Greetings, and welcome to the September 2019 edition of ReFlections!

We are delighted to announce that Dr. Adela Osman is joining the ReFlections editorial team as Assistant Editor. Adela, who is Chief Medical Research Officer, RGA Reinsurance Company of South Africa Limited, has been a valuable member of RGA’s medical team for three years. She has more than nine years of experience in the insurance medicine field, most recently specializing in product development. We look forward to her leadership and contributions in the years to come.

A special thank-you goes out to Peter Barrett as he steps down from his service as co-editor of ReFlections over the last three years. He will continue in his busy U.K.-based role as Senior Vice President, Head of Global Support Team Underwriting, Claims and Medical Support, RGA.

This issue has several interesting and informative articles. First up is Part II of Dr. Newman L. Harris’s (Consultant CMO, RGA Australia) interesting and detailed exploration of ICD-11’s new approach to classifying chronic pain – information critical for insurance medicine professionals.

Also in this issue is an examination and update of the diagnostic and therapeutic modalities of Alzheimer’s disease from Dr. Lisa Duckett, Vice President and Medical Director, U.S. Mortality Markets, RGA. This is Dr. Duckett’s second article in ReFlections in which she adds significant information and insight. We present a Brief Report from Dr. Daniel D. Zimmerman, Senior Vice President, Chief Medical Director, Global Support Team, RGA, on the latest developments in ongoing efforts to create a universal flu vaccine – a topic of extreme interest to insurers worldwide.

The Longer Life Foundation (LLF) page features an interview with Bettina Mittendorfer, Ph.D., the new director of LLF’s Longevity Research Program (LRP). Dr. Mittendorfer’s career-long focus on nutrition’s impact on health is a great match for LRP’s mission, which she plans to broaden to encompass how obesity affects a range of disease states.

We hope you enjoy this issue and look forward to continuing to bring you top-caliber thought leadership.

Sincerely,
Dan and Adela
PART II: PROPOSED NEW CLASSIFICATION AND NOMENCLATURE FOR CHRONIC PAIN

Abstract

The most recent version of the International Classification of Diseases, 11th Revision (ICD-11), is introducing a new approach to classifying chronic pain that stratifies it in ways which will be new to many readers of ReFlections. It will be critical for insurance medicine professionals to understand the concepts within this new nosology as it will likely impact how underwriters assess risk and may even affect how claims are assessed and adjudicated.

This article is Part II of Dr. Harris’s exploration of this new pain nosology. Part I, which was featured in the May 2019 edition of ReFlections, focused on discussing chronic pain in general as well as chronic primary pain syndromes. Part II will address chronic secondary pain syndromes.

Background

Please see Part I of this article in the May 2019 edition of ReFlections for previous background discussion. [http://www.rgare.com/knowledge-center/media/articles/part-i-proposed-new-classifications-and-nomenclatures-for-chronic-pain]

Chronic Secondary Pain Syndromes

These pain syndromes are conditions related to other diseases, which are the underlying cause(s) of the pain presented. The proposed new ICD-11 codes become relevant as a co-diagnosis when pain issues warrant specific care; that is, when persistent pain becomes a problem in its own right above and beyond that of the causative pathology, which is not always associated with pain. In some instances, the pain might persist longer than the precipitating disorder.

• Chronic cancer-related pain

  This is pain caused directly by cancer (either a primary tumor or metastases) or by the treatment(s) for it. Persistent pain is generally prevalent in cancer survivors and chronic secondary pain syndromes include neuropathic and musculoskeletal pain. (Note that pain caused by chemotherapy or radiation is coded in this category. However, pain caused by surgical treatment of cancer is coded as chronic post-surgical or post-traumatic pain, described in the following section.)

• Chronic post-surgical or post-traumatic pain

  Irrespective of projected expectations of normal healing times, pain experienced after a surgery or other trauma is considered chronic if said pain is still felt three months after the surgery or trauma (so as to maintain consistency with the new code’s definition of “parent entity”). In other words, such pain may not be reflective of persistent primary pathology. In both post-surgical and post-traumatic conditions, neuropathic disturbance is common. On average, in 30% of cases, chronic peripheral neuropathic pain may be given as a co-diagnosis.
• **Chronic neuropathic pain**

Chronic neuropathic pain is subdivided into chronic peripheral and chronic central neuropathic pain. This type of pain is caused either by a lesion affecting or by a disease involving the somatosensory nervous system. Typically, such pain is experienced in the innervation territory pertinent to the damaged nervous system structure. It may occur either spontaneously or in response to sensory stimulation.

A diagnosis of chronic neuropathic pain requires that a patient have a history of nervous system injury, be it physical, chemical, or metabolic, the pain from which is associated with a specific neuroanatomical distribution. Similarly, associated sensory loss(es) or other neurological derangement(s) must be consistent with the innervation territory of the damaged nervous structure.

Confirmation of chronic neuropathic pain requires identification of the lesion or disease involving the nervous system via, for example, imaging, histopathology, or neurophysiological testing. The diagnosis cannot be applied purely on the basis of obtained history.

• **Chronic secondary headache or orofacial pain**

The definitional language for this type of pain cross-references substantially with that used by the International Headache Society (IHS), which was fully implemented in ICD-11’s chapter on neurology. That classification differentiates among the following:

– primary (idiopathic) headaches
– secondary (symptomatic) headaches
– orofacial pains including cranial neuralgias

Chronic headache and orofacial pain are defined as conditions which occur for more than two hours a day and for at least 50% of the days during a minimum three-month period. This classification category includes only chronic secondary headache and chronic orofacial pain; chronic primary headache is listed under chronic primary pain syndromes. In addition, the types of chronic orofacial pain detailed in the ICD-11 classification are more varied than those in the IHS classification, and include chronic dental and temporomandibular conditions.

• **Chronic secondary visceral pain**

This type of pain is defined in ICD-11 as “persistent or recurrent pain that originates from internal organs of the head and neck region and the thoracic, abdominal, and pelvic cavities.” Such pain can be perceived in the tissues of the body wall (i.e., skin and muscle) as well as in other areas that are receiving the same sensory innervation as the internal organ(s) where the pain (“referred visceral pain”) originates. The diagnostic entities within this category are further subdivided according to the dominant underlying causative mechanisms for the pain, such as mechanical factors, vascular factors, or ongoing inflammation.

Visceral pain due to cancer is classified as chronic cancer-related pain, while pain due to functional or unexplained mechanisms is classified as chronic primary pain.

• **Chronic secondary musculoskeletal pain**

This pain is defined as “persistent or recurrent pain that arises as part of the disease process directly affecting bone(s), joint(s), muscle(s), or related soft tissue(s).” This category is limited to nociceptive pain and therefore does not include pain experienced in musculoskeletal tissues that does not actually arise from those tissues, such as pain related to neural compression or somatic referred pain.
This diagnostic category is further subdivided according to the underlying etiologic mechanisms, such as inflammation, infection, autoimmune causes, dysfunctional metabolic disturbance(s), structural or anatomical changes in the affected tissues, or chronic musculoskeletal pain secondary to diseases of the motor nervous system; e.g., spasticity after central nervous system injury or the rigidity seen in Parkinson’s disease.

Pain disorders with musculoskeletal manifestation for which the cause is incompletely understood, such as non-specific pain or chronic widespread pain, are included in the section on chronic primary pain and are reviewed in Part I of this article.

**Severity and Other Extension Codes In ICD-11**

Extension codes, which were first introduced with ICD-10, provide more details than the stem code and are available for all chronic pain conditions. These pertain to pain severity, how the pain progresses over time, and evidence of psychological and social factors in the pain state. (See Table I.)

In assessing the severity of pain states, consideration is given to subjective measures of pain intensity, pain-related distress, and pain-related functional interference. Of course, the validity of these measures can be clouded by the need to rely on subjective patient reporting. Therefore the potential exists for reported pain to be influenced by current and long-term patient attitudes and/or beliefs (personal and cultural), patient anxiety, depression, related unconscious processes, and even perhaps conscious manipulation by the patient.

Temporal (over time) pain characteristics are to be coded as follows:

- continuous pain
- episodic recurrent pain
- continuous pain with pain attacks

Psychological factors can include evidence of problematic cognition such as catastrophization and ruminating, behaviors such as avoidance or endurance, and emotions such as fear or anger. Psychosocial factors encompass how the pain impacts the patient’s relationships with others.

The use of these extension codes is encouraged in instances where psychological or social factors are judged to contribute to the onset, maintenance, and/or exacerbation of pain, or are regarded as relevant consequences of the pain. They are not to be used to imply a causal or an etiological relationship, as all chronic pain is regarded as a multifaceted biopsychosocial phenomenon.

**Scope and Coordination**

In due course, these new ICD-11 classifications are intended to be coordinated with the World Health Organization family of international classifications of various health/morbidity factors, which also include The International Code of Functioning (ICF) and the International Code of Health Interventions (ICHI). This is seen as being of particular importance in the classification of chronic pain conditions, as both systems assess pain and any associated impairments. The draft of the functioning properties pertaining to
Table 1: Specifiers or Extension Codes in ICD-11

<table>
<thead>
<tr>
<th><strong>Pain severity</strong></th>
<th></th>
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<tbody>
<tr>
<td><strong>Pain intensity</strong></td>
<td>Pain intensity may be assessed verbally or on a numerical or visual rating scale. For the severity coding, the patient should be asked to rate average pain intensity for the best week on a numerical rating scale (NRS) ranging from 0 (no pain) to 10 (worst pain imaginable), or on a 100-mm visual analog scale (VAS) ranging from 0 mm (mild pain) to 100 mm (severe pain):</td>
</tr>
<tr>
<td>Mild pain:</td>
<td>NRS 1-3, VAS &lt;31 mm</td>
</tr>
<tr>
<td>Moderate pain:</td>
<td>NRS 4-6, VAS 31-54 mm</td>
</tr>
<tr>
<td>Severe pain:</td>
<td>NRS 7-10, VAS 55-100 mm</td>
</tr>
<tr>
<td><strong>Pain-related distress</strong></td>
<td>Pain-related distress may be assessed by asking the patient to rate the pain-related distress experienced in the past week (multifactorial unpleasant emotional experience of a cognitive, behavioral, emotional, social, or spiritual nature due to the persistent or recurrent experience of pain) on an NRS ranging from 0 (no pain) to 10 (worst pain imaginable), or a VAS ranging from 0 mm (no pain-related distress) to 100 mm (extreme pain-related distress):</td>
</tr>
<tr>
<td>Mild distress</td>
<td>NRS 1-3, VAS &lt;31 mm</td>
</tr>
<tr>
<td>Moderate distress</td>
<td>NRS 4-6, VAS 31-54 mm</td>
</tr>
<tr>
<td>Severe distress</td>
<td>NRS 7-10, VAS 55-100 mm</td>
</tr>
<tr>
<td><strong>Pain-related interference</strong></td>
<td>Pain-related interference during the past week may be assessed by asking the patient to rate it on an NRS ranging from 0 (no interference) to 10 (unable to carry on activities), or a VAS ranging from 0 mm (no interference) to 100 mm (unable to carry on activities):</td>
</tr>
<tr>
<td>Code 0</td>
<td>No interference</td>
</tr>
<tr>
<td>Code 1</td>
<td>Mild interference; NRS 1-3, VAS &lt;31 mm</td>
</tr>
<tr>
<td>Code 2</td>
<td>Moderate interference; NRS 4-6, VAS 31-54 mm</td>
</tr>
<tr>
<td>Code 3</td>
<td>Severe interference; NRS 7-10, VAS 55-100 mm</td>
</tr>
<tr>
<td><strong>Overall severity</strong></td>
<td>Overall severity combines the ratings of intensity, distress, and disability using a three-digit code. Example: A patient with a moderate pain intensity, severe distress, and mild disability will receive the code 231. The severity code is optional.</td>
</tr>
<tr>
<td><strong>Temporal characteristics of the pain</strong></td>
<td>The temporal course of a patient’s pain can be coded as “continuous” (the pain is always present), “episodic recurrent” (there are recurrent pain attacks with pain-free intervals), and “continuous with pain attacks” (there are recurrent pain attacks as exacerbations of underlying continuous pain).</td>
</tr>
<tr>
<td><strong>Presence of psychosocial factors</strong></td>
<td>This extension code permits coding problematic cognitive (e.g., catastrophizing, excessive worry), emotional (e.g., fear, anger), behavioral (e.g., avoidance), and/or social factors (e.g., work relationships) that accompany the chronic pain. The extension code is appropriate if there is positive evidence that psychosocial factors contribute to the cause, maintenance, and/or exacerbation of the pain and/or associated disability and/or when the chronic pain results in negative psychobehavioral consequences (e.g., demoralization, hopelessness, avoidance, withdrawal).</td>
</tr>
</tbody>
</table>

Source: Treede et al. 7
persistent pain, based on the ICF domains, was developed jointly by the International Association for the Study of Pain (IASP) and the International Society for Physical and Rehabilitation Medicine (ISPRM).

ICD-11 Pain Nosology: Implications for Underwriting and Claims Management

Incorporation of this new classificatory system into the ICD-11, and subsequent common clinical use, may pose some challenges as medical, administrative, and related industries become accustomed to the new terminologies. We can reasonably anticipate initial uncertainty pertaining to these diagnoses. Debate may also be triggered regarding the utility and applicability of these new codes as they are incorporated into common parlance.

There is likely to be some imprecise application of the terms and codes as medical practitioners acquire familiarity with the novel and rather precise set of underlying criteria. In addition, all involved may need to query which diagnostic system has been used to reach a diagnosis, especially if imprecise terminology such as “chronic pain disorder” is used in attending physician statements.

Perhaps the sophistication of this new system will precipitate a broader interest in the hypothesis of a shared genetic, inflammatory, and/or neuroendocrine etiology of pain contributing to some psychiatric disorders as well as conditions such as chronic primary pain disorders (e.g., irritable bowel syndrome and fibromyalgia).

Some have criticized these new categories for seeming to reject psychiatric etiology as a primary contributor to certain pain states. From a clinical perspective, one might suggest that, in fact, primary pain disorder categories serve to properly integrate all facets of the individual, without laboring over insoluble questions and often pejorative and unprovable conclusions pertaining to the degree to which one factor contributes to the pain. Advancing technology may afford us more sophisticated assessment of illness in years to come and provide a basis of reconsideration of nosological classification. From an insurer’s perspective, given the lack of objective clinical information which can be gleaned in relation to some presentations, abandonment of the potential for a clearly psychiatric attribution in the ICD system may prove challenging, and could compromise the planning and provision of appropriate therapies and interventions.

In some situations, a condition may meet ICD-11 diagnostic criteria for a pain disorder while also satisfying criteria as a mental illness under the Diagnostic and Statistical Manual, Fifth Edition (DSM-5). This may invite debate as to whether or not the condition can be considered a mental illness. Insurers will need to think carefully about how they respond to such situations, and policy document wordings may warrant some preemptive adjustments. While there will be greater acceptance of terminology pertaining to chronic primary pain disorders, we should not lose sight of our current vigilance pertaining to the common association of such presentations with psychiatric vulnerabilities or even frank mental illness. Closer attention to other possible indicators of mental illness (e.g., past treatment for insomnia, family histories) may improve underwriting decisions and claims management.
A projected set of mortality and morbidity data for field testing/assessment of these categories was made available to ICD users in 2017 and updated in 2018. After consideration, the World Health Assembly endorsed the ICD-11 in May 2019. Countries around the world are now expected to start reporting health data using ICD-11 from 2022 onward. Usable mortality and morbidity data pertaining to these new diagnoses will be unavailable for several years, but once these diagnoses are formally adopted by the ICD-11, pertinent research will fill journals, addressing questions of reliability and validity of these diagnoses, and will promote our understanding and insights into these new codes and definitions.

**Conclusion**

An understanding of the new nosology of chronic pain may prove essential for insurance medicine professionals as the terms are adopted in the near future. This understanding will assist in assessing risk and adjudicating claims, as well as providing insight into current biological constructs underpinning the biopsychosocial facets of chronic pain syndromes.

**References**


THE CHANGING FACE OF ALZHEIMER’S DISEASE: CURRENT KNOWLEDGE, AREAS OF RESEARCH INTERESTS, DRUG DEVELOPMENT

Abstract
Alzheimer’s disease (AD) was first described over a century ago and since then, the major histologic features of the disease have been extensively studied. Amyloid plaques and phosphorylated tau protein tangles do not reveal the entire story for development of Alzheimer’s dementia. Many efforts related to therapeutic and pharmacologic interventions have fallen short. It is time to re-evaluate this devastating disease, look at possible etiologies and focus research in different areas of understanding in this complex disease.

As the world’s population ages and demand for health care resources increase, society will have to accommodate the increasing burden of chronic diseases characteristic of the aging population. Prevention and treatment of AD becomes imperative. Research must look into different avenues of disease development. Currently, the only consistent research finding that is effective in prevention of disease is lifestyle modification: healthy diet, regular exercise, smoking cessation and moderate alcohol intake. Lifestyle modification has influence on the development of disease and may be the best way to avoid it altogether since therapeutic alternatives are not effective.

Current Understanding of Alzheimer’s
Alzheimer’s disease (AD), currently the most common form of dementia in the U.S., is reaching epidemic proportions. Recent data estimates 5.7 million Americans are living with AD, and an additional 11.6 million have mild cognitive impairment.1 The rapidly aging U.S. population means the number of AD cases will most likely triple in the next 30 years.2 Not only is the U.S. impacted by an aging population, worldwide the number of people living with dementia in 2017 was estimated to be close to 50 million. The number of dementia cases globally will nearly double every 20 years, to 75 million in 2030 and to 131.5 million in 2050. China, India, and other developing nations have the fastest-growing elderly populations due to improved health care, which has extended life expectancies.3 Women make up the majority of individuals living with AD, attributable to greater longevity and biological factors.4 Lifetime risk of AD for women at age 65 is 21.1% and for men is 11.6%.1, 5 Survival after diagnosis is influenced by multiple factors, including age at diagnosis, gender, presence of psychotic features, motor system involvement, and medical comorbidities.6 On average, survival after diagnosis ranges from four to eight years if comorbid conditions are present, and best-case scenarios for survival may be up to 15 to 20 years.6, 7

Unfortunately, neither a cause nor a cure for this devastating disease has yet been found. Most recent research efforts have focused on the role of amyloid plaques and neurofibrillary tangles (NFTs). These abnormal proteins are found in the brains of individuals with AD and are composed primarily of phosphorylated tau protein. It has become clear, however, that abnormal

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Dr. Lisa Duckett is Vice President and Medical Director for RGA Reinsurance Company. In this role, she provides support for facultative underwriting and underwriter education through presentations, one-on-one interactions, and articles related to underwriting topics.

Trained as an internal medicine doctor, Dr. Duckett is board-certified in insurance medicine as well as geriatric medicine. She has been in the insurance industry for 20 years, after 12 years spent in clinical medicine. Her true love is geriatric medicine, and she has done extensive research into the mortality risks and unique qualities of the older-age cohort.
proteins by themselves do not explain the disease’s etiology. Further research into the systems that support protein homeostasis in the brain and regulate inflammation and protein removal is underway, and may be what is needed to develop a more complete understanding of the pathology of AD.

**Amyloid Plaques and Neurofibrillary Tangles**

The characteristics of amyloid and tau proteins in brains of individuals with AD were elucidated in the 1980s. Both proteins are generated in the normal course of brain function, but can become toxic if they aggregate abnormally in the brain.

The amyloid beta (A\(\beta\)) protein is a peptide formed by neurons in the cortex of the brain – particularly in the hippocampal area, which is where memory function is housed. However, as A\(\beta\) is released into the brain’s extracellular spaces, it can become distorted, forming chains of A\(\beta\) oligomers that conglomerate to form insoluble amyloid plaques. These plaques grow in size and interfere with neuronal function by destroying dendritic connections between cells.

Amyloid plaques accumulate in the brain in a predictable manner, and their presence can be detected in the brain by testing for it in cerebrospinal fluid (CSF) and by PET (positron emission tomography) scans using radiotracers that bind selectively to A\(\beta\) protein. PET scans are reliable predictors of brain amyloid plaque burden. These imaging findings, however, are not specific to the brains of individuals with AD. Plaques are also found in brains of individuals with other neurodegenerative disorders, such as Lewy body dementia and cerebral amyloid angiopathy, and in those of cognitively healthy older individuals as well.

NFTs are composed of hyperphosphorylated tau protein. When normal, this protein is part of the structural support system of neurons that maintain integrity of the neuronal axon. However, when tau protein accumulates, it leads to interruption of normal neuronal function and ultimately to death of neurons. Today, deterioration of cognition is seen as correlating more strongly with tau protein burden and distribution than with that of amyloid plaques.

Autopsy findings of people with late-onset dementia, particularly the oldest old (now frequently defined as age 90 and older) and even individuals with mild cognitive impairment (MCI), will exhibit multiple pathologies at autopsy, including vascular brain injury, Lewy body dementia, and hippocampal sclerosis.

**AD: A Vascular Disease?**

Large epidemiologic studies and an accumulation of scientific data associate vascular risk factors and vascular markers with subsequent development of dementia. The large database of 7,000 subjects of the Rotterdam Study has followed elderly individuals since 1990. This study group was compared to an age-matched control group. A series of reports comparing those who develop dementia and the nondementia group identified an association between the presence of vascular risk factors and the development of AD in older individuals. Risk factors confirmed by the Rotterdam Study as well as other independent studies include diabetes mellitus, atrial fibrillation, smoking, and atherosclerosis. Each of these risk factors directly influences perfusion to the brain in a negative manner.
Hypertension has been demonstrated in many studies to be a contributing factor to AD. Indeed, long-term follow-up of middle-aged men with hypertension in the Honolulu-Asia Aging Study noted a higher burden of NFTs and brain atrophy post-mortem compared to normotensive individuals with AD. Additional studies have substantiated the ill effects of long-term hypertension after following a large group of individuals with stroke history. In the 1990s, the FINMONICA Stroke Register in Finland, for one, began to track trends and determinants of vascular disease among participants. Early studies noted a relationship between middle-aged individuals with hypertension and hyperlipidemia and subsequent development of MCI and AD: the higher the blood pressure and lipid abnormalities, the higher the risk of developing cognitive impairment later in life. When both blood pressure and cholesterol are abnormal, the risk for both MCI and AD increases in a synergistic manner. Knowing that vascular risk factors can be modified, a group of researchers recently published their findings on the risk of developing dementia when healthy lifestyle habits are followed in individuals with varying degrees of genetic propensity for dementia. Results of the study demonstrate that unhealthy lifestyles with any degree of genetic predisposition will increase risk for dementia development. Hazard ratios, in this study, increased with dose-dependent exposure to unhealthy life styles combined with high polygenic risk scores. (Unhealthy lifestyles are defined in this study as: smoking, poor diet, no regular exercise, and high alcohol intake.) Controlling risk factors for vascular health is important and consistently demonstrates protective value in preventing dementia.

**AD: An Inflammatory Disease?**

Another area of research which has grown in importance is the role of neuroinflammation and its contribution to the development of AD. Post-mortem brain tissue indicates there is a prominent inflammatory response to the deposition of abnormal proteins in the brain. Aβ peptides have been shown to be cytotoxic in laboratory analysis, stimulating synaptic loss, mitochondrial dysfunction, and eventually neuronal death. Accumulation of cytotoxic misfolded amyloid protein in the brain is an example of a proteopathy, a condition in which the integrity of protein is controlled through phagocytosis and degradation of abnormal proteins in a healthy brain. However, AD creates an unhealthy environment where microglia cells have a central role in clearance of toxic proteins. With aging, disease, or genetic mutations, microglia cells become dysfunctional. Similar to other situations in which inflammation is nonproductive, microglia activity causes harm through propagation of inflammation by antigen-specific and nonspecific mechanisms. One novel therapeutic approach is to control brain inflammation through the inhibition of microglia activity.

**AD: An Infectious Disease?**

Many aspects of AD may be similar to known physiological responses to infection. One researcher has even posited a possible AD germ. Clues that an infectious etiology could be the root cause for AD include observation that various antibiotics have been reported to have beneficial effects on patients with AD. University of California San Francisco (UCSF) scientists have indicated that AD could be the result of tau and amyloid proteins behaving more like prions (i.e., infectious protein particles). Prions are proteins lacking nucleic acids that have the genetic capability to self-propagate. Two examples of cognitive-related prion diseases are Creutzfeldt-Jakob disease and mad cow disease. UCSF researchers have developed analytic tools to identify and quantify prion levels. Tau prion levels appear to correlate most closely with disease activity in middle-aged onset AD. The higher the levels, the higher the disease activity and risk for death. In older individuals with AD (late-onset), tau prion levels are much lower, suggesting slower propagation time and a less aggressive form of the disease. Another pathogen of interest is the herpes simplex virus (HSV). Researchers have demonstrated that Aβ and fibril
Development pathways mediate antimicrobial activities in the brain. Amyloid oligomers bind the glycoprotein molecules on the surface of herpes virus to engulf the virus and render it inactive. Herpes virus subtypes 6A and 7 have been identified in significant amounts in the brains of individuals with AD. In addition, there is a link between viral activity in the brain and pathologic changes of the brain in those with late-onset AD.29

Therapeutic Developments

Drug development for the treatment of AD has been very slow and disappointing. Initially, acetylcholinesterase inhibitors (AChEIs) were approved in 1993 by the U.S. Food and Drug Administration (FDA), based on the understanding that an acetylcholine deficit develops in the brain as a result of neuronal loss. AChEIs are considered symptomatic therapies, as they do not alter the progression of the disease, they do not have neuroprotective qualities,7 and no proven benefit has been demonstrated in MCI.2 Namenda (memantine), the only FDA-approved AChEI for moderate dementia, has been used successfully in treating behavioral disturbances in the advancing stages of the disease, but it has not been shown to be effective for arresting disease progression.30

Presently, approximately 200 compounds are being researched and developed for AD treatment or prevention. Challenges exist with the research and development of AD-specific pharmacologic agents, particularly since the disease moves very slowly and there is a very long preclinical interval before symptoms develop. Clinical trials need to extend over years and even decades, making trials expensive and lengthy.31

Biomarkers used to identify abnormalities in CSF and brain imaging are being used more frequently to identify patients for drug studies, especially those with preclinical and early symptomatic disease. Going forward, biomarkers will likely become the tool of choice to provide an objective measurement of response to potential therapeutic modalities, which should shorten time for clinical trials.32

Researchers are investigating the mechanism of clearance of Aβ from the brain across the blood-brain barrier (BBB) as another possible target for therapeutic intervention. The primary receptors for passage of Aβ across the BBB are lipoprotein receptor-related protein 1 (LRP1) and receptor for advanced glycation end products (RAGE). A soluble form of the LRP1 molecule sequesters the majority of amyloid peptides in the brain and reduces the plasma levels of the protein. However, in AD the function of the LRP1 molecule is disrupted, leading to production and aggregation as well as clearance of amyloid protein. Several immunotherapies are under investigation to promote clearance of Aβ, including passive immunization with monoclonal antibodies, either directly or through the activity of microglial cells or complement activation.33

Another area of research focus is chaperone molecules. These molecules are proteins that appear to inhibit the propagation of deformed amyloid fibrils and, in turn, reduce the toxicity of the abnormally folded amyloid protein. Harnessing the function of chaperone molecules could have therapeutic potential as a way to reduce the production of amyloid deposits in the brain.34 It is interesting to note that pathologic amyloid fibrils are associated with about 40 different diseases in addition to AD, including type 2 diabetes and mad cow disease.35

Stem cell therapies are in early phases of development as possible viable solutions for replacement of neurons, disease modeling, and drug development. Restoration of lost neurons and ineffective microglial cells via transplant or in situ stem cell self-renewal and differentiation may offer an effective addition to current AD treatments. Despite the excitement about cell replacement therapy in AD, challenges do remain. Transplantation data suggests that genetic and epigenetic backgrounds of donor cells are extremely important, so donor-to-donor variation of stem cells must be considered in relationship to propensity for disease development. In addition, transplantation of genetic defects that cause biochemical symptoms of AD must be corrected in donor cells before successful transplantation can occur.36, 37

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abnormally high levels of amyloid in the brain. The other transport molecule, RAGE, when bound to the soluble form of Aβ, appears to malfunction and facilitates amyloid passage across the BBB from the peripheral circulation into the brain and acts to promote endothelial inflammation and decreased blood flow. Inhibitors that block RAGE and Aβ interaction are plausible targets for intervention.

Insurance Industry Implications
Dementia is an extremely slow-moving disease with a very long preclinical stage – 15 to 25 years, according to some studies. Biochemical changes occur during this period without outward symptoms. Age is the most important risk factor in the development of dementia, and the presence of vascular risk factors such as smoking, diabetes, hypertension, sleep disorders (particularly obstructive sleep apnea), and atherosclerotic disease, both in the brain and in peripheral arteries, all increase the risk for later-life cognitive impairment. In addition, brain trauma, coronary artery bypass surgery, silent stroke seen on brain imaging studies, and medications such as benzodiazepines and anticholinergics (which treat disorders as diverse as asthma, incontinence, and Parkinson’s disease) have been associated with increased dementia risk.

Applicant mortality assessments should include evaluation of the presence and severity of risk factors for future AD, as well as family history. Older-age questionnaires that focus on subtle changes in cognition or memory function, mental status evaluation, brain imaging, and medical records can all help insurance underwriters develop a history for possible impaired cognition. Work and education history information can also be used to develop baseline cognition function profiles. Independence measured by performance of instrumental activities of daily living, as well as ability to manage finances and use technology such as e-mail, mobile phone, and the internet, should be included in cognitive screenings.

Use of social services may signal a loss of ability to manage instrumental activities of daily living, particularly when the use of in-home social or support services are initiated. However, education, physical activity, and social engagement may offset the negative influence of the aforementioned factors.

Corroboration of the facts by a family member or close friend would be optimal to verify the information acquired through the interview process. Any red flags should warrant additional investigation.

Conclusion
Normal aging manifests as slowed memory and learning acquisition that does not interfere with function in the community. Older-age underwriting will always be challenging due to the heterogeneous nature of the aging process. Biomarkers will continue to evolve and may become more commonly utilized in the diagnostic process, but today, brain imaging and cognitive screening tests are the methods used to diagnose dementia.

AD remains a puzzle that medical science has yet to understand fully. The disease presents many concerns and challenges, particularly since the global population is aging and rates of occurrence for dementia are likely to increase rapidly over the next 30 years. Potential etiologies for the disease are diverse and are the focus of ongoing research. Trials of pharmaceuticals to prevent and treat disease have been unsuccessful to date. Clearly, new avenues for research and development will have to be examined to address this complex disease.

References


The Elusive Universal Influenza Vaccine – Are We Any Closer?

Abstract

Insurers are susceptible to fluctuations in mortality experience due to varying severity of seasonal influenza from year to year. They are especially concerned with the rarer but dreaded threat of pandemic influenza posing significant risk to insured lives portfolios. Research to develop a universal influenza vaccine, often referred to as the Holy Grail of vaccine development, has been going on for quite some time with no success to date. This Brief Report will update the reader on the recent developments in the quest to develop the world’s first universal flu vaccine and how this quest, if successful, could impact an insurer’s bottom line.

Influenza Basics

There are two main epidemiological forms of influenza: seasonal and pandemic. Influenza A and B cause seasonal (annual) epidemics and lead to 300,000–500,000 deaths per year globally. Influenza A, which affects both animals and humans, is the only one documented that emerges periodically (and unpredictably) to cause pandemics. (B only affects humans.)

There have been four influenza pandemics in the last 100 years: 1918 (50,000,000+ deaths), 1957 (1,100,000 deaths), 1968 (1,000,000 deaths), and 2009 (151,700–575,400 deaths). Concern is growing that animal influenza viruses, which do not currently have sustained human-to-human transmission, could undergo a mutation that would confer efficient transmission among humans and cause the next pandemic.

Current strategies for seasonal vaccine production are essentially one year behind in terms of keeping up with flu virus variation. With regard to pandemic influenza risk, the current approach leads to making, testing, and stockpiling vaccines that may never be used. Furthermore, seasonal flu vaccines provide essentially no protection against an emerging pandemic strain.

New Focus on Universal Influenza Vaccine Research

The outer surface of all flu viruses displays two well-studied proteins: hemagglutinin (H) and neuraminidase (N). The H and N proteins are what classify and differentiate influenza viruses (and how strains of flu viruses get their names; e.g., H1N1, H3N2). The H protein has two components, a head and a stem. Typical seasonal flu vaccines target the head, but this region also experiences frequent antigenic changes, or “drifts,” necessitating new flu vaccines every year. The stem portion remains more constant over time and therefore represents an ideal focus for longer-lasting and broader-coverage universal flu vaccines. There is some new vaccine research also being directed at the N protein, but most remains focused on the H protein.
In February 2018, the National Institute of Allergy and Infectious Diseases (NIAID) published a Universal Influenza Vaccine Strategic Plan to chart the course for research priorities. It recommended the following: that a universal flu vaccine should be at least 75% effective; protect against two groups of influenza A viruses; have durable protection that lasts at least one year; and be suitable for all age groups. ¹

Then, in April 2018, the Bill & Melinda Gates Foundation issued “Ending the Pandemic Threat: A Grand Challenge for Universal Influenza Vaccine Development.” The goal of this challenge was to “identify novel, transformative concepts that will lead to development of universal influenza vaccines offering protection from morbidity and mortality caused by all subtypes of circulating and emerging influenza A subtype viruses and influenza B lineage viruses for at least three to five years.” ⁵ In addition, “it is envisaged that such a universal influenza vaccine would address the threat from both seasonal and pandemic influenza, thus alleviating the need for annual seasonal influenza vaccination campaigns.” ⁶ The Gates challenge seeks transformative approaches rather than incremental research.

The timing for such initiatives has never been better. The probability of successful development of a universal flu vaccine is more feasible now than even a decade ago due to advances in virology, immunology, vaccinology, deep gene sequencing, and structural biology. ¹ In fact, several universal flu vaccine clinical trials have recently been announced, indicating the research is now moving from theoretical to operational.

In vaccine development there are four phase types,⁶⁷ all of which are time-consuming, complex, and costly. A brief description of each follows:

- **Phase I**: Small-scale trials to determine safety in humans and the immune response evoked; conducted in individuals at low risk for the infection the vaccine is designed to prevent
- **Phase II**: Large-scale studies to look at the efficacy of the vaccine against artificial (i.e., intentional) infection and clinical disease; may include an at-risk population
- **Phase III**: Large-scale studies across several geographic sites to determine vaccine efficacy under natural disease conditions; includes an at-risk population
- **Phase IV**: The vaccine is licensed and introduced to the public, also called post-marketing surveillance

**Current Trials**

The National Institutes of Health (NIH) announced in April 2019 the opening of a Phase I clinical trial of an innovative universal influenza vaccine candidate, H1ssF_3928. The trial is being conducted at the NIH Clinical Center in Bethesda, Maryland (U.S.) and aims to enroll 53 healthy adults between the ages of 18 and 70. The researchers
will study how participants respond to the vaccine, which is directed toward the stem of the H protein, based on age and previous exposure to different influenza strains. Early reports on the study should be available in 2020.9

Two additional studies are being conducted by a private company. It has administered a pandemic universal influenza A vaccine to the first participants in a Phase II study being conducted in Antwerp, Belgium, according to a communication issued on June 5, 2019. Additionally, the company announced that it had administered the vaccine to 2,200 people in a Phase II field trial in Australia. In this case, the new vaccine was co-administered with the current quadrivalent seasonal flu vaccine to determine whether the combination might offer improved efficacy over the standalone seasonal vaccine. Results of these studies are also expected in 2020.9

An Israeli company has announced completion of enrollment for a Phase III universal flu vaccine trial in late 2018. It will enroll a second cohort during the 2019-2020 flu season. Results from this study will also be available in the second half of 2020.12

While not a clinical vaccine trial per se, the Cincinnati Children’s Hospital Medical Center announced on May 2, 2019, that it received a US$30 million federal grant to accelerate research on a universal flu vaccine. Specifically, these researchers will study how the immune systems of infants and growing children are imprinted by their first exposures to flu viruses. The research cohort will consist of individuals from Cincinnati and Mexico City.10

While news has generally been favorable and positive regarding the prospects and advancements of universal flu vaccine development, there have been some setbacks. A large pharmaceutical firm, for example, recently terminated a universal flu vaccine candidate after reviewing interim Phase I data. The reason: the vaccine had induced an immune response, but the boosting effect of a second dose was not as strong as expected. Additionally, the results were insufficient to conclude the benefit would be supra-seasonal.11

**Insurance Implications and Conclusions**

Actuaries and insurance medical directors have long studied and modeled the impact of mortality variation due to seasonal influenza and the greater risk of pandemic influenza. The latter is especially important, as modeling is required as part of regulatory reserving calculations. There is no doubt that the development and deployment of a successful universal influenza vaccine would have an immensely favorable impact on society as well as on insurers’ mortality risk liabilities. While not a focus of this article, it would also significantly reduce morbidity through lower health costs and hospitalization reimbursement.

Although a universal influenza vaccine has not yet been produced, recent developments in technology have advanced this search to a new stage. Overall prospects for success are greater now than at any time in history. While it may be too early for insurers to definitively expect morbidity and mortality improvements, it certainly may be time to at least begin planning for that day. **RF**
References


MEDICAL TEAM UPDATE
Marco Percque, M.D., has joined RGA’s Canada office in Montreal as a part-time independent consultant. His training includes obstetrics and gynecology as well as insurance medicine.
Recently, ReFlections had the opportunity to chat with Bettina Mittendorfer, Ph.D., the new director of the Longer Life Foundation’s Longevity Research Program (LRP). Here, she shares with us how her current focus on human longevity will inform LRP’s research directions in the coming years.

Your research focuses on metabolism, nutrition, and aging. How did you get interested in these topics, and what do you hope your research will accomplish, long-term?

When I was an undergraduate at the University of Vienna, I had the opportunity to spend some time at the University of Texas Medical Branch at Galveston (UTMB). There I met Dr. Robert Wolfe, who pioneered the use of stable isotope-labeled tracers for studying metabolism in vivo. I was immediately hooked, and decided to pursue my Ph.D. in his lab. My research focused on understanding the mechanisms responsible for age-associated muscle loss and sarcopenia. I then came to St. Louis to do my post-doctoral work with Dr. Samuel Klein, an expert in obesity research and the director of the Center for Human Nutrition at Washington University in St. Louis.

Metabolism, nutrition, obesity, and aging have naturally morphed together in my research, which focuses on improving human longevity. Integrating metabolic tracers, clinical imaging, cardio and physical function testing, and analysis of tissue biopsies has provided me with a better understanding of the pathophysiology of obesity-associated alterations in cardiometabolic function. It has also given me a better understanding of age-associated declines in metabolic and muscle health and physical function, which are major predictors of premature mortality. Ultimately, deep metabolic phenotyping combined with functional outcome measures is necessary to develop appropriate prevention and treatment strategies for age- and obesity-associated declines in health and premature mortality.
How do you see the global obesity epidemic evolving? Could it someday be treated pharmaceutically, or do you think the root causes of poor diet, lack of exercise, and stress need to be managed more effectively?

In my opinion, the primary focus needs to be on obesity prevention, meaning lifestyle modification (including diet, physical activity, and sleep) and stress reduction, both for individuals and via targeted public health efforts. Understanding how lifestyle factors affect physiological functions and the barriers to adopting proven beneficial strategies through targeted research will be key to implementing evidence-based best practices and developing effective treatment strategies. Pharmaceuticals and nutraceuticals will certainly play important roles. Ultimately, success will depend on finding an optimal balance of approaches and will likely require a shift in social norms.

We know the rate of mortality improvement has slowed over the last several years, mostly (but not exclusively) due to slowing mortality improvement from cardiovascular disease. Do you think obesity, diabetes, and other CV risk factors play a role?

The changes in mortality from cardiovascular diseases over the past decades include the rapid decline that coincided with the reduction in smoking, the introduction of statins, and focused blood pressure control efforts. These demonstrate the tremendous impact prevention and intervention strategies can have on CV disease prevalence and mortality. The high prevalence of obesity and its associated CV risk factors, including a sedentary lifestyle, are most likely responsible for much of the remaining CV disease risk and mortality.

As the new director of the Longer Life Foundation’s Longevity Research Program, what do you see the program accomplishing in the next three to five years?

The Longevity Research Program aims to stimulate and advance research to identify factors that assist in predicting mortality and morbidity and to improve people’s health and longevity. My hope is that the program will serve as an incubator of ideas by stimulating new collaborations and providing cost-effective opportunities for multidisciplinary research to test novel hypotheses and train young investigators.

An example is our proposed project that will evaluate the effect of dietary protein intake on cardiovascular health (e.g., endothelial function) in people at risk for developing type 2 diabetes. This project will involve a new translational collaboration among several clinical and basic science investigators. It will leverage the resources of a recently initiated NIH-funded randomized clinical trial that will evaluate the effect of high protein intake from animal and plant sources on key metabolic functions, including insulin sensitivity and beta-cell function, involved in the pathogenesis of type 2 diabetes.
Association of Stroke among Adults Aged 18 to 49 Years with Long-Term Mortality

Stroke is the second leading cause of death worldwide. Approximately 10% to 15% of all strokes occur in young adults between ages 18 and 49. However, information on the risk of death in this subgroup is limited because of the small number of stroke patients younger than age 50 included in previous studies.

This study, which was conducted in the Netherlands, aimed to investigate case fatality and cumulative 1-year, 5-year, 10-year, and 15-year mortality and trends over time of young adults who had and survived their first strokes for at least 30 days and were between ages 18 and 49. Results were stratified by age, sex, and stroke subtype. Causes of death and rates of excess mortality after stroke were compared with the general population.

Although both acute treatment and secondary prevention for stroke have improved over the past decades, and despite adequate treatment for stroke and treatment of associated risk factors according to current standards, more patients in this cohort were found to have died of malignancies and cardiovascular disease compared with the general population. In addition, the cohort’s mortality risk remained elevated up to 15 years later.

Editor’s Note: Not only is the increased mortality in these young individuals a concern, but the higher morbidity risk, especially malignancies, is worth noting, particularly in markets where living benefits are very popular. The study, it is hoped, may provide evidence for possible underlying disease mechanisms.

Association Between Life Purpose and Mortality Among U.S. Adults Older Than 50 Years

The aim of this study was to evaluate whether an association exists between life purpose and all-cause or cause-specific mortality among older adults in the U.S., using data from the Social Security Administration’s longitudinal Health and Retirement Study (HRS). A growing body of literature suggests that having a sense of purpose in life can be associated with physical and mental health and with overall quality of life. There is also evidence to suggest that elevated levels of inflammatory markers such as C-reactive protein and cytokines such as interleukin 6 are associated with increased mortality. This represents one possible mechanism through which purpose in life can influence mortality. However, to our knowledge, no studies have measured the impact of life purpose intervention(s) on health outcomes (including mortality), or on cytokines or other biomarkers.

The study revealed a significant association between life purpose and all-cause mortality as well as specific mortality attributed to heart, circulatory, and blood conditions. A stronger purpose in life was
associated with lower all-cause mortality. Other studies suggest that strong life purpose is associated with lower cortisol levels and lower levels of pro-inflammatory cytokines. Future research will focus on the mechanism of how life purpose may influence all-cause mortality and cause-specific mortality and on the appropriate timing of life purpose interventions.

**Editor’s Note:** These findings are likely to influence the way insurers underwrite the older generation of customers going forward, where social interaction and life purpose are of paramount importance.

**Cardiovascular Events and Mortality in White Coat Hypertension: A Systematic Review and Meta-analysis**


Hypertension, the most preventable cause of disability and premature mortality worldwide, is commonly diagnosed in a clinical setting with in-office blood pressure (BP) measurements. This systematic review and meta-analysis used observational studies with at least three years of follow-up, and evaluated the cardiovascular risk of untreated white coat hypertension (WCH) or treated white coat effect (WCE) compared with normotension (arterial BP in normal range). A total of 27 studies were included, comprising 25,786 participants with untreated WCH or treated WCE and 38,487 with normal BP.

The review found that compared with normotension, untreated WCH was associated with higher risk for cardiovascular events, all-cause mortality, and cardiovascular mortality. It also found no significant association between treated WCE and cardiovascular events, all-cause mortality, or cardiovascular mortality.

**Editor’s Note:** The long-term cardiovascular risk of isolated elevated BP is unclear. Despite recent guidelines that strongly recommend out-of-office BP monitoring (including ambulatory BP monitoring and self- or home monitoring), real-world practice has been slow to adopt this method. The findings of this meta-review advocate policies to support broader implementation of out-of-office BP monitoring in routine clinical practice. This might ultimately impact how insurers screen for, and underwrite, hypertension.

**Analysis of Whole-Exome Sequencing Data for Alzheimer Disease Stratified by APOE Genotype**


This study identified multiple possible novel associations for Alzheimer’s disease (AD) with rare variants in groups of individuals with and without APOE ε4 alleles that reinforce known pathways and suggest additional ones leading to AD. The ε4 allele of apolipoprotein E (APOE ε4) is considered the major genetic risk factor for AD and is a common cause of dementia in the elderly. This case-control whole-exome sequencing study of 10,441 individuals identified a possibly novel association of AD with a GPAA1 variant among those who lacked the APOE ε4 allele. This finding was replicated in independent data sets and supported by analyses of whole-genome and RNA sequencing data derived from human brain tissue. Other novel associations were identified among individuals with the APOE ε4 allele, and this supports the apparent involvement of genes in Alzheimer’s disease where the effects are dependent on the APOE genotype.

**Editor’s Note:** It is hoped that a better understanding of AD’s genetic profile will lead to earlier intervention and enhanced management of the disease. This will ultimately improve both quantity and quality of life and ultimately impact how the insurance industry views AD.
Physical Activity, Multimorbidity, and Life Expectancy: a UK Biobank Longitudinal Study

This study used UK Biobank datasets to extract data on 36 chronic conditions. Multimorbidity was defined using three sets of criteria, with physical activity (PA) categorized into low, moderate, and high, using questionnaires as well as wrist-worn accelerometers. Survival models were applied to calculate adjusted hazard ratios and predict life expectancy differences. The study showed that overall, for individuals age 45 with multimorbidity, moderate to high levels of physical activity can be associated with longer life. It also showed an inverse dose-response association between PA and mortality.

Editor’s Note: There has been a recent increase in wellness programs as part of the insurance offering globally. This study supports the notion that increased physical activity, even in the arena of multimorbidity, is critical to mortality and morbidity outcomes.

RGA THOUGHT LEADERSHIP PUBLICATIONS
RGA publishes content on many topics of interest to readers. Here are links to some recent publications:

1. Polygenic Risk Scores – A useful tool in our risk prediction toolkit? by Heather M. Lund, M.D. and Richard Russell, Ph.D, RGA

   https://www.rgare.com/knowledge-center/media/articles/a-human-approach-to-mental-and-nervous-claims

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

HIV: An Update, by Dr. Russell Hide, RGA (Duration 7:01)
https://www.rgare.com/knowledge-center/media/videos/hiv-an-update

Russell Hide, MB.BCh, Medical Officer, RGA South Africa, brings viewers up to date on the latest development in this global pandemic, discussing HIV’s history, the latest advances in antiretroviral and injectable therapies, and information related to improving longevity.