

ReFlections

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IN THIS ISSUE

- 2 Polygenic Risk Scores:
Combining Thousands of Genetic Variants
to Predict Disease**
By Richard Russell, Ph.D.
- 6 Recent Webcasts**
- 7 The Association of Loneliness, Social
Engagement and Social Activity with All-
Cause Mortality**
By Hilary Henly, FCII (DLDU/DLDC)
- 13 Longer Life Foundation –
Announcing 2018-2019 Grant Recipients**
- 14 ReCite**
Relevant articles to insurance medicine

FROM THE EDITORS

It is with pleasure that we bring you the September 2018 issue of *ReFlections*, RGA's global medical newsletter. We hope your year, both professionally and personally, is going along nicely.

With this issue, we are proud to introduce a new author, Richard Russell, Ph.D., Lead Health Data Scientist, U.K., Division of Global Research and Data Analytics (GRDA). In his article, he addresses polygenic risk scores (PRSs) and provides an update on the quickly advancing knowledge in this area of genetics research and risk assessment.

In our second feature article, Hilary Henly, Head of Underwriting, Ireland and Director, Divisional Underwriting Research, returns to present an innovative review of some non-traditional predictors of mortality and morbidity. Specifically, she discusses the impact of loneliness, social engagement, and social activity. Given the aging population and newer approaches to older age underwriting, this topic will be of significant interest to the reader.

The Longer Life Foundation (LLF) continues to celebrate its 20th anniversary in 2018. Recently, the newest group of grant recipients were announced and the researchers and their cutting-edge projects can be reviewed on page 13. Also, please click the page's link to the Foundation's 20th anniversary commemorative brochure, which highlights some of LLF's groundbreaking researchers and lists all grant recipients throughout its history.

Additionally, we have provided links to two new webcasts: the first, on mosquitos as disease vectors and their impact on global mortality and morbidity, from Eric Westhus, Ph.D., Data Scientist, Global Research and Data Analytics (GRDA); and the second, on liquid biopsies and epigenetics, from Daniel D. Zimmerman, M.D. Senior Vice President, Chief Medical Director, Global Support Team (GST). Both can be viewed at your convenience. Please turn to page 6 for details.

Please feel free to contact us at any time and provide your feedback and comments.

Thank you,

Peter and Dan

POLYGENIC RISK SCORES: COMBINING THOUSANDS OF GENETIC VARIANTS TO PREDICT DISEASE

Abstract

In recent years genome-wide association studies (GWAS) have discovered thousands of genetic variants associated both with diseases and complex traits. Geneticists had hoped these studies might transform precision medicine by enabling individualized disease risk prediction and treatments tailored to the variations in a person's genes (a field known as pharmacogenomics). Most common diseases, however, are not caused by single genetic mutations, which are far more accessible to precision medicine strategies. Instead, GWAS have revealed that the majority of common diseases have a polygenic architecture, wherein multiple genetic variants, each by themselves of small effect, cumulatively impact disease risk.

Advances in statistical and clinical genetics have started to demonstrate the power of polygenic risk profiling in the form of polygenic risk scores to identify individuals at higher (and lower) risk of disease. This article reviews recent developments in polygenic risk profiling and the predictive utility of polygenic risk scores to uncover a person's susceptibility to disease.

The Promise of Genetics and Genomics for Medicine

During the past decade, significant progress in genomic technologies has allowed scientists and clinicians to explore the human genome in incredible detail. Consequently, the growth in our understanding of genetics and genomics may have the potential to transform all aspects of precision medicine, including prevention of disease manifestation, accurate diagnosis and prognosis of disease, pharmacogenomics, and motivating lifestyle changes to improve health.

When coupled with the ever-decreasing cost of DNA sequencing (see Figure 1), the era of genomic medicine can now be considered truly under way. The first human genome cost \$2.7 billion and took almost 15 years to sequence. Now sequencing costs about \$1,000 and can be done in a few days. In a few years, some believe the whole genome will be sequenced for as little as \$100. As research continues to advance our understanding of genetics, genomic medicine will almost certainly lead to improvements in mortality and longevity, which will be positive for the life insurance industry and for society as a whole.

What is a Polygenic Risk Score?

A polygenic risk score (PRS) is a metric that condenses information from tens, hundreds, thousands or even millions ("poly") of a person's genetic variants ("genic") into a score that measures the individual's genetic predisposition to specific diseases or complex traits.

Genome-wide association studies (GWAS) are a relatively new way for geneticists to search among the millions of variants in the human genome and identify those associated with certain diseases or complex traits. These

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Richard Russell, Ph.D., is Lead Health Data Scientist in RGA's Global Research and Data Analytics unit. He is primarily focused on strengthening and enhancing RGA's global mortality and morbidity modeling capabilities for underwriting manual research, actuarial pricing and innovation projects. Prior to joining RGA in 2013, he was a postdoctoral research fellow in statistics at City, University of London. Richard's B.Sc. in biotechnology, M.Sc. in bioinformatics and Ph.D. in statistics are all from Imperial College, London.

genetic variants are known as single nucleotide polymorphisms or SNPs (pronounced “snips”). DNA has four different base nucleotides (DNA building blocks) and a SNP occurs when a nucleotide in a particular position in the genome is different.

Geneticists have observed that certain SNPs occur more commonly in people with a particular disease. Over the 13 years since the first GWAS was conducted (2005),² millions of SNPs have been found and isolated.

These SNPs have been shown to increase or decrease a person’s risk of developing complex diseases such as diabetes,³ breast cancer,⁴ and cardiovascular disease.⁵

Clinicians commonly test for high-penetrance single gene mutations such as *BRCA1* or *BRCA2*, two genes that confer increased risk for breast cancer. Such simple one-to-one relationships between a gene and susceptibility to disease, however, are very rare. Rather, the genetic architecture of most disease is overwhelmingly polygenic, with multiple SNPs, each of small effect, cumulatively affecting disease risk. No single SNP can be used in prediction, as the increase or decrease in risk is extremely small. However, merging information across thousands or even millions of SNPs can be useful in predicting disease risk.

It is hoped that as GWAS grow in sample size and more SNPs are investigated, researchers will uncover additional SNPs associated with common diseases as well as SNPs that can influence a person’s response to medications.

And so we come to PRSs. These scores, which are calculated based on an individual’s SNPs, are generally expressed as risk percentiles correlated against the risk of a particular disease in a given population. They are already proving most useful in terms of risk predictions in the extremes of the genetic risk distribution (see Figure 2).

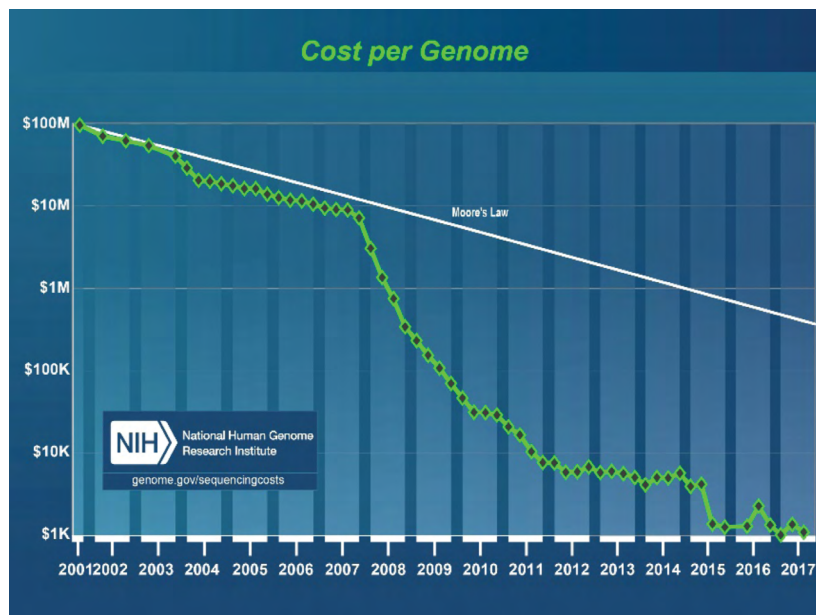
An individual with a PRS in the 100th percentile for diabetes, for example, would be considered to have the highest genetic risk. However, for an individual with a PRS closer to the population mean, the score would offer little additional risk information (i.e., the person’s predicted risk, based on his or her genetics, will be similar to the population’s average risk).

In the past few years, academic researchers have developed PRSs for many conditions and have tested them in their studies. The pertinent question, however, remains: will PRSs transform clinical risk assessment in terms of disease prediction, stratification, and prognosis? And could they impact insurance medicine, underwriting, product development, and claims experience?

Clinical Utility of Polygenic Risk Scores and Possible Applications

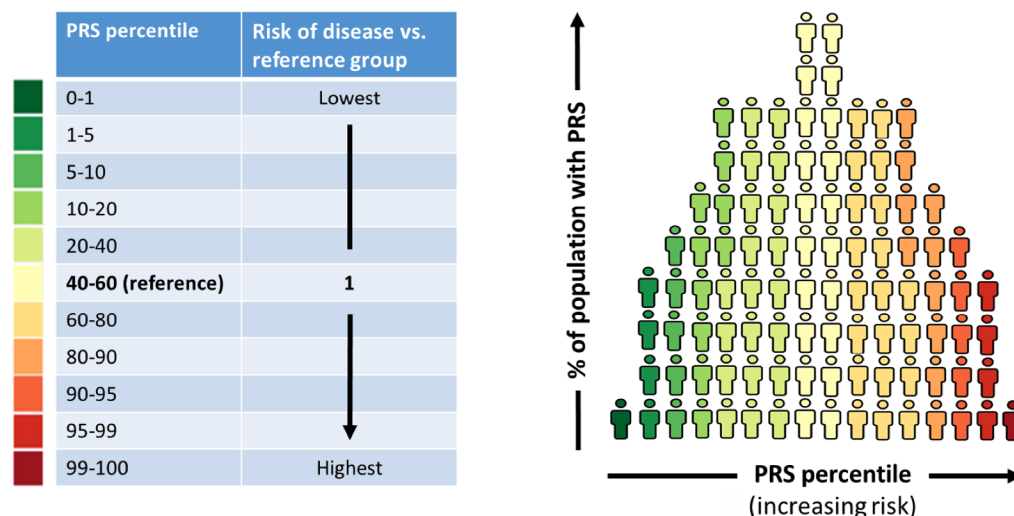
As PRSs are simple to calculate and remain constant over a lifetime, their potential in clinical medicine is vast. Several studies suggest PRSs could be integrated into clinical risk tools in the near future. For example, a PRS to predict coronary artery disease risk

Figure 1: Human Genome Sequencing – Historical Cost



Source: Wetterstrand KA. DNA Sequencing Costs: Data from the NHGRI Genome Sequencing Program (GSP).¹

Figure 2: PRS Distribution



Source: RGA

has already demonstrated that people with a PRS in the highest 5% have a threefold increased risk of experiencing the condition compared to individuals with lower PRSs.⁶ In a study on genetic risk and breast cancer, women whose PRSs were in the top 20% were shown to have a 17.2% lifetime risk of breast cancer compared to a 5.3% lifetime risk for women whose scores were in the lowest quintile.⁴

Another application of PRSs could be to redefine cancer screening algorithms. For instance, women with PRSs indicating higher breast cancer risk could be offered more regular cancer screenings. In the United Kingdom, breast cancer screening is first initiated in women 47 years of age. This screening decision is based on the 10-year risk of breast cancer in the average woman. Researchers, however, have now illustrated that women with PRSs in the 96th to 100th percentile attain this level of risk at just 37 years of age, while those with PRSs below the 20th percentile will never attain this level of risk in their lifetimes.⁴

Of course genetics only forms part of a person's disease risk profile. Environmental factors clearly also contribute, and an additive relationship is generally seen between these. For example, in coronary disease, an individual with a "healthy" lifestyle but at the highest level of genetic risk (i.e., a PRS in the highest quintile) has roughly the same risk of suffering a coronary event as does an "unhealthy" individual with the lowest level of genetic risk (i.e., a PRS in the lowest quintile).⁶ "Healthy" and "unhealthy" are defined here in terms of the individual's smoking, diet, and exercise habits and body mass index. This example emphasizes the importance of environment and lifestyle: while genetics contributes to the risk of a disease, it is not deterministic and differences in (or changes to) someone's environment can increase or decrease their overall risk. Identifying individuals at high genetic risk would allow targeted public health messages and lifestyle interventions to try to prevent disease manifestation.

Any application of PRSs for precision medicine would need to overcome significant challenges. Polygenic medicine represents a paradigm shift for clinicians: most are familiar with rare high-penetrance single gene mutations, but not with genetic predisposition based on a continuous risk score. Education for clinicians and the public will be imperative to hasten clinical uptake. Organizations such as the U.K. Department of Health's Genomics England, which runs the 100,000 Genomes Project, offer resources

to communicate information about genomic medicine with rare variants, but education on polygenic medicine is significantly lacking.

As the predictive accuracies of PRSs improve, commercial interest in them will undoubtedly grow as well. During the past year, the field has seen some interesting developments: in September 2017, Myriad Genetic Laboratories launched *riskScore*, a product which estimates a woman's polygenic risk of breast cancer based on 86 genotyped SNPs. A month later, the Scripps Translational Science Institute and The Scripps Research Institute in California released a smartphone app called MyGeneRank, which estimates a person's polygenic risk of coronary artery disease based on their 23andMe genetic data. In addition, a senior scientist at Helix, a U.S.-based company that provides direct-to-consumer (DTC) DNA testing as well as a marketplace for products based on DNA tests, was quoted just a few months ago as saying that most DTC DNA testing products will offer polygenic risk scores within the next three years.⁷

Conclusions

Disease prevention and early disease detection are critical for extending human longevity. During the past few years, hundreds of research papers have been published demonstrating that PRSs can capture important information about an individual's risk of developing common diseases. For heritable diseases, a person's genetic risk can be measured from birth (or even before birth); therefore, in theory, a newborn's PRS could enable disease prediction for him or her long before the typical age of onset of the disease and possibly decades before the disease's clinical risk factors become apparent.

Many scientific, clinical, and social obstacles must still be overcome to bring PRSs into clinical practice. Further improvements in polygenic risk profiling capabilities are essential. In particular, methods are needed to enable prediction estimates to be adjusted based on an individual's ancestry, demographics, and clinical information (most genetic research carried out to date has only been among populations of European ancestry). Other improvements might include using whole genome prediction models, machine learning, and artificial intelligence to increase prediction accuracy.

Regardless, the era of polygenic medicine is approaching fast: the leap in the scientific understanding of polygenic risk profiling and the explosion in public interest in genetics have brought us to a point where, in due course, PRSs will almost certainly have a place in clinical risk prediction and potentially in insurance risk stratification, if regulations allow. 

Rather, the genetic architecture of most disease is overwhelmingly polygenic, with multiple SNPs, each of small effect, cumulatively affecting disease risk.

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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. We hope you enjoy them and we look forward to continuing to bring you interesting and illuminating webcasts.



Mosquito Blues: A Tiny Fly with a Big Impact on Human Longevity

<https://www.rgare.com/knowledge-center/media/videos/mosquito-blues-a-tiny-fly-with-a-big-impact-on-human-longevity>

Eric Westhus, Ph.D., Data Scientist and member of RGA's Global Research and Data Analytics team, discusses mosquitos as disease vectors, their impact on global mortality and morbidity, how science is working to combat them, and what insurers need to know.



Epigenetics and Liquid Biopsies: Fact, Fiction or Both?

<https://www.rgare.com/knowledge-center/media/videos/be-kind-to-your-genes-an-insurance-perspective-on-the-fast-growing-field-of-epigenetics>

Daniel D. Zimmerman, M.D. Senior Vice President, Chief Medical Director, and a member of RGA's Global Support Team, discusses epigenetics – how genetic code expression can change due to environment and life choices. He also reviews liquid biopsies – an emerging non-invasive medical diagnostic methodology that could change how dread diseases are diagnosed and treated, and the potential impact of both on medicine and insurance.

THE ASSOCIATION OF LONELINESS, SOCIAL ENGAGEMENT, AND SOCIAL ACTIVITY WITH ALL-CAUSE MORTALITY

Abstract

"The worst loneliness is not to be comfortable with yourself."

– Mark Twain

Physical activity has long been associated with improved health and longevity. Even less physically demanding activities such as gardening, do-it-yourself (DIY) projects, and reading have this association. Mortality studies consistently indicate that over the long term, those who engage in social activities have reduced mortality risk, and social isolation and loneliness increase that risk. Indeed, the long-term impact of loneliness and social isolation has been compared to that of the current obesity crisis (an impact accurately predicted three decades ago), and poor social engagement's impact shown to be comparable to that of excess drinking and smoking.

Leisure time group physical activities are associated with lower risk of heart disease and all-cause mortality, and is also directly correlated to a lower risk of developing 13 types of cancers. Yet, because loneliness and social engagement are difficult to quantify, they are not currently used as part of the traditional underwriting process.

Introduction

As life expectancies rise, so too does the size of the aged population. According to the United Nations' "World Population Prospects 2017" report, persons over age 60 represent just over one eighth (13%) of the world's population. The segment, however, is growing at a rate of about 3% per year, and is projected to reach 1.4 billion by the year 2030.

Physical activity has long been associated with improved health and longevity. Those who complete two to three times the minimum recommended amount of aerobic activity per week are shown to have a 37% lower mortality risk compared to those who report no leisure time physical activity at all.¹ Even less physically demanding activities such as gardening, DIY projects, and reading have been associated with lower levels of mortality.

Clearly all of these factors are important considerations when underwriting an applicant for life, critical illness, and disability insurance. How to utilize this information in risk assessment is a challenging task, but perhaps it not unreasonable for the insurance industry to consider these non-traditional risk factors in the underwriting process.

Loneliness and Social Isolation

Social isolation and loneliness are two increasingly common risk factors for older-age individuals. Causes can include widowhood, feelings of social rejection, living alone, and feeling poorly understood by friends and family.

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Social isolation differs from loneliness in that a socially isolated person generally lives alone and has little to no contact or involvement with others. Loneliness generally tends to be a more subjective state, and is described as someone's perception of their relationships as well as a feeling of lack of connection to others.

Loneliness can influence several risk factors, including diet, smoking habits, and alcohol intake. In a 2016 meta-analysis of 35 articles, loneliness was found to be a risk factor for all-cause mortality in women (HR 1.26), in men (HR 1.44) and for both genders combined (HR 1.22).² Awang and Osman's 2017 research into loneliness in older adults noted that the odds of dying at younger ages were about 40% higher for those who report often feeling lonely than those who never did.⁴

Another meta-analysis examining loneliness and social isolation showed that the increased likelihood of death was 26% for those experiencing loneliness, 29% for social isolation, and 32% for living alone.³ Some studies have shown that increased mortality risk due to loneliness and social isolation is even greater than that from obesity.³ Therefore, insurers may want to consider utilizing this important evidence, if available, for risk stratification purposes.

Loneliness also has an impact on morbidity. A Chinese study found that lonely individuals had a higher incidence of dementia even after adjusting for sociodemographic factors (OR 1.31).⁵ Other studies found an association with increased vascular resistance, raised blood pressure, increased hypothalamic pituitary adrenocortical activity, and altered immunity.

Increased physical activity improves health and longevity but engagement with others in leisure time physical activities is important as well.



The data for social isolation differed somewhat. An analysis of data from the UK Biobank study cohort found that social isolation generated increased all-cause mortality (HR 1.73). Socially isolated people were also found to have an increased risk of death from neoplasms (HR 2.06) and diseases of the circulatory system (HR 1.68).⁷ Day, et al. identified 15 associated genetic variants in the UK Biobank study that contribute to loneliness and estimated the heritability of loneliness to be 4.2%. Interestingly, they also identified genomic loci that drive engagement in a sports club or gym, a pub or social club, and religious groups.⁸

Loneliness and social isolation have separately been found to be risk factors for coronary heart disease (CHD) and stroke. A systematic review and meta-analysis of 11 studies by Valtorta, et al. reported that poor social relationships were associated with a 29% increase in CHD incidence and a 32% increase in stroke incidence.⁹

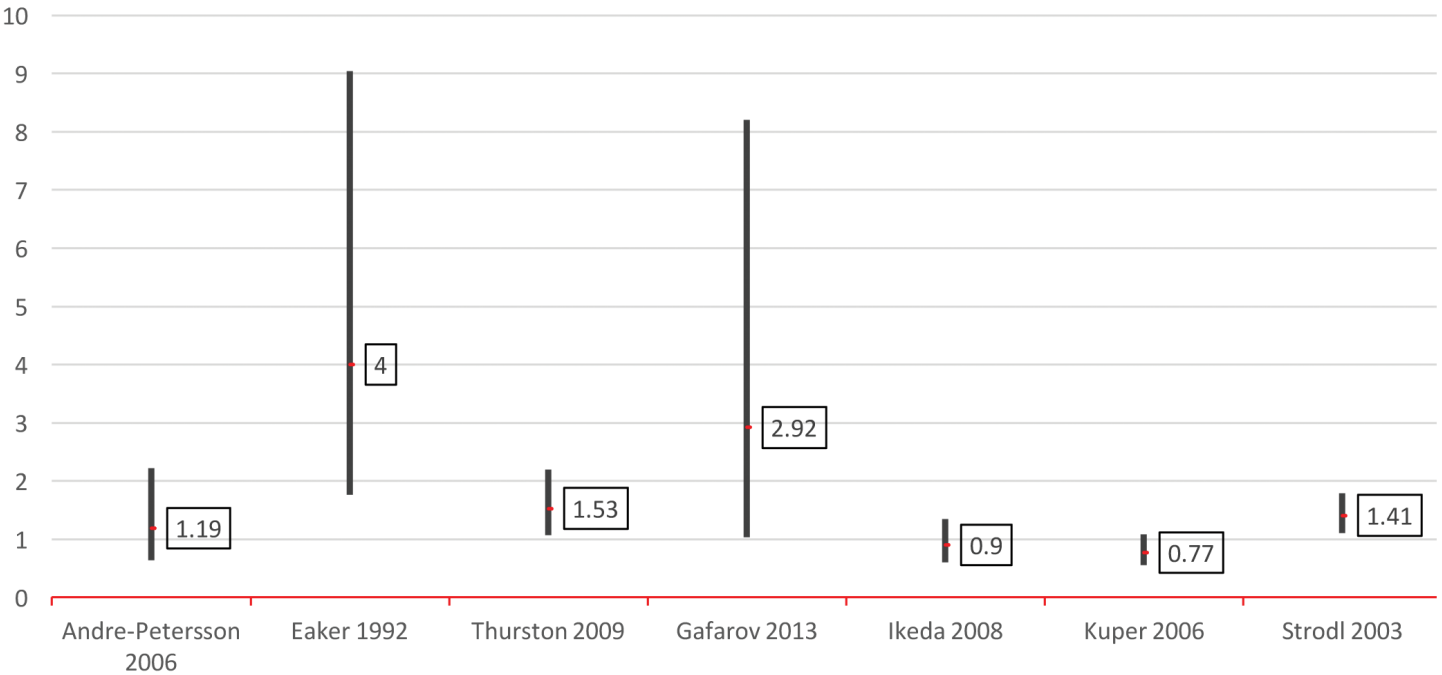
The seven studies included in Figure 1 show the increased risk of CHD for lonely or socially isolated individuals, with one study even showing a four-fold increase.

The positive health effect of adequate social networks is comparable with stopping smoking and exceeds the negative impact of obesity and physical inactivity.

Social Engagement

Adults who are socially engaged and have strong social networks have been shown to live longer. In recent decades, however, social interactions have increasingly moved online, which is changing how people interact with each other. As of March 2018, for example, 1.45 billion people were using Facebook daily, according to the company. Unfortunately, the increasing amount of time individuals spend on social media is

Figure 1: Relative Risk of New CHD When Comparing High Versus Low Loneliness or Social Isolation



Source: Adapted from Valtorta NK, et al. Loneliness and Social Isolation as Risk Factors for Coronary Heart Disease and Stroke: Systematic Review and Meta-Analysis of Longitudinal Observational Studies.⁹

reducing the amount of time that they would otherwise spend physically socializing in groups and engaging in activities.

Figure 2 shows the relative risks for all-cause and cause-specific mortality, taken from a study examining the relationship between social networks and mortality in Japan. The study found that single women had significantly higher risk of all-cause and circulatory system disease mortality, and socially isolated women had notably increased risk of cancer mortality. For men, the increased risk of mortality from non-cancer/non-circulatory disorders was more than double that of men who participated in activities such as hobbies or club events.¹⁰

A meta-analysis by Holt-Lunstad, et al. in 2010 concluded that the positive effect on health of having adequate social networks is comparable with that of stopping smoking, and exceeds the negative impact of other risk factors for mortality such as obesity and physical inactivity.⁹ The authors suggest that general medical evaluations and screenings could include a section on social well-being and should help to promote improvements of social networks.¹¹ Indeed, perhaps such screenings might be incorporated into wellness programs to improve mortality and morbidity outcomes.

Additionally, the recently released English Longitudinal Study of Ageing (ELSA) showed that those who reported higher enjoyment of life experienced fewer diagnoses of CHD, diabetes, arthritis, stroke or chronic lung disease, and had fewer instances of impaired mobility and impaired ADLs.⁶

Of all pets, dogs are considered the most beneficial for increasing physical activity and reducing cardiovascular risk.

Social and Physical Activity

Increased physical activity is known to improve health and longevity, but engagement with others in leisure time physical activities is important as well. Data from 12 U.S. and European cohorts showed that higher activity levels were associated with younger ages, higher educational attainments, lower body mass indexes (BMIs), and lower likelihood of being a smoker. Paradoxically, it was also linked to increased risk of prostate cancer (HR 1.05) and malignant melanoma (HR 1.27). However, the analysis also showed that

Figure 2: Relative Risks* by Social Network Variables for All-Cause and Cause-Specific Mortality for Men/Women

Variable	All-cause	All cancers	All circulatory	IHD	CVD	Non-cancer/ Non-circulatory
Rare or never visit with relatives (Reference: often or sometimes)	0.89/1.78	0.65/1.79	1.07/1.72	0.86/0.86	0.68/2.50	1.21/1.84
No friends (Reference: friends)	0.82/0.86	0.80/0.50	0.92/0.86	0.96/1.16	1.16/0.90	0.74/1.57
No participation (Reference: participates)	1.50/1.31	1.08/0.53	1.63/1.71	0.44/0.47	1.70/1.58	2.26/2.55

Source: Adapted from Iwasaki M, et al. Social Networks and Mortality Based on the Komo-Ise Cohort Study in Japan.¹⁰
*multivariate adjusted RR (age, area, occupation, education, smoking, alcohol, body mass index and chronic disease)

Figure 3: HRs for 12 U.S. and European cohorts with higher levels of leisure-time physical activity by cancer type



Source: Adapted from Moore SC, et al. Association of Leisure Time Physical Activity with Risk of 26 Types of Cancer in 1.44 Million Adults.¹²

higher levels of leisure time physical activity was associated with a 7% overall lower risk from all cancers.

Study results presented in Figure 3 show that leisure time physical activity is associated with lower heart disease and all-cause mortality risk and is directly correlated to a lower risk of 13 types of cancers. The most significant correlation was with esophageal adenocarcinoma, with a 42% risk reduction in the physically active participant.¹

According to the Health Survey for England 2016, an annual survey undertaken by the National Health Service to monitor health trends, 58% of women and 47% of men aged 75 and older reported less than 30 minutes per week of moderate physical activity. This is leaving a large number of older adults at increased mortality risk.¹³

Owning a pet can increase physical activity. Of all pets, dogs are considered to be the most beneficial for increasing physical activity and reducing cardiovascular risk. Dog ownership is also associated with reducing social isolation and improving perception of well-being. A 2017 Swedish nationwide cohort study on dog ownership and risk of cardiovascular disease and death, for example, showed that dog ownership was associated with a lower risk of all-cause mortality (HR 0.67) and cardiovascular death (HR 0.64) in single-person households.¹⁴

Conclusions

Underwriters, claims assessors and pricing actuaries are well aware of the traditional risks presented by raised blood pressure, obesity, high alcohol consumption as examples, but these other lesser-known risk factors discussed in this article are clearly of relevance. The question is: can underwriting applications incorporate them into the risk assessment process, given that they are usually self-reported risks and difficult to quantify in the same way as a blood test? It is worrying that mortality and morbidity risks from lack of social engagement and social isolation have been shown to be higher than from obesity, smoking and excess alcohol. It begs the question if we have been missing other vital mortality risk factors not traditionally used as part of the life assurance application process. 

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LONGER LIFE FOUNDATION'S 2018-2019 RESEARCH GRANT RECIPIENTS

The Longer Life Foundation (LLF) is proud to announce the 20th anniversary class of research grant recipients. These individuals are investigating some of the most important health issues of the day, from obesity and antibiotic resistance to diseases of the blood, liver, and brain. To find out more about LLF and the research funded to date, and to view its commemorative 20th anniversary report, please visit www.longerlife.org. 



INVESTIGATOR/TITLE OF RESEARCH PROJECT	DESCRIPTION
Samuel Klein, M.D., Director, Longevity Research Program <i>Complex Interaction Between Excess Adiposity and Health Aging</i>	This study will identify novel biomarkers and metabolic pathways associated with cardiometabolic disease and with a 20% weight loss. This is part of Dr. Klein's ongoing research studying differences between metabolically normal and metabolically abnormal obese individuals.
Jennie Kwon, D.O. (Year 2) <i>The Trajectory of the Fecal Microbiome in Patients with Multidrug-Resistant Urinary Tract Infections (UTIs)</i>	UTIs, especially those due to antibiotic-resistant organisms, can cause significant morbidity and mortality. Dr. Kwon will study the fecal microbiome and determine its relationship with multi-drug-resistant UTIs and UTI recurrence.
Dmitri Samovski, Ph.D. (Year 2) <i>Role of CD36 in the Obesity-Associated Fatty Liver Disease and Hepatic Insulin Resistance</i>	Non-alcoholic fatty liver disease is common and frequently encountered in insurance medicine. Dr. Samovski will continue to investigate a novel metabolic pathway to further understand how abnormal levels of fat accumulate in liver cells. This research may eventually enable the design of new therapeutic approaches.
Meredith E. Jackrel, Ph.D. <i>Restoring Proteostasis to Counter Human Disease</i>	Protein misfolding and aggregation is associated with numerous neurodegenerative disorders, including amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), Parkinson's disease (PD), and Alzheimer's disease (AD). Dr. Jackrel's research will look into novel ways in which these abnormal proteins might be dissolved and removed to restore cellular health.
Grant Challen, Ph.D. <i>Reducing the Risk of Blood Cancer with Age by Weeding Out Leukemia-Causing Stem Cells in the Bone Marrow</i>	Myelodysplastic syndromes (MDS) and acute myeloid leukemia (AML) are clonal hematopoietic malignancies with significant morbidity and high mortality that typically occur in people over the age of 65. Dr. Challen's research will investigate if these diseases can be prevented by eliminating cancer-causing stem cells from the bone marrow.
Brian DeBosch, Ph.D. <i>Leveraging Adaptive Hepatic Glucose Fasting Responses Against Cardiometabolic Disease</i>	Dr. DeBosch hypothesizes that the sugar trehalose can prevent damage to the myocardium by blocking the development of left ventricular hypertrophy and dysfunction via pathways in the liver. This study will further investigate this line of research.

Relationship between Clinic and Ambulatory Blood-Pressure Measurements and Mortality

Banegas JR, et al. N Engl J Med. 2018 April 19; 378:1509-20.

<https://www.nejm.org/doi/full/10.1056/NEJMoa1712231>

This Spanish study compared blood pressure (BP) measured in the clinic with that measured with 24-hour ambulatory devices and correlated the results with all-cause and cardiovascular mortality. The two groups were categorized as: sustained hypertension; white-coat hypertension; masked hypertension; and normotension. Median follow up was 4.7 years. 24-hour systolic BP was more strongly associated (HR 1.58) with all-cause mortality than the clinic BP. Masked hypertension (normal clinic BP and elevated ambulatory BP) was more strongly associated with all-cause mortality (HR 2.83) than sustained hypertension (HR 1.80) and white-coat hypertension (HR 1.79). Cardiovascular mortality paralleled the all-cause mortality results.

Editor's Note: *The results of this study are very relevant to risk assessment of insurance applicants. Often, only a single BP measurement is available. While ambulatory BP monitoring is not practical from an insurance underwriting perspective, in general, consideration could be given to offering it as a reconsideration tool or as a dynamic underwriting or wellness benefit.*

Sustaining Health-Protective Behaviors Such as Physical Activity and Healthy Eating

Dunton GF. JAMA. 31 May 2018.

<https://jamanetwork.com/journals/jama/fullarticle/2683633>

This short opinion piece reiterates the well-known fact that to attain significant health benefits, health-protective behaviors should be performed consistently and regularly. Furthermore, physical activity and healthy dietary intake should be an integral part of an individual's daily routine and last across the lifespan. The author suggests that study be given to microtemporal factors (minutes, hours, and days) that drive beneficial behavior versus the traditional focus on macrotemporal factors (weeks, months, or years). This may also allow a more individualized assessment and approach.

Editor's Note: *The concepts noted in this article are very important for insurers to consider as they develop post-issue wellness programs with the intent of improving mortality and morbidity. According to Matt Battersby, VP, Chief Behavioral Scientist at RGA, behaviors are largely driven by situational and contextual cues. That is why there should be more focus on changing the context in which people behave and make decisions rather than changing attitudes.*

Five-Year Risk of Stroke after TIA or Minor Ischemic Stroke

Amarenco P, et al. N Engl J Med. 2018 June 7; 378: 2182-90

<https://www.nejm.org/doi/full/10.1056/NEJMoa1802712>

The investigators studied individuals who had a transient ischemic attack or minor stroke and were followed for five years to determine further outcomes including stroke, acute coronary syndrome, or death from cardiovascular causes. Stroke occurred at a cumulative rate of 9.5%, with 43.2% of these occurring in the second through fifth year. The overall rate of cardiovascular events including stroke was 6.4% in the first year and 6.4% in the second through fifth years.

Editor's Note: *These data are extremely useful especially for those developing and pricing multi-pay critical illness products.*



Predictors of Unemployment After Breast Cancer Surgery: A Systematic Review and Meta-Analysis of Observational Studies

Wang L, et al. J Clin Oncol. 2018 May 14; 36(8):1868-79.

<http://ascopubs.org/doi/abs/10.1200/JCO.2017.77.3663>

This group reviewed 26 observational studies to explore factors associated with unemployment after breast cancer surgery. Unemployment after surgery was associated with high psychological and physical job demands, lower education level, lower income level, cancer stage II, III, or IV, and mastectomy versus breast-conserving surgery. Additional risk factors for unemployment included access to universal health care and receipt of chemotherapy.

Editor's Note: *Understanding contributing factors which may impact return-to-work can allow for a more holistic, empathetic, and effective approach to breast cancer claims management.*

Innovation for Pandemics

Gates B. N Engl J Med. 31 May 2018; 378: 2057-60.

<https://www.nejm.org/doi/full/10.1056/NEJMp1806283>

Despite successes in multiple global aspects of public health, Bill Gates warns of the continued lack of progress in pandemic preparedness. What is needed, he writes, is a globally coordinated approach to pandemics, including better early detection and response systems. He does point out some favorable initiatives, such as the current efforts to create a universal flu vaccine, and notes other good work is being directed towards antivirals and monoclonal antibody therapies. He also mentions research directions in RNA and gene delivery systems. Gates concludes by stating that we need a clear road map for a comprehensive pandemic preparedness and response system.

Editor's Note: *Awareness of pandemic risk and preparedness along with related actuarial modeling are critical activities for all insurers. Insurers would be well-advised to follow developments in pandemic risk mitigation and even offer to participate in discussions and planning to achieve the goal of global preparedness.*



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