cells in persistent pain. The traditional treatment model for chronic pain has been mechanistic: identify the generative mechanism and direct a specific corrective treatment modality, which should restore function and alleviate symptoms. In reality, this model is only effective for certain conditions.*

How neuroinflammation manifests during pain states – specifically, the impact of peripheral and central sensitization in chronic pain conditions – is a key factor that demonstrates the need for an approach to pain treatment that focuses less on specific mechanistic aspects of pain's generators and more on the overall health of the person experiencing the pain. Dr. Harris also wrote that "persistent pain should be considered a disease or condition in its own right." As such, treatment for an individual's chronic pain must holistically address the totality – the biological as well as the psychological and social factors.

Introduction

Chronic pain is a major societal burden that not only impacts individuals but also carries a significant socioeconomic toll. The prevalence of this condition across jurisdictions is approximately 20%. Chronic pain affects quality of life in many ways: through symptoms, functional limitations, social isolation, absenteeism, and possible disability.

The biopsychosocial model of illness – one that incorporates a condition's associated physical, mental, and environmental aspects – is today the predominant and heuristic approach to managing chronic pain. However, this model is often overlooked by pain medicine practitioners, who frequently treat pain only with biological means: medications, injections, invasive procedures, and surgeries that target the mechanisms suspected of causing the specific pain on neurological, physiological, or anatomical levels. The subtleties of how pain is expressed can frequently be lost to the expected outcome of applying precision-targeted medical treatments when what is truly sought by patients is relief of suffering, of which pain is but one component.

The biopsychosocial model of chronic pain is usually depicted as the Venn diagram in Figure 1. (next page)

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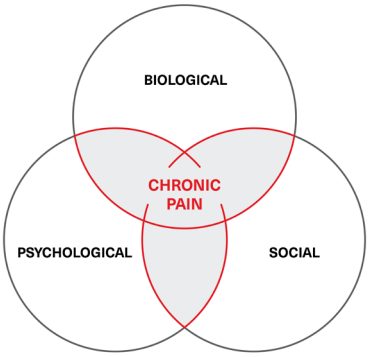
He is an Assistant Professor in the Department of Family Medicine at Queen's University, is on the staff of Humber River Hospital, and is a scientific board member for clinical trial reviews with Advarra IRB. He also performs independent medical examinations for third parties looking specifically at chronic pain presentations and case management. Dr. Kim has been a consultant to the Workplace Safety and Insurance Board in Canada for medical disability management.

Dr. Kim presents frequently on chronic pain and mental health. He has been active in continuing medical education for the insurance industry and the medical community. He received his MBA from the University of Toronto's Rotman School of Management.

Figure 1: Chronic pain biopsychosocial model



Medicine generally renders the treatment of human ailments as scientific endeavors, and for the most part this approach has worked. Experimentation, research, and clinical trials have usually been able to tease out many of the intricacies of human pathophysiology, enabling the development of effective treatments for many diseases. Relevant to the focus of this article, research has also shown the role glial cells play in basic aspects of chronic pain. Where the scientific method has faltered, however, has been in addressing non-biological expressions of pain and illness.

What should be clear from the biopsychosocial model (Figure 1) is that mental health plays a crucial role in the evolution and course of chronic pain states. Its impacts are demonstrated by the frequent concurrence of depression and anxiety with chronic pain. Depending on the data source, 70% to 85% of chronic pain sufferers may also have significant mental conditions; most often, depression. In addition, between 15% and 100% (mean 65%)[19] of those diagnosed with depression may also exhibit significant pain symptoms. These numbers demonstrate a compelling etiological commonality, and glial cells may play a role.

Glial Cells and Mental Health

There is no arguing that exposure to trauma, whether physical or mental, can impact an individual. Physical trauma can engender aberrant physiological processes that may lead to chronic pain, and exposure to psychological stressors can also trigger responses that may lead to pathological mental states such as depression and post-traumatic stress disorder (PTSD). The similarities between these two constructs are reflected in individual outcomes: not everyone who experiences trauma or stressors develops chronic pain and/or psychiatric morbidity. The underlying mechanism for triggering chronicity in both pain symptomatology and pathological mental states may lie with the neuroinflammatory role of glial cells.

Research has determined that oligodendrocytes, the cells that make the protective myelin sheaths that surround neurons and preserve nerve conductivity, are demonstrably fewer in number and generate irregular myelin coverage in brain tissues of mice that displayed social withdrawal after exposure to aggressive stressors. Mice that did not develop social withdrawal behavior and continued to interact normally showed healthy myelin and relatively abundant oligodendrocytes.[1, 2, 3, 4]

Research has also demonstrated that symptoms of depression can enhance inflammatory responses. This effect can specifically be seen in the production of interleukin-6 (IL-6), a proinflammatory cytokine.[5] As acute stress can result in measurable transient increases in systemic inflammation, a chronic depressive state can also sensitize an inflammatory stress response. In chronic pain, the process of central and peripheral sensitization propagated by neuroinflammatory glial cell activity also implicates IL-6 as a key regulatory mechanism. Thus, both chronic pain and depression (and most likely other impaired mental health states) are mirrored and accentuated through symptom magnification and physiological augmentation by a common inflammatory pathway.

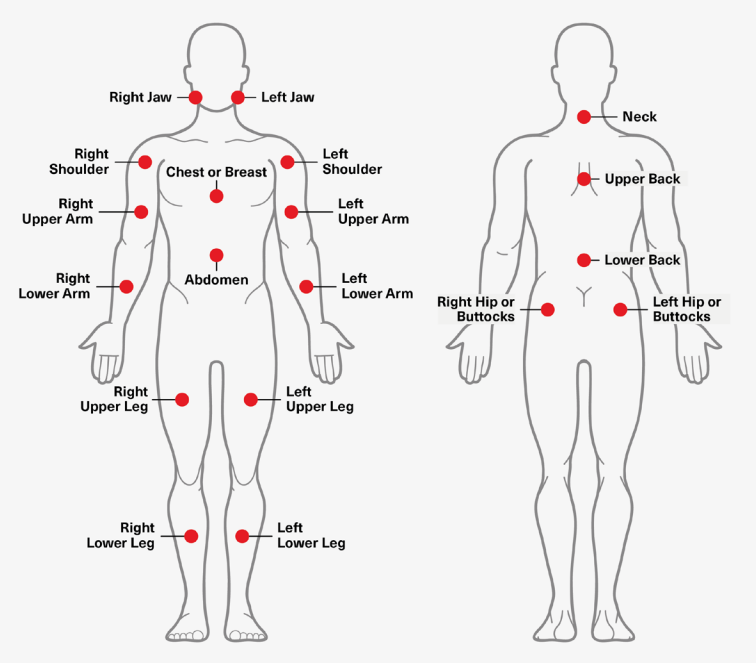
Case Study: Fibromyalgia

Fibromyalgia is one of the most difficult and frustrating chronic pain conditions to assess and treat. It is considered a "functional pain syndrome," in that it presents as pain with no obvious organic origin.[20] Because of this, fibromyalgia can be an effective model for demonstrating the biopsychosocial paradigm set forth in Figure 1.

A fibromyalgia diagnosis is one of exclusion, meaning it is arrived at in the absence of specific objective findings. Fibromyalgia is a condition which manifests with a variety of nonspecific symptoms, ranging from widespread musculoskeletal pain and fatigue to cognitive impairment, non-restorative sleep, and mood dysfunction. Given this broad constellation of potential symptoms, fibromyalgia can result in significant impairment for affected individuals. It is also a condition that arguably manifests in both a physical and mental context. It should additionally be noted that a diagnosis of fibromyalgia does not rule out the concurrent presence of other illnesses.

The currently used diagnostic framework for fibromyalgia, first developed in 2010 and revised in 2016, consists of the sum of two scores: the Widespread Pain Index (WPI) and the Symptom Severity Score (SSS). Developed by the American College of Rheumatology, the WPI scores fibromyalgia-related pain by assessing pain during the prior week in 19 specific places on the body. That assessment is to be done while taking current medicines and treatments and exempting symptoms from known diseases such as arthritis, lupus, and Sjogren's syndrome. The numerical score, which consists of the total number of places where pain was experienced, is the WPI.[21]

Figure 2: Calculating the WPI



Adapted from: *http://www.jlgh.org/Past-Issues/Volume-14-Issue-4/Ton-That_Fibromyalgia.aspx*[24]

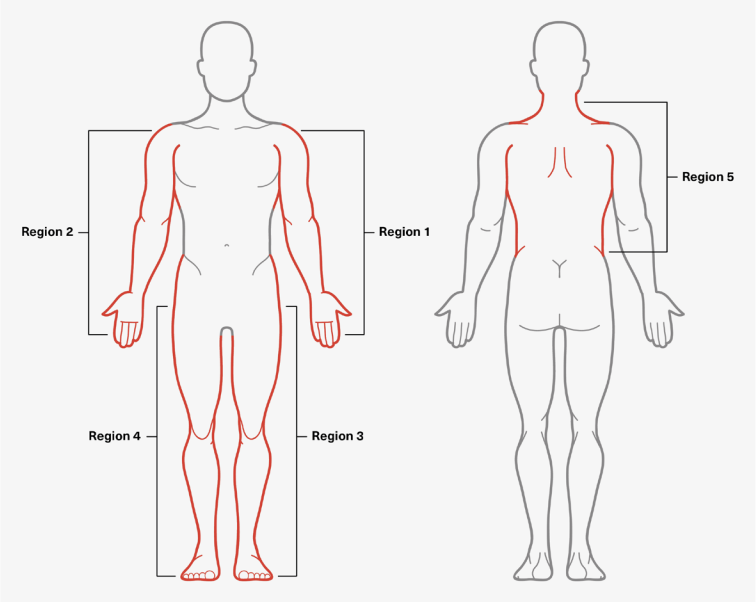
The SSS is a two-part calculation. In the first part, the patient assesses the severity of three categories of fibromyalgia symptoms: fatigue, waking unrefreshed, and cognitive symptoms (e.g., forgetfulness, concentration difficulties, mental slowness, language-related problems, reduced planning/organizational abilities). In the second, patients indicate which of a checklist of 41 non-fibromyalgia-related conditions and symptoms they are currently experiencing. The number of "yes" answers are then matched to a scoring range from 0 to 3.[21]

The totals of the WPI and SSS, once added together, yield an overall score that is today the accepted clinical tool for diagnosing fibromyalgia. However, each score's weight ultimately affects the final numerical score. A patient meets the diagnostic criteria for fibromyalgia if the following conditions are met:

- The WPI score (Part 1) is ≥7 AND the SSS (2a + 2b) is ≥5; OR the WPI score is from 4 to 6 AND the SSS is ≥9[22, 23]
- Generalized pain is present in four of the five regions depicted in Figure 3
- Symptoms and conditions have been present at a similar level for at least three months
- There is no other disorder present that would otherwise explain the pain

For example, if a patient's WPI score was 9 and SSS was 6, he or she would meet the diagnostic criteria. However: If the WPI was 5 and the SSS was 7, the patient would not.

Figure 3: Assessing Generalized Pain Regions



Adapted from: *http://www.jlgh.org/Past-Issues/Volume-14-Issue-4/Ton-That_Fibromyalgia.aspx*[24]

Etiological Mechanisms

Although the symptomatology of fibromyalgia has become much clearer over the years, its underlying pathophysiology is still not well understood. Currently, central sensitization of the nervous system is a widely accepted foundation for fibromyalgia's clinical presentation. Other identifying mechanisms include aberrant activity of the Diffuse Noxious Inhibitory Controls (DNIC), which is the ascending spinal pathway for pain sensation. Common to both central sensitization and DNIC malfunction is the link of neuronal activity, which would necessarily implicate glial cells and their activation as a component of the induction and perpetuation of chronic pain.

Recent research using positron emission tomography (PET) scan imaging studies has demonstrated that glial activation is present in fibromyalgia patients.[6] This finding is consistent with the association of fibromyalgia syndrome as a neuroinflammatory event. Translational

research is also implicating tumor necrosis factor alpha (TNF-α), which is generated by the microglia, as a key pathological factor in fibromyalgia.[7] The research further underlines the concurrence of mental health manifestations arising from the same neuroinflammatory process. Herein lies the inextricable connection within fibromyalgia of the duality of medical states affecting the individual. It is not unreasonable to extrapolate this occurrence to other chronic pain conditions.

Treatments

Treatment of fibromyalgia in an ideal setting is holistic, encompassing multiple medical therapy modalities and psychological interventions. Several classes of medications are currently used which now, in the context of research findings, can be rationalized by their mechanisms of actions on glial cell function.

- Antidepressant medications such as the serotonin-norepinephrine reuptake inhibitors (SNRIs) duloxetine and milnacipran, while acting primarily on neurotransmitter function, may also modulate glial function.[6] Older tricyclic antidepressants such as nortriptyline and amitriptyline may also have a modulating effect. Using antidepressants to simultaneously treat chronic pain and depression targets the etiological mechanism common to both.
- Anticonvulsants such as pregabalin and gabapentin dial back neuronal excitability, thereby modulating central sensitization and inhibitory controls (DNIC). Pregabalin has been shown in animal studies to demonstrate neuroprotective action and decrease proliferation of astrocytes in spinal cord damage.[8] Animal studies on multiple sclerosis also show that pregabalin enhances myelin repair and dampens glial cell activation.[9] It may thus be no coincidence that pregabalin is often used to augment antidepressant therapy.
- The use of an opioid antagonist in fibromyalgia is based on the assumption that its actions inhibit glial activation, thereby mitigating the neuroinflammatory process. Low-dose naltrexone can be custom-compounded into capsules to provide a dose far lower than the usual therapeutic dose. Typically, the action of naltrexone is to block opioid effects by competitive binding to the receptor and impacts the endogenous opioid effect, a mechanism postulated to be behind its efficacy in the treatment of alcohol use disorder.

In addition to medical therapy, psychological therapy modalities have also been validated for fibromyalgia relief in numerous therapeutic trials. Cognitive behavioral therapy (CBT), the most often used approach, has been found to be at least as effective as medical therapy. The foundation of CBT is that thoughts, feelings, emotions, and physical sensations are interconnected, and the persistence of negative feelings and thoughts may cause an individual to manifest aberrant behavior as well as engender physical symptoms such as pain. CBT is a short-term, problem-focused approach to dealing with an individual's internal cognitive-emotive processes and external stimuli. Along the same lines, mindfulness-based meditation and acceptance-commitment therapy (ACT) can also engage an individual's cognitive landscape as a means to ease physical sensations of pain.

Ultimately, what is clear is that strictly medical approaches cannot hope to deal with the effects of external factors that push and pull an individual through reflex actions, patterned behavior, and maladaptive responses, ultimately affecting clinical outcomes.

Conclusion

Will targeting glial cells successfully treat chronic pain and mental health conditions? In this review, two aspects of the biopsychosocial model and the common link of glial cell activity were discussed in an effort to address this question. Fibromyalgia is an example of a condition which demonstrates that despite finding specific pathophysiological mechanisms for treatment, the whole-person approach, addressing both medical and psychosocial factors, may ultimately enable a patient to overcome many of the physical manifestations of this illness.

Targeting glial cell function in chronic pain states may well refine a more encompassing treatment modality, but the multiple impacts of sociocultural influences on the other two domains of the biopsychosocial model cannot be easily measured in objective terms, nor can they be readily treated with medical therapy.

As for the assertion that chronic pain should be considered a disease in its own right, arguments will likely be raised regarding whether to classify pain as a primary or secondary manifestation of an illness within the context of pathophysiological mechanisms. Arguments might also be made that pain cannot beget pain, and thus the criterion for classifying pain as a disease may be lost to circular reasoning.[10] Clinicians will argue otherwise, but this debate is for another time and place.

When the mechanisms and complex etiologies of chronic and persistent pain states become more fully understood, underwriters, claims assessors, and insurance medical directors will be better positioned to assess risk, manage claims, and even potentially provide products or interventions to contribute to the restoration of health for those who experience chronic pain. ReF

References

1. https://elifesciences.org/articles/40855
2. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4679853/
3. https://www.hindawi.com/journals/cpn/2010/780645/
4. https://www.nature.com/articles/s41380-020-00930-0
5. https://doi.org/10.1016/j.bbi.2012.05.006
6. https://www.sciencedirect.com/science/article/pii/S0889159118302423
7. https://www.nature.com/articles/s41598-017-11506-4#citeas
8. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3051089/
9. https://pubmed.ncbi.nlm.nih.gov/28049030/
10. https://academic.oup.com/painmedicine/article/14/9/1284/1877623
11. https://journals.lww.com/pain/Fulltext/2019/03000/The_impact_of_anxiety_on chronicmusculoskeletal.13.aspx
12. https://www.tandfonline.com/doi/full/10.1080/00325481.2019.1574403
13. https://www.dovepress.com/pain-as-a-disease-an-overview-peer-reviewed-fulltext-article-JPR
14. https://doi.org/10.1155/2017/9724371
15. https://doi.org/10.1007/s11926-002-0038-5
16. https://oxfordmedicine.com/view/10.1093/med/9780190248253.001.0001/med-9780190248253-chapter-3
17. https://pubmed.ncbi.nlm.nih.gov/30586067/
18. https://jneuroinflammation.biomedcentral.com/articles/10.1186/s12974-016-0607-6#:~:text=Interleukin%2D6%20is%20an%20inflammatory,the%20development%20of%20pathological%20pain.
19. https://www.practicalpainmanagement.com/pain/other/co-morbidities/association-between-depressive-disorder-chronic-pain
20. https://academic.oup.com/bjaed article/16/10/334/2288619
21. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7230253/
22. https://southwest.devonformularyguidance.nhs.uk/documents/Referral-documents/fibromyalgia-criteria-\table.pdf
23. https://www.sciencedirect.com/science/article/abs/pii/S0049017216302086
24. http://www.jlgh.org/Past-Issues/Volume-14-Issue-4/Ton-That_Fibromyalgia.aspx

THE CONNECTION BETWEEN PHYSICAL AND MENTAL HEALTH: AN OVERVIEW

Abstract

Much has already been written about COVID-19's impact on our mental health. The World Health Organization (WHO) reported that in the first year of the pandemic, global prevalence of anxiety and depression increased by an estimated 25%, with the greatest impact among women, younger adults (ages 20-24), and people living in low- and middle-income countries.[1]

WHO also reported that the pandemic increased Global Burden of Disease (GBD) levels associated with mental health conditions, as measured by Disability-Adjusted Life Years (DALY). Mental health conditions are also estimated to account for approximately one-third of all Years Lived with Disability,[2] *a metric that is likely low due in part to the human bias of generally attributing illness to a physical condition when one is present.*

To fully understand how mental health conditions may drive GBD increases, we must understand the many linkages between human physical and mental health. While mental health is still a relatively young area of medical research, the more we learn, the more we understand that physical and mental health are fundamentally linked. Mental illness is not a diagnosis that stands alone, but rather is a foundational component of overall health, as it impacts physical, behavioral, and social well-being.

Many Clear Connection Points

- **Mental health disorders increase the risk for chronic physical health conditions.**
  People with serious mental illness are at greater risk of developing a variety of chronic health ailments, such as diabetes, heart disease, and respiratory conditions.[3] These conditions have the potential to impact nearly every system in the body. Population-based studies show that depression alone is an independent risk factor for stroke and for the development of type 2 diabetes and heart disease.[3, 4] Mental illness also increases the likelihood of developing a broad range of respiratory conditions such as chronic obstructive pulmonary disease (COPD), chronic bronchitis, and asthma.[3]
- **Conversely, many physical health conditions may increase the risk for mental health disorders.**
  People living with chronic conditions such as diabetes or heart disease have been shown to experience mood-specific mental health disorders such as anxiety and depression at a rate three times higher than that of the general population.[5] For individuals with fibromyalgia and chronic fatigue syndrome the prevalence is even higher, impacting more than a quarter of the population with those conditions.[5]

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Erin Crump is Vice President, Business Initiatives, and a member of RGA's Global Product Initiatives Team. A Toronto, Canada-based group and health insurance professional with almost 20 years of experience, her primary focus is on leveraging RGA's global group insurance expertise to anticipate and meet client needs and to grow the global group reinsurance business. She is based in Toronto.

Her background includes experience in pricing, underwriting, product development, human resources, marketing, and distribution. Prior to joining RGA, Erin served as Vice President, Individual & Mental Health for Green Shield Canada, where she was involved in the development and launch of a digital health line of business which sought to reduce health and morbidity costs through digital health programs. She has also held roles with Munich Re and Towers Watson.

Erin received a Bachelor of Mathematics degree (with honours) from the University of Waterloo, in Canada, in actuarial science with a minor in statistics. She is a Fellow of the Society of Actuaries (FSA) and a Fellow of the Canadian Institute of Actuaries (FCIA).

Further, many physical ailments may increase a patient's risk of developing new mental health disorders after diagnosis.[4] For example, the incidence of major depression increases following a heart attack or stroke, and patients living with cancer also face increased risk of developing a mental health disorder.

- **Mental health comorbidities can complicate the diagnosis and treatment of associated physical health conditions.**
  People living with mental health disorders may delay or avoid seeking help for the physical symptoms they are experiencing, which can adversely impact detection and diagnosis. In addition, once a physical condition is diagnosed, people with comorbid mental health disorders tend to have more difficulty adhering to recommended treatment plans for that condition, including medication adherence or blood glucose monitoring.[4] The presence of mental health disorders can therefore adversely impact the prognosis of conditions such as diabetes, stroke, and cancer.
- **Mental health disorders can affect the adoption of healthy behaviors.**
  Mental health disorders commonly occur concurrently with known unhealthy or risky behaviors, such as problematic use of alcohol or other substances.[6] People living with obesity are also more likely to also have a mental health disorder.[7]

  These disorders can make changing or adopting new, healthier behaviors more difficult. Looking at diabetes alone, patients with comorbid depression have greater difficulty making needed changes to their diet, increasing activity levels, or taking medications as prescribed.[4]

  More broadly, mental health disorders impact the key factors necessary for behavior change: it negatively impacts patients' perceptions of their capabilities to execute change, their ability to develop or maintain the social connections crucial to providing support, and their ability to accept opportunities to adopt new behaviors. Further, lack of motivation is a common symptom among those with many mental illnesses.
- **Mental illness can present as a physical condition in some patients.**
  It has been estimated that at least one-third of all physical symptoms are medically unexplained. Common symptoms in this category, including pain, fatigue, dizziness, and "somatization" (medically unexplained physical symptoms coupled with psychological distress) are found in conditions such as chronic fatigue syndrome, irritable bowel syndrome, fibromyalgia, and temporomandibular joint dysfunction.[4]

  Somatization adds significant costs to healthcare systems, and research evidence supports that when the underlying psychological distress is treated, whether with antidepressant medication or cognitive behavioral therapy, healthcare costs can be reduced by as much as a third.[4]

How Insurers Can Help

The increasingly evident connections between physical and mental health have obvious risk management implications on underwriting and claims management, particularly for occupational disability and income protection products. However, due to our deep understanding of mortality and morbidity and our connections to policyholders through the variety of available insurance products, insurers and reinsurers are uniquely positioned to play a more proactive role in meeting society's evolving mental health needs.

- **Provide meaningful insurance coverage for mental health conditions.**
  In some countries, it remains common to limit coverage for claims arising from mental health conditions. However, the more we learn, the more difficult it becomes to draw a clear line between physical and mental health. Claimants experiencing a mental health condition such as depression may not receive appropriate intervention during the early part of their claim should the insurer focus on this primary claim cause only. However, a claimant may already have or be developing a complicating physical condition such as a pain disorder for which cover cannot be limited, and because of this, the opportunity for early intervention, which would benefit both the claimant and the insurer, could be lost.

  On the other hand, a claimant who presents with a physical condition as a primary claim cause may well receive full necessary support, even though their condition may be complicated by the presence of mental health symptoms. As both individuals may experience the same level of impairment in performing their occupational duties, even though the primary driver may be different, their need for insurance cover and particularly early intervention to return to work would be the same.

  The increasing prevalence and awareness of mental health conditions over the last several years has governments and regulators around the world signaling a shift towards more equitable treatment of physical and mental health conditions in a variety of areas, including insurance. These trends, coupled with increasing customer awareness and desire for insurance products to keep pace with their evolving needs, suggest it would be a significant advantage for insurers to be proactive in creating mental health protection solutions.

- **Shifting mindsets from protection to prevention.**
  The concept of loss reduction is not new to insurers or claims managers, particularly as it relates to disability and medical coverage. Insurers are uniquely positioned at claim time to assess the full details of a claimant's situation and identify holistic interventions that may improve prognosis and reduce escalation or recurrence. These are increasingly including innovative mental health interventions. For example, insurers around the world are

dabbling with providing digital mental health apps to disability claimants early in the claim process to get critical interventions to claimants earlier while they wait to see a therapist. And, noting again the connection between physical and mental health conditions, these interventions are even being used with claimants where mental health is not the primary diagnosis, but where an increased risk exists of a mental health condition developing that is likely to adversely impact the prognosis of a physical condition such as cancer. Must insurers wait until a loss or illness occurs before taking action? When it comes to mental health, it has already been shown that the earlier the intervention, the more effective it may be. It is time for insurers to evaluate models for providing lower-intensity interventions to all policyholders to determine if claims could be avoided altogether.

- **Creating shared value through insurance.** Detection, prevention, and treatment of mental health conditions represents a significant and growing social issue – one already too big for governments to tackle on their own. If these challenges could be addressed, insurers would stand to benefit through reduced claims and claim severity as well as improved overall mortality and morbidity experience. Further, customers increasingly want to do business with companies that have purpose, are contributing to social progress, and generally care about customer wellbeing. Taking prevention one step further, insurers also have the opportunity to address mental illness as a social need through the products and services they offer. Life and health insurers have been applying this concept for many years via wellness programs attached to their protection products, which incentivize and reward customers who take steps to adopt healthy lifestyles. While the focus has traditionally been on physical activity, insurers are increasingly incorporating mental health themes through assessments and check-ins, rewarding behaviors which improve resilience and mental health literacy, and integrating themes of social connectivity and community.

Conclusion

In recent years and particularly in light of the pandemic, mental health has become recognized much more prominently as a leading factor in a person's overall health and wellness. Insurers clearly recognize this shift, as evidenced in the increasing incorporation of mental health needs into benefits and customer offerings. It would be advisable for our industry to keep a sharp eye on trends in mental health to be sure cover continues to recognize and incorporate consumer and market needs. RF

References

1. https://www.who.int/publications/i/item/WHO-2019-nCoV-Sci_Brief-Mental_health-2022.1
2. https://www.thelancet.com/journals/lanpsy/article/PIIS2215-0366(15)00505-2/fulltext
3. https://ontario.cmha.ca/documents/the-relationship-between-mental-health-mental-illness-and-chronic-physical-conditions/#:~:text=Mental%20illness%20can%20impact%20social,take%20care%20of%20their%20health.
4. https://www.thelancet.com/action/showPdf?pii=S0140-6736%2807%2961238-0
5. https://www.canada.ca/content/dam/phac-aspc/migration/phac-aspc/publicat/hpcdp-pspmc/28-4/pdf/cdic28-4-4eng.pdf
6. https://ontario.cmha.ca/addiction-and-substance-use-and-addiction/#:~:text=In%20Ontario%2C%20it%20is%20estimated,the%20population%20use%20substances%20problematically
7. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1913935/#:~:text=Obesity%20is%20associated%20with%20an,between%20obesity%20and%20mood%20disorder.

COLORECTAL POLYPS AS PRECURSORS TO COLORECTAL MALIGNANCY

Abstract

Recent developments and advances in the understanding and classification of colorectal polyps have been significant. This article will provide an in-depth review of the literature and outline changes in terminology and nomenclature. Having a good grasp of this information is essential in order to assess and stratify this risk fairly and appropriately.

Introduction

As of 2020, colorectal cancer (CRC) was the second most common type of cancer diagnosed and the third leading cause of cancer-related mortality. Like most other solid tumors, CRC is largely a consequence of progressive accumulation of abnormalities in tumor suppressor genes and oncogenes, which initiate and sequentially promote carcinogenesis.

More than 90% of CRCs are adenocarcinomas. Like many other solid tumors, CRC is a heterogenous disease with different subtypes that are distinguished by distinct clinical and molecular features. CRC originates in the glandular epithelium (colonocytes) of the large bowel. The process begins with an index genetic aberration in healthy epithelium, which gives the affected colonocyte a selective growth advantage and the opportunity for clonal expansion of cells at that site. These cells then proliferate in the colon mucosa and ultimately present as a polyp.

The initiating mutation of CRC usually occurs in the APC tumor suppressor gene, which is on chromosome 5. This gene participates in a number of functions, including suppression of abnormal cell proliferation. The silencing or inactivation of this gene results in aberrant functioning of the Wnt signaling pathway, a critical and highly conserved evolutionary pathway in animals that regulates cell communication, division, differentiation, and gene transcription.

An APC mutation is usually a spontaneous event at a particular site in the colon, but the causative chromosomal abnormality may be an inherited germline mutation. Germline mutations create a field defect in all colonocytes which exposes the entire colon to an increased risk of cancer. The APC germline mutation is responsible for familial adenomatous polyposis (FAP) syndrome, a rare type of inherited cancer predisposition syndrome characterized by hundreds to thousands of precancerous colorectal polyps (adenomatous polyps) which, if not removed, usually result in CRC at a young age.

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Dr. Paul Davis, Chief Medical Officer, RGA Australia, brings decades of experience as a cardiologist and in internal medicine to his role. In his 20 years with RGA, he has been influential in underwriting and claims management, education, medical research, and product development.

Dr. Davis received his Bachelor's degrees in Medicine and Surgery (with Honours) from Sydney University. He is a Fellow of the Royal Australasian College of Physicians (FRACP) and a member of several medical associations, including the Cardiac Society of Australia and New Zealand (CSANZ), the American Academy of Insurance Medicine (AAIM), and the Australian Life Underwriters and Claims Association (ALUCA).

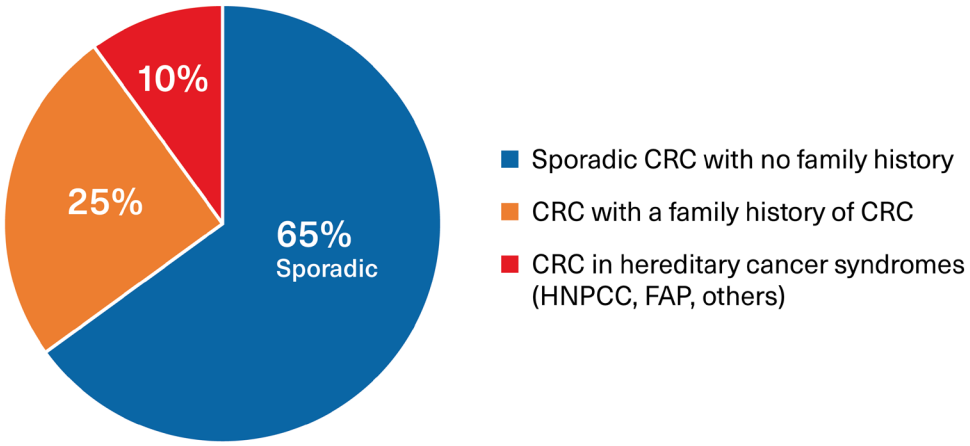
The transformation from an initially benign expansion of colonocytes into entities with increasing growth perturbation requires the sequential acquisition of additional genetic abnormalities. This accumulation of serial molecular alterations establishes a momentum of genetic instability, which results in affected cells developing increasingly abnormal characteristics leading to a final transformation into invasive cancer.

Most successful cancers contain many genetic abnormalities. It is estimated that an accumulation of 10 or 15 "hits" (i.e., abnormalities) in key signaling pathways is necessary for a cancer to establish. This process must begin during the short lifespan of a normal colonocyte. Each sequentially acquired abnormality provides affected cells with an incremental growth advantage which further enhances chromosomal instability and facilitates the neoplastic process.

Environmental factors are also established promoters of genetic instability and are known to affect gene structure and function. These factors may act as direct mutagens or exert adverse influences on gene expression. In addition, visceral obesity, smoking, lack of physical activity, alcohol consumption, western dietary patterns, and alterations in the colon microbiome are established promoters of carcinogenesis. All of these epigenetic factors influence the prevalence of sporadic cancers and may be responsible for familial clustering that can be seen in the absence of transmissible germline mutations. Most cancers occur in the absence of any family history while others have familial clustering as noted above.

Familial CRC clusters may result from a heritable germline mutation, such as FAP and Lynch syndrome (hereditary non-polyposis colorectal cancer [HNPCC]), although a substantial proportion are still the result of acquired mutations, possibly driven by common environmental exposures or other epigenetic influences. Epigenetic factors also play a role in the expression and penetrance of cancer in those with an identifiable genetic mutation. (Figure 1)

Figure 1: Proportions of Colorectal Cancers Associated with Sporadic and Hereditary Factors



Source: *RGA*

A family history of CRC increases individual cancer risk considerably. Indeed, the risk of cancer is doubled in those with one affected first-degree relative and quadrupled in those with at least two affected first-degree relatives.

Normal colon epithelium is renewed every few days, as older cells undergo apoptosis (programmed cell death) and are shed. The colon cell proliferation rate is of the order of 3-10 billion cells each day and this high turnover provides an enormous potential for the accumulation of genetic and epigenetic changes. Normal cell growth and division for tissue repair and organ maintenance is governed by genetically determined growth signals. Proto-oncogenes promote tissue growth while tumor suppressor genes inhibit cell proliferation and growth expansion. Mutations in proto-oncogenes, which cause them to be overexpressed, and mutations in tumor suppression genes which cause them to be silenced, are common promoters of colon tumorigenesis.

The DNA replication process occurring at cell division is surveilled by a DNA mismatch repair (MMR) system. This system identifies and repairs translation errors in newly synthesized DNA and limits material mutations. Defects in MMR promote the survival of spontaneous mutations, and also have a role in tumorigenesis which complements that of growth promoters. MMR genes are very prone to epigenetic influences.

It may take years for generations of cells to escape the body's multiple regulatory layers that are designed to suppress carcinogenesis, and for normal epithelium to transform into a cancer and acquire potential for tissue invasion and metastasis.

The Molecular Basis of Colorectal Cancer

At least three major molecular pathways (mutator phenotypes) form the basis for CRC initiation and development. Each is activated or influenced by chromosomal aberrations. These three pathways still require the accumulation of sequential defects, and the pathways are not mutually exclusive. (Figure 2)

- **Chromosomal Instability (CIN) pathway:** CIN is identifiable in approximately 85% of sporadic colon cancers and refers to high rates of gains or losses of portions of chromosomes which affect gene expression. CIN tumors are recognized by mutations in tumor suppressor genes (such as APC), oncogenic growth promoter mutations (such as KRAS and BRAF), and mutations in genes such as TP53, which both inhibits tumor suppression and negatively influences apoptosis. These mutations all represent gains in function for the growth of cancer cells.

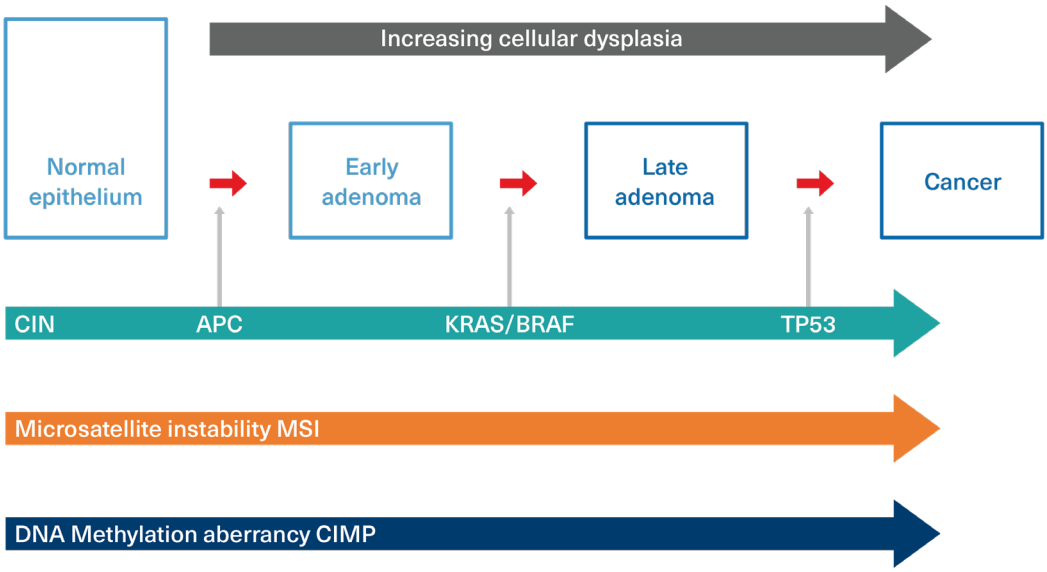
  In CIN, the cancer pathway is commonly initiated by inactivation of the APC tumor suppressor gene, promoted by early appearance of a KRAF or BRAF promoter mutation, and then enhanced by the later acquisition of a TP53 mutation.

  APC mutations have been identified in as many as 90% of sporadic CRC cases. In familial clusters of FAP syndrome, for example, all inherit a mutated copy of the APC tumor suppressor gene.
- **Microsatellite Instability (MSI) pathway:** MSI is another type of chromosomal instability. It refers to the presence of high numbers and frequencies of very small replication errors in DNA scattered throughout the genome. The progressive and repetitive accumulation of

these errors in a DNA sequence leads to a deficiency in the MMR system, which promotes a dramatic increase in mutation errors. MSI is identifiable in 15% to 20% of sporadic CRC cases and is responsible for Lynch syndrome or HNPCC.

- **Aberrant DNA Methylation pathway:** Not all genes are expressed at all times. DNA methylation plays a crucial role in gene expression and is a signaling tool which may be used to lock genes in the on or off position. Methylation sites are distributed throughout the genome in what are called CpG islands. Methylation at these sites can change the gene's expression and lead to gene silencing. Inappropriate silencing, particularly of tumor suppressor genes, may promote carcinogenesis. An abnormal CpG Island Methylator Phenotype (CIMP) is demonstrable in up to 30% to 35% of sporadic CRC cases and is a characteristic of tumors which develop in polyps with a serrated morphology (discussed below). CIMP positive tumors are commonly associated with KRAS and BRAF mutations and often exhibit microsatellite instability.

Figure 2: Molecular Pathways to Cancer



Adapted from: *Malki A, et al. Molecular Mechanism of Colon Cancer Progression and Metastasis: Recent Insights and Advancements. Int J Mol Sci. 2021; 22(1): 130.*[18]

Nomenclature and Classification of Polyps and the Risk of Malignant Transformation

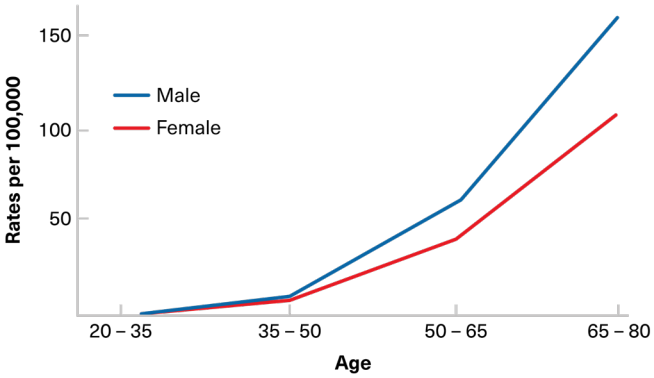
The acquisition of growth promotion characteristics in colonocytes results in the development of benign growths which expand and protrude into the bowel lumen in the form of polyps. While more than 90% of adenocarcinomas develop in benign polyps, most polyps do not harbor or acquire the requisite sequential carcinogenic mutations that promote transformation into overt malignancy.

The classification, terminology, and diagnostic criteria applied to polyps continue to evolve, particularly with respect to their molecular biology and potential for malignant change. An understanding of the various genetic pathways which induce and promote cancer transformation is central to polyp management and has led to the development of interventional strategies which have reduced CRC incidence and mortality.

The most recent classification of colorectal polyps appears in the World Health Organization (WHO) Classification of Tumors of the Digestive System, 5th Edition, published in 2019.

The prevalence of benign polyps increases with age. A significant increase generally begins between ages 40 and 50, predating the age-related incidence of invasive colorectal cancer (Figure 3).[1] In polyps destined for malignant transformation, the sequence from a benign precursor to a cancer usually occurs over several years, with this lag period providing an ideal opportunity for early screening detection.

Figure 3: Colon Cancer Incidence by Age – World



Adapted from: *Ballinger AB, Anggiansah C. Colorectal Cancer. BMJ. 2007; 335: 715-8.*[20]

Following detection and removal of an index polyp, subsequent surveillance intervals are governed by:

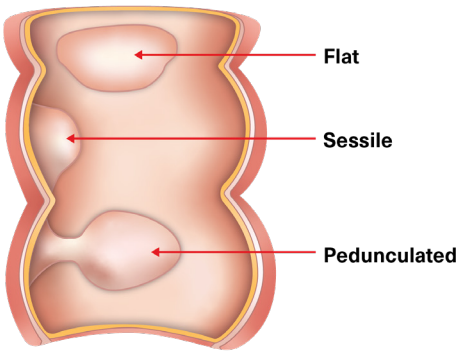
- Size (advanced size threshold defined as 10 mm)
- Number found (defined as >3)
- Classification (determined by histology)
- Presence or absence of any dysplastic features (determined by histology)

Morphological Descriptors

Two terms are used to describe the gross visual appearance of polyps found during a colonoscopy: Pedunculated (polyps with a stalk), and sessile (polyps that either have a broad base or are flat, with no stalk).

These gross features do not allow malignancy risk to be determined. Endoscopic removal is often easier for pedunculated polyps than for large sessile lesions. That caveat is recognized in some follow-up surveillance guidelines discussed below.

Figure 4: Pedunculated and Sessile Polyps



Source: *RGA*

Histological Classifications

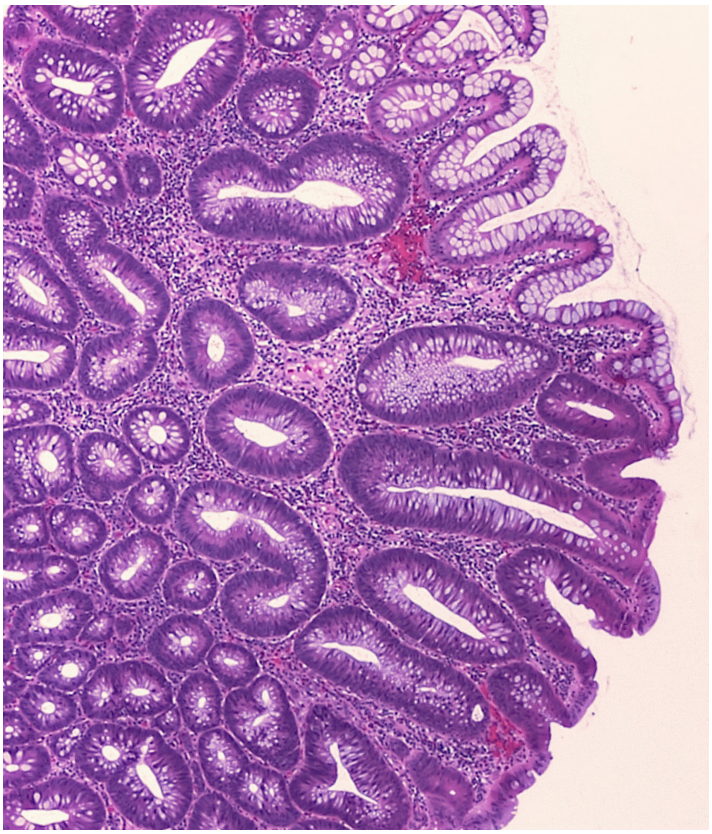
Two polyp types, conventional adenomas and serrated polyps, are defined using two distinct histological features. These features are now known to align with different pathways to carcinogenesis.

Conventional adenomas (previously known as adenomas or adenomatous polyps), are the most common type. They represent the classic cancer precursor lesion and account for most CRCs.

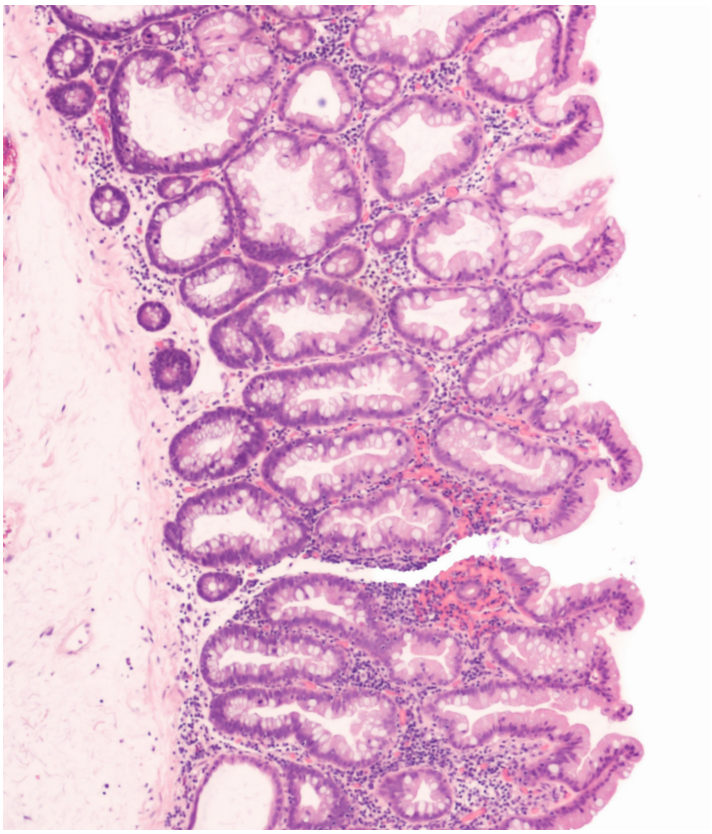
Serrated polyps (previously known as hyperplastic polyps or metaplastic polyps) are less common and traditionally were not considered precancerous. They are now classifiable into histological subsets on the basis of morphological and molecular profiles which label some as having malignant potential. The term "serrated polyp" now encompasses a number of entities, often with subtle differences in architecture which may be difficult to distinguish. Hyperplastic polyps (HP), currently considered a subset of serrated polyps, are the most common serrated polyp type (75%) and have the lowest malignancy potential.

Table 1: Polyp Types - Descriptors	
Conventional adenomas	**Serrated polyps**
Represent approximately 70% of all polyps	Represent approximately 30% of all polyps
Defined by a "layered" appearance of epithelial cell growth	Defined by a "serrated" or "sawtooth" appearance of epithelial cell growth
APC gene mutation is common (>90% of all adenomas)	Most remain classifiable as HPs with little or no malignant potential
All have malignancy potential	Premalignant subsets of serrated polyps are now recognized
Malignancy develops via a conventional pathway	BRAF (or KRAS) gene mutation is common in premalignant subsets (75%-90%)
Malignancy risk is 10%	Malignancy develops via a "serrated pathway"
Account for 85% to 90% of all sporadic CRC cases[1]	Account for 10% to 15% of all sporadic CRC cases[1]

Figure 5: Histology – Adenomatous and Serrated Polyps



Adenomatous Polyp - Conventional Adenoma



Serrated Polyp

Source: *Shutterstock*

Table 2: Malignant Pathway Descriptors for Conventional Adenomas and Serrated Polyps	
Polyp Pathway and Type	**Pathway Descriptor***
Conventional pathway	**Major carcinogenic chromosomal mutations**
Conventional Adenomas (75% of all CRCs)	• APC mutation common (>90%) • KRAS and BRAF mutations less common
Serrated pathway	**Major carcinogenic chromosomal mutations**
Serrated Polyps (25% of all CRCs)	• BRAF mutation common (80%) • KRAS mutation less common (30% of traditional serrated adenomas) • APC mutations less common (20% of traditional serrated adenomas)
***Mutational characteristics exposing polyps to cancerous change**	
• Sporadic mutations acquired during cell division OR • Global change in the DNA of colon mucosa (may be heritable)	

Description and Nomenclature

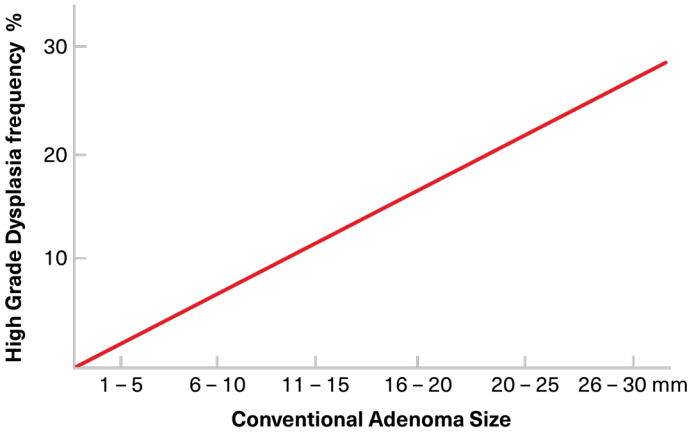
Conventional Adenomas

Conventional adenomas are the most common type of colon polyp. The term "conventional adenoma" is current nomenclature in surveillance guidelines and has replaced the older terms "adenomatous polyp" and "adenoma" in order to distinguish it from the adenomas now described in serrated lesion classifications. (The older nomenclature can still be found in some pathology reports.)

Most cancers arise in conventional adenomas and progress via a well-described "adenoma-carcinoma" sequence. Although only 10% of conventional adenomas will transform into malignancy, the majority harbor mutations in the APC cancer suppressor gene, a major gatekeeper against CRC. APC mutations are highly associated with both conventional adenoma development and malignant transformation. This transformation may be reflected in varying degrees of dysplasia on microscopy.

Conventional adenomas are the precursor polyps in most sporadic and familial CRCs and in those CRCs associated with heritable FAP and HNPCC syndromes. In sporadic CRC, APC mutations are spontaneously acquired in somatic cells with overt malignancy developing only after a long period of other sequential genetic aberrations, influenced by epigenetic factors. In familial cancers, APC mutations may be passed down via germlines, and most of these adenomas are pedunculated and small. Most conventional adenomas cluster in the distal (left) colon, occurring commonly in the rectosigmoid region. Larger adenoma size is associated with an increasing prevalence of dysplasia and malignancy (Figure 6).[3] Polyps <10 mm are rarely malignant and any cancerous change may take as long as 10 years. Polyps >10 mm, however, are more likely to harbor cancer, with benign polyps of that size transforming into cancer over a period of two to five years.

Figure 6: Relationship of Conventional Adenoma Size to Likelihood to Presence of High-Grade Dysplasia



Adapted From: *Markowitz AJ, Winawer SJ. Management of Colorectal Polyps. CA: A Cancer Journal for Clinicians. 1997 Mar/Apr; 47(2): 93-112.*[3]

Conventional adenomas usually have a smooth surface, but some contain components of a villous or frondlike architecture. The two are termed "smooth conventional adenomas" and "villous conventional adenomas," respectively. Sessile adenomas (flat or slightly raised with no stalk) are more likely to contain villous components than pedunculated adenomas.

Conventional adenomas are subclassified by the degree to which they exhibit villous architecture. While this introduces another layer of complexity in nomenclature, it has been argued as material on the basis of malignancy potential.

Table 3: Conventional Adenoma Nomenclature

Villous Characteristics	Type	Prevalence
None	Tubular adenoma	80%
Villous architecture <80%	Tubulovillous adenoma	10%
Villous architecture >80%	Villous adenoma	10%

Traditionally, villous architecture in serrated polyps has been considered an independent predictor of cancer risk and death. Although recent data suggests that the risk may not be as high as previously thought, most surveillance guidelines maintain villous-specific protocols. The European Society of Gastrointestinal Endoscopy (ESGE), however, makes recommendations in its guidelines irrespective of villous components.

Serrated Polyps

Serrated polyps are less common than conventional adenomas and their terminology continues to evolve. The majority are sessile. Serrated polyps are responsible for approximately 20% of sporadic cancers although the majority of these polyps do not become cancerous. The prevalence of serrated polyps is 20%-40% in average risk individuals with the majority being hyperplastic.[6]

Serrated polyps tend to appear at younger ages than conventional adenomas. While prevalence steadily increases with age, it does not seem to have as sharp a rise in prevalence with age as do conventional adenomas. While previously considered to represent a benign homogenous population, the recognition that this polyp category contains some entities that carry cancer-precursor mutations has resulted in the description of three main subtypes. In 2019, the WHO expanded the number of subtypes in order to better stratify the spectrum of associated malignancy risk and in recognition of the difficulties sometimes experienced at histological examination. They are:

- Hyperplastic polyps (HP), known as metaplastic polyps in older nomenclature
- Sessile serrated adenomas (SSA) or sessile serrated polyps (SSP) or sessile serrated lesions (SSL)
- SSA/SSP/SSL with dysplasia
- Traditional serrated adenomas (TSA) (also known as traditional serrated polyps)

HP is by far the most prevalent serrated polyp and has the lowest malignancy potential. HPs are small (<5 mm), sessile, and mostly cluster in the left colon. SSA/SSP/SSL are also sessile, but are larger than HPs (20% >10 mm) and mostly cluster in the right colon.

Large sessile lesions are subject to incomplete piecemeal endoscopic resection and early recurrence. Surveillance guidelines reflect these potential surgical difficulties.

Table 4: Serrated Polyps – Nomenclature and Characteristics

Type	Relative Frequency	Size	Characteristics	Histology	Dysplasia	Malignancy Potential
Hyperplastic polyp (HP)	80%-90%	<5 mm	Sessile/flat	Serrated, normal architecture	Nil; risk increased if larger size	• Nil to low • 20% (+) carry BRAF mutation
Sessile serrated adenoma (SSA), sessile serrated polyp (SSP), sessile serrated lesion (SSL)	15%-20%	<10 mm	Sessile/flat	Serrated, distorted architecture	+/-	• High • 80% (+) carry BRAF mutation
Traditional serrated adenoma (TSA)	1%-5%	>10 mm	Pedunculated	Serrated, distorted architecture	+/-	• High • BRAF, KRAF, or APC mutation

The pathway to cancer in serrated polyps, known as the serrated pathway, is different from that of conventional adenomas. Mutations in the BRAF gene are common for both SSA/SSP/SSL and TSA, and these lesions are considered to be at high risk of developing colorectal cancer. The oncogenic gene prevalence is much less common in HP. Gene expression is again influenced by epigenetic factors such as smoking, type 2 diabetes, alcohol consumption, and dietary factors such as red meat consumption.

SSA/SSP/SSL begins to appear in the mucosa of the right colon as early as the third decade of life, becomes clinically significant around age 50, and then incidence increases rapidly from 55-70 years of age. Increases in SSA/SSP/SSL incidence track with the age-related prevalence of DNA methylation in colonic mucosa coupled with the presence of the BRAF mutation.[12] SSA/SSP/SSL tends to grow more rapidly than conventional adenomas and are overrepresented as precursor lesions in interval colorectal cancers (CRCs diagnosed within 60 months of a negative colonoscopy).[12]

HPs are distinct from other serrated polyps in that they have not traditionally been seen as having the potential to transform into cancer. Although the label "adenoma" continues to be avoided, it is now recognized that HPs may harbor oncogenes and may not always be as innocuous as previously thought. Subsets of HPs may become dysplastic or transform into SSA/SSP/SSL and behave as precursor lesions. Polyps that transform have a high prevalence of the BRAF mutation.

Clinically, HPs are considered high-risk if they are multiple, large (>10 mm), or dysplastic, or if they occur in the context of a family history of serrated polyposis syndrome (SPS).

Serrated Polyposis Syndrome (SPS)

SPS has been described and is associated with excess CRC risk in the proband and in first-degree relatives, although a clear heritability pattern has not yet been established.

SPS is characterized by the presence of multiple serrated polyps. It is the most common polyposis syndrome and has a much higher prevalence than FAP. Mean age at diagnosis (45 years) is younger than that of patients with SSA/SSP/SSL (57 years) who do not meet criteria for SPS.[7]

Given the absence of any genetic marker, a diagnosis of SPS is defined by the WHO as follows:

- A lifetime total of >20 serrated polyps of any size (≥5 proximal to the rectum), or
- A lifetime total of ≥5 serrated lesions/polyps proximal to the rectum, all being at least 5 mm in size with at least two measuring >10 mm

An SPS diagnosis in individuals with any type of serrated polyp who have a family history of SPS had been considered a diagnostic criterion but was abandoned by WHO in 2019.

SPS carries high malignancy risk, and concurrent CRCs have been reported in as many as 15% to 30% of patients at time of diagnosis. Although as many as 70% with SPS will meet its diagnostic criteria at the first screening colonoscopy when it is discovered, it may take years and a number of colonoscopies to accumulate enough polyps for a confirmed diagnosis. This may result in under-diagnosis of SPS, although the risks associated with lack of early recognition may be mitigated by treating individual serrated polyps with care and in accordance with current accepted surveillance guidelines.

Overall risk of malignancy with SPS may be as high as 30% to 70% (compared to 100% for FAP), but the five-year risk falls to 1% once a diagnosed individual is admitted to surveillance programs. No germline genetic marker has yet been identified despite the excess risk of CRC in first-degree relatives (risk ratio=5).

Implications of Dysplasia in Histological Reports

Dysplasia describes pathological appearances reflecting abnormal cell growth characteristics that fall short of actual cancer. Dysplasia results from DNA damage and is viewed as a progression towards cancer transformation, if not an indication that transformation to cancer may have established. Although some would argue that, by definition, any neoplasm or new uncharacteristic cell growth is some degree of dysplasia, adenoma cells may have essentially

normal histological morphology and may therefore not be described as dysplastic.

In pathology reports, colon lesions are usually described either as non-dysplastic or as associated with low, intermediate, or high grades of dysplasia. The degree of dysplasia in polyps is predictive of their outcomes and influences surveillance recommendations. Increasing severities of dysplasia reflect increasing aberrancy in cellular proliferation and an expression of the serial acquisition of sinister oncogenes.

Small polyps (<10 mm) contain only the earliest of genetic alterations, and only small numbers of these will develop or acquire the additional genetic changes necessary to stimulate uncontrolled accelerated cell division, marked dysplasia, and the development of cancer.

High-grade (or severe) dysplasia (HGD) now embraces the same histological characteristics as carcinoma *in situ* (CIS). Some authorities have abandoned the term "CIS" and instead use the term "epithelial lesions in the gastrointestinal tract," and "HGD" has replaced "CIS" in some attending physician statements. High-grade dysplasia can only be found in <10% of conventional adenomas and sessile serrated adenomas in average risk populations, reflecting the fact that most polyps do not become cancerous.

Index Screening for Colorectal Polyps

Screening protocols for colorectal polyps vary by country and authority and continue to evolve. In low-risk individuals with no symptoms, no inflammatory bowel disease, and no family history of cancer, screening generally commences between 45 and 50 years of age.

Recommended screening modalities for average risk individuals include:

- Annual fecal occult blood (FOB) test (including high-sensitivity guaiac-based FOB tests)
- Annual fecal immunochemical test (FIT)
- Colonoscopy every 10 years
- Multitarget stool DNA test every three years

Surveillance After Polyp Resection

Updated protocols for surveillance in those with an index polyp have been published and are available online from the European Society of Gastrointestinal Endoscopy (ESGE) (2020), Cancer Council of Australia (2019), and the U.S. Multi-Society Task Force on Colorectal Cancer (2020).[8, 9]

In general terms, surveillance recommendations after polyp resection in average risk individuals is influenced by the following polyp aspects:

- Histology (conventional adenoma vs serrated polyp)
- Size
- Number
- Presence or absence of dysplasia
- Villous vs smooth architecture

While low-risk polyps may not require increased surveillance (return to regular screening intervals), others may require repeat colonoscopies at shorter intervals.

For males with low-risk polyps, five year intervals may be recommended if they have metabolic syndrome.

Conclusions

Colorectal cancer (CRC) is the second most common type of cancer diagnosed and the third leading cause of cancer-related mortality despite screening opportunities which are unsurpassed in oncology in terms of proven effectiveness.

As screening becomes more frequently accessed and adopted, insurers need to recognize the very high prevalence of polyps and understand their malignancy potentials. While careful screening with follow-up surveillance can reduce CRC incidence and mortality, as colonoscopies are being undertaken at increasing rates, pressure is increasing on medical services.

Screening guidelines continue to emphasize the importance of high-quality examinations, with resections being undertaken and patients followed up with care and rigor. Reassurance that a desired outcome will be achieved following resection of polyps detected during screenings requires an understanding of polyp classification and behavior and a grasp of the procedures involved.

Finally, risk assessment of individuals with high-risk precancerous lesions must be undertaken with reference to the pathology of index lesions discovered and ensuring that surveillance protocols, appropriately tailored to the individual's circumstances, are in place and followed.

The author would like to thank Dr. Radhika Counsell, Consulting Medical Officer, RGA, for her peer review of this article.

References

1. https://pubmed.ncbi.nlm.nih.gov/31455888/
2. https://doi.org/10.2147/CMAR.S166186
3. https://doi.org/10.3322/canjclin.47.2.93
4. https://www.nejm.org/doi/full/10.1056/nejmcp063038
5. https://europepmc.org/article/med/30407260
6. https://pubmed.ncbi.nlm.nih.gov/31323292/
7. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5605346/
8. https://pubmed.ncbi.nlm.nih.gov/32572858/
9. https://www.gastrojournal.org/article/S0016-5085(19)41479-0/fulltext#%20
10. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5461371/
11. https://pubmed.ncbi.nlm.nih.gov/31563625/
12. https://pubmed.ncbi.nlm.nih.gov/30346367/
13. https://pubmed.ncbi.nlm.nih.gov/29928381/#:~:text=Abstract,and%20CpG%20island%20methylator%20phenotype.
14. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2874430/
15. https://pubmed.ncbi.nlm.nih.gov/27798442/
16. https://pubmed.ncbi.nlm.nih.gov/29318445/
17. https://pubmed.ncbi.nlm.nih.gov/2841597/
18. https://www.mdpi.com/1422-0067/22/1/130
19. https://www.cancer.org.au/health-professionals/clinical-practice-guidelines/colorectal-cancer
20. https://pubmed.ncbi.nlm.nih.gov/17916855/

Longer Life Foundation

An RGA/Washington University Collaboration

The Longer Life Foundation (LLF), a collaboration of RGA and Washington University School of Medicine in St. Louis, is proud to announce its newest research grant recipients. These individuals are investigating some of the most important health and wellness issues of the day. To find out more about the LLF and the research it has funded to date, please visit www.longerlife.org or reach out to Dr. Dan Zimmerman at dzimmerman@rgare.com or Dr. Preeti Dalawari at preeti.dalawari@rgare.com.

Longer Life Foundation 2022-2023 Grants	
Investigator, Project Title	**Project Description**
Anuja Java, M.D., M.S.C.I. (Year 2) The Role of Complement in Hypertensive Disorders of Pregnancy	Preeclampsia is a severe complication of human pregnancy characterized by high blood pressure and signs of damage to other organ systems. Despite intensive research efforts, preeclampsia's causes are not well understood. It may involve the complement system, as prior research revealed mutations in complement proteins. This study will focus on these mutations to determine if they are damaging and likely causal of preeclampsia.
Nathan Stitziel, M.D., Ph.D. (Year 2) Targeting Receptor Interactions with SVEP1, a Circulating Biomarker of Longevity in Humans	SVEP1 is a novel biomarker of age and longevity in humans that is causally associated with risk of multiple age-associated chronic diseases. Although the cellular receptor and signaling pathway responsible for SVEP1's role in these diseases was previously unclear, the investigator in his first year identified a high affinity interaction between SVEP1 and a cell surface receptor named PEAR1. This year's funding will enable Dr. Stitziel to assess how SVEP1 interacts with this novel receptor and develop a method to measure levels of SVEP1. This research will expand our understanding of how SVEP1 influences disease and the therapeutic potential of targeting it as a treatment for many age-associated diseases.
Bettina Mittendorfer, Ph.D., Director, Longevity Research Program (LRP) (Year 1 of 3) Dietary Protein and Cardiovascular Health	This grant supports the LRP's ongoing research into potential links, mechanisms, and impacts of diets too high in protein on cardiovascular outcomes. The focus of LRP's work is now on assessing a high protein diet's impact on platelet and endothelial functioning, both of which can influence cardiovascular pathology. .

Longer Life Foundation 2022-2023 Grants	
Investigator, Project Title	**Project Description**
Peter Kang, M.D. (Year 1) Defining the Role of Neuroinflammation in Vascular Cognitive Impairment	Cerebral small vessel disease (CSVD) and vascular contributions to cognitive impairment and dementia (VCID) are leading causes of disability and cognitive impairment in older adults. Though manifestations of CSVD and VCID are common, the underlying mechanisms of disease remain unknown. This project will use novel and noninvasive MRI techniques and fluid biomarkers to understand the role neuroinflammation plays in the development of CSVD/VCID, and to help determine who may be at the highest risk for disease progression.
Jessica Silva-Fisher, Ph.D. (Year 1) Long Non-Coding RNAs as Markers of Multiple Myeloma (MM) Progression	MM accounts for about 13% of all hematologic malignancies and 1% of overall cancers. Despite advances, it is still incurable. The goal of this investigation is to understand why and how MM progresses to address the critical need for better prognostic markers, improve diagnoses, and create targeted therapies.
Milan Chheda, M.D. (Year 1) Glioblastoma and the Aging Brain	Brain tumors increase in frequency with age. This study's goals include: preventing glioblastoma recurrence; determining whether senescent cells increase cell proliferation and DNA damage; and determining if senolytic therapy can prevent tumor recurrence.
Laura Marks, M.D., Ph.D. (Year 1) Pathogenesis and Molecular Epidemiology of S. Aureus Isolates Associated with Invasive Infections Among People Who Inject Drugs (PWID)	S. aureus causes one of the most deadly types of bloodstream infections. Little is known about where these infections originate – whether from the skin or the environment. This investigator will study people who inject drugs, who are at some of the highest risks of invasive S. aureus infections, as well as matched control patients, to identify if bacteria recovered from the skin or the environment match those strains causing these serious bloodstream infections.

DR. ALPERS RETIRES FROM THE LLF

After many years chairing the Longer Life Foundation's Scientific Review Committee, **Dr. David J. Alpers** has retired from that post as of August 2022.

The benefit to the LLF and its investigators of Dr. Alpers' prodigious knowledge of clinical medicine and of research has been incalculable. Over the years, he has successfully mentored many young researchers as they embarked on their careers, providing the intellectual support they needed to develop grant proposals and then conduct their research successfully.

Dr. Bradley Evanoff, who has recently co-chaired the Scientific Review Committee, assumed sole leadership in August 2022. The LLF is looking forward to the experience which Dr. Evanoff will bring to the Foundation. To read more about Dr. Evanoff, please see this link.

MEDICAL TEAM UPDATE

Dr. Kim-Anh Vu has joined RGA's U.S. Mortality Markets medical team as Vice President and Medical Director. She was born in Vietnam and came to the U.S. in 1975. Her undergraduate degree is from the University of Cincinnati, where she graduated Summa Cum Laude with a Bachelor of Science in both chemistry and biology. She earned her M.D. from Ohio State University College of Medicine and completed her residency in Family Medicine. She has more than 20 years of experience in private practice and urgent care medicine. Before joining RGA, Dr. Vu spent six years as an associate medical director with Ohio National Life Insurance Company.

Dr. Manisha Kalaver has rejoined RGA's India office as a Medical Consultant, seven years after her initial time with RGA. She received her medical (MBBS) degree from the University of Mumbai and has more than 15 years of experience in medical underwriting, risk management, product development, and client training. Prior to her recent return, she was Chief Medical Officer in Gen Re's India office, and earlier was Chief Underwriter with Tata AIA Life.

Dr. Sakae Tonoya is retiring from RGA in September 2022. A stalwart of the RGA medical team and ambassador for the profession, Dr. Tonoya first joined RGA Japan in January 2003 as Chief Medical and Claims Research Director. In October 2007, he moved to Sydney to become Vice President and Regional Medical Director at RGA Asia Pacific Pty Ltd., and in April 2011, returned to Japan to provide technical medical support to the Asia Pacific region and Global functions.

Known to many globally, his industry contributions as a subject matter expert and mentor are far-reaching. RGA's medical and technical teams, in particular, benefited substantially from his depth of knowledge, patience, and wisdom. He will be very much missed, and we wish him the best.

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.

What Lies Beneath: Photoplethysmography (PPG) Solutions for Insurance

Dr. Steven Woh, MBBS
(IMU, Malaysia), Chief Medical Office and Claims Manager, RGA

Leigh Allen
Associate Vice President, Strategic Survey Research, RGA

Epidemic Within a Pandemic: Opioid Misuse and Mortality Risk Through 2020

Julianne Callaway, FSA, ACAS, MAAA
Vice President and Actuary, Strategic Research, Global Actuarial Pricing and Research, RGA

Kaitlyn Fleigle ASA, CERA
Senior Assistant Actuary, Strategic Research, Global Actuarial Pricing and Research, RGA

Johanna Svensson
Intern, Strategic Research, Global Actuarial Pricing and Research, RGA

Antimicrobial Resistance (AMR) – A Global Burden, An Individual Problem

Hilary Henly, FCII
FCII, Global Medical Researcher, RGA International Reinsurance Company dac

Advances in Neurotechnology Poised to Impact Life and Health Insurance

Hilary Henly, FCII
FCII, Global Medical Researcher, RGA International Reinsurance Company dac

Non-Substance Use Addiction in the Technological Era

Hilary Henly, FCII
FCII, Global Medical Researcher, RGA International Reinsurance Company dac

Industry-Wide Research Initiative Provides Key COVID-19 Insights

Jason McKinley, FSA
Actuary, Global Research and Data Analytics, RGA

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

Five Areas of Medical Innovation in Critical Illness (CI)

Dr. John Lefebre, FRCPC
Vice President and Senior Global Medical Director, Global Medical, RGA

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

Dr. Adela Osman, MBBCh
Chief Medical Research Officer
RGA South Africa

COVID-19 Brief: Remote Learning and Children with Neurodevelopmental Disorders

Diana Bosworth
Knowledge Management and Information Specialist, Global Actuarial Pricing and Research, RGA

The Case for Wellness Programs In Life and Health insurance

Julianne Callaway, FSA, ACAS, MAAA
Vice President and Actuary, Strategic Research, Global Actuarial Pricing and Research, RGA

Matt Berkley
Strategic Research Communications Lead, Global Actuarial Pricing and Research, RGA

COVID-19 Brief: Genome Sequencing Opens Doors for Effective Disease Management and Treatment

Gayathri Ravi Shankar
Knowledge Management and Information Specialist, RGA

Peter Rodes
Vice President, Consumer Engagement, RGAX

Colon Cancer: A Growing Risk for Young and Middle-Aged Adults

Colin M. DeForge
Executive Director, Underwriting, U.S. Mortality Markets, RGA

Dr. Valerie Kaufman, DBIM, FACC
Senior Vice President and Chief Medical Officer, U.S. Mortality Markets, RGA

Lauren Garfield, Ph.D., MPH
Underwriting Research Consultant, U.S. Mortality Markets, RGA

Traumatic Spinal Cord Injuries: The Underwriting Significance

Dr. Maryam Shapland, DBIM
Vice President and Medical Director, U.S. Mortality Markets, RGA

Why Stretching is Beneficial for the Mind and Body

Jared Godwin
Business Development Actuary, RGA
South Africa

Sleep Apnea Mortality Risk Higher for Younger Women

Anthony Woods
Lead Data Scientist, Global Data and
Analytics, RGA

ReCite

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

Association of Sitting Time with Mortality and Cardiovascular Events in High-Income, Middle-Income, and Low-Income Countries

Li S, et al. JAMA. 2022 Jun 15.
https://jamanetwork.com/journals/jamacardiology/article-abstract/2793521

This population-based cohort study included 105,677 participants aged 35 to 70 years in 21 high-income, middle-income, and low-income countries to investigate the association of sitting time with mortality and major cardiovascular disease (CVD). The group was recruited starting January 1, 2003, and followed up with until August 31, 2021, with a median follow up of 11.1 years.

The study found that higher sitting time amounts were associated with increased risk of all-cause mortality and major CVD, and that the association was more pronounced in low-income and lower-middle-income countries. When compared with individuals who reported sitting times of less than four hours per day and high physical activity levels, participants who sat for eight or more hours per day experienced 17% to 50% higher associated mortality and CVD risk across physical activity levels, and the risk attenuated as physical activity levels rose.

Editor's Note: *Measuring sedentary time along with physical activity is likely to form an important strategy in risk assessment as well as helping to ease the global burden of premature deaths and CVD.*

Optimism, Lifestyle, and Longevity in a Racially Diverse Cohort of Women

Koga HK, et al. Journal of the American Geriatrics Society. 2022 Jun 8.
https://agsjournals.onlinelibrary.wiley.com/doi/epdf/10.1111/jgs.17897

Growing evidence suggests positive psychological factors are associated with less morbidity and mortality risk. In this study, 159,255 participants from the Women's Health Initiative (WHI) study completed a validated measure of optimism and provided other demographic and health data at baseline. (The WHI study was conducted from 1993 to 1998 of 161,808 postmenopausal American women who were between the ages of 50 and 79 at enrollment.) The aim of the current study was to examine associations of optimism with longevity across racial and ethnic groups and determine if a healthy lifestyle is a possible mediating pathway for this association.

The study found that higher optimism was associated with longer lifespans and a greater likelihood of achieving exceptional longevity (survival to age >90) overall and across racial and ethnic groups. The contribution of lifestyle to these associations was modest.

Editor's Note: *With an aging global population and a shift in the insurance needs of this group, psychological factors like optimism and social connections are likely to form an important part of their risk assessment in the future.*

Trajectory of Long COVID Symptoms After COVID-19 Vaccination: Community-Based Cohort Study

Ayoubkhani D, et al. BMJ. 2022 May 18.
https://www.bmj.com/content/bmj/377/bmj-2021-069676.full.pdf

This study sought to estimate the associations between COVID-19 vaccination and long COVID symptoms in adults with SARS-CoV-2 infection before vaccination. It included 28,356 participants in the U.K. Office for National Statistics COVID-19 Infection Survey between the ages of 18 and 69 who received at least one dose of an adenovirus vector or mRNA COVID-19 vaccine after testing positive for SARS-CoV-2 infection. Researchers then measured the presence of long COVID symptoms at least 12 weeks after infection for a period of seven months.

During the follow-up period, 23.7% of the participants reported long COVID symptoms of any severity at least once. A first vaccine dose was associated with an initial 12.8% decrease in the odds of long COVID with subsequent data compatible with both increases and decreases in the trajectory, while a second dose was associated with an initial 8.8% decrease and then subsequent decreases of 0.8% per week. Heterogeneity was not found in associations between vaccination and long COVID by sociodemographic characteristics, health status, hospital admission with acute COVID-19, vaccine type (adenovirus vector or mRNA), or duration from SARS-CoV-2 infection to vaccination.

Editor's Note: *Vaccination may contribute to a reduction in the population health burden of long COVID symptoms and this is a notable factor when assessing risk for living benefits.*

Successful 10-Second One-Legged Stance Performance Predicts Survival in Middle-Aged and Older Individuals

Araujo CG, et al. British Journal of Sports Medicine. 2022 Jun 21.
https://bjsm.bmj.com/content/early/2022/06/22/bjsports-2021-105360

It is well established that in humans, balance diminishes after age 50, leading to increased risk of falls and adverse health outcomes. The aim of this observational study was to assess whether the ability to complete a 10-second one-legged stance (10-sec OLS) was associated with all-cause mortality and whether the ability added relevant prognostic information beyond ordinary demographic, anthropometric, and clinical data.

Researchers drew on 1,702 participants between the ages of 51 and 75 (68% men) currently in the ongoing CLINIMEX Exercise cohort study in Brazil. CLINIMEX, which began in 1994, seeks to assess associations between various factors, such as measures of physical fitness, exercise-related variables, and conventional cardiovascular risk factors, with ill health and death. As part of their routine check-ups, participants were asked to stand on one leg for 10 seconds without any additional support. Participants were given three attempts.

As expected, the ability to perform the test decreased with age. Of the total participants, 20% were unable to perform the 10-sec OLS at all. That figure rose to about 70% for those ages 76 to 80, and to nearly 90% for those ages 81 to 85.

After accounting for age, sex, and underlying conditions, an inability to stand unsupported on one leg for 10 seconds was associated with an 84% heightened risk of death from any cause (as compared to their peers with better one-legged static balance) within the next decade.

Editor's Note: *Balance assessment is not routinely included in health checks nor in risk assessment of older lives. This rapid test provides instant and objective feedback and could be a great adjuvant to mortality and morbidity risk assessment for this group.*

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.

Respiratory Outcomes and Lung Transplantation in COVID-19 Patients (9:34)

Hilary Henly
FCII, Global Medical Researcher,
RGA International Reinsurance Company dac

For COVID-19 patients, lung transplantation is truly a last resort. RGA's Hilary Henly explores respiratory failure from COVID-19, long-term health outcomes after infection, and assessment criteria for lung transplantation.
https://www.rgare.com/knowledge-center/media/videos/respiratory-outcomes-and-lung-transplantation-in-covid-19-patients

Climate Change and Life Insurance Implications (25:14)

Dr. Georgiana Willwerth-Pascutiu, DBIM
Vice President and Medical Director, Global Medical, RGA International

Chris Falkous, FIA
Vice President, Senior Biometric Insights Actuary, Global Data and Analytics, RGA

Climate change impacts the fundamentals of human existence: water, air, food, and shelter. RGA's Dr. Georgiana Willwerth-Pascutiu and Chris Falkous explore the effects of suboptimal temperatures on mortality and estimate impacts under various climate pathways. The pair also touch on roles policymakers, individuals, and the insurance industry can play in mitigating climate risks.
https://www.rgare.com/knowledge-center/media/videos/climate-change-and-life-insurance-implications

Immunotherapy: Transforming Cancer Survival (29:48)

Dr. Radhika (Radi) Counsell, MBBS
Consulting Medical Director, RGA UK

Precision medicine is transforming cancer care, and immunotherapy is transforming precision medicine's role. Immunotherapy works by enhancing the immune system rather than directly attacking cancer cells. Dr. Radi Counsell, RGA's clinical oncologist, discusses how modern approaches to immunotherapy are transforming cancer survival rates for individuals fighting aggressive cancers. Dr. Counsell also examines the underwriting and claims adjudication implications.
https://www.rgare.com/knowledge-center/media/videos/immunotherapy-transforming-cancer-survival

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