

ReFlections

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FROM THE EDITORS

Welcome to the May 2016 edition of ReFlections! This is our second issue of the year and it continues our ongoing mission to educate, inform, and enlighten.

This edition contains two very timely articles. The science of genetics is becoming an increasingly important element in both the diagnosis and treatment of many disease conditions. In the first article, Dr. Sheetal Salgaonkar, Medical Director, India, provides an in-depth review of the role of genetics in the rapidly-changing diagnostic criteria, risk stratification, and treatment of individuals with chronic lymphocytic leukemia (CLL).

In the second article, Dr. Heather Lund, Chief Medical Officer – Asia, discusses the relatively new but increasingly popular Cancer Reimbursement product and its design, underwriting and claims issues.

We are confident you will find both of these articles informative and that they will enrich your knowledge of insurance medicine.

ReCite, our medical literature review section, has also been updated with several recently published and relevant articles of interest to both underwriters and medical directors.

Finally, The Longer Life Foundation remains actively engaged in its research function. Our update provides information about groundbreaking research on obesity conducted by an LLF-supported investigator who is also a member of the foundation's advisory committee.

We want to make this newsletter useful and practical to all our readers. Please feel free to provide feedback and suggestions to us!

Thank you,
Phil, Dan and Neil

CHRONIC LYMPHOCYTIC LEUKEMIA – AN UPDATE

Abstract

The clinical understanding and treatment of chronic lymphocytic leukemia (CLL), the most prevalent adult leukemia in the West, has experienced several advances over the past decade. Research on genetic aspects of CLL has expanded medical understanding of its risk stratification, uncovered a new precursor condition – high-count monoclonal B-cell lymphocytosis (MBL) and overall elicited a sizable transformation of CLL's treatment framework. Traditional chemotherapy-based regimens, which cause severe adverse effects in the elderly and in patients with comorbidities, are now being paired with (and in some cases supplanted by) targeted therapies such as the recently developed monoclonal antibody immunotherapy drugs ofatumumab and obinutuzumab and the targeted kinase inhibitors idelalisib and ibrutinib. These drugs are not only filling a major unmet need of those with newly diagnosed or resistant CLL, but also may reduce or even potentially eliminate the need for chemotherapy. Indeed, the American Society of Clinical Oncology (ASCO) named these new therapy options for CLL the Cancer Advance of the Year in its Clinical Cancer Advances 2015 report.

This article focuses primarily on recent advances in the clinical understanding and treatment of CLL and prognostic implications for insurers.

Background

Chronic lymphocytic leukemia (CLL) is a slow-developing cancer that is characterized clinically by the overproduction and accumulation of small mature-appearing (but functionally incompetent) B lymphocytes in blood, bone marrow and lymphoid tissues.¹

CLL is the most common adult leukemia in Western societies, with an incidence of 4.2:100,000/year. However, it is relatively rare in Asia³ and Africa. The reason for this geographical diversity is not clear, but the etiopathogenesis is suspected to be more likely due to genetic than environmental factors.⁴

The risk of developing CLL increases progressively with age. Nearly 70% of patients are 65 years of age or older, and its risk is 2.8 times higher for men than for women.²

Diagnosis

CLL was once thought to be a homogenous static disease, in which B lymphocytes accumulated largely due to lack of normal cell death. Recent research, however, has established CLL as a heterogeneous disease exhibiting constant turnover of malignant B lymphocytes at varying rates. This heterogeneity translates into varying clinical courses and responses to treatment.^{5,6}

More than 80% of CLL patients are diagnosed incidentally. Ten percent

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of CLL patients present with the characteristic symptoms of fever and night sweats, and approximately 20% to 50% present with enlarged and palpable lymph nodes, hepatomegaly and splenomegaly. A small percentage also experience unexplained weight loss and frequent infections.

Diagnostic criteria for CLL developed by the National Cancer Institute's Working Group^{19,25} includes the following:

- A peripheral blood B lymphocyte count of at least $5 \times 10^9/l$ (5,000/ μl)
- Clonality of the circulating B lymphocytes should be confirmed by flow cytometry
- The presence of atypical lymphocytes, cleaved cells or prolymphocytes should not exceed 55% of peripheral lymphocytes
- The lymphocytes should be monoclonal B lymphocytes, expressing B lymphocyte surface antigens CD19, CD20, and CD23 with low surface immunoglobulin and the T-cell antigen CD5
- Each clone of leukemia cells is restricted to expression of either kappa or lambda immunoglobulin light chains

Small lymphocytic lymphoma (SLL) is considered the same as CLL by the 2008 World Health Organization (WHO) classification of hematological malignancies due to their identical immunophenotypes. A confirmed diagnosis of SLL requires the presence of lymphadenopathy and/or splenomegaly, and an absolute lymphocyte count in the peripheral blood of less than $5 \times 10^9/l$.²⁶

**More than 80%
of CLL patients
are diagnosed
incidentally.**

Monoclonal B-cell lymphocytosis (MBL), which today is recognized as a precursor condition to CLL, was first described in 2005.²⁷ MBL is currently defined as the presence of fewer than 5,000 monoclonal B lymphocytes/ μl in the blood in the absence of lymphadenopathy, organomegaly, or cytopenia. Based on the size of the clone, MBL can be segregated into two groups:

- Clinical or high-count MBL with $\geq 0.5 \times 10^9/l$ clonal B cells. This is a preleukemic disorder; progression to CLL occurs in 1% to 2% of MBL cases per year.
- Low-count MBL, with $< 0.5 \times 10^9/l$ clonal B cells. This is seen in approximately 5% of the general population, especially among individuals older than age 70. It has little or no apparent clinical significance.

Table 1 (below) lists the diagnostic differentiators for CLL, SLL and MBL.

TABLE 1: DIAGNOSTIC DIFFERENTIATORS FOR CLL, SLL AND MBL ²⁸			
	CLL	SLL	MBL
Clonal B cells in peripheral blood	$\geq 5000/\mu l$	$< 5000/\mu l$	$< 5000/\mu l$
Lymphadenopathy/organomegaly	Possible	Yes	No
Disease-related symptoms	Possible	Possible	No
Lymph node biopsy	Not required	Required	Not required

Two clinical staging systems are used to predict CLL median survival rates (Table 2, below).^{29,30} In Europe, the Binet staging system is more widely used, whereas in the U.S. the Rai system is more commonly applied.

TABLE 2: BINET AND RAI STAGING SYSTEMS FOR CLL^{29,30}

Stage	Definition	Median Survival
Binet system		
Binet A	Hemoglobin (Hb) ≥ 10.0 g/dl, thrombocytes $\geq 100 \times 10^9/l$, < 3 lymph node regions	> 10 years
Binet B	Hb ≥ 10.0 g/dl, thrombocytes $\geq 100 \times 10^9/l$, ≥ 3 lymph node regions	> 8 years
Binet C	Hb < 10.0 g/dl, thrombocytes $< 100 \times 10^9/l$	6.5 years
Rai system		
Low risk		> 10 years
Rai 0	Lymphocytosis $> 15 \times 10^9/l$	
Intermediate risk		> 8 years
Rai I	Lymphocytosis and lymphadenopathy	
Rai II	Lymphocytosis and hepatomegaly and/or splenomegaly with/without lymphadenopathy	
High risk		6.5 years
Rai III	Lymphocytosis and Hb < 11.0 g/dl with/without lymphadenopathy/organomegaly	
Rai IV	Lymphocytosis and thrombocytes $< 100 \times 10^9/l$ with/without lymphadenopathy/organomegaly	

The expanding role of genetic analysis

Studies of somatic copy number variations in genomes using karyotyping, fluorescence in situ hybridization (FISH) or single nucleotide polymorphism arrays have identified several genomic mutations that impact the diagnosis, progression and treatment of CLL. The most recurrent diagnostic variations are deletions of chromosome 13q (55% of cases), 17p (7%), 11q (6% to 18%); and trisomy 12 (12% to 16%).^{7,8}

These chromosomal aberrations might not be wholly responsible for CLL's clinical heterogeneity. Mutations of genes such as IgHV (immunoglobulin heavy chain variable) and the protein coding genes TP53, NOTCH1 and SF3B1 also have implications in prognosis and treatment interventions.⁹ The mutation status for IgHV¹⁹ is generally detected using molecular analysis. About 50% of CLL patients present with unmutated IgHV.^{20,21} These patients have higher genetic instability and higher risk of gaining unfavorable genetic mutations, resulting in shorter overall survival rates.



FISH analysis is usually performed to detect if the long arm of chromosome 17p, where the TP53 gene resides, has been deleted.¹⁶ Patients with a detectable del(17p) mutation or deleted TP53 have the poorest prognoses, with a median overall survival of two to five years.^{17,18} An extended FISH analysis can also detect additional cytogenetic abnormalities, such as del(11q) or trisomy 12, both of which may have therapeutic consequences. The formerly poor prognosis of patients with del(11q) has improved with the chemotherapy cocktail FCR (fludarabine, cyclophosphamide and rituximab).¹⁹

Clonal evolution refers to the process whereby cancer cells accumulate genetic and epigenetic changes over time, giving rise to new subclones. In CLL, the heterogeneous nature of the disease likely fuels clonal evolution, which is a key point in its progression, relapse, and chemotherapy resistance.²² Over time, 25% of CLL patients develop a new genetic abnormality in coding or non-coding genes.⁹ Across studies, genetic lesions dominating at relapse have been consistently detected in smaller subclones at earlier stages, suggesting the emergence of fitter subclones together with genetic diversification.²³ The most consistent lesions detected in these studies have been pre-existing TP53 mutations, resulting in highly genomically complex clones at relapse.¹⁶ Chemotherapy exposure has also been shown to result in clonal evolution by inducing de novo mutations conferring major fitness of the related subclones.²⁴

Treatment

There is currently no evidence that early, risk factor-guided intervention with chemoimmunotherapy can alter the natural course of early-stage CLL.⁴ “Watch and wait,” therefore, remains the standard first-line care for patients with early-stage asymptomatic CLL.

For active symptomatic CLL, the International Workshop on CLL (IWCLL) has specified the following criteria for treatment:³¹

- Unintentional weight loss of 10% or more within the previous six months
- Significant fatigue
- Fevers higher than 100.5°F (38.0°C) for two or more weeks without other evidence of infection
- Night sweats for more than one month without evidence of infection
- Cytopenia not caused by autoimmune phenomena
- Symptoms or complications from lymphadenopathy, splenomegaly or hepatomegaly
- Lymphocyte doubling time (LDT) of less than six months (only in patients with more than 30,000 lymphocytes/ l [$30 \times 10^9/l$])
- Autoimmune anemia and/or thrombocytopenia poorly responsive to conventional therapy

The presence in the genome of del(17p) or of a TP53 mutation without the above-mentioned conditions are not indications for treatment.

Whether to administer chemoimmunotherapy depends on patient age (e.g., >65 to 70), fitness level score of >6 (as measured by the Cumulative Illness Rating Scale [CIRS]) and renal function (e.g., creatinine clearance <30 to 50 ml/min).³² Front-line treatment of CLL is based mainly on the stage and the specific genetic mutation expressed.

TABLE 3: PROGNOSTIC SUBGROUPS AND ASSOCIATED RISK GENETIC FACTORS IN CLL AT DIAGNOSIS^{9,10,11,12,13,14}

Category	Associated Genetic Factors	Therapeutic Strategies
Very high risk	del(17p)*/TP53 mutation and/or BIRC3 mutation	TP53-independent drugs (e.g., rituximab) Bruton's tyrosine kinase (BTK) inhibitors Allogeneic hematopoietic stem cell transplantation (HSCT)
High risk	del(11q)*/ ATM gene and/or NOTCH1 gene mutation and/or SF3B1 gene mutation	Fludarabine, cyclophosphamide, rituximab (FCR)
Intermediate risk	Trisomy 12 Normal karyotype/FISH	Watch and wait
Low risk	Isolated del(13q)*	Watch and wait
*higher percentages of deleted nuclei have negative impact on prognosis		

For fit patients (no comorbidities) without the TP53 mutation, the frontline standard of care is chemoimmunotherapy – specifically FCR. This is based on high response rates (40% to 50% complete response), prolongation of median progression-free survival (PFS) and median overall survival compared with administration of fludarabine and cyclophosphamide or of chlorambucil alone.^{33,34,35,36}

FCR has its own challenges, as it is associated with significant myelosuppression and infections, making it unsuitable for elderly patients and for patients with comorbidities. For older patients with comorbidities and without the TP53 mutation, regimens can include reduced-intensity FCR, chlorambucil + CD20 monoclonal antibody (rituximab, obinutuzumab, or ofatumumab), or bendamustine + CD20 monoclonal antibody.

For patients with the TP53 mutation, prognosis is generally poor, even after FCR therapy.³⁹ It is therefore recommended that they be treated with the newer inhibitors ibrutinib (which inhibits the enzyme Bruton's tyrosine kinase [BTK]) and idelalisib (a phosphoinositide 3-kinase inhibitor), along with rituximab, in both frontline and relapse settings. For transplant-fit patients responding to treatment with these inhibitor drugs, allogeneic hematopoietic stem-cell transplantation (HSCT) may also be considered. HSCT is the only modality with documented curative potential in CLL.⁴⁰

The breakthrough monoclonal antibody immunotherapy drugs obinutuzumab and ofatumumab were approved by the U.S. Food and Drug Administration (FDA) in 2013 and 2009, respectively. The combination of obinutuzumab and chlorambucil was more effective than chlorambucil alone or chlorambucil combined with rituximab, and more than doubled the average time to progression (TTP). The combination of ofatumumab and chlorambucil was also been shown to be superior to single-agent chlorambucil, with an average TTP of 22.4 months versus 13.1 months for chlorambucil alone.³⁸

Newest treatments and therapies

▪ B-cell receptor (BCR) pathway inhibitors

Currently ibrutinib and idelalisib are approved in the U.S. and Europe for treatment of CLL. Ibrutinib irreversibly inactivates BTK, which is essential for BCR signaling, and nuclear factor- κ B (NF- κ B), one of the proteins that regulates the expression of genes influencing, among other things, B lymphocyte development and cellular proliferation. Ibrutinib is approved for the treatment of CLL patients who have received at least one round of prior therapy and as the primary therapy for CLL patients presenting with chromosome 17p13.1 deletion.^{41,42}

Acalabrutinib, a second-generation selective BTK inhibitor, has shown promising results for relapsed CLL patients and was recently recommended for orphan drug designation in Europe. It has fewer side effects than ibrutinib, and has shown promise regarding safety and efficacy, including for those with chromosome 17p13.1 deletion.⁴⁴

Idelalisib is a selective and reversible inhibitor of PI3K δ , the delta isoform of the enzyme phosphoinositide 3-kinase, which regulates cellular growth and proliferation in leukocytes. In combination with rituximab, idelalisib is a safe and effective new treatment option for patients with relapsed CLL, including those with poor prognostic factors. In a study, patients treated with idelalisib and rituximab lived, on average, 10.7 months without the disease progressing, compared with approximately 5.5 months for participants treated with a placebo plus rituximab.⁴⁵

▪ B-cell lymphoma-2 (BCL-2) antagonists

BCL-2 is a prosurvival protein which causes apoptosis resistance and accumulation of long-lived clonal lymphocytes in CLL. Venetoclax (ABT-199, RG7601, GDC-0199), a potent BCL-2 inhibitor, has been granted breakthrough designation by FDA for ultra-high risk populations with relapsed/refractory del(17p) CLL. A recent study showed that the overall response rate was 79%, the complete response rate 20%, and the 15-month progression-free survival estimate 69%.⁴⁶

▪ Chimeric antigen receptors (CARs-T)

Recent clinical studies are investigating the use of chimeric antigen receptor (CAR) modified T cells to treat CLL. CAR-modified T cells have been developed to target antigen CD19 expressed on CLL cells. Treatment of bulky, relapsed, refractory and high-risk CLL with anti-CD19 CAR-modified T cells can result in sustained remissions in small numbers of patients.⁴⁷

Insurance considerations

CLL is undergoing a rapid and exciting transition right now, from what was, for many, a fatal disease to one that can be controlled for extended periods of time with an array of relatively well-tolerated therapies that to date exhibit very modest long-term risks.

Molecular genetics is changing CLL by offering superior prognostication and treatment strategies. As the understanding of and treatment frameworks for this condition continue to evolve, so are its underwriting risk classifications. Some early-stage favorable cases now exhibit insurable (albeit moderately reduced) life expectancies. Morbidity concerns with CLL, however, still are negatively impacting the ability to consider living benefits coverage.

Promising new therapies for relapsed, refractory and high-risk CLL have shown a remarkable increase in overall survival and progression-free survival, which could impact terminal illness products as the policy terms may no longer be fulfilled.

While developing critical illness products, insurers would be advised to evaluate precursor CLL conditions such as high-count MBL along with early-stage CLL to prevent unanticipated claims, as these conditions may not meet the “serious illness” spirit of the product, given their long life expectancies and the “watch and wait” treatment approach.

Survival in CLL patients over time has improved significantly due to the many new targeted therapies, which are improving not only response rates and progression-free survival, but also overall survival. Additionally, patients who are ineligible for conventional therapies who have relapsed or whose conditions are resistant now have new options, offering the chance of effective treatment. As these trends continue to evolve, insurers will need to watch and track them carefully. 

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RGa MEDICAL TEAM UPDATE

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CANCER REIMBURSEMENT – A NICHE SOLUTION

Abstract

"While there are several chronic diseases more destructive to life than cancer, none is more feared."

— Charles Mayo¹

The development of new and innovative products is a key success factor for insurers. Various stakeholders across different disciplines are involved throughout the product development cycle, the culmination of which can be the introduction of a novel indemnity offering. There are several considerations throughout the process, but from the consumer's perspective in order for there to be sufficient traction, there has to be a tangible need for the specific protection being offered. One such product is Cancer Reimbursement insurance. This article will address aspects of this product's development journey.

Background

Critical illness insurance, now well-entrenched in most insurance markets, is a product that meets an increasingly prevalent consumer need: a lump sum payment upon diagnosis of a condition that can impact life expectancy and quality of life, so as to ease the threat of financial loss. This cover is and will remain popular, but its current complexities, which have evolved over its past three-plus decades of existence, can overwhelm an average consumer at the point of sale.

Medical and hospital reimbursement insurance products are complex as well, and significant coverage gaps can exist in both private and state-provided reimbursement cover.

A solution? The simple yet elegant, contained yet comprehensive, niche indemnity solution known as Cancer Reimbursement (CR) insurance. Essentially a tailored hybrid product, CR provides comprehensive cover for the diagnosis, management, and ancillary care expenses incurred upon diagnosis of a defined incident cancer or a cancer in situ.

Public awareness of the threat of cancer is increasing, which is driving interest in targeted insurance protection.

CR as a product was first conceived of and launched in Asia towards the end of 2012. To date, its growth has averaged 25% per year – not unexpected as Asia accounts for 60% of the world population and half the global burden of cancer.² Lifestyle factors, sociocultural norms and ethnic heterogeneity contribute to this significant cancer burden. Smoking prevalence among males in Indonesia, China, Malaysia, and Korea, for example, is about twice that of males in the U.S. Dietary habits, outdoor air pollution and the burden of cancer-related chronic infections also offer some explanations for this prevalence.

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Heather M. Lund, MBBCh, is Chief Medical Officer – Asia at RGA Reinsurance Company. She provides medical consultation expertise and technical assistance for reinsurance underwriting and claims assessment, supporting actuarial business development, marketing and pricing teams across the Asia region. A native of South Africa, Heather's Bachelor of Medicine, Bachelor of Surgery (MBBCh) degree is from the University of the Witwatersrand in Johannesburg. Her background is in Family Medicine with a special interest in maternal health. She is a frequent contributor to medical publications and has also served on program committees of the International Committee for Insurance Medicine (ICLAM) and the Academy of Insurance Medicine in Asia (AIMA).

Cancer's reach is widespread, its effects significant and its associated burdens well understood, especially by those who receive the diagnosis, their families and communities. As medical science's understanding of the many cancer conditions advances, doctors are increasingly able to provide clear explanations of its risks, the etiologies and prognoses of different cancers, and the newer, more effective personalized testing and treatment options that are available.

Still, although survival has improved – the current five-year average survival rate is approximately 65% – cancer remains a significant diagnosis. Cancer Reimbursement cover aims to protect against some of the impact associated with such a life-changing finding.

Cancer Reimbursement – product features

The cancer care continuum involves highly specialized, multi-disciplinary, empathetic, attentive, and personalized care.

CR products generally have a per-cancer and overall lifetime maximum payment limit, and cover up to three incidences. A histopathologically distinct subsequent cancer is paid only if diagnosed one year after the preceding cancer occurrence.

Covered treatments include comprehensive medical care in and out of hospital settings, cancer surgery (including reconstructive surgery), home nursing care, assistive medical appliance expenses, rehabilitation and palliative care.

Allied medical services and supportive counseling are also reimbursed. Chiropractor consultations are also generally covered, but with limited per-visit payouts. Products can also cover complementary therapeutic modalities specific to a region's diverse sociocultural traditions, such as in- and outpatient Chinese medicine consultations and treatment. In addition, CR can cover donor expenses for transplantation costs, second medical opinion referral services and a hospital companion bed for an accompanying spouse or family member. Finally, the product pays a small compassionate death benefit upon the death of the insured.

Most CR policies exclude conditions diagnosed within the five years preceding policy inception unless the specific impairment was fully disclosed and accepted at underwriting stage. Some exclusions that currently apply include, but are not limited to, the following:

- Any treatments, tests, services or supplies that are not medically necessary, or any charges that are in excess of what is deemed reasonable and customary

- Non-medical services, such as guest meals, medical report charges
- Any experimental, unproven or unconventional medical technology, such as stem-cell therapy, and/or any procedure, therapy, drugs or medicines not yet approved by the government, relevant authorities and/or recognized medical association in the country or region where the treatment is sought
- Genetic testing undertaken to determine a genetic predisposition
- Over-the-counter medicines and nutrient supplements
- Vaccinations and immunizations received by an insured to prevent a covered cancer

Underwriting guidelines – cancer risk assessment under the microscope

The unique risk assessment needs of cancers necessitated the development of product-specific underwriting guidelines for CR. Simply adapting the critical illness guidelines for a targeted cancer product would not work, as each specific cancer risk and its cost of care must be isolated and rated accordingly.

Broadly, the underwriting approach separates disclosed medical conditions into two groups: impairments for which a clear and established cancer risk exists; and impairments that do not have any associated cancer risk. Additional premium loadings or exclusions appropriate for an applicant's relative cancer risk are most commonly used for the first group of impairments. For example, chronic hepatitis B carriers might receive an additional loading for the associated hepatocellular carcinoma risk unless there is additional information available that can allow for an alternative decision. Other impairments where no appreciable cancer link exists can, for the most part, be accepted at standard rates.

Many common impairments are encountered at underwriting for which a slightly higher overall relative risk of cancer exists but where it might be arguable that this risk is not significant enough to be assigned an extra premium. At the same time, comorbidities need to be weighed and properly assessed, and the potential for any occupational exposure must be considered. The guidelines would also have to accommodate an early-stage carcinoma in situ diagnosis as a claim trigger. Underwriting philosophies are company-specific, and pricing assumptions are important too, but ultimately evidence should drive the underwriting decision and rating.

Specific cancer risk, however, cannot always be separated out. For example: How might an applicant with Type 2 diabetes be underwritten for CR cover? This increasingly common impairment presents various challenges at the risk assessment stage, particularly for rider benefits. Most of diabetes' critical illness risk is related to its well-known macro- and microvascular outcomes. Epidemiologic evidence is conflicting for overall cancer risk in diabetes, but consistently points to excess risk for site-specific cancers.³ (Most study populations have only included Type 2 diabetics due to the relative prevalence of this type.) Meta-analyses show an increased risk for cancer in diabetics. Similar evidence exists for individuals who have metabolic syndrome and those considered prediabetic.

The complex pathophysiology of diabetes encompasses a range of chronic hormonal abnormalities, chronic inflammation and oxidative stress. This milieu, together with a genetic susceptibility, can initiate carcinogenesis. The association may also be due to the risk factors shared by cancer and diabetes, which include aging, obesity, diet, smoking and physical inactivity. Some of this overlap is accommodated in the base ratings, but the synergism remains an important risk assessment consideration.

Interestingly, evidence suggests diabetes might have a protective effect on prostate cancer incidence. As prostate cancer is not prevalent in men in Asia, this might explain the finding of a lower "all cancer" risk in men in some studies.⁴

Hepatocellular carcinoma risk, however, is about two to three times higher for diabetics. Since most epidemiologic studies

indicate such increases in relative risk of hepatocellular carcinomas in diabetics, it must be questioned whether diabetes is a direct risk factor or whether diabetes-related diseases such as obesity and nonalcoholic fatty liver disease (steatosis) might also be implicated.

Hepatitis B and C infections have also been shown to be more frequent in diabetic patients. Ultimately the exact mechanism of this association remains unclear but as hepatocellular carcinoma is more prevalent in Asia, it requires due consideration in a product intended for this region. Hepatitis B and C also increase the relative risk for cancers of the pancreas, kidney, endometrium, colon, and rectum and bladder.⁵

In a comparison of overall survival rates in cancer patients with and without diabetes, a systematic review and meta-analysis showed that those cancer patients with pre-existing diabetes are at increased risk for long-term, all-cause mortality compared with those without diabetes.⁶

The presence of rheumatic conditions is another example of where benefit assessment for a cancer-only product requires a considered, research-based risk assessment approach. Evidence points to overall increased cancer risk for some of these conditions.⁷ An international multi-site cohort study of cancer risk for individuals with systemic lupus erythematosus⁸ found evidence that suggests a standardized incidence rate for these individuals of 1.14 for all cancers, with higher rates for lymphomas and leukemias.

In a mini-review of malignancies in autoimmune rheumatic diseases,⁹ Szekanecz and colleagues summarized some of the rheumatic diseases associated with an increased risk for cancer.

TABLE 1: RHEUMATIC DISEASES WITH INCREASED RISK FOR MALIGNANCIES	
Sjögren's syndrome	Lymphoproliferative diseases
Rheumatoid arthritis	Lymphoproliferative diseases (cancer?)
Systemic lupus erythematosus	Lymphoproliferative diseases
Systemic sclerosis	Lung, skin and esophageal cancer
Dermatomyositis	Ovarian, lung and gastric cancer

Caution must be exercised when underwriting cases where the absolute cancer risk might be negligible but the overall mortality risk is significant. This situation should raise certain ethical considerations in terms of the relative need for cancer coverage. CR product applicants with impairments that might have precluded them from obtaining life cover will need to be individually considered, and with great care. For example, this product might seem to meet the need of an applicant with multiple cardiovascular risk factors or adverse associated health outcomes that would otherwise attract very sub-standard terms. Such applicants might need to be referred for additional consideration. Of course, the risk of anti-selection also exists and must be investigated and mitigated wherever possible.

Claim considerations

Cancer Reimbursement products need to state explicitly which cancers as well as pre-cancerous conditions are and are not covered. The products would do well to maintain consumer friendliness, but need to be strictly aligned medically as well. This is particularly important given the rapid ongoing advances in medicine and accompanying new understanding and even re-classification of certain neoplastic entities. The advances are enabling better categorization, prognostication, and treatment of cancer, but clarity is needed in order to accommodate improvements in both diagnosis and outcomes.

Ongoing feedback from claims assessors is also critical, in order to monitor cancer trends in the insured population. Any anti-selection concerns need to be raised.

Healthcare is local, but contentious contractual challenges could arise with the interpretation of some exclusions. For example, the concept of “medically necessary” and which therapies might be deemed “experimental treatments.” The latter category is usually defined as those treatments which have not yet been established as being effective for a particular medical condition. (These are usually in Phase III or earlier clinical trials.) Drug treatments that are later in the trial process have usually undergone appropriate clinical scrutiny, including publication in peer-reviewed medical journals as well as approval by relevant regional drug licensing authorities. While there are contractual

definitions in this respect, both medical advancement and the hope that often accompanies newer cancer treatment modalities will need to be carefully managed and monitored at the claim adjudication stage.

Product enhancements and pricing future cancer care

What does the future of cancer care look like? Thoughts along these lines often present more questions than answers. Will there be more home-based care? Will medical advances, including those in the genetic, epigenetic and proteomic space, offset or add complexity to the construction, definitions and associated pricing structures of cancer products? What trends are we likely to expect in terms of cancer screening in the future, and what will their potential impact be?

A recent viewpoint in medical literature challenges current cancer screening trends, arguing that overall mortality should be the benchmark for advocating screening, not disease-specific mortality (as is currently the case), in order to avoid overdiagnosis and overtreatment.¹⁰ While this debate might be academic right now, life insurers need to observe this sentiment as well as the drive towards more comprehensive and less invasive early cancer detection testing. Another ever-important consideration for the insurance industry is the upward trend of a more informed, engaged, and empowered consumer.

Monitoring of the rapidly expanding pipeline of new targeted and customized cancer therapies will need to be vigilant. The first anti-cancer immunotherapy appeared in the mid-1990s and by May 2015, 171 such therapies were in active development.¹¹ These new therapies offer tremendous promise, but the research and development of these innovative agents comes at substantial cost.

Another consideration of this expansion in drug therapy options is the earlier incorporation of newer therapies into first-line or initial cancer treatment protocols, as opposed to being used as second-line or as salvage therapy. Cancer vaccines (both preventative and therapeutic), oncolytic virus therapy and gene therapy need to be added to the current list of innovative cancer treatment advances. Additionally, the use of precision genome editing as a therapy, using CRISPRs (Clustered Regularly Interspaced Short Palindromic Repeats) genome editing technology, will certainly be one to watch closely.



It is imperative to explore constantly ways in which both existing preventive strategies as well as new advances in diagnosis and treatment can be harnessed to aid future product development or enhancements.

Cancer: are we still at war?

The analogy of war is often used in the context of fighting against cancer. Public awareness of this enemy continues to increase, as well as knowledge of the lifestyle changes necessary to ward it off. There are also now new recruits in this war, such as enhanced imaging capabilities, targeted prevention and treatment strategies and novel tactical battle plans aided by advances in analytic capabilities. No doubt cancer still is to be feared as many of its aspects continue to defy clear, rational explanation, but there is also a more optimistic outcome trajectory than ever before.

Through new product ideas, vigilant risk assessment with research-based guidelines, careful claims adjudication and ongoing research into the likely future trends of incidence, survival and the impact of comprehensive cancer care, the insurance industry can continue to play a crucial and ongoing supportive role in the battle against cancer, and serve the fight well. 

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LONGER LIFE FOUNDATION: IN THE NEWS

One area of investigation which has received substantial support throughout the Longer Life Foundation's 17-year history is that of obesity and its relationship to health and longevity.

Very recently, Dr. Samuel Klein, the William H. Danforth Professor of Medicine and Nutritional Science at Washington University School of Medicine in St. Louis as well as a member of the Longer Life Foundation's Board of Advisors and a past LLF grant winner, published the results of research into the effects of varying levels of weight loss on human health.

Dr. Klein led what is believed to have been the first investigation that separated weight loss outcomes for those who lost 5% of their weight from those who lost 10% or more. (A loss of 5% to 10% of body weight is a commonly recommended therapeutic target for obese individuals.)

The research, which appeared in the article "Effects of Moderate and Subsequent Progressive Weight Loss on Metabolic Function and Adipose Tissue Biology in Humans with Obesity," published February 22, 2016 in the journal *Cell Metabolism*, determined that 5% weight loss "improved adipose tissue, liver and muscle insulin sensitivity, and β cell function, without a concomitant change in systemic or subcutaneous adipose tissue markers of inflammation". Additional weight loss, according to the research summary, "further improved β cell function and insulin sensitivity in muscle and caused stepwise changes in adipose tissue mass, intrahepatic triglyceride content and adipose tissue expression of genes involved in cholesterol flux, lipid synthesis, extracellular matrix remodeling and oxidative stress." These results, the summary continued, "demonstrate that moderate 5% weight loss improves metabolic function in multiple organs simultaneously, and progressive weight loss causes dose-dependent changes in key adipose tissue biological pathways."

An article about Dr. Klein's research in *The Source*, the magazine of Washington University in St. Louis, quoted him as saying: "You get the biggest bang for your buck with 5% weight loss." Another interesting finding of the investigation was that inflammatory markers, which are elevated in the obese, did not change much when study subjects lost a moderate amount of weight, meaning that metabolic function could improve while markers of inflammation remain unchanged. This element of the research will require further study. Dr. Klein would like to expand the investigation to incorporate individuals with Type 2 diabetes.



The Longer Life Foundation is a not-for-profit partnership between RGA and the Washington University School of Medicine, an internationally recognized academic medical institution located in St. Louis, Missouri (U.S.). Founded in 1998, LLF supports and funds independent research into longevity and enhancing quality of life and wellness. Please visit our website, www.longerlife.org, for more information.

For more information about this investigation, please go to <https://source.wustl.edu/2016/02/in-obese-patients-5-percent-weight-loss-has-significant-health-benefits/> for the article in The Source, and to <http://www.ncbi.nlm.nih.gov/pubmed/26916363> to access the abstract of the article in *Cell Metabolism*. 

For more information about LLF-funded obesity research, please visit our website, www.longerlife.org, to read about these recent investigations:

Jun Yoshino, M.D., Ph.D.

Identification of Novel Blood Biomarkers and Mediators of Obesity-Induced Insulin Resistance (2015)

Xiong Su, Ph.D.

Monomethyl Branched Chain Fatty Acids (mmBCFAs) as Potential Biomarkers for Risk of Obesity-Associated Metabolic Disease (2012)

Elisa Fabbrini, M.D., Ph.D.

Assessment of Potential Novel Immune Biomarkers to Identify Obese Persons at Increased Risk for Cardiometabolic Disease (2010-2011)

Mortality Trends Among People with Type 1 and Type 2 Diabetes in Australia: 1997-2010

Harding JL, Shaw JE, Peeters A et al. Diabetes Care. 2015 Apr; 38(4):733-4.

<http://www.ncbi.nlm.nih.gov/pubmed/25805865>

All-cause mortality trends in a cohort of diabetics were analyzed from 1997 to 2010. For type 1 diabetes, SMRs decreased in males from 4.2 to 3.08 and decreased in females from 3.92 to 3.46. For type 2 diabetes, SMRs decreased in males from 1.4 to 1.21 and decreased in females from 1.56 to 1.22. Cardiovascular disease (CVD) rates decreased in type 2 diabetes from 44.5% to 29% in males and from 45.5% to 31.6% in females. Most of the excess mortality in diabetics was attributable to CVD. These results are consistent with other studies and reflect an increasing attention to CVD risk factor modification in diabetic populations.

On-Demand Preexposure Prophylaxis (PreP) in Men at High Risk for HIV-1 Infection

Molina JM, Capitant C, Spire B et al. N Engl J Med. 2015 Dec 3;373(23):2237-46.

<http://www.ncbi.nlm.nih.gov/pubmed/?term=n+engl+j+med+2015%3B373%3A2237-46>

A double-blind, randomized trial of combination tenofovir and emtricitabine vs. placebo taken prior to sexual relations in men who have sex with men to determine its effectiveness in HIV prevention. After 9.3 months, the relative reduction of new infections in the treatment group was 86%. The two individuals in the treatment group who acquired HIV during the study were later determined to have been non-adherent to the medication. Both continuous and intermittent preexposure prophylaxis (PreP) is now being seen among insurance applicants. While there may be inherent risk related to other exposures, this study indicates that the use of PreP can effectively reduce the risk of acquiring HIV.

Second Cancer Risk Up to 40 Years After Treatment for Hodgkin's Lymphoma

Schaapveld M, Aleman BM, van Eggermond AM et al. N Engl J Med. 2015 Dec

24;373(26):2499-511.

<http://www.ncbi.nlm.nih.gov/pubmed/26699166>

A large Dutch study of individuals treated for Hodgkin's lymphoma between 1965 and 2000, in which incidence of secondary tumors was analyzed by treatment era. At a median follow up of 19.1 years, the standardized incidence ratio of a second cancer was 4.6 in comparison with the general population. The risk remained increased even after 35 years. The overall incidence of second solid cancers did not differ according to treatment era (1965-1976, 1977-1988, 1989-2000), despite clinical reductions in the size of radiation fields and chemotherapy dosages. Survivors of Hodgkin's lymphoma are commonly seen in insurance underwriting and need to be assessed carefully for lifelong additional morbidity and mortality risk.

A Randomized Trial of Intensive Versus Standard Blood-Pressure Control

The SPRINT Research Group et al. N Engl J Med. 2015 Nov 26;373(22):2103-16.

<http://www.ncbi.nlm.nih.gov/pubmed/26551272>

Randomized control trial of more than 9,000 individuals with increased cardiovascular risk and without diabetes treated to a target systolic blood pressure of less than 120 mm Hg (intensive) vs. less than 140 mm Hg (standard). The trial was stopped after a median follow-up of 3.26

years due to significantly lower rate of primary composite outcome in the intensive-treatment group. Importantly, all-cause mortality was significantly lower in the intensive-treatment group (HR 0.73; 95% CI, 0.60-0.90; $P=0.003$). These results could impact clinical treatment guidelines and have favorable implications for mortality and living benefits products.

Atrial Fibrillation as Risk Factor for Cardiovascular Disease and Death in Women Compared With Men: Systematic Review and Meta-Analysis of Cohort Studies

Emdin CA, Wong CX, Hsiao AJ et al. BMJ. 2016 Jan 19;352:h7013.

<http://dx.doi.org/10.1136/bmj.h7013>

Previous studies report conflicting data on the effect of atrial fibrillation (AF) on the risk of death and cardiovascular disease in women. This meta-analysis of 30 studies with over four million participants concluded that women with AF experience increased ratio of relative risks for all-cause mortality (1.12), stroke (1.99), cardiovascular mortality (1.93), cardiovascular events (1.55), and heart failure (1.16), as compared with men. The authors stated it might be appropriate for clinicians to consider more aggressive treatment of risk factors in women with AF as they seem to be at higher proportional risk of death and cardiovascular disease. Insurers might consider these results when developing or refining underwriting guidelines or mortality and living benefits products. 

RECENT PRESENTATIONS

Anticipating Infectious Disease Impacts in an Increasingly Globalized World



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 of BlueDot

Presenter: Dr. J. Carl Holowaty, DBIM

Senior Vice President, Chief Medical Director (Retired)
RGA Reinsurance Company

New infectious diseases are emerging faster today than ever before, just as many known diseases are reemerging. 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, and what tools are available to help the insurance industry better plan for and respond to tomorrow's inevitable epidemics.

Electronic Health Records Data: Are You Ready?

Presenter: Sue Wehrman



Vice President, Electronic Health Records Initiatives
RGA Reinsurance Company

Moderated by: Kathryn Cox

Senior Vice President, Business Development, U.S. Markets
RGA Reinsurance Company

We discuss RGA's 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. 



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