ReFlections

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IN THIS ISSUE

FROM THE EDITORS

We would like to take this opportunity to wish our readers a very Happy New Year and hope you have a successful year ahead.

Articles by two new authors are being featured in this edition of *ReFlections*. The first, by Dr. Karneen Tam, Medical Consultant, RGA Asia Pacific, provides an in-depth discussion on cardiovascular and kidney complications related to diabetes mellitus and the mitigating effects of newer classes of medication. The second continues the *ReFlections* tradition of providing updates on the growing importance of electronic health records (EHRs) and digital health data initiatives. Jennifer Thoreson, R.N., AALU, Executive Director, Underwriting Services, U.S. Mortality Markets, RGA, provides a comprehensive overview of the current state of EHRs, how EHRs now compare with attending physician statements, and the benefits and challenges both bring to risk assessment.

Infectious diseases continue to be a topic of great concern for medical professionals, researchers, public health officials, and insurers. We are therefore pleased to feature an exclusive interview with Michael T. Osterholm, Ph.D., MPH, a global expert in infectious disease epidemiology. He discusses current and evolving trends and risks in this area.

We are also pleased to announce the 2019-2020 research grant awards funded by the **Longer Life Foundation**. These annual awards continue to support cutting-edge research into factors and determinants of morbidity and mortality, conducted at Washington University in St. Louis School of Medicine.

Please enjoy this edition of *ReFlections*! We always look forward to hearing from you.

Thank you,

Dan and Adela

NEW DEVELOPMENTS IN CARDIORENAL PROTECTION IN TYPE 2 DIABETES MELLITUS

Abstract

Cardiorenal complications represent advanced stages of progression for type 2 diabetes mellitus (T2DM). These complications are two major drivers of DM-related mortality and morbidity. Results of Cardiovascular Outcome Trials (CVOTs) on some recently developed agents suggest that possible ways now exist to mitigate these destructive cardiorenal vasculopathies. This review focuses on currently available CVOT findings for two classes of agents in particular: sodium glucose cotransporter 2 (SGLT-2) inhibitors and glucagon-like peptide 1 receptor agonists (GLP-1 RAs).

DM and the Deadly Impact of Comorbid Cardiovascular and Renal Diseases

Diabetes mellitus (DM) has come to be viewed as having reached pandemic status worldwide. According to the International Diabetes Federation (IDF) Diabetes Atlas, 9th Edition, one of every 11 adults around the world currently lives with this disease, and even more alarmingly, one of every two adults who now has DM is undiagnosed.[1]

This population requires relevant and appropriate risk cover and support from the insurance industry. However, as DM is highly heterogeneous in phenotype, clinical presentation, metabolic profile, progression, and control, insurers must be vigilant in monitoring its ever-changing epidemiology as well as mortality trends driven by clinical advances.

Cardiovascular Diseases

Over the past several decades, cardiovascular disease (CVD) mortality has been decreasing among general populations in high-income countries. A reduction in CVD risk has also been observed among people living with DM in these countries, but as prevalence of DM has risen, so will the number of people with CVD.

CVD is the chief cause of death in DM. Observational studies in the U.S., Canada, Australia, and Iceland report an approximate 50% reduction in the relative risk of CVD mortality in the general population, but excess risk of death due to CVD in DM populations is approximately two to four times that of non-DM populations. It is also estimated that about 50% of individuals with type 2 diabetes (T2DM) will die of it, with the majority of deaths due to coronary artery disease, followed by stroke.[1, 2] The IDF estimates that in high-income countries, prevalence of CVD among those with DM may be as high as 16% in the younger (28-44) age band, and jumps to 41% for those in the 56-66 age band. In study groups where the mean age was 53-67, prevalence of stroke ranged from 3.5% to 10%.[3]

Insufficient data exists about CVD prevalence among DM populations in low-income countries, but approximately 75% of those with DM are known to live in low- and middle-income countries, and DM prevalence in those countries is known to be accelerating.[3]

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Dr. Karneen Tam is a medical consultant for RGA Reinsurance Company's Asia Pacific region. Based in South Africa, she is a diabetologist with an MBBCh from the University of the Witwatersrand, South Africa and an M.Sc. in Diabetes from University of South Wales, Cardiff, Wales (U.K.). Before coming to RGA, Dr. Tam was a Chief Medical Officer for several South African direct and reinsurance companies.

Dr. Tam has extensive clinical experience in general medical and specialist diabetes care spaces. She has a strong interest in non-communicable disease management, particularly in how nutrition and lifestyle modifications can be preventative therapies and how digital tools can enhance health care delivery.

In terms of heart failure (HF) specifically, T2DM confers a two- to five-fold excess risk of its development. For those living with both existing HF and T2DM, the latter confers a 60% to 80% higher risk of death. In addition, the association between DM and HF is bidirectional; among individuals with HF, DM prevalence is four times higher.[5]

DM also worsens prognoses for individuals who experienced HF with reduced ejection fraction (HFrEF) and those who experienced preserved ejection fraction (HFpEF).[4] For people living with DM who are 65 or older with existing HF, risk of death leaps tenfold.[5]

Diabetic Nephropathy

The coexistence of chronic kidney disease (CKD) and DM fuels an additive effect on mortality and morbidity: higher risk for arrhythmia, acute coronary syndrome, and congestive heart failure; and earlier and higher mortality rates during and after hospitalization.[4, 7]

Globally, diabetic nephropathy (DN) is the leading cause of end-stage renal disease (ESRD). This microangiopathic condition is found in approximately 30% of those with type 1 diabetes mellitus (T1DM) and 40% of those with T2DM. As the worldwide prevalence of DM increases, so does that of DN, and its prevalence is further exacerbated by longer survivals of affected individuals due to improved DM management.[2] In addition, DN-associated mortality, which rose a dramatic 94% from 1990 to 2012, is now considered responsible for most of the excess mortality risk in DM as well as a significant driver of cardiac mortality.[6]

ESRD is expected to cause a significant worldwide future disease burden. Although incidence has been declining in Scandinavian countries and Australia, increases have been detected in several other countries, including the U.S., the Republic of Korea, and Singapore.[2] As global prevalence of DM is projected to reach a staggering 700 million by the year 2045, the correlating increase in ESRD is expected to be devastatingly high as well.[1]

Pathophysiological Mechanisms in DM-Related Kidney Disease

Although vascular dysfunction due to ongoing hyperglycemia may be the precipitating event for DN, DN results from a multidimensional and multicellular process. Its progression is driven by hyperglycemia and hypertension, two key risk factors which are exacerbated by oxidative stress, inflammation, and fibrosis.[8]

The pathophysiological development of DN begins with a thickening of the glomerular basement membrane (BM), coupled with tubular and capillary BM thickening. Next comes loss of endothelial fenestration, with mesangial enlargement, glomerular hypertrophy, and loss of podocytes. Subsequent mesangiolysis, associated with exudative obstructions of small arterioles, glomerular capillaries, and microaneurysms, further compromises the integrity of the glomerulus. Late stages in the development of DN are characterized by interstitial inflammation and glomerulosclerosis.[6, 8]

These processes are accompanied by hemodynamic alterations, including rising intra-glomerular pressures, hyperfiltration, and changes in permeability, leading to progressive albuminuria.[8, 9]

The renin-angiotensin-aldosterone system (RAAS) is also implicated in altered kidney function in DM. In early DM, a rise in arterial pressure and renal vascular resistance can be observed, accompanied by increased renin activity.[9]

The two main characteristics of DN are progressive albuminuria and declining estimated glomerular filtration rate (eGFR). Renal damage correlates to the duration and magnitude of hyperglycemia, with incidence beginning to rise after 10 years of DM. DN generally manifests as some degree of proteinuria, which may progress to ESRD. Subsequent renal replacement therapy or transplant are both associated with high morbidity and mortality.[8, 9, 10]

It should be noted that in DM, proteinuria does not correlate absolutely to deteriorating glomerular filtration. Microalbuminuria (albumin loss of between 30 and 300 mg/day) may regress, as seen in the Diabetes Control and Complications Trial (DCCT) and Epidemiology of Diabetes Interventions and Complications (EDIC) follow-up study of T1DM cohorts after six to 10 years of optimal DM management. Also, in some, DN develops without any preceding albuminuria, as seen in the United Kingdom Prospective Diabetes Study (UKPDS), which looked at clinical and therapeutic implications for people with T2DM.[10] In addition, and more importantly, approximately 40% of the T2DM cohort in the UKPDS study did not develop renal dysfunction.

A small long-term U.S. study also showed that in the absence of renal disease, 20-year mortality risk for individuals with T1DM did not increase compared with the general population.[11]

Pathophysiological Mechanisms in DM-Related Cardiovascular Disease

In CVD, DM is an independent risk factor. The two conditions share many metabolic dysfunctions, including obesity, hypertension, and hyperlipidemia.

Multiple health factors can increase CVD risk for those with DM, including:[12]

- hyperglycemia
- hyperinsulinemia (and insulin resistance)
- inflammation
- oxidative stress
- endothelial dysfunction
- hypercoagulability
- dyslipidemia

These factors are known, collectively and synergistically, to promote atherosclerosis, which leads to macrovascular and microvascular damage throughout the body. Macrovascular disease complications include: ischemic heart disease, which can lead to myocardial infarction (MI) and cardiomyopathy; cerebrovascular disease, which can lead to stroke and paralysis; and peripheral vascular disease, which sometimes requires amputation of affected extremities. Microvascular complications can include retinopathy, nephropathy, and neuropathy.

Ischemic heart disease may result in cardiomyopathy, but DM can directly alter myocardial function and structure via metabolic mechanisms that are independent of hypertension, valvular disease, or coronary artery disease.

A wide range of metabolic dysfunctions are implicated in DM-associated cardiomyopathy: aberrant insulin signaling; mitochondrial dysfunction and calcium mishandling aggravating the energy mismatch; rise in oxidative stress and advanced glycation products; inflammation; activation of the RAAS; autonomic neuropathy; and microangiopathy.

The characteristic features of DM-associated cardiomyopathy are an initial subclinical phase of myocardial fibrosis and cardiac remodeling, leading to left ventricular hypertrophy, myocyte stiffness, and cell signal alteration. There is then progression to diastolic dysfunction with preserved ejection fraction and later to systolic dysfunction, leading eventually to HFrEF. This process typically results from long-standing and poorly controlled DM.[5, 14]

Can Cardiorenal Diseases be Treated Effectively in DM?

For many decades, DM management focused primarily on glycemic control. However, the tight glycemic control arm of the UKPDS did not yield significant CVD improvement. Indeed, a meta-analysis of several large prospective randomized controlled trials showed a rise in adverse events as glycemic control was tightened.[15, 16] Anti-hyperglycemic agents can cause several adverse effects, such as weight gain, hypoglycemia, and even HF.[7] Furthermore, the efficacy of oral agents tends to taper off over time, resulting in an increasing medication burden.

For the past two decades, DN treatment has focused on blood pressure and glycemic control with renin-angiotensin system (RAS) blockade, but prevalence of CKD among people living with DM has remained at around 30% to 40%.[17]

Cardiovascular Outcome Trials (CVOTs)

CVOTs, which were first mandated by the U.S. Food and Drug Administration (FDA) in 2008, were put in place to ensure that newly approved anti-DM agents demonstrated no CV harm compared to standard care treatments. Results of these trials have shown not only cardiac safety with most of these agents, but also, in some cases, a reduction in CVD and nephropathy progression. The strength of the CVOT evidence has resulted in adjustments in international treatment guidelines for T2DM with existing CVD and CKD.[18]

Sodium Glucose Cotransporter 2 (SGLT-2) Inhibitors

The first CVOT that focused on an SGLT-2 inhibitor was completed in 2016 for empagliflozin, a drug first approved for use in 2014 by the European Medicines Agency (EMA) and the FDA. This CVOT, EMPA-REG OUTCOME, conclusively demonstrated that among the T2DM population with established CVD and moderate to severe renal dysfunction at baseline, empagliflozin could lower glucose levels safely within the context of standard care, improve CVD mortality, and improve renal outcomes. (Treatments for this population included treatment for hypertension and hyperlipidemia.) The trial also showed the relative risk reduction for cardiovascular death vs. placebo was 38%, and for HF, 35%. In addition, reduction in composite renal outcomes, which included renal function decline, ESRD, and renal death, was 46%.[4]

CVOTs conducted more recently for two newer SGLT-2 inhibitors, CANVAS Program (for canagliflozin) and DECLARE TIMI 58 (for dapagliflozin), supported the findings for empagliflozin. Relative risk reductions for HF with the two agents were 33% and 27%, respectively, and for renal composite outcomes, 40% and 47%, respectively.[4]

A meta-analysis of several observational studies that drew from national registries of 12 countries with wide geographic and diverse population representations provided real-world evidence to back the results of these CVOTs. This study supported the conclusions about the beneficial effect of these medications for HF reduction in those with baseline HF and as primary prevention in those with no baseline HF.[4, 19]

In addition, the results of the recent CREDENCE CVOT demonstrated the additional renal benefits of adding canagliflozin to a baseline RAS blockade in a DM population with moderate to advanced renal impairment. The eGFR of the recruited cohort was 30 to < 90ml/min/1.73m². (An eGFR of 60 or above is considered normal.) CV death or hospitalization for HF for the cohort taking canagliflozin was reduced by 30%. Concerns of limb amputation risk from the earlier CVOTs have been eased by the comparable adverse effect rates between the active and placebo arms.[20]

A meta-analysis of three SGLT-2 inhibitor studies published September 2019 by Neuen et al. concluded that these medications prevent major kidney damage in T2DM by decreasing dialysis requirement and transplantation, and reduce the likelihood of death due to CKD.[21]

Hypothesized Mechanisms of Action of SGLT-2 Inhibitors:[4, 5, 9, 13]

- Renal reabsorption of filtered glucose in the proximal tubules of the kidneys is mostly attributed to the action of SGLT-2, while SGLT-1 is responsible for the remaining 10%. Inactivation of SGLT-2 by inhibitors has pleiotropic effects.[4] It causes glucose wasting, which effectively lowers glucose toxicity and reduces the caloric burden, thus contributing to weight loss.
- The correlating diuretic effect also lowers blood pressure, which reduces load on the left ventricle along with myocardial oxygen consumption.
- Increased ketone production shifts the myocardial fuel demand away from fatty acids to ketones, which are a more efficient fuel substrate for the myocardium.
- The concomitant natriuresis reactivates the renal tubule-glomerular feedback loop, which causes vasoconstriction of the afferent glomerular arteriole, thus lowering intra-glomerular pressure, resulting in reduced albuminuria.
- Lowering sodium in the myocyte seems to preserve mitochondrial calcium and reverses an energy mismatch, mitigating oxidative stress buildup.
- Reduction in arterial stiffness, inflammation, and oxidative stress have also been observed.
- The impact on glucose lowering, however, is only moderate, averaging 0.6% to 1.2%.

Glucagon-Like Peptide-1 Receptor Agonists (GLP-1 RAs)

CVOTs for members of this class of medications offered reassurance of glucose lowering efficacy, favorable safety profiles, and absence of cardiac harm when compared with standard care.[7] Two specific agents, liraglutide and semaglutide, demonstrated in the LEADER and SUSTAIN-6 CVOTs (respectively) added CV benefits such as reduction of CV death, MI, and stroke in T2DM individuals with high baseline risk, including multiple risk factors or existing CVD.[7]

The primary composite reduction of major adverse cardiovascular events (MACE) due to these medications ranged from 13% to 26%. Some generated higher reductions in stroke, which was the main driver for overall MACE reduction. These benefits do not correlate strictly to the magnitude of body mass reduction nor of glycemic lowering.[7] The findings of the recently published REWIND study, which investigated dulaglutide, have shown favorable stroke reduction but no significant difference in all-cause mortality or HF when compared to placebo.[23]

The actions of GLP-1 RAs are pleotropic. Receptors for GLP-1 are found in multiple sites throughout the human body. Significant glycemic lowering is seen as resulting from members of this class of agents, but weight loss and blood pressure lowering are variable.[7]

Renal function deterioration was a secondary outcome of the GLP-1 RA LEADER and SUSTAIN-6 CVOTs. There was a general trend of improvement seen in the progression of nephropathy, driven mainly by reduction in macroalbuminuria. There was, however, no definitive evidence of any impact on the hard outcomes of renal disease such as the need for renal replacement therapy for ESRD.[17, 19]

The initial exenatide CVOT, EXSCEL, did not show better cardiac outcome in candidates receiving exenatide compared with those receiving standard care, but the composite renal outcomes were meaningfully reduced in the exenatide group.[22]

Current FDA-approved GLP-1 RAs include exenatide, liraglutide, lixisenatide, albiglutide, dulaglutide and semaglutide. The CVOTs for these agents did not uniformly show CV and renal benefits. Where there were benefits, the degree was variable. They did, however, all show effective and safe lowering of hyperglycemia, body mass, cholesterol levels, and blood pressure to varying degrees. These benefits may indirectly contribute toward CV and renal improvements over and above the direct mechanisms.[7, 17, 19, 22]

Hypothesized Mechanisms of the Action of GLP-1 RAs:[5, 9, 17, 22]

- GLP-1 is released from intestinal cells in response to food ingestion, with a consequent paracrine function that potentiates insulin release commensurate to the rise in the blood glucose level.
- Receptors for GLP-1 are distributed throughout the body. GLP-1 RAs display discernable pleotropic influences.
- Effects of GLP-1 RAs on the pancreas include increased insulin sensitivity and less beta cell apoptosis. GLP-1 RAs also reduce post-prandial glucagon secretion and hyperlipidemia, slow gastric emptying, and contribute to weight loss.
- Other hypothesized cardiorenal protective mechanisms of GLP-1 RAs include:
  - Reduction of inflammation and the infarct size in the ischemic heart
  - Restoration of left ventricular function
  - Improved endothelial function (via reactivation of endothelial nitrous oxide synthase)
  - Stimulation of tubular natriuresis (which may reactivate tubule-glomerular feedback)
  - Modulation of cAMP/PKA signaling
  - Possible minimization of oxidative and inflammatory injuries
  - Reduction of RAS activity, glomerular atherosclerosis, and renal hypoxia

Conclusion

Cardiovascular outcomes trials have resulted in updates to international guidelines for treating individuals with T2DM where there is also established atherosclerotic CVD, CKD, and HF. The updates recommend, depending on baseline pathology, treatment with GLP-1 RAs and/or SGLT-2 inhibitors after standard first-line treatments.[18]

Interestingly, cardiorenal benefits observed after administering these agents did not correlate to the magnitude nor the temporal trend of the glycemia lowering effect, thus strongly suggesting that other mechanisms might be at play. Still, other benefits were seen, including weight loss, blood pressure reduction and, in some instances, lipid profile improvement.

It is groundbreaking that, even in individuals with established DM-related CVD, DN and HF, there are now treatment options that may bring about cardiac and renal improvements. At this time, the effect is known to be mild to moderate. Results of longer therapeutic durations will become available over time. Current investigations are looking into the value of these treatments as primary prevention, with the potential to prevent or postpone cardiorenal complications in T2DM. Indeed, some studies in this area on the T1DM population have also been completed, and more are under way.

These new-generation agents enable profile-specific and individualized treatment methodologies that are approaching those of personalized medicine. For every individual along the multiple points of DM's treatment path, potential opportunities exist to arrest disease progression and prevent major complications, which may lead to significant improvements in quality of life and survival for people living with DM.

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MEDICAL TEAM UPDATE

Dr. Summer Zhu has joined RGA as Regional Medical Director, Asia Pacific. She is currently based in Sydney, Australia.

ELECTRONIC HEALTH RECORDS VS. ATTENDING PHYSICIAN STATEMENTS

Abstract

RGA has been studying the evolution of Digital Health Data (DHD) for the past decade and has developed tools that can aid our clients in optimizing their use of electronic health records (EHRs) in underwriting. To many, the EHR and the Attending Physician Statement (APS) have become interchangeable terms referring to patient medical records. In this article, for clarity, an APS refers to the handwritten or typed notes that contain office visit summaries and medical histories as well as the imaging and test and procedure results that make up a patient's medical file. An EHR denotes the digitized version of these records. Much of the information in an APS may be contained in an EHR, but in digitizing, some of the detail and clarity may be lost due to constraints in how the information can be recorded. Reviewing this data has given RGA underwriters some valuable insights into how best to reconcile EHRs with traditional medical records. While we are excited about the potential utility of DHD and believe it has become an important underwriter resource, we do not yet think an EHR should routinely be substituted for an APS. Many in the industry are currently working to understand and define use cases around DHD, and it may be helpful to share some lessons learned.

DHD and Underwriting: Still a Lot to Learn

Today's electronic health records (EHRs) are the result of the ongoing drive to digitize the information contained in physician patient records. They aim to automate and streamline provider workflow and are increasingly used by medical professionals and service providers to maintain patient histories and records. However, the EHR and its structured digital data is still not a perfect substitute for the unstructured data found in many attending physician statements (APSs).

There are several reasons for this: first, an EHR might not always provide a full and comprehensive view of the history, longevity, and severity of each condition in a record. For instance, the cancer diagnostic codes in an EHR may not always include tumor stage or grade, and the cardiac diagnostic codes may not provide the detail available in an echocardiogram or cardiac catheterization report.

Interoperability also continues to be a challenge. Sometimes the lack of coding detail depends on which medical entity is providing the EHR. A primary care physician, for example, might not have the diagnostic detail found in a specialist's records if good interoperability does not exist. This can be especially true if the specialist is outside of the primary physician's practice or network.

Surprisingly, information such as "status" of a specific condition or "effective time" (when that condition first emerged) are both optional EHR fields. In addition, digital information-gathering and recordkeeping are not yet universal practices in the medical profession: EHRs are only available from providers or practices which have chosen to implement these systems.

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Jennifer Thoreson, R.N., AALU, is Executive Director, Underwriting Services, U.S. Mortality Markets, at RGA. With the company since 2004, she currently directs a team of underwriters working on innovations such as evaluating digital health data, developing automated and accelerated underwriting rules, and applying data science techniques to underwriting data. She also is a member of RGA's Underwriting Manual Review Committee.

Jennifer's extensive background in underwriting includes roles as a Senior Underwriter with RGA and General American Life Insurance Co., a group life underwriter for Paragon Life Insurance, and a health underwriter for National Casualty Company.

Her Bachelor of Science (B.S.) degree in Health Science is from South Dakota State University, and her R.N. Diploma is from the Lutheran School of Nursing, in St. Louis. Jennifer also has two years of clinical nursing experience at St. Mary's Hospital, Clayton, Missouri. She is an Associate of the Academy of Life Underwriting (AALU) and has completed eight LOMA exams.

The digital medical history in an EHR may be limited, as unstructured data can be difficult to standardize and interpret on an automated basis. Underwriters often need the unstructured data found in an APS for diagnoses such as alcohol and drug abuse or depression.

Finally, diagnostic codes in EHRs may be based on a differential and not a final diagnosis, especially if a test or procedure was ordered to confirm or rule out a diagnosis. The actual diagnosis is therefore not always clear or needs to be found in another medical record.

Cases with substantial complexity are more likely to need detailed and unstructured information along with hands-on underwriter analysis. Figure 1 lists examples of impairments that may be found in complex cases.

Figure 1: Common diagnoses that may require more information than an EHR provides	
Alcohol abuse / addiction	Drug abuse / addiction
Cancer	Multiple sclerosis
Coronary artery disease	TIA (transient ischemic attack)
Depression	Valvular heart disease

EHR Utility

Right now, it is most effective to use digital health data to underwrite cases rated standard or better or cases that are likely declines. Figure 2 provides examples of impairments that are good candidates for underwriting using the EHR. For these cases, EHRs can add value in many ways, as they contain information that can supplement, complement, or even take the place of basic evidence items. For example, vital sign information in an EHR, such as build and blood pressure, could be used in lieu of a paramedical exam for certain age and face amount bands. An EHR could also speed verification of application disclosures by validating clean applications or highlighting nondisclosures.

EHRs can be particularly helpful when verifying applicant MIB codes. Certain MIB codes might require additional investigation, and the ICD or SNOMED codes contained in an EHR could provide the needed information, eliminating the necessity (or at least reducing the time needed) for a follow-up applicant tele-interview.

An EHR that provides information pertaining to specialist referrals can help underwriters target requests for additional information from specialist medical records. Also, effective dates and statuses in an EHR can provide a good timeline, which can help an underwriter determine if additional information is needed. As an example, a diagnostic code for depression in full remission last noted 10 years ago may need no additional information, whereas that same code, if noted one year ago, may require additional information.

Finally, EHRs can be part of an underwriting department's "Heads up" or "Triage" program, identifying cases that could be processed with no or minimal underwriter review or cases that could go to a junior underwriter for processing.

Figure 2: Common applicant disclosures that may be underwritten with only an EHR	
Anxiety	Gastroesophageal reflux disease (GERD)
Asthma	Hypertension
Basal cell carcinoma	Hernia
Benign prostatic hypertrophy or prostatitis	Hypercholesterolemia
Build (overweight)	Hypothyroidism/Hyperthyroidism
Cholecystitis	Osteoarthritis

Room for Improvement

As we have studied the use of digital data found in EHRs, we have found that there is room for further refinements.

Sometimes a medication is indicated as having been prescribed, but a diagnosis code matching that medication's purpose does not appear. For example, an EHR might indicate a prescription for metformin that instructs the patient to take one tablet daily by mouth with evening meals for diabetes, but a diagnosis code indicating the purpose of the prescription is not included.

Also, some medical providers use very general diagnostic codes in EHRs that makes it difficult for underwriters to assess the risk. For example, an EHR might contain SNOMED code 41368006, indicating urethral disease, but not the additional codes that would provide the specificity an underwriter would need. Figure 3 shows the range of types of codes that can appear in one person's EHR.

Indications of active or inactive statuses can also be helpful but they are not always updated, and these indications need to be compared with a date. For example, one EHR contained a status of "generalized enlarged lymph nodes" with an onset date of November 13, 2017, which was still marked "active" in a 2019 record. However, no update had been provided since the initial date of diagnosis. In another instance, a condition was diagnosed three years ago and never mentioned again, yet medications were still being prescribed for it. This is where an APS, with details and dates for every visit, can be helpful.

Doctor instructions on prescriptions can help an underwriter as well. For example, one EHR indicated three drugs had been prescribed: trazadone, an anti-depressant, with instructions to take half a tablet by mouth at bedtime for sleep; hydrocodone, with instructions to take as needed for post-surgical pain; and Revatio, a treatment for pulmonary hypertension, with instructions to take three tablets one hour prior to sexual activity. The doctor's instructions clarify why a medication is prescribed, which can be especially helpful when medications have more than one use or are prescribed for off-label uses.

Figure 3: Examples of Codes, Code Descriptions, and Dates in an EHR

Applicant Demographics: 55 Y/O Female, Non-Smoker; Height 5'3"; weight 155; BP 125/85

Code Value	Code Set	Code Description	Date Reported
14760006	SNOMED	Constipation (disorder)	11/20/2018
23595009	SNOMED	Gastroesophageal reflux disease (disorder)	1/29/2018
59621000	SNOMED	Essential hypertension (disorder)	1/29/2018
267434003	SNOMED	Mixed hyperlipidemia (disorder)	1/29/2018
1076151100019101	SNOMED	History of pulmonary embolism on long-term anticoagulation therapy (situation)	1/29/2018
61582004	SNOMED	Allergic rhinitis (disorder)	10/27/2017
711150003	SNOMED	Long-term current use of anticoagulant (situation)	10/27/2017
193462001	SNOMED	Insomnia (disorder)	10/27/2017
00822004	SNOMED	Hyperlipidemia (disorder)	10/27-2017
2788600009	SNOMED	Chronic low back pain (finding)	2/17/2017
239873007	SNOMED	Osteoarthritis of knee (disorder)	2/17/2017
414916001	SNOMED	Obesity (disorder)	3/29/2016
48694002	SNOMED	Anxiety (finding)	12/3/2015
81576005	SNOMED	Closed fracture of phalanx of foot (disorder)	9/8/2015
064.00	ICD-9	Constipation, unspecified	9/12/2013
21897009	SNOMED	Generalized anxiety disorder (disorder)	9/12/2013
415.19	ICD-9	Other pulmonary embolism and infarction	8/28/2013
280.0	ICD-9	Iron deficiency anemia, unspecified	3/6/2013
626.8	ICD-9	Other disorders of menstruation and other abnormal bleeding from female genital tract	4/18/2012
724.2	ICD-9	Lumbago	12/17/2010
49218002	SNOMED	Hip pain (finding)	12/17/2010
698.3	ICD-9	Lichenification and lichen simplex chronicus	12/17/2010
631.81	ICD-9	Esophageal reflux	4/3/2007
564.1	ICD-9	Irritable bowel syndrome	4/3/2007
692.9	ICD-9	Contact dermatitis and other eczema, unspecified cause	2/8/2007
35489007	SNOMED	Depressive disorder (disorder)	11/14/2006
717.9	ICD-9	Unspecified internal derangement of knee	8/30/2006
718.31	ICD-9	Recurrent dislocation of joint, shoulder region	8/30/2006
780.52	ICD-9	Insomnia, unspecified	8/30/2006
38341003	SNOMED	Hypertensive disorder, systemic arterial (disorder)	8/30/2006
472.0	ICD-9	Chronic rhinitis	8/30/2006
715.90	ICD-9	Osteoarthrosis, unspecified whether generalized or localized, site unspecified	8/30/2005
724.2	ICD-9	Lumbago	9/10/2005
727.43	ICD-9	Ganglion, unspecified	3/23/2004
599.0	ICD-9	Urinary tract infection, site not specified	3/23/2004
466.0	ICD-9	Acute bronchitis	10/7/2003
478.1	ICD-9	Other diseases of nasal cavity and sinuses	9/21/2003
477.8	ICD-9	Acute rhinitis due to other allergies	8/4/2003
461.9	ICD-9	Acute sinusitis, unspecified	8/4/2003
719.46	ICD-9	Pain in joint, lower leg	12/3/2002
726.90	ICD-9	Enthesopathy of unspecified site	3/30/2001
278.00	ICD-9	Obesity, unspecified	11/24/2000

Ready for Prime Time? Not Quite…

EHRs are here to stay. Although they may be long and repetitive and may contain gaps and digital noise, they are also deep, rich sources of applicant medical data. However, EHRs should not yet routinely be substituted for APSs. It will be the insurance industry's challenge to discover how best to access the information nuggets in EHRs and stitch them together so that repetition is deleted and digital noise quieted, enabling the information to be digested and well-utilized in underwriting.

TODAY'S CHALLENGES IN INFECTIOUS DISEASE

ReFlections recently had the opportunity to interview Michael T. Osterholm, Ph.D, MPH, a highly respected and globally recognized public health, biosecurity, and infectious disease expert. Dr. Osterholm generously shared his time and observations with *ReFlections.*

With regard to infectious diseases, what keeps you up at night?

Right now, several things. The near-future risk of a pandemic, especially for influenza, tops the list, but I am also concerned about the worldwide resurgence of polio, measles, and sexually transmitted infections. How vector-borne diseases are spreading in developing countries where urbanization is ramping up faster than infrastructure is also a worry, as well as newer diseases such as acute flaccid myelitis, which public health officials are still trying to figure out. Increased worldwide travel and migration are also making the spread of disease faster and more efficient.

Speaking of influenza, what do you think are the chances for successful development of a universal flu vaccine? How long do you think it might take?

Fortunately, this is one area where a lot of major investment and interesting research is taking place. I am optimistic we will have an influenza vaccine that will be highly protective against many strains of influenza virus and will protect for many years. However, this type of vaccine won't be available for at least another five to seven years.

Australia's 2019 flu season was described by some as a particularly bad one. Can that provide any information about what the Northern Hemisphere might expect?

First, you simply can't predict the coming influenza season from the one just past. Even though Australia's flu season was a severe one with increased morbidity, there have been seasons in the past where what happened during one season in one hemisphere was not followed by a similar trend in the other.

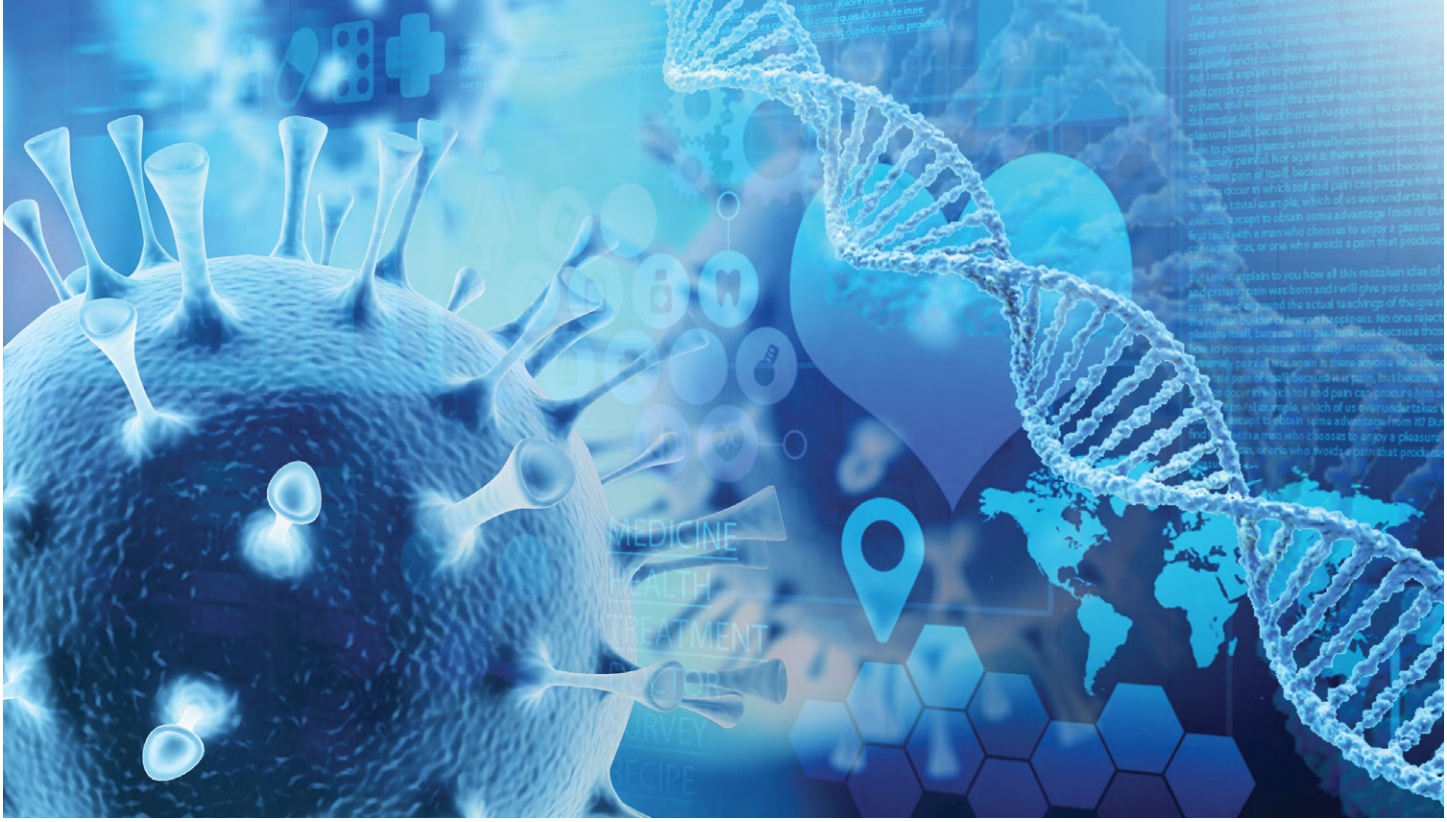
That being said, it has become clear that most influenza vaccinations, especially in the U.S., are given far too early. Flu is rarely seen in the general population before December, and flu vaccine efficacy generally begins to significantly reduce in four to six months. As U.S. vaccination programs tend to coincide with the beginning of the school year (late August/early September), this mismatch needs attention.

ABOUT THE EXPERT

Michael T. Osterholm, Ph.D, MPH
http://www.cidrap.umn.edu

Michael Osterholm, Ph.D, MPH, founded and leads the Center for Infectious Disease Research and Policy (CIDRAP), which is part of the University of Minnesota's Department Office of the Vice President for Research. Under his aegis, CIDRAP, which was founded in 2001, consults with corporations and other organizations and governments, providing information and research and teaching preparedness for outbreaks and related crises. (RGA is an executive member of the CIDRAP Leadership Forum.)

Dr. Osterholm is also Regents Professor, McKnight Presidential Endowed Chair in Public Health at the University of Minnesota, a professor in the University's School of Public Health, College of Science and Engineering, and an adjunct professor at its Medical School. He has been an advisor to the U.S. Department of Health and Human Services on issues related to bioterrorism and public health preparedness and to the Centers for Disease Control and Prevention, and was most recently a science envoy for health security for the U.S. Department of State. He consults frequently with the World Health Organization and with U.S. governmental organizations on issues related to epidemiology and bioterrorism. He has authored more than 315 papers and abstracts, is a frequent lecturer on topics related to the epidemiology of infectious disease, and has received several honors, awards, and major research grants.



Can you tell us more about acute flaccid myelitis (AFM)?

As far as we know, it is most probably caused by an enterovirus, but scientists don't yet know how the virus causes the disease or why it has a bi-yearly surge pattern. Research is progressing, but one of the challenges is the relatively small number of cases makes it hard to study. *(**Editor's Note:** AFM is a rare disease that affects spinal cord gray matter. It mostly affects young children with symptoms that include weakness of the limbs, loss of muscle tone, and decreased or absent reflexes.)*

In 2014, the report "Review on Antimicrobial Resistance" stated that by 2050, 10 million deaths a year may be attributable to antimicrobial resistance (AMR). What are your thoughts?

I agree with this assessment – and this is yet another thing that keeps me up at night. By 2050, if things don't change, we will likely see 10 million deaths annually from infectious diseases that can't be treated – more than the projected mortality for cancer and diabetes combined. Look at *Candida auris*: it wasn't even on the radar two years ago, and now it has many strains with high levels of drug resistance. It's a real challenge in hospital settings.

What needs to change? AMR needs to be a real priority. Right now, the U.S. spends about $1 billion a year on AMR, but given the current issues, the need is really for more. My hope is that governments will make the effort now to prioritize the need to combat AMR.

Are there best practices insurance companies should follow when managing pandemic risk, especially for influenza?

Awareness of the potential impact and managing expectations are probably the two most important things. Predicting an influenza pandemic's severity is very difficult, as they generally come in several waves – at least two in the first year – and the second wave can be far worse than the first. Then there is making sure preparations are in place to ensure a company's business activities can continue: will there be people who can come to work, to turn on the lights, respond to emails and phone calls, and maintain processes?

Is there a Disease X – an unknown future disease – that insurance companies need to be concerned about? If so, how can they prepare?

A disease we're keeping an eye on is Chronic Wasting Disease (CWD). Much like Mad Cow Disease, it is animal-borne. Currently, it affects only cervids (deer, elk, moose), but the prion that causes it is mutating

quickly. Although human transmission has not been documented yet, as with Mad Cow, it could just be a matter of time, as hunters are eating animals that test positive for infection, and there has been resistance among some U.S. hunters to have their killed cervid tested for CWD before consumption. Epidemiologists are watching CWD closely, tracking both human and animal exposure, and are working toward more reliable tests.

What value does CIDRAP add for its consulting clients such as RGA? How does it enhance information-gathering and business outcomes and benefit both society and bottom lines?

Companies need authoritative, up-to-date knowledge of infectious diseases. Scientists and public health experts are making steady progress, but many diseases are still flourishing. For insurance companies, the threat is from more than just well-known conditions such as influenza: morbidity and mortality from measles and polio is again on the rise, new infectious diseases are emerging, and the rapidly developing pace of AMR is a constant worry. Companies need to plan for their own futures, and to align their plans with local and national infrastructures. What we provide is in-depth, up-to-the-minute knowledge – we have a news team that collects timely, accurate knowledge and disseminates it daily – and the experience and expertise to help companies know what can pop up in a crisis and orchestrate well-coordinated response plans.

> **I am optimistic we will have an influenza vaccine that will be highly protective against many strains of influenza virus and will protect for many years.**

What is your fear for the future? What is your hope?

Probably we should say “fears”. What has become clear to me over the years is that public health is really an issue of national security. Pharmaceutical supply chains are one concern, as they can be compromised by natural disasters, wars (trade or military), and epidemics. Another is the growing distrust of science, which in epidemiology is translating into resistance to vaccination. The forces driving this resistance are powerful and well-funded, and in terms of disease are resulting in outbreaks of diseases thought to have been eradicated.

Public health is also not a static issue. It is constantly evolving, and the epidemiology piece is a worldwide challenge. Meeting it will take resources. My hope is that the focus of the medical profession and of governments on these issues will improve, so that the world can meet today’s challenges and the challenges to come.

Longer Life Foundation

An RGA/Washington University Collaboration

THE LONGER LIFE FOUNDATION (LLF) ANNOUNCES 2019-2020 RESEARCH GRANTS

The **Longer Life Foundation** recently awarded its 2019-2020 grants to fund early-stage research to ten leading investigators at Washington University in St. Louis School of Medicine.

Now in its 21st year, the **Longer Life Foundation**, a collaboration of RGA and Washington University in St. Louis School of Medicine, has been funding pilot and feasibility research studies that add to medical science's ability to understand, prevent, and treat diseases and, ultimately, improve the human condition. This research also helps insurers improve risk stratification and will hopefully allow the industry to provide more cover to more people.

Please visit the LLF website, www.longerlife.org, or contact **Dr. Daniel Zimmerman**, Managing Director of LLF, or **Dr. Dave Rengachary**, Deputy Managing Director of LLF, for more information. If you are interested in getting involved with LLF and being a part of its cutting-edge research, please feel free to reach out.

Longer Life Foundation 2019-2020 Research Grants

Researcher	Project Title
Luigi Adamo, M.D., Ph.D. (Year 1)	Myocardial Aging as a B Lymphocyte-Dependent Event
Grant Challen, Ph.D. (Year 2)	Reducing the Risk of Blood Cancer with Age by Weeding Out Leukemia-Causing Stem Cells in the Bone Marrow
Brian DeBosch, Ph.D. (Year 2)	Leveraging Adaptive Hepatic Glucose Fasting Responses Against Cardiometabolic Disease
Michelle Elvington, Ph.D. (Year 1)	C3(H2O) as a Marker of Human Malignancy
Meredith E. Jackrel, Ph.D. (Year 2)	Restoring Proteostasis to Counter Human Disease
Sungsu Kim, Ph.D. (Year 1)	A Pathogenic Role for Senescent Schwann Cells in the Aging-Associated Impairment of Nerve Regeneration
Lei Liu, Ph.D. (Year 1)	Innovative Data Mining for Biological Age
William McCoy, M.D., Ph.D. (Year 1)	Targeting *Cutibacterium acnes* RoxP to Decrease Morbidity and Mortality of Indwelling Medical Devices
Joshua Mitchell, M.D. (Year 1)	Predicting Cardiovascular Toxicity of Targeted Cancer Therapy
Bettina Mittendorfer, Ph.D. (Director, Longevity Research Program)	Dietary Protein and Cardiovascular Health

The Longer Life Foundation's mission is to fund and support the study of factors that either predict mortality and morbidity of select populations or influence improvements in longevity, health, and wellness.

ReCite

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

Natural History of Adrenal Incidentalomas With and Without Mild Autonomous Cortisol Excess: A Systematic Review and Meta-analysis

Elhassan YS, et al. Annals of Internal Medicine. 2019 July 16; 171: 107-16.
https://annals.org/aim/article-abstract/2736920/natural-history-adrenal-incidentalomas-without-mild-autonomous-cortisol-excess-systematic

Adrenal incidentalomas are mostly either benign non-functioning adrenal tumors (NFATs) or adenomas causing mild autonomous cortisol excess (MACE). Incidental detection of adrenal masses by imaging is increasingly common in clinical practice, owing to the ever-increasing use of cross-sectional imaging. Generally, NFATs do not require surgery, whereas whether MACE adenomas should be removed is controversial despite several studies suggesting that MACE might result in increased risk for cardiometabolic disease and death. This study sought to summarize the available literature and undertake a systematic review and meta-analysis of the natural history of NFAT and MACE adenomas to better guide their management.

The meta-analysis found that only a small proportion of patients with NFAT or MACE had tumor growth or changes in hormone production during follow-up, and no patients developed adrenal cancer. Also, patients with both types of tumors, but more so with MACE, presented with high prevalence and incidence of cardiovascular events such as hypertension, obesity, dyslipidemia, and type 2 diabetes. Finally, those with MACE were more likely than those with NFAT to develop or show worsening of these factors during follow-up. Of note, reported statistics for all-cause and cardiovascular mortality in patients with NFAT during follow-up were similar to those for patients with MACE.

Editor's Note: *Applicants with either NFAT or MACE, or both, carry increased risk for cardiometabolic comorbid conditions. It warrants both clinical follow-up and further scrutiny of cardiac risk factors when underwriting for mortality and living benefits.*

Overall Mortality After Diagnosis of Breast Cancer in Men vs. Women

Wang F, et al. JAMA Oncology. 2019 Sept 19; 5(11): 1589-96.
https://jamanetwork.com/journals/jamaoncology/article-abstract/2751525

Survival differences between male and female patients with breast cancer have been reported, but the underlying factors associated with the disparity have not been fully studied. The aim of this study was to compare mortality of male and female patients with breast cancer, and quantitatively evaluate the factors associated with any sex-based disparity discovered. In total, 16,025 male (mean age 63.3; standard deviation [SD] 13.0 years) and 1,800,708 female (mean age 59.9; SD 13.3 years) patients with breast cancer were included in the study.

Male patients had higher mortality than female patients across all stages. Clinical characteristics and undertreatments were associated with a 63.3% excess mortality rate for male patients. However, sex remained a significant factor associated with overall mortality (adjusted hazard ratio [HR], 1.19; 95% confidence interval [CI], 1.16-1.23) as well as mortality at three-year (adjusted HR, 1.15; 95% CI, 1.10-1.21) and five-year (adjusted HR, 1.19; 95% CI, 1.14-1.23) follow-ups, even after adjustment for clinical characteristics, treatment factors, age, race/ethnicity, and access to care.

Editor's Note: *The disparity in mortality between male and female patients with breast cancer appeared to persist after accounting for clinical characteristics, treatment factors, and access to care, suggesting that other factors – particularly additional biological attributes, treatment compliance, and lifestyle factors – should be identified to help in eliminating this disparity. This will certainly shape our views when considering the mortality risk of this group going forward.*

Sleep Duration and Myocardial Infarction

Daghlas I, et al. Journal of the American College of Cardiology. 2019 Sept; 74(10).
http://www.onlinejacc.org/content/74/10/1304

This study sought to investigate associations between sleep duration and incident myocardial infarction (MI), accounting for joint effects with other sleep traits and genetic risk of coronary artery disease, and to assess causality. Among 461,347 members of the UK Biobank (UKB) database cohort free of relevant cardiovascular disease, the authors estimated multivariable-adjusted hazard ratios (HR) for MI (5,128 incident cases) across habitual self-reported short (<6 hour) and long (>9 hour) sleep durations. They also examined joint effects with sleep disturbance traits and calculated a coronary artery disease genetic risk score, also using UKB data.

The authors conducted two-sample Mendelian randomizations (MRs) for short (24 single nucleotide polymorphisms) and continuous (71 single nucleotide polymorphisms) sleep duration with MI (n = 43,676 cases/128,199 controls) and replicated the results using UKB data (n = 12,111 cases/325,421 controls).Compared with sleeping six to nine hours per night, shorter sleepers had a 20% higher multivariable-adjusted risk of incident MI (HR: 1.20; 95% CI: 1.07 to 1.33), and longer sleepers a 34% higher risk of incident MI (HR: 1.34; 95% CI: 1.13 to 1.58). These associations were independent of other sleep traits. Healthy sleep duration mitigated MI risk even among individuals with high genetic liability (HR: 0.82; 95% CI: 0.68 to 0.998).

Editor's Note: *Sleep duration and quality has been associated with several diseases, including dementia and cardiovascular events. Prospective observational and MR analyses support short sleep duration as a potentially causal risk factor for MI. Investigation of sleep as a risk factor might become part of routine underwriting practices in the future.*

Medium and Long-Term Risks of Specific Cardiovascular Diseases in Survivors of 20 Adult Cancers: a Population-Based Cohort Study Using Multiple Linked U.K. Electronic Health Records Databases

Strongman H, et al. The Lancet. 2019 Aug 20; 394(10203): 1041-54.
https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(19)31674-5/fulltext

The past few decades have seen substantial improvements in cancer survival, but concerns exist about long-term cardiovascular disease risk in survivors driven by cardiotoxic treatment effects, mechanisms directly related to cancer biology, and shared risk factors. This study used large-scale electronic health records data from multiple linked U.K. databases to quantify absolute and relative risks of a comprehensive range of cardiovascular diseases in survivors of the 20 most common site-specific adult cancers. It covered more than 90% of all cancer diagnoses and compared with cancer-free controls from the general population. It also investigated the extent to which relative risk differences are driven by shared risk factors, demographic characteristics, and use of chemotherapy and radiotherapy.

Findings suggested that venous thromboembolism risk was elevated in survivors of 18 of 20 site-specific cancers compared with controls. HRs decreased over time but remained elevated more than five years after diagnosis. Researchers also observed increased risk of heart failure or cardiomyopathy in patients after ten of 20 cancers.

Elevated risks of arrhythmia, pericarditis, coronary artery disease, stroke, and valvular heart disease were observed for multiple cancers, including hematological malignancies. HRs for heart failure or cardiomyopathy and venous thromboembolism were greater in patients without previous cardiovascular disease and in younger patients. However, absolute excess risks were generally greater with increasing age. Increased risks of these outcomes seemed most pronounced in patients who had received chemotherapy. The findings show that more tailored strategies to minimize and manage cardiovascular risk are needed for people who survive cancer.

Editor's Note: *Survivors of most site-specific cancers had higher risks of cardiovascular disease compared with those without diagnosed cancer. Patterns of risk varied by cancer site and by specific cardiovascular disease outcomes. This could have a significant impact in markets where critical illness benefits reinstate and where plans are able to pay more than 100% of the sum assured. Pricing impacts and underwriting practices need to be aligned to minimize these risks.*

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.

Lifestyle-Related Mortality
Julianne Callaway, Strategic Research Actuary, RGA (running time: 7:52)
https://www.rgare.com/knowledge-center/media/videos/lifestyle-related-mortality

The World Health Organization has identified the rise of non-communicable diseases as a profound global threat. Spending excessive time behind a computer or on a couch, using tobacco products, or eating fatty foods can all have negative effects on longevity. To understand the relationship between lifestyle behaviors and mortality, RGA investigated two national, health-related, mortality-linked data sets provided by the Centers for Disease Control and Prevention (CDC). This webcast discusses the findings.

Liquid Biopsies: Fact, Fiction, or Both?
Daniel D. Zimmerman, M.D., Senior Vice President and Global Support Team Chief Medical Director, RGA (running time: 17:30)
https://www.rgare.com/knowledge-center/media/videos/liquid-biopsies-fact-fiction-or-both

The fast-developing science of liquid biopsy is becoming an increasingly important clinical tool in the investigation and diagnosis of diseases such as cancer, with the added bonus of being non-invasive. In this webcast, Dr. Zimmerman discusses this rapidly developing technology and the impact it is likely to have on both clinical and insurance medicine.

RGA THOUGHT LEADERSHIP PUBLICATIONS

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

The HIV/AIDS Epidemic: What's New (Part I)
Hilary Henly, Chartered Insurer / FCII (DLDU/DLDC),
Head of Underwriting, Ireland; Director, Divisional Underwriting Research,
RGA International Reinsurance Company dac
https://www.rgare.com/knowledge-center/media/research/the-hiv-aids-epidemic-what-s-new

Kratom: The New Opioid?
Hilary Henly, Chartered Insurer / FCII (DLDU/DLDC),
Head of Underwriting, Ireland; Director, Divisional Underwriting Research,
RGA International Reinsurance Company dac
https://www.rgare.com/knowledge-center/media/research/kratom-the-new-opioid

Underwriting Opioid Risk: One Doctor's Journey
Elissa Del Valle, M.D., Vice President and Medical Director, RGA
https://www.rgare.com/knowledge-center/media/articles/underwriting-opioid-risk-one-doctor-s-journey

Underwriting Vaping-Related Lung Injury: Five Questions with RGA's Dr. Dave Rengachary
Dave Rengachary, M.D., Senior Vice President and Chief Medical Director, U.S. Mortality Markets, RGA
https://www.rgare.com/knowledge-center/media/articles/underwriting-vaping-related-lung-injury-five-questions-with-rga-s-dr.-dave-rengachary

Global Health Brief: Navigating Allergen-Specific Immunotherapy
Dipta Rai, M.D., Associate Director, Health Claims Management,
RGA Malaysia
https://www.rgare.com/knowledge-center/media/articles/global-health-brief-navigating-allergen-specific-immunotherapy

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