ReFlections

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IN THIS ISSUE

FROM THE EDITORS

Welcome to the September 2021 issue of *ReFlections*! We hope you, your families, and your loved ones continue to be safe and well. The pandemic is turning out to be more challenging than any of us could have anticipated, keeping top of mind and focus on our role and responsibilities as insurers of life and health.

This issue offers several informative articles that delve into the scientific and medical discoveries that are pushing medical frontiers forward in exciting ways. The first, by Dr. Maryam B. Shapland, Vice President and Medical Director, U.S. Mortality Markets, a new author for *ReFlections*, is an excellent review of reactive thrombocytosis, an important condition to understand. Dr. Heather Lund, Regional Chief Medical Officer, Asia, returns to *ReFlections* with an extensive and detailed piece providing much of the latest research and thinking about multiple sclerosis. The third article, from frequent *ReFlections* contributor Hilary Henly, FCII, Global Medical Researcher, is on the topic of pharmacogenomics, a fast-expanding and vitally important component in the field of precision medicine.

We also are proud to announce the 2021-2022 grants awarded by The Longer Life Foundation, RGA's research collaboration with Washington University School of Medicine in St. Louis. The eight newest grants represent our 24th year of supporting cutting-edge and highly pertinent research into topics relevant to clinical and insurance medicine.

We hope you find the articles in this issue relevant and informative. Please don't hesitate to let us know how we can continue to improve *ReFlections* for you.

Dan and Adela

REACTIVE THROMBOCYTOSIS: A BENIGN ENTITY?

Abstract

Thrombocytosis, a condition defined as having a platelet count of more than 450,000 per microliter of blood (450 x 10^9/L), can be either physiologic in nature or due to primary or secondary causes. Secondary or reactive thrombocytosis (RT) is far more prevalent than primary or clonal thrombocytosis, and the presence of comorbid conditions in RT, a transient rise in platelets, and lack of genetic mutations favor a secondary etiology. Clinical manifestations of RT can range from no symptoms (most common) to acute thrombosis (rare), and elevated platelet counts may also be a predictor of underlying disease and of mortality. Recent studies of thrombocytosis in patients with COVID-19 infection have shown that elevated platelet counts are predictive of poorer prognosis. Therefore, it is essential for an underwriter to identify RT, as RT is not always a benign entity, which means outcomes can vary.

This article will focus on RT, which is the most common cause of thrombocytosis. It will contrast RT to primary thrombocytosis (PT), outline the factors that favor a diagnosis of RT versus PT, discuss RT's clinical manifestations and prognosis, and explore RT's mortality risks and underwriting considerations, particularly in light of the current pandemic.

Introduction

Reactive thrombocytosis (RT), also known as secondary thrombocytosis, is a proliferation of platelets caused by a response to growth factors released from an inflammatory or malignant condition, whereas primary thrombocytosis (PT) is caused by an underlying myeloproliferative or myelodysplastic neoplasm.[9]

Platelets are the smallest formed elements that circulate in the blood, with a half-life of about four days. They are fragments of larger multinucleated cells called megakaryocytes, with no nuclei of their own. Platelets are an integral component of coagulation, as proteins on the surface allow platelet adhesion, leading to the formation of a platelet plug.

A normal platelet count ranges from 150,000 to 450,000 platelets per microliter of blood. An abnormally elevated count of >450,000/microL is known as thrombocytosis. Its differential diagnosis is broad. Causes of thrombocytosis can be physiologic (exercise, parturition) and can also be primary/clonal (e.g., essential thrombocythemia, polycythemia vera, primary myelofibrosis, and other hematologic malignancies) as well as secondary/reactive (due to infectious and inflammatory diseases, neoplasms, anemia, trauma, surgery, asplenia, and iron deficiency).

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A Common Clinical Finding

Thrombocytosis is a common incidental clinical finding, present in 1.5% to 2.2% of the population older than age 40 who are in a primary care setting.[4] The incidence of PT (also known as essential thrombocythemia), by comparison, is relatively low, at 1-2.5/100,000 per year.[16] Even in extreme thrombocytosis cases, where platelets were greater than 1 million/microL, PT accounted for only 14% of cases. The likelihood of thrombocytosis being due to RT is markedly higher. In fact, in a recent study 777 adults presenting with thrombocytosis revealed that in routine clinical practice, RT accounted for 97% of cases (see Table 1).[5]

Table 1: Causes of Thrombocytosis

Condition	Adults (n=777)	Platelet Count of 1000x10^9/L (n=280)	Children (n=663)
Infection	22%	31%	31%
Rebound thrombocytosis	19%	3%	15%
Tissue damage (surgery, etc.)	18%	14%	15%
Chronic inflammation	13%	9%	4%
Malignancy	6%	14%	2%
Renal disorders	5%	NS	4%
Hemolytic anemia	4%	NS	19%
Postsplenectomy	2%	19%	1%
Blood loss	NS	6%	NS
Primary thrombocytosis	3%	14%	0%

From Platelets, 4e. Academic Press, 2019.[5]

RT: Diagnosis of Exclusion

Given the prevalence of RT in clinical practice (and therefore in underwriting), it is important to understand how it is diagnosed. Several factors point toward a reactive etiology rather than a primary cause. The presence of, for example, a comorbid condition such as an infection, a connective tissue disease, bleeding, splenectomy, trauma, or postoperative state would favor a diagnosis of RT, whereas the absence of these conditions would suggest PT.

In adults, acute infection, tissue damage, chronic inflammatory disorders, and malignancy are the most common causes of RT, with one or more of these present in more than 75% of RT cases.[6] Transient platelet elevation is also more likely due to RT, whereas concerning signs and symptoms such as vasomotor symptoms, hepatosplenomegaly, and thrombosis tend to be more indicative of PT. If PT is suspected, one would likely see further clinical investigations such as bone marrow biopsy, flow cytometry, and genetic studies.

A growing number of acquired driver mutations causing platelet proliferation through aberrantly activated signaling pathways have been identified, most commonly JAK2V617F.[9] Indeed, the latest revision (2016) of the World Health Organization's diagnostic criteria for essential thrombocythemia (i.e., PT), cited the presence of the JAK2, CALR, or MPL mutation as a criterion, along with a platelet count higher than 450,000/microL and an abnormal bone marrow biopsy. In addition, a minor criterion for PT includes absence of evidence that would result in an RT diagnosis.[3]

Clinical Setting Determines Risk

RT is typically a clinically silent and transient condition. No clear correlation exists between symptoms and platelet counts; even patients with platelet counts of >1 million/microL due to RT are usually asymptomatic.[9]

The risk of thrombotic complications from RT is considered to be low, occurring in only 1.6% of patients in one large case series, with all thrombotic events identified as venous and occurring in patients with other risk factors, such as a postoperative state or with underlying malignancy.[6]

Interestingly, RT in patients with iron deficiency anemia has been associated with a twofold thrombosis risk compared with patients with iron deficiency anemia alone.[15] The cause of this association is still not completely understood; however, it is postulated that platelet activation is an ongoing process in iron deficiency and that the frequent comorbidity of iron deficiency with a number of clinical conditions that have known thrombotic risk, such as inflammatory bowel disease and cancer,[1] contributes to this phenomenon.

There have rarely been case reports of arterial thrombosis occurring in the setting of RT. In one case report, a 55-year-old female presented with symptoms of left hemiparesis.[8] She was diagnosed with a right middle cerebral artery stroke from a right carotid thrombus, which was ultimately determined to be due to RT (>1 million/microL) secondary to iron deficiency anemia. She was treated with plateletpheresis, a process in which platelets are removed from the bloodstream. Given that the overall risk of thrombosis is considered to be low in RT, treatment with anti-platelet therapy such as aspirin is usually not indicated. Still, treatment can be considered for patients with platelets of >1 million/microL with complications of thrombocytosis, or for patients at risk of developing such complications.[12]

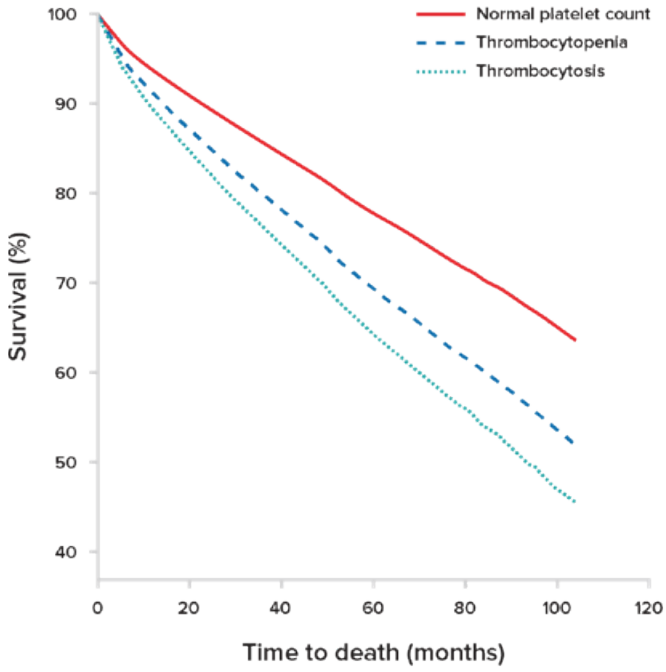
RT as a Predictor of Poor Outcomes

The presence of RT in infections and cancer may also be predictive of poor outcomes. In a recent study of 421 patients admitted for acute infectious disease, 32 had thrombocytosis with mean peak platelet counts of 527,000/microL. The study authors found that those with thrombocytosis had an increased length of stay, more bacteremia, and increased mortality, with 6.25% of the RT group dying in comparison to 2% of the non-thrombocytosis (control) group.[13] This elevated mortality risk has been validated in other investigations on hospitalized patients, with one study showing a 30-day mortality risk 2.5 times higher in those with RT of >500,000/microL compared to those with normal platelet counts.[10]

Thrombocytosis is a risk marker for cancer. A 2017 prospective study of more than 31,000 patients with thrombocytosis in a primary care setting found that males with thrombocytosis had an 11.6% incidence of cancer in the year following their thrombocytosis diagnosis, and females had an incidence of 6.2%. This compares with 4.1% of males and 2.2% of females who had normal platelet counts. The incidence of cancer rose with age and with higher platelet counts.[4]

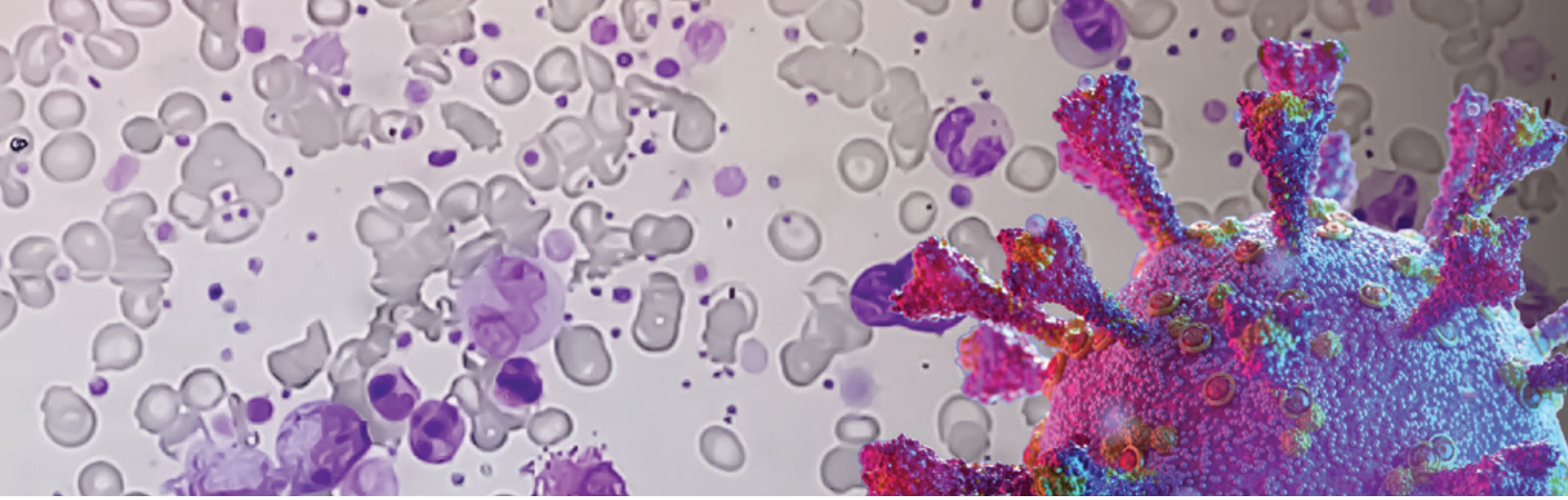
Researchers have also found that an abnormally high platelet count for elderly patients can be an independent predictor of mortality.[11] In a study of a large outpatient cohort of asymptomatic elderly individuals, platelet counts and their association with mortality were examined. In a median follow-up period of 3.3 years with a total of 134,132 patient-years of observation, a significant association with increased mortality was found in these patients for both thrombocytosis and thrombocytopenia, with a hazard ratio (HR) of 1.75 for thrombocytosis (see Figure 1). This association persisted across all ethnic groups.

Figure 1. Overall Survival Curves Stratified by Platelet Count



Overall survival curves are stratified by platelet counts after adjustment for all covariates including gender, ethnicity, anemia, neutropenia, and age-adjusted Charison comorbidity index. Both thrombocytopenia and thrombocytosis independently and significantly decreased overall survival compared to that of patients with normal platelet counts (P<0.01).

Adapted from Msaouel, P. Haematologica.[11]



Thrombocytosis and COVID-19

Significant attention has been paid to thrombosis and COVID-19, as it is thought that elevated platelet counts could be an indicator of cytokine storm, endothelial injury, and/or thrombopoietin release stimulating lung megakaryocytes to produce platelets.[2] A literature search of 20 studies with more than 3,500 patients with COVID-19 revealed that higher levels of platelet-to-lymphocyte ratios (PLR), a reflection of a patient's inflammatory state, were seen in severe COVID-19 disease compared to non-severe disease.[7] This validation of PLR as a prognostic marker in cardiac conditions, tumors, sepsis, pneumonia, and acute respiratory distress syndrome, suggests that RT might also be used as an independent prognostic marker of disease severity in COVID-19.

Reports of central venous sinus thrombosis (CVST) occurring after COVID-19 vaccination has led to further investigation into the hematologic sequelae of the SARS-CoV-2 virus. Remarkably, researchers have identified a novel underlying mechanism for thrombosis in 22 patients presenting with CVST after receiving the ChAdOx1 nCoV-19 (AstraZeneca) vaccine. These patients did not have thrombocytosis; rather, they were thrombocytopenic. In addition, antibodies to platelet factor 4 were identified in 21 of these patients.[14] The authors note, however, the risk of venous thromboembolism after vaccination does not appear to be higher than the background risks in the general population. In fact, a preprint study showed that the incidence of CVST after COVID-19 diagnosis was 10 times higher than CVST incidence after receiving the mRNA vaccine.[17] It is evident from these studies that COVID-19 continues to wreak havoc on the hematologic equilibrium of these patients.

RT is typically a clinically silent and transient entity… however, it may be predictive of a poor outcome in acutely and chronically ill individuals.

Underwriting Considerations

Given what we know about RT, there are several considerations when underwriting thrombocytosis, particularly in light of the ongoing COVID-19 pandemic.

- RT is a much more common entity than PT; statistically, a majority of those with thrombocytosis have RT.
- It is essential to determine whether a finding of thrombocytosis is reactive or primary.
- RT is typically a clinically silent and transient entity with a relatively low thrombotic risk.
- RT is associated with higher mortality in acutely ill patients.
- RT is an independent predictor of mortality in asymptomatic elderly individuals.
- Elevated platelets are associated with worse outcomes in individuals hospitalized with COVID-19.

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NEW TREATMENT PARADIGMS IN THE MANAGEMENT OF MULTIPLE SCLEROSIS

Abstract

Younger adults (ages 20-30), with a slight female predominance, are the global population most impacted by multiple sclerosis (MS). A full understanding of this progressive and disabling acquired autoimmune disease of the central nervous system (CNS) still eludes the medical profession. Most likely caused by complex gene-environment interactions, with the latter being the more significant factor, recent advances in MS diagnosis and treatment are translating into earlier detection and better treatment outcomes. This opens the potential for long-term remission and even cure in small subsets of affected individuals, although long-term outcomes of the emerging disease-modifying therapies (DMTs) are currently largely unknown. This article will highlight some of the new paradigms in understanding and managing MS and associated implications for risk assessment.

Challenging Previously Held Views

MS is a chronic condition of variable course in which the patient's immune system attacks the nerve fibers (axons) of the patient's central nervous system (CNS). Diagnosis is based on the most recent (2017) revision of the McDonald Criteria for the Diagnosis of Multiple Sclerosis, which was first developed in 2001 and is reviewed and updated every five years.[1] While there are many nuances in the diagnostic process, at the most basic level, confirming MS requires evidence of CNS damage that is both disseminated in time (DIT) and in space (DIS), i.e., being able to show a timeline for the damage and where in the nervous system it occurred.

Table 1 shows the combination of clinical findings, imaging and laboratory tests used by the McDonald Criteria to confirm a diagnosis.

A finding of oligoclonal bands in cerebrospinal fluid (CSF) tests can now be used to demonstrate DIT and confirm a diagnosis, as this indicates intrathecal antibody production. This finding can also be used to assess treatment response and prognosis, as it has been shown to associate with higher risk of a subsequent MS attack.[1]

Advances in magnetic resonance imaging (MRI) technology, including volumetric and functional imaging, are also expanding the role of imaging in MS beyond its current clinical application of disease activity estimation to include assessment of treatment response and long-term clinical outcomes.

Recently, researchers have trained a machine learning algorithm to predict the progression of disability and possible responses to treatment based on an analysis of early MRI abnormalities.[2] The research defined three MS subtypes from the results, with one subtype showing the highest risk of progression and rate of relapse, yet also demonstrating the most significant treatment response. This data-driven approach and similar insights into what influences progression has the potential to be used in future clinical

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Table 1: The 2017 McDonald Criteria

Clinical Episodes	Objective Clinical Lesions	Additional Requirements to Satisfy Diagnosis
2 or more	2 or more	None
2 or more	1	Dissemination in Space (evidenced either by MRI or via second clinical attack implicating a different CNS site)
1	2 or more	Dissemination in Time (evidenced by MRI, CSF test, or via second clinical attack)
1	1	Dissemination in Space AND Time (evidenced by MRI, CSF test, or via second clinical attack)
0/Progressive at Onset	N/A	• One year of disease progression PLUS two of the following three: ◦ DIS in the brain (periventricular, cortical or juxtacortical, or infratentorial regions) ◦ DIS in the spinal cord ◦ Positive CSF

Source: Thompson AJ, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald Criteria. Lancet Neurology[1]

trials to stratify patients, individualize treatment, and might even be a crucial step toward finding new treatments.

Current limitations of treatment stratification in MS are due partly to the lack of clear pathophysiological boundaries of the currently identified clinical phenotypes.

The clinical distinctions made among the three subtypes are:

- Relapsing remitting MS (RRMS): This is the most commonly encountered form. It is characterized by periods of stability (remission) followed by episodes of symptom exacerbations (relapses). A second clinical attack typically occurs within the first two years after an untreated RRMS episode.
- Secondary progressive MS (SPMS): More than half of RRMS patients advance into SPMS 10 to 15 years after onset. In SPMS, symptoms worsen progressively without remission and disability accumulates.
- Primary progressive MS (PPMS): This is MS's most rapidly progressive form. It is characterized by symptoms that gradually and steadily worsen over time from initial presentation without relapses and remissions, and comprises about five to 15% of all cases.

Two related conditions along the diagnostic continuum are also described:

- Clinically isolated syndrome (CIS): This would be a patient's first clinically recorded inflammatory demyelinating CNS event. Such events do not generally fulfill all the diagnostic criteria for MS. However, they may indicate a patient's possible predisposition toward the development of clinically definite MS. The cumulative risk of developing the disease after a single episode of optic neuritis was assessed in a small Italian study in 2000. The study suggested a probability of 13% after two years, 30% after four years, 38% after six years, and 49% after eight and ten years.[3] Contemporary ophthalmological and neurological management would therefore most likely include an MRI scan after a first episode of optic neuritis.
- Radiographically isolated syndrome (RIS): In this, brain lesions characteristic of MS are incidentally found in MRIs performed for other conditions in asymptomatic patients.

All of these clinical distinctions are currently being challenged. Additionally, the MS diagnostic continuum is expanding to include preclinical (asymptomatic) or prodromal (early signs and symptoms, such as RIS) disease. This is becoming increasingly important for

insurers, as those diagnosed as having RIS are not eligible for treatment according to current guidelines, yet one study found that approximately one-third of these individuals progress to MS within five years.[4]

Furthermore, neurodegeneration can be present from the clinical onset of MS, with progressive atrophy already often seen on early MRI scans in MS patients. This begs the question whether some or all MS patients might benefit from early treatment intervention that could limit or prevent end-organ damage.

On the opposite end of the disease spectrum, only limited treatments are available for those with PPMS. Its rapid progression has to date made it difficult to assess treatment effects and has thus produced disappointing clinical trial results. In some instances, PPMS diagnoses have been reclassified to another subtype so that the patient could obtain treatment, challenging the reasonability of the current stratification of disease states.

Thus, similar to other neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease, a shift toward preclinical screening and diagnosis of MS for at-risk groups will need to be considered both from the potential of studying preventive strategies (although these may take several years to produce meaningful results) and from a clinical and disease outcome perspective.

This shift could impact all insurance product lines quite significantly. Mortality, morbidity, and healthcare benefits would each be impacted differently. Although mortality and disability could show improvements over time, critical illness and health products would potentially be the most adversely affected by any fundamental change in the diagnostic and/or disease management approach.

Trends in Outcomes and Current Treatment Eligibility

Treatment of MS used to focus only on episodes of disease relapse. In recent years, newer approaches using disease-modifying therapies (DMTs) earlier in the course have increasingly been employed and have improved outcomes. As mentioned, quantifying treatment efficacy in terms of clinical trial outcomes has been challenging, owing to the inherent limitations of adequately measuring long-term disease outcomes using short-term studies, but analyses of trends seen in long-established MS registries have indicated secular improvements in both patient longevity and functional outcomes.

In recent years, newer approaches using disease-modifying therapies (DMTs) earlier in the disease course have increasingly been employed and have improved outcomes.

Although predating many of the newer treatment advances, a 2015 population-based Canadian study found that survival improved over a 27-year time period for the MS population but remained somewhat lower than for a matched population without MS.[5] Median survival from birth in the MS population was 75.9 years vs. 83.4 years in the matched population. The impact of comorbidity was also considered and was associated with increased mortality as expected, but not greater than in the matched study population.

In the long-term EPIC (expression/genomics, proteomics, imaging, and clinical) single-center prospective observational cohort, originally set up at the University of California in San Francisco in 2004, individuals with RRMS were recently found to transition to SPMS at a median of 16.8 years after disease onset.[6] Outcomes in this contemporary and actively managed cohort are currently assessed using clinical measures (relapses), radiographic measures (MRI activity), and progression of disability using various disability scales, the most common being the Kurtzke Expanded Disability Severity Scale (EDSS).

In a very recent study, the effect of DMTs on long-term disability in people with MS was assessed using observational data from the MSBase registry, an international registry which focuses on the study of MS and other neurological diseases.[7] Comparing disability outcomes over 15 years or more of follow-up during periods of DMT treatment versus no treatment in patients with RRMS, worsening disability was approximately 20%

lower for treated patients, with a 67% reduction in the need for a walking aid.

Evidence supports the notion that everyone with a diagnosis of RRMS should be treated with DMT, and that earlier treatment is associated with better outcomes.

Treatment for other clinical phenotypes includes for those with CIS but who also have additional clinically silent lesions in the brain or spinal cord imaging. This is in line with an overall trend toward treating those with CIS to delay onset of clinically definite MS, those with SPMS who have clinically active disease or new lesions on imaging, and those with PPMS who are younger (age ≤55 years) or are showing active disease on MRIs.

When treatment is indicated, shared decision-making is advocated, and individualized treatment plans are becoming the norm.

Contemporary MS management requires a broad, multilayered approach to controlling acute attacks, managing disease progression, and treating debilitating symptoms.

Rising to the Treatment Challenge

In MS, regardless of the clinical disease type, inflammation leads to nerve cell damage with subsequent axonal damage (axonal transection) and demyelinating sclerotic plaque formation, which disrupts nerve conduction throughout the CNS leading to eventual and irreversible neurological damage. The goals of treatment include suppression of inflammation and active disease, and a deceleration of progressive disease with concomitant preservation of function. An ultimate aspiration would be cure.

Contemporary MS management requires a broad, multilayered approach to controlling acute attacks, managing disease progression, and treating debilitating symptoms. Treatments can be classified into DMTs (MS-specific) and symptomatic (non-MS-specific) therapies.

Many different classes of MS-specific DMTs are available, each of which has different mechanisms of action and routes of administration. Table 2 (on p.12) lists the currently approved DMTs, their mechanisms of action, routes of administration, relative potency, brief description of major adverse effects and monitoring requirements, and current indications.

The first DMT was approved almost 30 years ago. Before this, there were no known drug treatment options that affected MS disease progression at all. Since then, several DMTs have been approved, including nine within the last two years alone.

New therapies that work at various points along the disease continuum have broadened the landscape for significant improvements. DMTs for MS have been found to decrease the frequency of relapses, reduce the number of MRI findings, and reduce patient short-term disability. Although caution is advised when interpreting the variation across populations and time periods studied, treatment with DMTs can reduce the annualized relapse rate (a measure of treatment efficacy) by 29% to 68%, compared with placebo or comparator drug.[8] Data are limited, but some DMTs may even slow the underlying neurodegenerative (atrophy) process, although the overall impact of these newer modalities may not yet be fully appreciated.

There has also been a shift in understanding the role B-cells may play in the immunopathogenesis of MS away from a purely T-cell-mediated pathogenesis, hence the introduction of B-cell-depleting DMTs.

As with many other diseases, treatment risks and benefits must be considered before choosing the appropriate therapeutic approach. For MS, this could involve starting with less potent DMTs and stepping up to a more potent medication as disease activity requires. The alternative is to begin with a more potent DMT as first-line therapy, which although not confirmed in any randomized trial as yet, might be the preferred option in terms of tolerability and adherence as well as reducing the risk of SPMS conversion and permanent disability. This is the big debate emerging in MS management.

An emerging MS treatment goal and outcome measure is NEDA (no evidence of disease activity). Achieving NEDA means that for MS patients currently being treated with drugs, the disease is stable (i.e., no new relapses, no progression in disability, and no new or enlarging lesions showing up on MRIs). Long-term persistence of NEDA at this time is still unknown and probably unlikely, and clinical relapses after a period of NEDA might represent a later stage of overall disease activity.[6, 9] This goal has led to treatment escalation earlier in the disease course or early treatment with more potent therapies as first-line treatments.

NEDA is currently defined and evidenced by these clinical parameters:

- NEDA 1 and 2 – absence of relapses and disease progression
- NEDA 3 – adds no clinical activity and no inflammatory MRI activity
- NEDA 4 and 5 – adds normalizing MRI atrophy, and normal biomarker levels (i.e., normal CSF neurofilament levels)

Types of Treatments

Some regimes start with oral therapies, which have intermediate efficacy and risk. Women with MS who wish to conceive would need to be appropriately counseled and treated, given the teratogenic potential of many of the DMTs.

Disease-specific DMTs

- Maintenance/escalation therapy: active and ongoing therapy scaled over time that are either immunomodulatory (interferon beta, glatiramer acetate, teriflunamide) or immunosuppressive (fingolimod, or monoclonal antibodies [mAb] such as natalizumab and ocrelizumab).
- Immune reconstitution therapy: short-course therapy resulting in long-term, qualitative immune function changes and disease remission (which is the closest to a potential cure). Treatments include alemtuzumab, HSCT (impacting the innate and adaptive immune systems), and cladribine (impacting the adaptive immune system).
- PPMS-specific therapy: Ocrelizumab is currently the only approved DMT for treatment of PPMS. As a B-cell depleting treatment, it is thought specifically to reduce B-cell-mediated inflammation implicated in the neurodegenerative process. Premedication with a corticosteroid and antihistamine are required.

  Treatment for mild relapses may not be necessary, but high-dose systemic steroids are used for moderate to severe relapses. Plasma exchange is also sometimes tried for relapses that are either severe or refractory to steroid treatment.

Symptomatic and other non-DMS treatments

As MS progresses, supportive treatments may be needed for CNS damage or associated conditions such

as bladder dysfunction, neuropathic pain, cognitive or gait impairments, psychiatric comorbidities, or sleep disruption. Comorbid conditions worsen the trajectory and associated disability in MS. Treatment, especially of associated depression or anxiety disorders (present in up to 50% of those with MS), leads to improved patient quality of life and usually correlates with better treatment adherence.

Supervised lifestyle and wellness modifications seem also to impact outcomes positively, although evidence for this is modest. Smoking cessation must be strongly encouraged, as smoking has a negative impact on prognosis. Very little robust evidence exists for the impact of dietary modifications in MS. Psychological support is crucial throughout and rehabilitation is especially necessary for progressive disease.

Multidisciplinary care, although not formally studied in randomized trials, is intuitively advisable wherever possible, given the complex nature of the disease and its multiple associated comorbidities.

Table 2: DMTs and Corresponding Considerations, Indications

DMT	Mechanism of action	Class	Efficacy (generalized from clinical evidence)	Administration route	Required monitoring	Rare aftereffect	Indication
Fingolimod Siponimod Ozanimod	Immuno-suppressive, can cross blood-brain barrier	Sphingosine 1-phosphate (S1P) receptor modulators	High	Oral	CBC, LFT, U&E, TFT, eye and skin examination	Bradycardia, heart block, infections, macular edema	RRMS, CIS, SPMS
Interferon beta	Immuno-modulatory	Interferons	Moderate	SC or IM	CBC, LFT, U&E, TFT ,	Liver toxicity	RRMS, CIS, SPMS
Glatiramer acetate	Immuno-modulatory	Amino acid copolymer	Moderate	SC	CBC, LFT (sometimes none)	Skin necrosis	RRMS, CIS, SPMS
Teriflunomide	Immuno-modulatory	Pyrimidine synthesis inhibitor	Moderate	Oral	CBC, LFT, U&E	Teratogenicity, hepatotoxicity	RRMS, CIS, SPMS
Dimethyl fumarate; Diroximel fumarate	Pleiotropic	Fumarates	High	Oral	CBC, LFT, U&E	Infections, liver toxicity	RRMS, CIS, SPMS
Cladribine	Immune reconstitution	Purine analogue	Very high	Oral	CBC, U&E, TFT, age-appropriate cancer screenings,	Malignancy, infections, and teratogenicity	RRMS, SPMS
Ocrelizumab (Anti-CD20) Ofatumumab (Anti-CD20) Natalizumab (Anti-α4 integrin receptor) Alemtuzumab (Anti-CD52)	Immuno-suppressive Immune reconstitution	Monoclonal antibodies	High/ Very high	IV, SC	CBC, LFT, U&E, TFT, screening for underlying infections (TB, HIV, JCV, Hepatitis B and C)	Malignancy, Hepatitis B reactivation, tuberculosis, hypersensitivity reactions, autoimmune conditions (thyroid, immune thrombo cytopenic purpura [ITP])	PPMS, RRMS, CIS, SPMS

Source: From McGinley, et al. and Dobson, et al.[8, 9]

Table 3: Prognostic Consideration in MS

Favorable factors	Unfavorable factors
• Female • Relapsing-remitting onset • Sensory symptoms or optic neuritis only • Younger age (<30) at onset • Low number of relapses early in disease course (<2 in first two years) • Complete recovery of neurological function following relapse • Long time (>5 years) until assignment of an EDSS score of 4 • Low rate of increase in lesion load on MRIs	• Male • Progressive onset • Motor symptoms, cerebellar symptoms, or bowel/bladder problems • Older age (>30) at onset • High number of relapses early in disease course (>2 in first two years) • Incomplete recovery of neurological function following relapse • Short time (<5 years) until assignment of EDSS score of 4 • High rate of increase in lesion load on MRIs, particularly in first five years after MS diagnosis

How Long Should Treatment Continue?

Once started, treatment is usually lifelong. Breakthrough disease (relapses, attacks) or adverse side effects might necessitate a change in medication. The question regarding duration of treatment, however, can become particularly challenging to answer if treatment is started at the CIS or RIS stage.

Regular neurologic examinations and MRIs are necessary, including individualized laboratory investigations based on concomitant DMT or other therapy, to keep track of the course and speed of the disease.

Trials are ongoing to evaluate whether treatment can be discontinued in patients with nonactive disease. Observational studies have suggested that a group who might benefit from a discontinuation of treatment, as they have a low risk of disease recurrence, are older individuals who have been stable clinically and radiographically for at least four years.

What Are the Prognostic Indicators?

The most important factors indicating poor prognosis for MS seem to be the number and type of attacks, presence of highly active disease, more extensive disease burden detected on imaging, and poor or partial recovery between relapses.[10]

High frequency of relapses in the first few years is a bad prognostic sign, as the average relapse rate in first few years is approximately one per year. In terms of type of attack, vision loss as a presenting symptom is associated with a better outlook whereas primary bulbar symptoms, motor attacks, or ataxia are associated with a poorer prognosis. Additional clinical factors associated with a worse prognosis are male gender, older age of onset, multifocal presentation, cognitive impairment, and involvement of pyramidal and cerebellar symptoms. These are represented in Table 3.

Conclusion

Medical science's understanding of MS continues to advance, particularly with respect to improvements in its diagnosis and treatment. Earlier diagnosis and improved imaging and other investigative tools are likely to impact disease outcomes positively.

In terms of emerging treatments, hematopoietic and mesenchymal stem cell therapy as well as remyelination therapies are being studied in ongoing clinical trials but are not yet part of standard medical care. The impact of a breakthrough treatment that could repair or reverse the significant and debilitating progression of the disease would be tremendous. The cost implications of these advances would need to be considered and balanced with the benefit of being able to restore function and reduce progressive disease and disability. Nevertheless, it is an exciting time in the evolution of the understanding and management of MS. This will be an area to continue to observe very closely for any improvements that might meaningfully impact risk assessment. RF

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PHARMACOGENOMICS: THE FUTURE OF PRECISION MEDICINE

Abstract

Pharmacogenomics is the branch of precision medicine that studies how a person's genes affect their responses to drugs. It studies the different components of the genome that control the metabolism of drugs and how drug treatments can be adapted to a person's individual genetic make-up, while pharmacogenetics is the study of specific genetic variants that causes different drug responses in people. Although both terms overlap, pharmacogenomics takes a wider look at the overall genetic picture, rather than focusing on how single genes affect the action of pharmaceutical drugs.[1]

Background

Genetic variants influence drug therapy and play a fundamental role in the treatment outcome of diseases such as cancer, human immunodeficiency virus (HIV), heart disease, and hypertension. A genetic variant is a difference in genetic sequences among people. It has been estimated that 97% of individuals have high-risk variants that affect drug absorption, distribution, metabolism, and excretion. Data from the 1000 Genomes Project, which ran between 2008 and 2015, has contributed to the identification of several genomic variants that impact drug treatment.[2]

Variants can be influenced by heritability, epigenetic stimuli such as exercise, diet, smoking, air pollution, and a combination of these factors. Variants can also help to explain how responses to drugs can differ from person to person, adverse drug reactions (ADR), and differing therapeutic outcomes in diverse ethnic populations. Research has already found that between 40% and 70% of patients either do not respond adequately to drug treatment or they experience ADRs, and 30% of hospital admissions for ADRs are life-threatening. Understanding drug-gene interactions is allowing treatments to be personalized, which is resulting in better safety outcomes for the patient.[3]

If genomic information is routinely available in a person's health record, it could be used to make more beneficial and faster treatment decisions.[3]

Benefits of Pharmacogenomics

For variants that have been identified, therapies can be personalized using an individual's genetic profile to optimize treatment outcomes by selecting specific drug treatments or altering drug dosage levels.

The benefits of pharmacogenomic testing for a patient include reduced drug toxicity and hospital admissions, and improved treatment efficacy and general health. However, challenges remain, such as the current lack of guidelines and training around testing, and ongoing regulatory and ethical concerns. For many patients, there is significant concern as to who (or

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which entity) will have access to their test results and how that access might affect their insurability. Legislation often prohibits the use of genetic test results in insurance, but this means insurance applicants may miss out on certain benefits to them because of genetic testing.

The cost of testing differs across laboratories and by country, but a once-in-a-lifetime test for the genetic variants which affect commonly prescribed drugs may be less costly in the long run than carrying out regular blood tests to measure drug concentrations over a lifetime.

Pharmaceutical Labeling

The U.S. Food and Drug Administration (FDA) publishes a list of approved drugs (currently at 178) with pharmacogenomic labeling that contains information on indications for use, dosage recommendations, and warnings. The label information for abacavir, for example, a drug used to treat Human Immunodeficiency Virus (HIV), includes a warning for patients with the HLA-B*5701 allele, as a portion of these patients develop severe hypersensitivity reactions to the drug.[3]

The benefits of pharmacogenomic testing for a patient include reduced drug toxicity and hospital admissions, and improved treatment efficacy and general health.

Demonstrating how important pharmacogenomics has become, the annual proportion of new FDA drug approvals with pharmacogenomic labeling has increased nearly threefold, from 10.3% in 2000 to 28.2% in 2020.[5]

Common Genetic Variants

Cytochrome P450 enzymes (CYPs) are primarily responsible for the metabolization of pharmaceutical drugs. Most CYP genes that encode for enzymes involved in drug metabolism have genetic variants. Importantly, there are three phenotype variants: ultra-rapid metabolizers, extensive (normal) metabolizers, and poor metabolizers. The most significant variants are observed in the CYP2C9, CYP2C19, CYP2D6, CYP3A4, and CYP3A5 genes. CYP3A4 and CYP3A5 contribute to the metabolism of approximately half of all drugs, while CYP2D6 acts on a quarter of all prescription drugs.[1]

Liver enzymes change the chemical make-up of drugs, sometimes making them more effective or less effective. Variants in the CYP2C19 gene, a liver enzyme involved in the processing or metabolizing of at least 10% of commonly prescribed drugs, is known to impact dosage levels for blood thinners such as warfarin and clopidogrel.[6] As warfarin has a narrow dosage range for treatment, genetic testing is available to assess if patients are especially sensitive to warfarin and therefore might require monitoring on a more frequent basis.[7]

The liver enzyme CYP2D6 plays a major role in human metabolization and in the elimination of commonly prescribed drug classes, including opioids, antiestrogens, antiarrhythmics, antipsychotics, antidepressants, β-blockers, antihypertensives, and antihistamines. People with extra copies of the CYP2D6 gene produce too much CYP2D6 enzyme, which means they process drugs of the listed classes extremely quickly. Meanwhile, some have copies of the CYP2D6 gene that do not work, which means they process these drugs very slowly.[6]

Evidence to date shows that the prevalence and frequency of variants in drug-related genes is highly diverse across different ethnic populations. Roughly half of all functional variants in these genes are unique to individuals of African, South Asian, East Asian, Finnish, non-Finnish European, and Latino ancestry.[2]

Effects on Disease Outcomes

Pharmacogenomics plays a significant role in cancer therapy, helping healthcare practitioners make appropriate drug choices and avoid drug toxicity. For example, 5-fluorouracil (5-FU) is widely used in the treatment of colorectal cancer, but resistance to it as well as the presence of toxicity remain a problem. Variants in the DPD gene have been identified in 3% to 5% of individuals, and those deficient in the DPD enzyme are

known to experience higher 5-FU toxicity.[8] In another example, variants in the GSTM1 and GSTT1 genes, which play a role in detoxifying cancer drugs, can reduce the efficacy of cisplatin, carboplatin, and oxaliplatin.[9]

Pharmacogenomic biomarkers have also emerged as an important tool in predicting recurrence of mood disorders. A recent meta-analysis showed that in 1,737 patients, pharmacogenetic-guided therapy achieved much better outcomes, with patients 1.7 times more likely to achieve symptom remission compared to patients who did not receive this guided therapy.[10]

Insurance Implications

Some health insurance policies already offer patients access to genetic tests, which may lead to more successful treatments and survival outcomes. Coverage of tests for KRAS, EGFR, HER2, and BRAF are common, but few policies cover tests for PMIRARA, CD25, or G6PD. The life insurance industry could benefit by exploring opportunities to apply pharmacogenomics to innovative product development. Pharmacogenomic benefits could, for example, be judiciously used to promote better disease control, improve the potential to avoid adverse drug reactions, and improve efficacy and survival. The principles of clinical validity and clinical utility should also be considered when recommending any type of genomic testing to ensure real benefit. Of course, insurers must keep in mind the legal, ethical, and cost barriers in using pharmacogenomic information.

The life insurance industry could benefit by exploring opportunities to apply pharmacogenomics to innovative product development.

Conclusions

Personalized medicine and the use of pharmacogenomic biomarkers has been successful in improving patient outcomes through better drug efficacy and fewer adverse drug reactions. The evaluation of genetic markers to predict drug responses and health outcomes is opening new pathways in the prevention and treatment of diseases such as cancer, heart disease, and viral illnesses. The wider implementation of pharmacogenomics in clinical care could pave the way for life insurance companies to offer more favorable terms to insurance applicants and improved benefits to insurance policyholders. RGA

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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 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. Daniel D. Zimmerman at dzimmerman@rgare.com or Dr. Dave Rengachary at drengachary@rgare.com.

Longer Life Foundation 2021-2022 Grants	
Investigator and Project Title	**Project Description**
Alex Holehouse, M.Sc., Ph.D. (Year 2) Predicting the Functional Impact of Genetic Variation Within Intrinsically Disordered Protein Regions	This project addresses a critical barrier to progress in understanding the molecular basis of disease. Intrinsically disordered proteins and protein regions (collectively referred to as IDRs) are protein regions that do not fold into a set 3D structure.
Anuja Java, M.D. The Role of Complement in Hypertensive Disorders of Pregnancy	This proposal aims to identify rare and common genetic variants associated with preeclampsia and functionally characterize the variants to determine their clinical significance. This may help to identify high-risk patients who could be treated with anti-complement therapy to prevent short- and long-term complications.
Devesha Kulkarni, M.Sc., Ph.D. (Year 2) Defining the Role of Intestinal Immune Cell Balance and its Association with Obesity	In the last 10 years, researchers have identified the role of dysbiosis (imbalance in gut microbiota) in the development of obesity and its related comorbidities. The results of this study will form the scientific basis for therapeutic approaches to prevent or reverse obesity and associated diseases.
Hrishikesh Kulkarni, M.D., MSCI Targeting the Amplification Loop Between Mitochondria and Complement Activation in Acute Respiratory Distress Syndrome (ARDS)	The overarching goal of this project is to enhance both the survival and quality of life after acute respiratory distress syndrome (ARDS), a major cause of mortality due to both infectious and sterile causes.

2021-2022 Grants	
Kathryn Lindley, M.D. (Year 2) Angiogenic Imbalance and Diastolic Dysfunction in Preeclampsia	Preeclampsia during pregnancy is associated with the development of future cardiovascular disease (CVD). Recent epidemiologic studies suggest that rather than being a marker of CVD, preeclampsia is mechanistically linked to the development of CVD. The goal of this study is to identify preeclampsia-related biomarkers associated with left ventricular diastolic dysfunction, which may help identify women at high risk for future CVD.
Patrick Lyons, M.D. Determining Causes and Potential Preventability of Clinical Deterioration Among Oncology Inpatients	This proposal aims to develop knowledge of the pathways that deteriorate clinically in hospitalized cancer patients, under the scientific premise that early identification of these pathways can improve outcomes through tailored evidence-based interventions.
Bettina Mittendorfer, Ph.D., Director, Longevity Research Program (Year 3 of 3) Dietary Protein and Cardiovascular Health	The goal of this three-year LRP project is to evaluate the effect of dietary protein (plant vs. animal origin) on cardiovascular health and to determine the physiological and cellular mechanisms involved. This topic is particularly important because consumption of protein-fortified plant-based foods is now a popular trend.
Nathan Stitziel, M.D., Ph.D. Targeting Receptor Interactions With SVEP1, a Circulating Biomarker of Longevity in Humans	SVEP1 has emerged as a novel circulating biomarker of age and longevity in humans that is causally associated with risk of multiple age-associated chronic diseases. In this proposal, the investigator will assess how circulating SVEP1 influences the behavior and cellular signaling of endothelial cells, a key cell type involved in the SVEP1-associated diseases that is constantly exposed to circulating proteins.

LLF Welcomes Dr. Preeti Dalwari, Director of Member Engagement

The Longer Life Foundation is proud to announce that Dr. Preeti Dalwari, Medical Director, U.S. Mortality Markets, RGA, has been named Director of Member Engagement for the Longer Life Foundation. The newly created role will serve to drive outreach and increase meaningful engagement by members of the insurance industry with the LLF.

MEDICAL TEAM UPDATE

RGA welcomes **Dr. Megan Leivant**, Vice President and Medical Director, U.S. Mortality Markets, to our global team of medical doctors. Based in Carmel, Indiana (U.S.), Dr. Leivant is board-certified in internal medicine and practiced outpatient internal medicine for a decade before transitioning to insurance medicine in 2018. She has earned FLMI Level 1 and ALU Level 1 Certificates and is working toward her FLMI and FALU designations, as well as her board certification in insurance medicine.

Dr. Lisa Duckett recently retired as Vice President and Medical Director, U.S. Mortality Markets. All of us at RGA would like to thank Lisa for her years of great service and wish her well in her new endeavors.

ReCite

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

Associations Between Physical Multimorbidity Patterns and Common Mental Health Disorders in Middle-Aged Adults: A Prospective Analysis Using Data From the UK Biobank

Ronaldson A, et al.
The Lancet. 2021 June.
https://kclpure.kcl.ac.uk/portal/en/publications/associations-between-physical-multimorbidity-patterns-and-common-mental-health-disorders-in-middleaged-adults-a-prospective-analysis-using-data-from-the-uk-biobank(cc704bed-f088-41eb-85c2-276e5ae4ca52).html

This study aimed to identify specific patterns of physical multimorbidity, defined as the presence of two or more physical long-term conditions, and to examine the extent to which these specific patterns could predict future common mental health disorders in 154,367 middle-aged adults enrolled in the UK Biobank database.

Prospective associations were assessed between physical multimorbidity status at baseline assessment (2006-2010) and findings of depression and anxiety at follow-up (2016) according to the Patient Health Questionnaire (PHQ)-9 and the Generalised Anxiety Disorder Assessment (GAD)-7.

Compared to those with no physical multimorbidity, having two, three, or four physical conditions was prospectively associated with emergent and persistent depression and anxiety at follow-up in a dose response manner. Respiratory conditions and pain/gastrointestinal conditions were the strongest predictors of new onset depression and anxiety.

Editor's Note: *These findings might have significant implications for the way we view multimorbidity in the underwriting process in the future.*

Age at Menopause and Risk of Ischemic and Hemorrhagic Stroke

Welten SJGC, et al.
AHA Stroke. 2021; 52(8): 2583-91.
https://www.ahajournals.org/doi/10.1161/STROKEAHA.120.030558

Data was analyzed from 16,244 postmenopausal women, aged 26 to 70 years at recruitment, who were enrolled in the European Prospective Investigation into Cancer and Nutrition – Netherlands cohort between 1993 and 1997. Participants were followed for occurrence of stroke until January 1, 2011. All analyses were adjusted for age, smoking, systolic blood pressure, and body mass index.

A total of 830 strokes (571 ischemic, 162 hemorrhagic, 97 unclassified) were identified. Earlier menopause was associated with an increased risk of total stroke. Compared with women who had experienced menopause between 50 and 54 years of age, women who underwent menopause before age 40 had a 1.48x higher risk of total stroke. In continuous analyses, the study also observed a 2% lower total stroke risk for each year menopause was delayed. The risk between earlier menopause and stroke was confined only to ischemic stroke and not hemorrhagic stroke. The association with age at menopause was also stronger for natural menopause than for surgical menopause.

Editor's Note: *Whether this should have clinical consequences such as intensified risk factor control should be subject of further studies and might be crucial to cardiovascular risk profiling of females.*

Initial Observations on Age, Gender, BMI and Hypertension in Antibody Responses to SARS-CoV-2 BNT162b2 Vaccine

Pellini R, et al.
The Lancet EClinical Medicine. 2021 June 04.
https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(21)00208-X/fulltext

The goal of the study was to analyze the antibody titre seven days after the second dose of the BNT162b2 (Pfizer) vaccine in a group of 248 healthcare workers (HCWs), and thereafter to investigate how antibody titre changes in correlation with age, gender, BMI, and hypertension.

After the second dose of the vaccine, 99.5% of participants developed a humoral immune response. The geometric mean concentration of antibodies among the vaccinated subjects after the booster dose was higher than that of human convalescent sera. Multivariate linear regression analysis of arbitrary units per milliliter (AU/mL) by age, gender, and BMI multivariate was performed by the inclusion of covariates. This analysis demonstrated that younger age and female gender are statistically associated with differences in antibody response after vaccination, whereas BMI and hypertension have no statistically significant association.

Editor's Note: *Insurers will need to be aware that the development of tailored vaccination strategies might impact underwriting in the future as more data emerges to assess immunogenic efficacy and the correlation with age, gender, and BMI.*

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.

The Promise of Liquid Biopsy in Advancing Cancer Diagnosis and Treatment (running time: 41:48)
Dr. Radhika Counsell, MBBS, Consulting Medical Officer, RGA UK
https://www.rgare.com/knowledge-center/media/videos/the-promise-of-liquid-biopsy-in-advancing-cancer-diagnosis-and-treatment

Liquid biopsy is one of the most promising new areas of investigation in cancer treatment and cure. This webcast provides an in-depth introduction by Dr. Counsell to liquid biopsy – what it is, its current and potential future role in cancer care and treatment, and its implications for insurers.

Cannabis: A New Era (running time: 10:45)
Hilary Henly, FCII, Global Medical Researcher, RGA
https://www.rgare.com/knowledge-center/media/videos/cannabis---a-new-era

With cannabis becoming an increasingly used product, this webcast provides an important view into its legal status worldwide, its growing and evolving utilization in medical, wellness, and recreational settings, and its implications for insurance medicine and insurers.

RGA THOUGHT LEADERSHIP PUBLICATIONS

RGA publishes content on many topics of interest to insurers. Here are links to some recent publications:

Better Living Through Genetics: First-of-a-Kind Global Survey Reveals Evolving View of an Emerging Science
By Carmela Tedesco, Vice President, Business Initiatives Lead, RGAX, and Leigh Allen, Director, Global Surveys and Distribution Research, RGA
https://www.rgare.com/knowledge-center/media/articles/better-living-through-genetics-first-of-a-kind-global-survey-reveals-evolving-view-of-an-emerging-science

Bridging the Insurance Care Gap for Mental Health Disorders
By Dipali Jawalkar, Executive Director, Underwriting, RGA Hong Kong
https://www.rgare.com/knowledge-center/media/articles/bridging-the-insurance-care-gap-for-mental-health-disorders

Calorie Restriction (CR) – What Is It and What Does the Research Tell Us?
By Hilary Henly, FCII, Global Medical Researcher, RGA
https://www.rgare.com/knowledge-center/media/research/calorie-restriction-(cr)-what-is-it-and-what-does-the-research-tell-us

Duration of Natural and Vaccine-Induced COVID-19 Immunity: What We Know and What We Need to Learn
By Hilary Henly, FCII, Global Medical Researcher, RGA
https://www.rgare.com/knowledge-center/media/research/duration-of-natural-and-vaccine-induced-covid-19-immunity-what-we-know-and-what-we-need-to-learn

Gene Re-Education: How Gene Therapy Promises to Challenge and Transform Insurance
By Barb Tomlin, BSN, M.S., Director (Ret.), ROSE Consulting Group – Quota Share, and Mari-Pat Pusey, MBA, Senior Product Director, OptumRx
https://www.rgare.com/knowledge-center/media/articles/gene-re-education-how-gene-therapy-promises-to-challenge-and-transform-insurance

Global Health Brief: Prognostic Genomics and Breast Cancer
By Dr. Elizabeth Gil Aguilar, Medical Manager – Health (Ret.), Latin America, RGA
https://www.rgare.com/knowledge-center/media/articles/global-health-brief-prognostic-genomics-and-breast-cancer

mRNA Vaccines: Is The Future Now?
By Hilary Henly, FCII, Global Medical Researcher, RGA
https://www.rgare.com/knowledge-center/media/research/mrna-vaccines-is-the-future-now

New Medication for Alzheimer's Disease: What You Need to Know about Aducanumab
By Dr. Dave Rengachary, DBIM, FALU, FLMI, Senior Vice President and Chief Medical Director, U.S. Mortality Markets, RGA Reinsurance Company
https://www.rgare.com/knowledge-center/media/articles/what-you-need-to-know-about-aducanumab

Redefining Wellness: Global Survey Sheds New Light on Opportunities for Insurers
By Carmela Tedesco, Vice President, Business Initiatives Lead, RGAX, and Leigh Allen, Director, Global Surveys and Distribution Research, RGA
https://www.rgare.com/knowledge-center/media/articles/redefining-wellness-global-survey-sheds-new-light-on-opportunities-for-insurers

Worth a Shot: An Industry Case for Vaccination
By Dr. Daniel D. Zimmerman, Senior Vice President, Head of Global Medical, RGA Reinsurance Company, and Hilary Henly, FCII, Global Medical Researcher, RGA
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