RGA

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LETTER FROM THE EDITOR

Dear readers:

This edition of ReFlections, the first in 2015, highlights RGA's global operations. Dr. Sheetal Salgaonkar, Medical Director of our office in Mumbai, India, shares her insights into trends in pulmonary diseases. Hilary Henly, Head of Underwriting (Ireland) and Director, Divisional Underwriting Research, has provided the second part of her article on the increasing relevance of biomarkers for underwriters. Dr. Keiko Imuro, Chief Underwriting Officer for our Mexico City office, utilizes her experiences as a pediatrician in discussing the many challenges of underwriting the pediatric insurance applicant. Lastly, Jeff Heaton, EHR Information Scientist, continues to provide us with information related to Electronic Health Records, specifically regarding the value of Continuity of Care Documents for underwriters. I hope that you find all of these articles interesting.

This is the last edition of ReFlections that I will edit. Over the past 15 years, I have had the privilege of working with many talented people to provide articles that would enlighten and stimulate you. I have certainly appreciated all the feedback and words of kindness over the years. I am looking forward to my retirement from the life insurance industry in April, and all the challenges and opportunities that will entail. I am confident that Dr. Philip Smalley, the next editor of ReFlections, will continue to provide you with topical, thoughtful articles from the RGA associates who contribute to our medical underwriting operations. I know he will appreciate any feedback on how to improve ReFlections, so please do not hesitate to contact him!

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TRENDS IN RESPIRATORY DISEASES

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Respiratory diseases are a major cause of morbidity and mortality. The magnitude of the problem is staggering. Hundreds of millions of people are burdened with chronic respiratory conditions. Four million people die prematurely from chronic respiratory diseases each year[1] [2], and 90% of these deaths occur in low- and middle-income countries. Developed countries experience high levels of asthma, chronic obstructive pulmonary disease (COPD) and lung cancer[3]. In developing countries, major problems include tuberculosis (TB) and other respiratory system infections.

Four external, modifiable drivers are responsible for a substantial percentage of the disease burden represented by the major lung diseases: tobacco, outdoor air pollution, household air pollution, and occupational exposures to lung toxins. The Forum of International Respiratory Societies, in its recent report entitled "Respiratory Disease in the World: Realities of Today – Opportunities for Tomorrow," identified five conditions that are primary contributors to the global burden of respiratory disease: asthma, chronic obstructive pulmonary disease, acute respiratory infections, tuberculosis, and lung cancer[4].

The Big Five global respiratory conditions[2 4]				
Disease	Major preventable risk factors	Estimated global disease frequency	Global deaths/year	Comments
COPD	Cigarette smoking, indoor smoke, occupational gases and particles, outdoor air pollutants, asthma	200 (prevalence)	Unavailable	Fourth leading cause of death worldwide.
Asthma	Genetic predisposition, environmental allergens, air pollutants, dietary factors, abnormal immunological responses	238 (prevalence)	0.18	Increasing in prevalence worldwide
Acute respiratory infections	Low immunization rates, poor nutrition, overcrowding, HIV infection	Unavailable	4	The most common chronic diseases in children and the leading overall cause of death in developing countries. Pneumonia is the leading cause of death in children under five years of age. The greatest single contributor to the overall burden of disease in the world as measured by DALY (disability-adjusted life year) loss
TB	HIV infection, overcrowding	8.7 (incidence)	1.4	Approximately 80% of global HIV-TB cases occur in Africa. Multidrug-resistant TB is increasing globally.
Lung cancer	Cigarette smoking, passive cigarette smoke exposure, biomass fuel smoke, inhaled radon and asbestosis	1.6 (incidence)	1.37	The most common cause of cancer death.

Source: Forum of International Respiratory Societies, 2013.

Definition of abbreviations: COPD = chronic obstructive pulmonary disease; DALY = disability adjusted life years; HIV = human immunodeficiency virus; TB = tuberculosis

Acute Respiratory Infections

Respiratory infections account for more than four million deaths annually and are the leading cause of death in developing countries[5]. Respiratory tract infections are caused by many viral and bacterial pathogens[6] and are the second most common cause of morbidity and mortality worldwide[7 8 9]. Lower respiratory tract infections come second in the Global Burden of Disease (GBD) rankings, after ischemic heart disease[6 9].

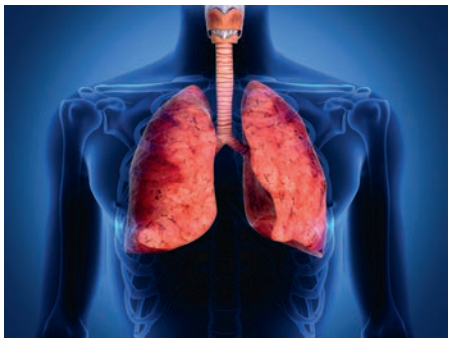
The emergence of difficult-to-treat known and novel bacterial, viral, and fungal respiratory tract pathogens with epidemic potential is of major global concern. The past century has seen several epidemics of new viral respiratory tract infections, most of which emerged from interactions between people and animals[10]. Some of these include severe acute respiratory syndrome coronavirus (SARS-CoV), avian influenza viruses H5N1, H7N9, and H10N8, variant influenza virus A H3N2, swine-origin influenza virus A H1N1, human adenovirus type 14, and the Middle East respiratory syndrome coronavirus (MERS-CoV). Unfortunately these microorganisms do not respect international boundaries, and ease of global travel and airborne spread make them a persistent threat to global health security[11].

Pneumonia is the most common acute respiratory infection. In children under five years of age, pneumonia accounts for 18% of all deaths, or more than 1.3 million annually[12], and kills far more than HIV or malaria[5]. Pneumonia occurs several-fold higher in the elderly and HIV-infected individuals. Streptococcus pneumonia remains the most frequent bacterial cause of pneumonia. Pneumonia can also lead to chronic respiratory diseases such as bronchiectasis.

Tuberculosis

Tuberculosis causes about 1.3 million deaths every year[13]. Globally, about three million cases of tuberculosis every year remain undiagnosed and these infected individuals continue to spread the disease, especially in high-burden TB countries such as Cambodia[13], China[13], India[40], the Philippines[13] and Vietnam[13]. Though the global incidence of drug-susceptible tuberculosis is declining, the emergence of multidrug-resistant (MDR) and extensively drug-resistant (XDR) tuberculosis during the past decade is threatening to reverse this trend. This is further complicated by co-morbid infections, especially HIV, mainly in Africa. Nearly half a million cases of multidrug-resistant tuberculosis are diagnosed worldwide every year and a third of patients with this disease will die because of failure of diagnosis or unavailability of appropriate treatment[13].

The World Health Organization has set the goal of eliminating TB by the year 2050. Efforts in its global Stop TB strategy has led to advances in TB diagnostics and drugs and, to a lesser extent, TB vaccines. Two diagnostics which have made significant advancement are the Xpert MTB/RIF assay nucleic acid simplification test, for simultaneous detection of mycobacterium tuberculosis DNA and rifampicin resistance in sputum[14] and the detection of mycobacterial cell wall lipoarabinomannan (LAM) in urine to diagnose tuberculosis in patients with advanced HIV disease[15]. Several new effective antimicrobials, including delamanid, bedaquiline, and linezolid, have recently become available for clinical use, but a combination regimen for drug-resistant tuberculosis needs urgent validation in a prospective clinical study in intermediate-burden and high-burden settings[16].



Asthma

Asthma is a common chronic non-communicable disease that affects as many as 334 million people of all ages in all parts of the world[17]. It is concerning that the global burden of asthma, which is already substantial in terms of both morbidity and economic costs, seems to be increasing rapidly as the world becomes more westernized. The recent Global Burden of Disease study estimated that asthma was the 14th most important disorder in terms of global years lived with disability. Currently, 14% of the world's children and 8.6% of young adults (ages 18-45) experience asthma symptoms, and 4.5% of young adults have been diagnosed with asthma and/or are being treated for asthma. The burden of asthma is greatest for children of ages 10-14 and the elderly of ages 75-79[18].

Though the prevalence of asthma is increasing, evidence suggests that asthma mortality and health care utilization rates continue to plateau and/or decrease. The number of deaths due to asthma in 2009 was approximately 27% lower than the number of deaths in 1999[19]. The number and rate of hospital discharges also both decreased by 24% between 2003 and 2010[20].

Asthma has global distribution, with a relatively higher burden of disease in Australia and New Zealand, some countries in Africa, the Middle East and South America, and northwestern Europe. Environmental factors are much more likely than genetic factors to have caused the large increase in the numbers of people in the world with asthma.

Chronic Obstructive Pulmonary Disease (COPD)

It is estimated that there are at least 210 million persons in the world with COPD, and that this group of conditions causes three million deaths annually[4]. The disease burden from COPD appears to be growing despite the development of new therapeutics such as long-acting antimuscarinic agents, long-acting beta-agonists, inhaled corticosteroids, and phosphodiesterase inhibitors.

COPD is now the third leading cause of death in the world[21 23]. This is much earlier than the predicted ranking by 2030 as per the World Health Organization. The burden of COPD is projected to increase substantially in Asia and Africa in the coming decades, mostly as a result of increased tobacco use in those regions[21].

More than 1.1 billion people worldwide smoke, with 82% of smokers residing in low- and middle-income countries[22]. Although many high-income countries have witnessed decreases in smoking rates, overall smoking prevalence has continued to increase in many low- and middle-income countries[24]. Tobacco smoking is a well-established major risk factor, but emerging evidence suggests that other risk factors are important, especially in developing countries. As an estimated 25% of patients with COPD have never smoked, the burden of non-smoking COPD is much higher than previously believed. About three billion people, half the worldwide population, are exposed to smoke from biomass fuels compared with 1.01 billion people who smoke tobacco, which suggests exposure to smoke from the burning of biomass fuels might be the biggest risk factor for COPD globally[25].

Lung Cancer

Lung cancer has been the most common cancer in the world for several decades. There are estimated to be 1.8 million new cases in 2012 (12.9% of the total), 58% of which occurred in the less developed regions. The disease remains as the most common cancer in men worldwide (1.2 million, 16.7% of the total) with the highest estimated age-standardized incidence rates in Central and Eastern Europe (53.5 per 100,000) and

Eastern Asia (50.4 per 100,000). Notably low incidence rates are observed in Middle and Western Africa (2.0 and 1.7 per 100,000 respectively). In women, the incidence rates are generally lower and the geographical pattern is a little different, mainly reflecting different historical exposure to tobacco smoking. Thus the highest estimated rates are in North America (33.8) and Northern Europe (23.7) with a relatively high rate in Eastern Asia (19.2) and the lowest rates again in Western and Middle Africa (1.1 and 0.8 respectively)[26].

Lung cancer is the most common cause of death from cancer worldwide. It is estimated to be responsible for nearly one in five deaths (1.59 million, 19.4% of the total). Additionally, lung cancer survival rates continue to be poor[27 28]. Age-adjusted lung cancer death rates in the U.S. over a period of six decades shows a declining trend in males whereas females show a rising trend, mainly because of the decline in smoking among males and a concurrent increase in smoking among females[27]. Because of its high fatality (the overall ratio of mortality to incidence is 0.87) and the relative lack of variability in survival in different world regions, the geographical patterns of mortality closely follow those of incidence[26].

Due to lung cancer's high mortality, various controlled trials of screening for lung cancer using sputum examinations, chest radiography or chest CT (computed tomography) scans have been carried out. The current evidence does not support screening for lung cancer with chest radiography or sputum cytology. Annual low-dose CT screening is associated with a reduction in lung cancer mortality in high-risk smokers, but further data are required on the cost effectiveness of screening and the relative harms and benefits of screening across a range of different risk groups and settings[29].

Interstitial Lung Disease

Though not one of the Big Five, respiratory diseases remain incomplete without the mention of interstitial lung disease (ILD). More than 300 different conditions are included among the total number of ILDs.The most important ILDs are sarcoidosis, idiopathic pulmonary fibrosis (IPF) (previously called cryptogenic fibrosing alveolitis, mainly in the U.K.), extrinsic allergic alveolitis, ILD as a feature of connective tissue disorder, drug-induced ILD and pneumoconiosis.

Data from ILD registries show that the most frequent ILDs are IPF and sarcoidosis, which together comprise about 50%[30]. IPF is the most common and severe form of idiopathic interstitial pneumonia (IIP). It is irreversible, has an unpredictable and variable clinical course and is associated with extremely poor prognosis, with a death rate worse than that of many cancers (three-year survival, 50%)[31 32 33].

There are no large-scale studies of the incidence or prevalence of IPF on which to base formal estimates. A study from the U.K. reported an overall incidence rate of only 4.6 per 100,000 person-years, but estimated that the incidence of IPF increased by 11% annually between 1991 and 2003[34]. This increase was not felt to be attributable to the aging of the population or increased ascertainment of milder cases. Another study from the U.S. estimated the incidence of IPF to be between 6.8 and 16.3 per 100,000 persons, using a large database of healthcare claims in a health plan[35].

Prevalence estimates for IPF have varied from 2 to 29 cases per 100,000 in the general population. The wide range in these numbers is likely explained by the previous lack of a uniform definition used in identifying cases of IPF, as well as by differences in study designs and populations. It is unknown if the incidence and prevalence of IPF are influenced by geographic, ethnic, cultural, or racial factors.

Mortality rates for pulmonary fibrosis (PF) increased steadily in the U.S., England and Wales, Scotland, Australia, and Canada from the late 1970s to the early 1990s. A U.S. study showed that mortality rates from pulmonary fibrosis further increased from 1992 to 2003. With the advent of better diagnostic facilities and improved overall life expectancy, incidence of ILD will most likely continue to further increase[36].

A study published in October 2014 revealed that mortality from IPF is also increasing steadily worldwide. It is estimated that in 2014, there will have been between 28,000 and 65,000 deaths in Europe and between 13,000 and 17,000 deaths in the U.S. Increasing mortality rates may be due to true increases in incidence, but some of the trends may relate to changes in diagnostic or coding practices[37].

After years of ineffective treatment, two new drugs – pirfenidone and nintedanib – have shown promise for patients with IPF[38 39].

Conclusion

Insurers are seeing increasing numbers of applicants and claimants with respiratory diseases. Scientific advances over the past several years have been reducing mortality from asthma, acute respiratory infections and other conditions. Interacting environmental factors, however, are generating substantial increases in global incidence trends for the more severe chronic respiratory diseases: asthma, COPD, interstitial lung disease and drug-resistant tuberculosis. These are substantially increasing morbidity trends as well as health care costs. Knowing these global trends will be useful in life underwriting and for underwriting living benefits such as CI, TPD, IP and Hospitalization.

Summary

- The Big Five contributors to the global burden of respiratory disease are: asthma, chronic obstructive pulmonary disease, acute respiratory infections, tuberculosis and lung cancer.

- Respiratory tract infections are the second most common cause of morbidity and mortality worldwide. Pneumonia is the most common serious respiratory infection in children under five years of age, accounting for 18% of all deaths.
- Although the global incidence of drug-susceptible tuberculosis is declining, the emergence of multidrug-resistant (MDR) and extensively drug-resistant (XDR) tuberculosis strains during the past decade are threatening to reverse this trend.
- Mortality from asthma as well as hospitalization due to asthma is decreasing, but the prevalence of asthma is increasing. Asthma is the 14th most important disorder in terms of global YLDs (years lived with disability).
- COPD is now the third leading cause of death in the world. Interestingly, 25% of COPD patients have never smoked.
- Lung cancer is the most common cause of death from cancer worldwide. Annual low-dose CT screening is associated with a reduction in lung cancer mortality in high-risk smokers.
- Mortality from idiopathic pulmonary fibrosis, one of the most frequently found interstitial lung diseases, has been increasing steadily worldwide. This might be due to true increases in incidence, but could also be due to changes in diagnostic and/or coding practices. ■

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BIOMARKERS: CAN THEY ADD VALUE? (PART 2)

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Part 1 of this article, "Do Biomarkers Mean Business?", which was published in the Fall 2014 issue of ReFlections (http://www.rgare.com/knowledgecenter/Pages/ReFlectionsFall2014.aspx), discussed the biomarker NT-proBNP. This second part takes a look at three more biomarkers: proPSA (specifically p2PSA), red cell distribution width (RDW) and cystatin C.

New biomarkers are constantly being discovered and research continues into their application in clinical practice. Not all biomarkers can be used as screening tools for insurance purposes, but they can still provide useful information within a blood profile when assessed at underwriting stage and must not be discounted. It is important that biomarkers are properly interpreted and that the underwriter understands the data presented and how it affects the overall risk profile.

What is proPSA?

Due to the inherent problems with prostate-specific antigen (PSA) values and false positive results, several new biomarkers for prostate cancer (PCa) have been discovered in recent years. These include p2PSA, a prostate cancer-specific isoform of free PSA (fPSA), which is more concentrated in peripheral gland cancer tissue and is almost solely expressed by prostate cancer cells[3]. It is also notably higher in patients diagnosed with PCa[1].

There is a need for new biomarkers not only to identify early prostate cancer but also the more aggressive cancers for which treatment is most beneficial. So far, studies have shown that p2PSA rises with increasing Gleason scores (GS) and is higher in aggressive cancers [8].

Further to this, the U.S. Food and Drug Administration has approved the Prostate Health Index (PHI), which incorporates p2PSA, fPSA and total PSA (tPSA) with the formula [(p2PSA / fPSA) x √(tPSA)][4]. The PHI has been shown to be 2.5 times more specific in detecting prostate cancer in patients with PSA values in the 4-10 ng/mL range, resulting in a 31% reduction in unnecessary biopsies[2]. Both p2PSA and PHI have also been found to be the only raised biomarkers in those with PSA < 4 ng/mL and a negative digital rectal exam (DRE) several months before a diagnosis of PCa is made[3].

The following evidence supports the association between these new biomarkers and Gleason scores greater than or equal to 7, with PHI additionally found to be a useful clinical marker for men with a family history of prostate cancer[1]:

- Catalona et al. showed %p2PSA (p2PSA/fPSA x 100) significantly improved specificity for PCa for PSA in the 2-4 ng/mL range, identifying 90% of cancers including all extra-capsular tumors and 96.6% with GS > 7[1].
- Sokoll et al. examined data from 119 men with PSA 2.5-4 ng/mL, and found that at a sensitivity of 75%, specificity for %p2PSA was considerably greater than for %fPSA (59% v. 33%)[1].
- Heidegger et al. showed that p2PSA was able to distinguish aggressive PCa from benign conditions one to four years before diagnosis in Caucasians in their early 60s, with the highest predictive values at one to two years[5], as shown in the table below. They also found that preoperative p2PSA values were significantly higher in PCa with nodal involvement (> T3a) compared to men with organ-confined cancer (< T2c) in years 1, 2, 3 and 4 before diagnosis. Levels were highest for those with GS > 8 and lowest for those with GS < 6[5].

Time Before Diagnosis	p2PSA pg/mL (Benign)	p2PSA pg/mL (Cancer)	PSA ng/mL (Benign)	PSA ng/mL (Cancer)
1 year	8.5	17.2	2.6	3.7
2 years	8.0	1.9	3.8	4.0
3 years	11.9	15.8	3.7	3.9
4 years	14.1	17.1	2.8	3.5

- A study by Mikolajczyk et al. of 380 men with PSA 4-10 ng/mL showed that p2PSA, with a sensitivity of 90%, would have resulted in 36% fewer biopsies[1].
- In a multicenter European study by Lazzeri et al. of patients with a total PSA of 2-10 ng/mL, PCa was diagnosed in 40.1%. The %p2PSA and PHI were found to be the strongest predictors of PCa at initial biopsy, being significantly more accurate than PSA or %fPSA. At a PHI cut-off of 28.8, 116 biopsies could have been avoided, with PCa overlooked in six cases but none being GS > 7[6].

These studies would indicate a close correlation between higher values of p2PSA and a diagnosis of prostate malignancy. PSA is organ- but not cancer-specific, and can be raised in the presence of benign prostatic hyperplasia (BPH), in genitourinary infections or post DRE[1]. A second problem with PSA values is its low specificity (below 10 ng/mL), where cancer is still detected in up to 25% of patients, with an even higher percentage of patients undergoing needless biopsy[4]. Treatments for indolent cancers can lead to complications such as urinary incontinence, erectile dysfunction and/or hormonal changes[5].

In 2012, the United States Preventive Services Task Force issued a Grade D recommendation ("discourage the use of this service") against prostate cancer screening for men of all ages. While there would be one fewer prostate cancer death

for every 1,000 men screened, there would also be 30-40 men with subsequent incontinence or erectile dysfunction[7].

The Melbourne Consensus Statement, created by a group of international experts and the European Association of Urology, recommended baseline screenings of men in their 40s, but also stated that PSA testing should not be considered on its own but as part of a multivariable approach to prostate cancer detection[7].

Studies to date indicate that p2PSA is a cancer-specific biomarker for prostate cancer and is significantly elevated in blood serum correlating to Gleason score.

Most recently, in October 2014, the Canadian Task Force on Preventative Health Care recommended against screening using the PSA test in the general population, based on the harms outweighing the benefits of a 0.1% reduction in deaths due to prostate cancer using screening.

What is Red Cell Distribution Width (RDW)?

Red cell distribution width is a measure of the variation in the size of circulating erythrocytes that can help to identify causes of microcytic anemias such as iron deficiency and thalassemia trait and of macrocytic anemias due to B12 or folate deficiency and bone marrow disorders.

RDW is reported either as coefficient of variation (CV) or standard deviation (SD). RDW-CV (%) is calculated by (standard deviation of RBC/mean MCV) X 100[10]. A normal RDW-CV reference range is between 11% and 14.5%[11]. A high RDW, known as anisocytosis, can be caused by thalassemias or iron deficiency. A higher RDW is also associated with older age and impairments such as diabetes, heart failure and chronic kidney disease[12]. RDW has also been investigated as a predictive marker for risk of myocardial infarction (MI) and in the progression of some cancers. Higher RDW values so far appear to have a linear relationship with increased comorbidities and mortality in patients with coronary artery disease. Studies below also show that increased RDW is associated with an increase in all-cause mortality.

Some studies have shown that higher RDW is strongly associated with increased mortality and risk of cardiovascular disease[9].

- 2,550 patients from the National Health and Nutritional Examination Survey III group (NHANES III) were grouped into quartiles of RDW <13.1%, >13.1% -<13.6%, >13.6% -<14.1% and > 14.1%. Mortality in Q4 with the highest RDW values was nearly four times higher than that of those in the first quartile[12].
- An evaluation of seven community-based studies by Patel et al. in 2009 found that when compared to an RDW of <12.5%, mortality risk was nearly double for those with RDW 14% - 14.9% (HR 1.77, 95% CI 1.53-2.04) and more than double for those with RDW >14.9% (HR 2.51, 95% CI 2.1-2.91). Mortality risk increased by 14% for every 1% increase in RDW (HR 1.14, 95% CI 1.11-1.17)[13].
- A study by Arbel et al. evaluated the predictive value of RDW for cardiovascular morbidity and all-cause mortality over a five-year period, using data from a cohort of quarter of a million patients. They found that compared to patients with RDW < 12%, a significant association with increased morbidity and mortality occurred as follows[9]:

RDW	HR all-cause mortality	HR major cardiac event
> 17%	8.2 (95% CI 4.4-15.2 P< 0.001)	1.32 (95% CI 1.09-1.64 P<0.001)

- A retrospective study by Spell et al. on cases of colon cancer diagnosed over a five-year period found that of the 127 patients diagnosed with right-sided colon cancer, 84% had elevated RDW, and of the 98 with left-sided colon cancer, only 50% had elevated RDW[15].
- The Tromsø Study looked at whether RDW was associated with the risk of a first MI. During the 15-year followup of those who had experienced a first MI, each 1% increment in RDW was associated with a 13% increased risk of a second MI (HR 1.13, 95% CI 1.07-1.19). Those with an RDW greater than the 95th percentile had a 71% higher risk of MI than those who placed in the lowest quintile (HR 1.71, 95% CI 1.34-2.2). It also showed that the risk of CV mortality increased by 22% for a 1-SD increase of RDW (HR 1.22 95% CI 1.14-1.31), and was more than twice as high for those in the highest quintile when compared to the lowest[14].

Based on studies to date, an independent relationship has been shown to exist between higher RDW values and the risk of cardiovascular events. However, larger studies would still be needed to evaluate fully the usefulness of RDW as a biomarker in this context.

What is Cystatin C?

Cystatin C is a protein found in all nucleated cells in the blood. It is filtered by the glomeruli in the kidneys, with almost all being reabsorbed within the proximal tubules. When renal function is reduced, these proteins accumulate in the blood. The more commonly measured creatinine is a byproduct of muscle cells and is influenced by muscle mass, physical activity and diet as well as by age and gender. Kidney disease disproportionately affects the elderly as kidney function declines over time, and cystatin C has been shown to be more sensitive than creatinine in detecting mild to moderate reduction in estimated glomerular filtration rate (eGFR). It is also released into the bloodstream at a relatively consistent rate and holds a significant advantage over creatinine in that it is not influenced by age, gender, race, muscle mass and/or most medications[16].

In 2007, the European Society of Cardiology recommended the use of cystatin C for predicting MI and long-term mortality in patients with non-ST elevation acute coronary syndrome[17]. The NHANES III study reported that cystatin C-based estimation of renal function was more strongly associated with all-cause mortality as well as with cardiovascular mortality than creatinine-based estimation of renal function [22]. Furthermore, high levels of cystatin C have been associated with poorer outcomes in those diagnosed with colorectal, lung and melanoma cancer, and patients with relapse of B-cell non-Hodgkin's lymphoma were found to have significantly higher levels than those without recurrence[21]. The prognostic power of cystatin C is further illustrated in the following studies:

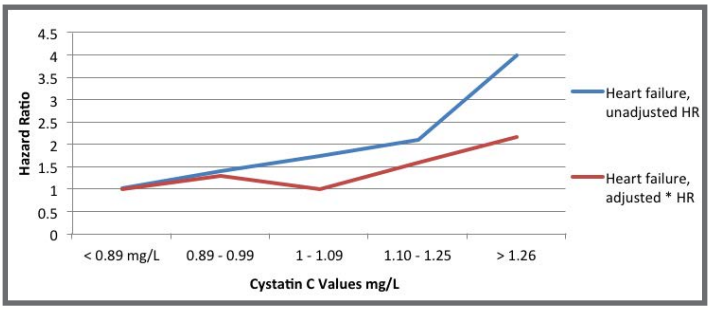
- The Tromsø Study found that cystatin C was a risk factor for all-cause mortality in women. A 38% increased risk for all-cause mortality was found when the upper cystatin C quartile was compared with the lowest, after adjustments for cardiovascular risk factors. Interestingly, this association was not found in men[22].
- The NHANES III study looked at cystatin C levels in those 60 years of age and in a 25% random sample in those between 12 and 59 years of age. Those with high cystatin C were found to be mostly male, hypertensive and older lives. When comparing participants with low values to those with medium or high levels of cystatin C, the study showed that they were at higher risk of all-cause and cause-specific mortality. A sample of data is provided in the table below[23]:

Serum cystatin C level (mg/L)	Relative risk of all-cause mortality	Relative risk of cardiovascular mortality	Relative risk of cancer mortality	Relative risk of non-CVD mortality
> 90th percentile	4.36	7.44	2.45	3.15
10th-90th percentile	3.45	4.59	2.36	2.99
<10th percentile	1 (reference)	1	1	1

- A study by Shlipak et al. published in 2005 on cystatin C in elderly patients found it to be a stronger predictor than creatinine of the risk of death and cardiovascular events. The hazard ratios were found to be as follows[20]:

Cystatin C (mg/L)	<0.89	0.9-0.99	1-1.1	1.11-1.28	1.29-1.39
All-cause mortality (adjusted)	1	1.08	1.23	1.34	1.77
Death from cardiovascular causes (adjusted)	1	1.33	1.93	1.99	2.48
MI (adjusted)	1	0.97	1.26	1.14	1.44
Stroke (adjusted)	1	1.22	1.17	1.15	1.43

- A study by Sarnak et al. of the Cardiovascular Health Study found that participants in the higher quintiles for cystatin C were more likely to be white, older, have a history of hypertension and coronary heart disease (CHD), higher triglycerides and lower HDL cholesterol. Those in the highest quintile were also associated with a four-fold risk of heart failure in univariate analysis and twice the risk when adjusted for multivariate risk factors[18] (see chart below):



- The Cardiovascular Health Study, funded by the National Heart, Lung and Blood Institute (NHLBI) in 2005, found that the 20% with the highest levels of cystatin C had a two-fold risk of death from all-cause mortality as well as CAD and a 50% higher risk of MI and stroke compared to those with the lowest levels of cystatin C[17].

Cystatin C is a more useful tool than creatinine in the detection of mild renal dysfunction where eGFR is measured at >60 mL/min/1.73m[17] and thus its use might be considered in underwriting where there is some question about renal function[22]. It is important to note, however, that levels of cystatin C may be altered by rapid cell turnover, uncontrolled thyroid disease or corticosteroid use, so this must be factored in when assessing test results for underwriting purposes[19]. In addition, the cost of the cystatin C test (US$4.00) is substantially more than that of creatinine ($0.20), but it is still cheaper than other frequently-ordered clinical tests such as BNP ($15.00) or Troponin T ($10.00), so cost should not be a prohibitive factor when considering cystatin C's use as a biomarker when developing underwriting assessments[19]. ■

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PEDIATRIC UNDERWRITING

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A basic principle in insurance is the concept of insurable interest. In life insurance, it means a policyholder must establish that he or she has an authentic financial interest in the person insured.

Pediatrics is the branch of medicine that oversees the health of a human being in his/her first years of life. Its scope includes newborn until adolescence.

Insurance products for children can include life, health, critical illness and personal accident covers. Disability products are not usual.

Living benefits policies for health and critical illness protect parents and children from the financial toll of a life-threatening illness. Health insurance plans can be diverse: some are built on a major expenses health insurance base; others cover hospitalization and/or surgeries on an indemnity base; and still others cover preventive medicine services.

Critical illness policies are also offered specifically for children. The list of insurable conditions for these policies should be clearly different than the product offered traditionally for adults. A typical juvenile CI policy can cover 30 or more conditions, with those most commonly included being cancer, type 1 diabetes mellitus, cystic fibrosis, hemophilia, Kawasaki disease, rheumatic fever with heart valve complications, encephalitis, major head trauma, major burns, and major organ transplants. Some female-specific CI products offer cover for pregnancy-related complications and certain congenital conditions, and would serve to provide some cover to the newborn child.

General personal accident insurance cover pays medical expenses due to an accident or pays a benefit for funeral expenses. These policies usually have low face amounts, and are acquired by individuals in a enrolled group such as a school or club.

In the case of life insurance for children, policies generally have small face amounts and the plans are structured as endowment or whole life. In certain markets, insurance can be purchased on the life of a child, but if the child dies before reaching age 14, no benefit will be paid and premiums will be returned.

As an initial step in underwriting a child's application an Agent's Report should be obtained, showing how the sum insured was determined. Applications for large face amounts need to be evaluated carefully. The underwriting process information on the total amount of existing life cover on the child should also be taken into consideration, to avoid over-insurance.

There are some general guidelines associated with pediatric underwriting:

- Parent or parents should have insurance on their own lives of at least two times the amount of insurance of the child.
- The parents' finances should be examined. Their income and net worth should not raise concerns of speculative intentions.
- All children in the same family should be insured equally. Whenever only one or some children in the same family are chosen for insurance, this should raise a red flag, as it could suggest possible anti-selection.
- The sum assured applied for must make sense in terms of policy type, term and reason for cover.

Pediatric Morbidity and Mortality

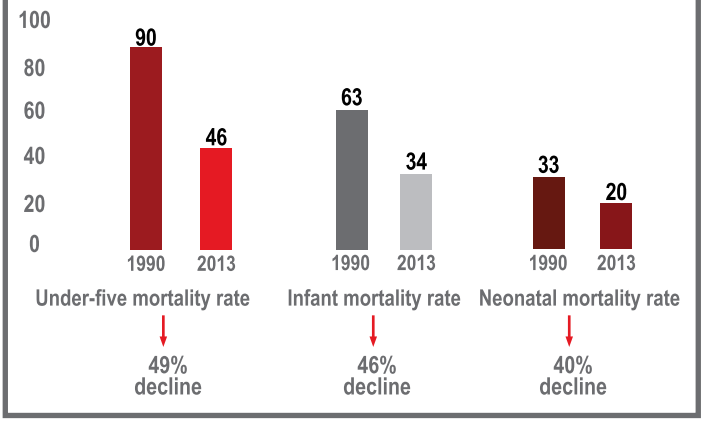
A child's growth and development can be divided into four stages:

- Infancy (0 - 2 years)
- Preschool years (3 - 5 years)
- Middle childhood years (6 - 12 years)
- Adolescence (13 - 19 years)

Each of these stages has its particular characteristics. Morbidity and mortality for each stage are different as well.

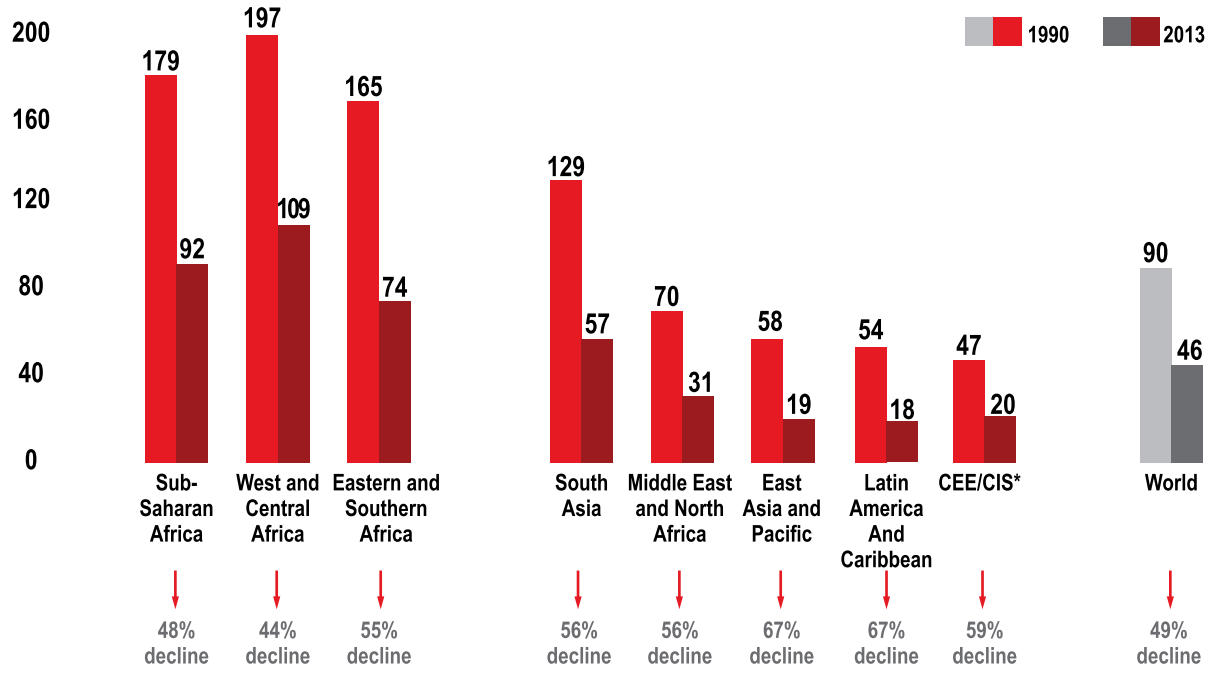
Substantial global progress has been made in reducing child deaths since 1990. According to the Levels & Trends in Child Mortality Report 2014, the global mortality rate for children under five years of age (infancy and preschool stages) has dropped 49% – from 90 deaths per 1,000 live births in 1990 to 46 per 1,000 in 2013. In addition, the global neonatal mortality rate (deaths occurring within 28 days of birth) declined by 40%, from 33 deaths per 1,000 live births in 1990 to 20 in 2013[1].

Figure 1: Global under-five mortality rate 1990—2013
(deaths per 1,000 live births)



Source: United Nations Inter-agency Group for Child Mortality Estimation (UN IGME), as published in: Committing to Child Survival: A Promise Renewed - Progress Report 2014. UNICEF, New York 2014.

Figure 2: Global under-five mortality rate by region, 1990 and 2013
(deaths per 1,000 live births)

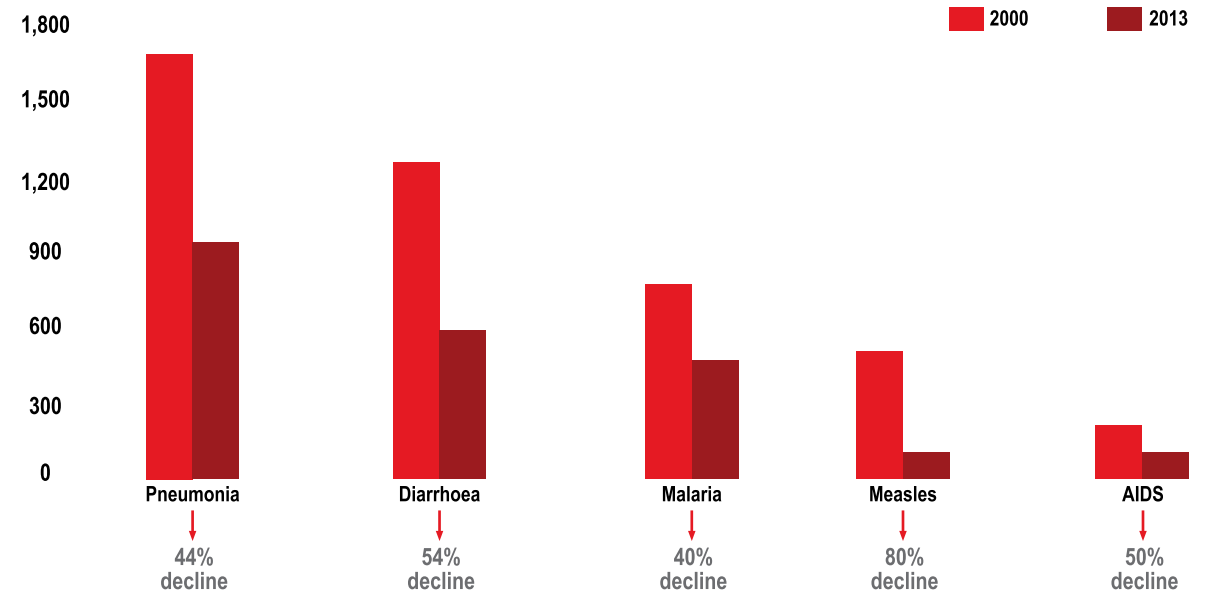


Source: UNICEF analysis based on United Nations-agency Group for Child Mortality Estimation (UN IGME), as published in UNICEF: Committing to Child Survival: A promise renewed-Progress report 2014, UNICEF, New York 2014.

For children under the age of 5, the leading causes of death include: pre-term birth complications (17%); pneumonia (15%); intrapartum-related complications (complications during labor and delivery) (11%); diarrhea (9%) and malaria (7%). In addition, nearly half of under-five deaths globally are attributable to undernutrition[2].

Figure 3: Child deaths from leading infectious diseases have declined dramatically during the last decade

Global under-five deaths from five infectious diseases, 2000 and 2013 (in thousands)



Source: The World Health Organization (WHO) and the Child Health Epidemiology Reference Group (CHERG) provisional estimates, 2014.

Prematurity

Prematurity used to be an important cause of neonatal mortality, but technological advances and improvements in medical knowledge in the field of neonatology have increased survival rates for premature babies. Still, the probability of death during the first week of life for babies born prematurely can be six times higher than for babies born after 37 weeks of gestation, and the probability for all premature infants to die before the age of one is three times higher[3].

Expenses related to the care of premature babies have also increased. The average hospital stay for premature babies, often in intensive care, is three months. Expenses are not limited to this stage: some health problems can continue for many years. Several studies done in the U.K. show that expenses from hospital admissions accumulated during the first 10 years of life of children born prematurely are twice those of children born at term[4].

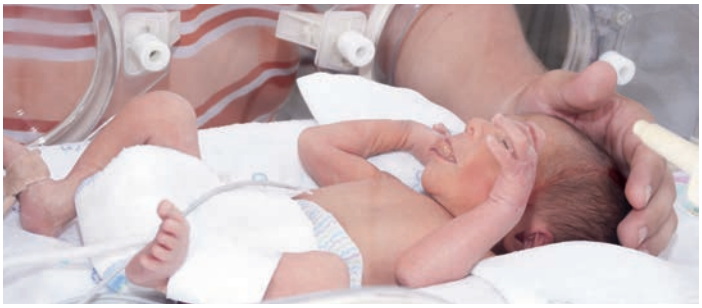
In 2013, almost one million newborns (36%), whether full-term or premature, died the day they were born, and an additional one million (37%) died within six days of birth. Some 0.8 million neonatal deaths (27%) occurred between day 7 and day 27 of life[1].

At least 90% of babies born after 28 weeks of gestation survive.

Prematurity can have long-term effects, including medical, developmental and/or mental problems or issues. These can continue until later childhood and can sometimes last into adulthood. Common long-term complications include:

- Bronchopulmonary dysplasia (BPD) (chronic lung disease). Premature babies might need oxygen for some months. Some improve slowly, while others can develop lung damage and pulmonary hypertension. These babies are also at major risk to develop respiratory infections such as pneumonia and bronchiolitis.
- Impaired growth and development.
- Mental or physical developmental delays or disabilities (intellectual disability, learning disabilities, cerebral palsy).
- Retinopathy, blindness.
- Loss of hearing.

In the long term, children born prematurely also have a higher risk of developing cardiovascular diseases, hypertension and diabetes as adults, and could also have a higher risk of developing cancer[5 6 7].



Congenital Conditions and Abnormalities

Other important causes of morbidity and mortality in the first years of life are congenital conditions – defects that develop during pregnancy and are present at birth. They can be visible or microscopic, evident or occult, and can present sporadically or in several family members. In addition, they are not necessarily inherited.

Congenital abnormalities, such as malformations and genetic diseases, may cause chronic disabilities and can have a substantial impact on the affected, their families, health systems and society.

The list of these conditions and abnormalities is very long, and includes:

- Heart malformations
- Central nervous system malformations
- Inborn errors of metabolism
- Down syndrome
- Marfan syndrome

Causes of these conditions can vary. For example:

- Chromosomal abnormalities: Down, Turner, Klinefelter syndromes
- Genetic abnormalities: hemophilia, thalassemia, cystic fibrosis, Huntington's disease, Marfan syndrome
- Environmental: a virus, or alcohol/drug use during gestation

Most congenital defects, unfortunately, do not have a recognizable cause.

Among the most common congenital abnormalities are:

- **Patent Ductus Arteriosus (PDA):** This is one of the most frequent congenital heart malformations in children[8]. Diagnosis generally occurs at the pediatric stage, although approximately 2% of cases are discovered in adulthood. The condition leads to increased pulmonary blood flow and pulmonary arterial hypertension, manifesting clinically as cardiac failure, but it can also be asymptomatic. Treatment consists of the surgical or medical closure of the arterial duct. This defect was the first to be resolved surgically, and in recent decades its treatment has dramatically evolved.

  PDA in premature and low-birth-weight children is associated with significant comorbidity and mortality due to hemodynamic instability. Asymptomatic patients with a small duct present a normal life expectancy, but they do have a life-long risk of endocarditis. Those with a moderate to large duct with important hemodynamic consequences can develop irreversible changes in the vasculature of the lungs and pulmonary hypertension.

  Occasionally treatment does not take place in the pediatric age, which leads to the persistence of the patent arterial

ductus into adulthood, which depending on the size of the short-cut, favors an increase in lung blood flow and the risk of vascular obstructive pulmonary disease (Eisenmenger syndrome). Mortality in adults, without treatment, is reported at 1.8% per year.

- **Atrial and Ventricular Septal Defects (ASD/VSD):** These are also common congenital heart defects. VSD is the most common congenital heart defect, present in 14% to 17% of all babies born each year. ASD represents 6% to 10% of congenital heart defects, and is the most frequent cause (40%) of noncyanotic congenital heart disease in adults.

  Children with this defect can be completely asymptomatic, and small septal defects usually close spontaneously and do not require treatment. Those affected should still be followed up with to ensure the defect has completely closed and that there are no complications, for they may become symptomatic in adult life. Complications from ASD are arrhythmias, especially atrial fibrillation, heart failure, endocarditis, pulmonary hypertension and strokes. Complications from VSD are aortic regurgitation, heart failure, endocarditis, and pulmonary hypertension.

- **Central nervous system congenital abnormalities:** These constitute important causes of disability among children. They include neural tube defects such as anencephaly, encephalocele and spina bifida, which are the most frequent central nervous system malformations, with prevalence varying between 0.8 - 1 for every 1,000 babies born alive. Genetic and environmental causes include maternal folic acid deficiency, maternal exposure to rubella virus and to valproic acids, radiation, and folic acid antagonists such as trimethoprim, carbamazepine, phenytoin and phenobarbital. The rate of occurrence for neural tube defects is 1.5% - 5%, and for anencephaly alone can reach 10%[9 10].

  The prognosis for brain malformation depends on the severity. For anencephaly, the prognosis is always fatal. Encephaloceles are classified depending on the region involved. Long-term evolution shows high mortality, and most of the survivors have severe disabilities.

  Spina bifida (meningocele or myelomeningocele) has an incidence of 1/1000. This defect can be closed (15%) or open (85%). Hydrocephalus is the most important complication for lumbo-sacral myelomeningoceles and is present in 90% of cases, and Chiari II malformation is present in 70% of cases. Other associated abnormalities include hip dislocation, foot deformities, contractures or flaccid paralysis. A child's ability to walk varies with the level of the spina bifida lesion. In any case, the child should receive physical therapy, and orthopedic surgery may be necessary to enable the child to stand upright and be ambulatory. Other concerns are elimination functions: there is also a high risk for urinary tract infections and bowel dysfunction as poor peristalsis predisposes to constipation. Intellectual capacity in children with neural tube defects is in a wide range; however, most are at low-normal to borderline levels.

  With adolescence, scoliosis may become apparent and be associated with syringomyelia. Kidneys might be affected due to chronic recurrent infections and calculus, and lead to loss of renal function. Affected individuals may become obese and less ambulatory. The transition into independent adulthood is very difficult, and psychosocial problems are major.

  When the spina bifida defect is closed health problems may be similar, but hydrocephalus is rare and intelligence is usually normal.

- **Down Syndrome:** This condition is due to chromosomal abnormalities, and its most constant characteristic is intellectual disability: IQs vary between 20 and 80. The great majority (95%) of Down syndrome infants have a 21 trisomy (extra copy of chromosome 21). In 4% of sporadic cases and 1/3 of familial cases the affected child has 46 chromosomes, which includes an abnormal chromosome 21. Mosaicism of the 46/47 type can also occur, and may have milder symptoms.

  About one-third of children with Down syndrome have congenital heart disease, and most have a septal defect. Leukemia is 20 times more common than in unaffected children. Other complications these children can present and which becomes more common as they grow older include infectious diseases due to abnormalities in their immune system, dementia, seizures, Alzheimer's disease, sleep apnea, obesity, hearing and vision problems, and thyroid dysfunction.

  Life expectancy for these individuals has improved dramatically; people with this condition can now live to age 60 or older. Generally, children with Down syndrome reach key developmental milestones later than other children. However, with appropriate support and treatment, many with Down syndrome lead happy, productive lives.

- **Marfan syndrome:** This is a connective tissue disorder caused by a genetic defect. In the majority of cases it is inherited, but up to 30% of the patients have no family history. In this disease there is a progressive involvement of organs and systems: skeletal, cardiovascular, ocular, skin, lungs.

  There are three forms of presentation:

  Neonatal Marfan: Very few cases have been reported. Prenatal ultrasounds will show cardiomegaly with severe tricuspid regurgitation, and at birth there

are skeletal and skin abnormalities (long limbs with delicate fingers, the appearance an elderly individual, hypotonia) and cardiovascular lesions (mitral and tricuspid severe regurgitation, cardiomegaly, aortic and pulmonary dilation, arrhythmias, mitral prolapse, ascending and descending aortic aneurysms). Death occurs in hours or days from heart failure.

Infantile Marfan: Usually seen in children before the age of 16. The non-cardiac manifestations are arachnodactyly, facial and palate abnormalities, scoliosis, and chest deformities. Cardiovascular lesions are present in 55% of the cases, and most are asymptomatic. Aortic dilation is found in 42% of the affected children, and most of the patients have cardiovascular compromise when reaching skeletal maturity. The most common cardiovascular lesions are mitral prolapse, aortic root dilation and mitral regurgitation. In this type of Marfan, average age of death is 16.3 months, and 74% have heart failure. During the early ages, morbidity and mortality are more related to mitral valve disease and in later childhood/ adolescence, to aortic valve compromise.

Classic Marfan: This is the most frequent and known presentation and can be found in children, adolescents and adults. Cardiovascular diseases are the most important cause of mortality and the most common of them is aortic dilation. Its incidence depends on age: 40% - 80% in children and 80% - 100% in adults. It has a negative prognosis due to its progressive nature, leading to valvular incompetence, dissection and rupture. In 70% of the cases one sees progressive eye problems: crystalline subluxation, glaucoma, cataracts, and retinal detachment.

- **Inborn Errors of Metabolism:** These genetic disorders were first described at the beginning of the last century and were considered rare. Since then, the number of known inborn errors of metabolism has increased and now are known as important causes of pediatric-age disease. In some cases effective treatment is available. In others, however, even though there is no known treatment, informed decisions about future offspring can be made. Clinical manifestations can vary. Common situations are acute metabolic disease in the newborn (which can be confused with sepsis), intellectual disability, vomiting and encephalopathy in an infant or older child, hypoglycemia, hyperammonemia or acidosis at any age.

Accidents

Unintentional injuries are the leading cause of death among children and adolescents, accounting for nearly a third of all deaths among children between the ages of one and 14, and more than four in ten of all deaths among teens ages 15 to 19. Most injuries and deaths of children due to accidents happen in the home or on the streets, in schools, or at recreation centers.

Accidents with young children usually occur at home, and are the result of falls, mouth burns (from food heated in microwave ovens), electrical burns (on hands), choking, asphyxiation or drowning, and amputation of a finger. As children grow older and are standing up and walking, the risk of a different type of injury increases. In addition to the previously mentioned causes, children can swallow foreign objects (coins, small toys), experience boiling water burns and esophageal burns due to the ingestion of caustic substances, suffer dog bites and traffic-related injuries, or while they are in a vehicle, experience head, chest and/or abdominal trauma.

At preschool age, a child's range of activities increases and so does the accident risk. In this age range, accidents can result from the use of bicycles, skates and skateboards, causing fractures and serious head, chest and abdominal trauma. Going to school increases the possibility of sports injuries. During adolescence, there is an increase in injuries due to sports, moving vehicles (bicycles, motorcycles, cars) and guns.

Traffic-related injuries are highest for children from 5 to 19 years of age. In teenagers, lifestyle-related issues such as use of alcohol, drugs and participation in dangerous avocations should be considered.

Severe head trauma is present in 80% of accidental deaths in children. Boys are more likely than girls to experience injuries and to die as a result of an injury. The difference exists regardless of the child's age and across all OECD countries. It may relate to differences in behavior, or in the type of activities in which boys and girls engage[11].

Cancer

From ages 5 to 14, a third leading cause of death is cancer. The most common types of cancer in children are different from those seen in adults. They are: leukemias, brain and other central nervous system tumors, neuroblastoma, Wilms' tumor, lymphomas, rhabdomyosarcoma, retinoblastoma and bone cancers (i.e., osteosarcoma and Ewing's sarcoma).

Lifestyle-related risk factors seem to play a major role in many types of cancer in adults and usually take many years to influence. In childhood cancers, however, lifestyle factors do not seem to play a role. There may be some environmental factors, such as radiation exposure, but in most cases external cause has not been demonstrated. Some children inherit mutations that increase their risk to develop cancer and the cause is not known.

Each year in the U.S. approximately 13,400 children between birth and 19 years of age are diagnosed with cancer. About one

in 300 boys and one in 333 girls will develop cancer before reaching age 20. In 1998, cancer was the most common cause of death by disease for children and adolescents.

While the incidence of childhood cancer has changed only slightly, the overall survival rate for childhood cancer has increased drastically. Today, the overall five-year survival rate for childhood cancers is close to 80%. Because treatment cure rates have increased, the population of childhood cancer survivors has also increased. Currently there are estimated to be 270,000 such survivors in the U.S. This equates to one in 640 young adults between the ages of 20 to 39 being a survivor of childhood malignancy. Survival has its cost, however: two-thirds of those who survive will later face at least one chronic health condition (heart or lung damage, second cancer, infertility, cognitive impairment, growth deficits among others)[12].

Underwriting

Underwriting a child's risk may already be challenging even when the child is apparently healthy. A child has a longer life expectancy, is still undergoing changes due to ongoing growth and development, and is constantly experiencing the effect of environmental physical, biological and social influences.

In making an underwriting assessment of a child, an underwriter should consider the prenatal and neonatal history as well as whether the pregnancy and delivery were normal or if there were complications. It is important also to review parental lifestyle issues (e.g., whether use of tobacco, alcohol and/or drugs was present), as well as parental occupational hazards.

Infectious disease risk in children can be prevented through proper immunization. It is important to consider insurability of children whose parents have chosen not to vaccinate them. Red flags are expressed parental concerns about autism and the measles-mumps-rubella (MMR) vaccine, multiple sclerosis and the hepatitis B vaccine, and sudden infant death syndrome and the diphtheria-tetanus-pertussis vaccine, despite scientific evidence that does not support these associations. Some juvenile critical illness policies cover infectious diseases such as polio, and a valid question is whether a claim for childhood polio should proceed in cases where parents have chosen not to provide the vaccine.

Physical growth and development of psychomotor milestones should also be considered in the course of underwriting. Just as underwriting for the elderly should introduce cognitive testing, an age-appropriate approach should be taken when considering an insurance application for a child. ■

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WHAT DOES THE CONTINUITY OF CARE DOCUMENT HOLD FOR UNDERWRITERS?

By Jeff Heaton
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The Continuity of Care Document (CCD) is a type of Electronic Medical Record (EMR). It is used to provide a detailed summary of a patient's current health profile and past care in order to enable a patient's smooth transition from one medical provider to another and maintain appropriate care.

The CCD is an important part of the Stage 1 and 2 "meaningful use" criteria set forth by the U.S. government. Financial incentives are available to U.S. healthcare providers that can demonstrate they are "meaningfully using" their Electronic Health Record (EHR) technology. Because the CCD is part of this incentive structure, the availability of this document in the U.S. will likely increase.

The information contained in the CCD is organized into 17 sections that describe the patient's condition and ongoing treatment. All health providers must adhere to the standard CCD format in order to ensure acceptable levels of uniformity. This format is controlled by Health Level Seven International (HL7), a not-for-profit standards development organization accredited by the American National Standards Institute (ANSI).

Because the CCD is an electronic record, coded in the common computer standard of XML, it can be integrated easily into existing computer systems and has the potential to add considerable value for automatic and computer-assisted underwriting. A wide variety of tools are available for this format.

Medical conditions described in a CCD make use of standard coding systems such as the Systematized Nomenclature of Medicine (SNOMED) and Logical Observation Identifiers Names and Codes (LOINC). This standardization makes the CCD more easily understood by computer systems. The CCD is also required to be readable by humans, which XML enables quite handily.

Figure 1

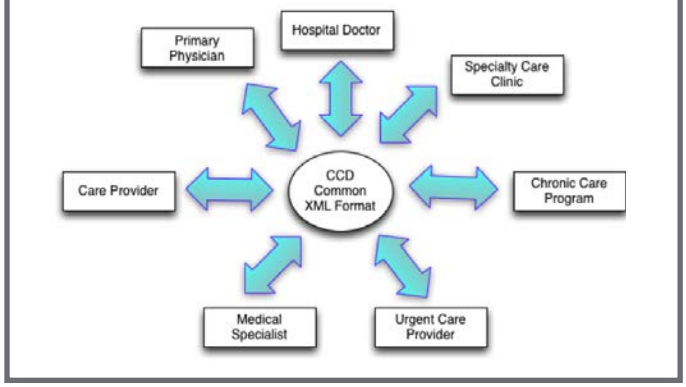

Figure 1 shows how a CCD might allow information interchange among several different providers. Each provider might use a different EHR software system, but the document's common format allows for smooth communication.

Contents of a CCD

- Header
- Purpose
- Problems
- Procedures
- Family history
- Social history
- Payers
- Advance directives
- Alerts
- Medications
- Immunizations
- Medical equipment
- Vital signs
- Functional stats
- Results
- Encounters
- Plan of care

Most of this data can be easily read both by humans and by computers. To see the XML document, simply double-click a CCD, and it will open in the default Internet browser.

Figure 2 (below) shows sample information from the "header" section of a CCD.

Actual patient data is shown in black. The XML tags are brown, and are delimited by "less than" (<) and "greater than" (>) angle brackets. The tags explain what the data is. Each block of data identifies the patient whose information is contained in this CCD document. The <given/> <family> tag, for example, tells us the patient's family name is "Heaton". The patient's birth date of January 15, 2014 (in the <birthTime value=> field, entered as 20140115000000), is also clearly evident.

Figure 2

```
<recordTarget contextControlCode="OP" typeCode="RCT">
  - <patientRole>
      <id extension="55555"/>
    - <addr use="HP">
        <streetAddressLine>16600 Swingley Ridge Road</streetAddressLine>
        <city>Chesterfield</city>
        <state>MO</state>
        <postalCode>63017</postalCode>
      </addr>
      <telecom value="tel:+1-6365550000" use="HP"/>
      <telecom use="WP" nullFlavor="UNK"/>
    - <patient>
      - <name use="L">
          <given qualifier="CL">Jeff</given>
          <given/>
          <family>Heaton</family>
        </name>
        <birthTime value="20140115000000"/>
      - <maritalStatusCode>
          <originalText>MARRIED (M)</originalText>
        </maritalStatusCode>
      </patient>
    </patientRole>
</recordTarget>
```

Medical information is similarly presented. The excerpt in Figure 3, for example, shows how an allergy to the antibiotic drug Amoxicillin Potassium Clavulanate is encoded in the CCD.

The existence of the allergy condition is indicated using the SNOMED code 416098002. The actual drug name is indicated using a First DataBank Generic Sequence Number (GSN), which in this case is 1901. Such mixing of coding

Figure 3

```
<code code="416098002" codeSystemName="SNOMED" displayName="Allergy to Drug"/>
<participant typeCode="CSM">
  - <participantRole classCode="MANU">
      - <playingEntity classCode="MMAT">
            <code code="1901" codeSystem="FDB" displayName="Amoxicillin Pot Clavulanate"/>
            <name>Amoxicillin Pot Clavulanate</name>
        </playingEntity>
    </participantRole>
</participant>
```

standards is fully supported by the CCD standard. Other common coding standards used in the document include RxNorm, GPI (Generic Product Identifier) and NDC (National Drug Code).

As can be seen from Figures 2 and 3, it is entirely possible to read a CCD without any special software. However, for underwriters working with large volumes of CCDs, specialized reader software that will extract information and hide the XML tags will be useful. Such software can also "crosswalk" among different coding standards.

CCDs in Underwriting

The CCD is designed to distill a patient's complete medical file down to only the pertinent information a new provider might need to continue care appropriately. Like most medical documents, the CCD was not specifically designed for insurance company usefulness. Nevertheless, it contains a wealth of information that will be of value to an underwriter.

Adoption of the CCD by healthcare providers will likely mean underwriters will see this document with increasing frequency.

Although from an underwriting perspective, the information in a CCD can be useful, a complete decision would not typically be able to be made from the document. A CCD generally carries information about procedures, problems, and medications that could result in a denial. However, much of the other information in the CCD serves as an overview of the applicant's current medical status. Additional medical documents such as attending physician statements (APS), lab reports, motor vehicle reports, financial statements and others will be needed to make a well-informed underwriting decision. This is particularly true for insureds with more complex medical situations.

What the Future Might Hold for the CCD

The CCD was first selected by the Healthcare Information Technology Standards Panel (HITSP) as the format for exchange of clinical information, and then recognized in 2008 by the U.S. Secretary of Health and Human Services for this use. Since then, it has been adopted into many EMR systems. This adoption, along with the inclusion of CCD in "meaningful use" initiatives, means the document will continue to become more common in the U.S.

CCDs are also seeing increased use by government agencies and medical researchers interested in compiling reports based on analytics provided by aggregate information obtained from CCDs from large groups of individuals. The standardized format of a CCD makes it relatively easy to aggregate data from many individuals. The data, which is de-identified and so no longer contains information that can link to any individual patient, is then used to forecast and analyze trends in segments of the population. Several government agencies and medical researchers are already using CCD data to advance medical research and promote public health. ■

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Jeff Heaton is the EHR Information Scientist for RGA Electronic Health Records (EHR) Initiatives team. In one of his first tasks, he was asked to create a utility to allow an underwriter to enter information on a code-by-code basis. This required mapping the CDC-provided XML files to an Oracle database, while preserving the hierarchical nature of the codes.

LONGER LIFE FOUNDATION: LATEST PEER-REVIEWED ARTICLES

Over the past four years, the number of articles published in peer-reviewed scientific publications about research supported by the Longer Life Foundation, or citing past LLF support, has skyrocketed.

From 2010 to now, 64 articles (or two-thirds of the total) have been published in a range of journals about LLF-supported research in nutrition and obesity, ageing, diabetes, cancer, cardiovascular conditions, and other topics.

The following articles were published in 2014:

1. **Energy requirements in nonobese men and women: results from CALERIE**.
   Redman LM, Kraus WE, Bhapkar M, Das SK, Racette SB, Martin CK, Fontana L, Wong WW, Robert SB, Ravussin E, for the CALERIE Study Group.
   Am J Clin Nutr. Jan 2014.
   http://ajcn.nutrition.org/content/early/2013/11/20/ajcn.113.065631
2. **Low protein intake is associated with a major reduction in IGF-1, cancer, and overall mortality in the 65 and younger but not older population.**
   Levine ME, Suarez JA, Brandhorst S, Balasubramanian P; Cheng CW, Madia F, Fontana L, Mirisola MG, Guevara-Aguirre J, Wan J, Passarino G, Kennedy BK, Wei M, Cohen P, Crimmins EM, Longo, VD
   Cell Metabolism 19, 407-17, March 4, 2014.
   http://www.longerlife.org/publications/Low-protein-intake-Cell-Metabol-2014.pdf
3. **Optimal body weight for health and longevity: bridging basic, clinical, and population research.**
   Fontana L, Hu FB. Aging Cell (2014) pp 1-10
   http://www.longerlife.org/publications/Optimal-body-weight-for-health-and-longevity-ac14.pdf
4. **Postprandial plasma incretin hormones in exercise-trained versus untrained subjects.**
   Weiss EP, Royer NK, Fisher JS, Holloszy JO, Fontana L.
   Med Sci Sports Exerc. 2014 Jun; 46(6): 1098-103
   http://www.ncbi.nlm.nih.gov/pubmed/24576859
5. **Cytochrome P450 gene variants, race and mortality among clopidogrel treated patients following acute myocardial infarction.**
   Cresci S, Depta JP, Lenzini PA, Li AY, Lanfear DE, Province MA, Spertus JA,. Bach RG.
   Circ Cardiovasc Genet 2014 Apr 24 (epub)
   http://www.ncbi.nlm.nih.gov/pubmed/24762860
6. **Medical research: treat ageing.**
   Fontana L, Kennedy BK, Longo VD, Seals D, Melov S.
   Nature 2014 Jul 24;511(7510):405-7
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   Weiss EP, Royer NK, Fisher JS, Holloszy JO, Fontana L.
   Med Sci Sports Exerc. 2014 Jun;46(6):1098-103.
   http://www.ncbi.nlm.nih.gov/pubmed/24576859
8. **CHRNA5 variant predicts smoking cessation in patients with acute myocardial infarction.**
   Chen LS, Bach RG, Lenzini PA, Spertus JA, Bierut LJ, Cresci S.
   Nicotine Tob Res 2014;16:1224-1231
   http://www.ncbi.nlm.nih.gov/pubmed/24727484
9. **Urinary concentrations of aquaporin-1 and perilipin-2 in patients with renal cell carcinoma correlate with tumor size and stage but not grade.**
   Morrissey JJ, Mobley J, Song J, Vetter J, Luo J, Bhayani S, Figenshau RS , Kharasch ED.
   Urology 2014Jan;83(1): 256.
   http://www.ncbi.nlm.nih.gov/pubmed/24239027

The Longer Life Foundation is a not-for-profit partnership between RGA and Washington University's School of Medicine, created in 1998. The LLF supports and funds independent research into longevity and enhancing quality of life and wellness.

UPCOMING WEBCASTS FROM RGA

Wednesday, March 25, 2015

Anticipating Infections Disease Impacts in an Increasingly Globalized World

New infectious diseases are emerging faster today than ever before, just as many known diseases are reemerging. A confluence of phenomena – from population growth, urbanization, increasing human exposure to animal pathogens, climate change and overburdened healthcare systems, to shifting attitudes toward vaccination, the threat of bioterrorism, mass gatherings and air travel – is driving risks for the emergence and spread of infectious diseases. In an increasingly globalized world, tomorrow's epidemics could infect millions and have vast health and economic consequences. This webcast will cover what we currently know about emerging global infectious diseases, reflecting on events from the 1918 Spanish flu to the current Ebola epidemic in West Africa. We will also discuss what tools are available to help the insurance industry better plan for and respond to tomorrow's inevitable epidemics.

Look for a follow-up email on March 25 with webcast access information.

Presenter: Dr. Kamran Khan, MPH, FRCPC
Clinician-Scientist, Division of Infectious Diseases,
St. Michael's Hospital
Associate Professor, Division of Infectious Diseases,
University of Toronto
Founder, BlueDot

Presenter: Dr. J. Carl Holowaty, DBIM
Senior Vice President, Chief Medical Director
RGA Reinsurance Company

Wednesday, May 20, 2015

Electronic Health Records Data: Are You Ready?

Because electronic health records (EHRs) are having such a huge impact on the life insurance industry, RGA has dedicated resources monitoring this space and developing tools to leverage EHRs in the sale of insurance. In our second webcast covering EHRs, RGA will discuss our vision for EHRs with respect to life insurance, current initiatives related to these records, and strategies for utilization of structured and unstructured data from electronic medical data sources. This webcast will also include an update on EHR adoption, meaningful use and interoperability in the United States.

Presenter: Sue Wehrman
Vice President, Electronic Health Records Initiatives
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Moderated by Kathryn Cox
Senior Vice President, Business Development
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