ReFlections

RGA's Global Medical Newsletter

Peter Barrett
Senior Vice President, Head of GST Underwriting, Claims and Medical Support
pbarrett@rgare.com

Daniel D. Zimmerman, M.D.
Senior Vice President, Chief Medical Director, GST
dzimmerman@rgare.com

FROM THE EDITORS

The year is moving along quickly and we are already well into the second quarter. We're hoping this newest edition of *ReFlections*, RGA's global medical newsletter, finds all of you doing well.

We're pleased to introduce a new author: Akhilesh Pandey, Senior Underwriter – Research and Manual Development, who is based in RGA's Mumbai office. He has written a comprehensive and detailed review on the natural history, pathophysiology, and genetics of hepatitis B.

Dr. Paul Davis, MB.BS (Hons), FRACP, Chief Medical Officer, RGA Australia and one of RGA's most experienced medical directors, presents an erudite perspective on the evolving clinical definition of myocardial infarction over time and the implications for insurers providing living benefit coverage for this condition.

The growing importance of understanding genetics in cancer is highlighted in an article on the subject by Dr. John J. Lefebre, BSc (Hons), MD, FRCPC, Medical Consultant, RGA International. Dr. Lefebre, based in Toronto, is another highly respected RGA medical director who in his article describes various types of mutations

associated with multiple cancer types and provides a quick review of basic genetics.

During 2018, the 20th anniversary year of the **Longer Life Foundation (LLF)**, we are pleased to bring you another in the series of interviews with former grant recipients from Washington University School of Medicine in St. Louis. In this edition, we profile Stephen T. Oh, M.D., Ph.D. Dr. Oh specializes in research on myeloproliferative neoplasms, and he kindly sat down with us to provide insight into these disorders, which are not uncommonly encountered during insurance underwriting and claims.

We are also pleased to announce that two new webcasts – one by Dr. Georgiana Pascutiu, Medical Director, Global Support Team, and one from Eric Westhus, Ph.D., Data Scientist, Global Research and Data Analytics – are now directly accessible to you for viewing at your convenience. Please see page 27 for details.

As always, if you have any comments or questions regarding *ReFlections* feel free to contact us. Meanwhile, we hope you enjoy this edition!

Thank you,

Peter and Dan

THE EVOLUTION OF THE DEFINITION OF MYOCARDIAL INFARCTION: IMPLICATIONS FOR INSURERS

Abstract

Myocardial infarction is a major trigger for living benefits claims and the survivability of infarction is such that a history is increasingly common in applicants.

Medical definitions of infarction have changed markedly over the last century, from what was initially a postmortem diagnosis of a condition that was considered inevitably fatal to a condition defined by circulating biological markers and where survival is the expectation.

Population demographics and the evolution of concepts as to how infarction should be defined and classified in various clinical settings have resulted in changes in incidence that have driven a need to continually monitor and revise pricing, underwriting, and claims models.

The basic tenet that a diagnosis of infarction is made when death of myocardial cells occurs as a result of inadequate blood supply has not changed, but assays of biological markers that reflect cell death have become surrogates for histopathological proofs.

Central to the triage of patients with coronary syndromes is a capacity to reliably distinguish unstable angina from infarction. The improved analytical discriminatory power of assays of circulating biological markers over time has resulted in a diagnosis of infarction being assigned to some who would previously have been diagnosed otherwise. The capacity to detect smaller and smaller infarcts than was previously possible has changed the relative proportions of those labeled infarction and unstable angina.

This article traces the history of the definition of infarction, documents the current standardized position, and looks at the potentials for change as technologies advance and medical opinion evolves.

Background and History

Until the end of the 19th century infarction was considered a fatal entity only diagnosable post-mortem. The diagnosis required evidence of thrombotic occlusion of a coronary artery in the context of sudden death, or death within a short period of time following the onset of chest pain.

That prevailing concept was re-examined by Dr. James Herrick in 1912 in the first classification of the clinical features of coronary obstruction. Herrick disputed the long-held view that infarction was inevitably fatal in providing clinical evidence that it was often survived without necessarily being associated with major morbidity.[1, 2] Acceptance of that view drove a need to define reliable parameters for diagnosing infarction in those with chest pain who had not succumbed to sudden death and who presented to medical attention.

In Herrick's time the diagnosis was based purely on clinical grounds with ischemic chest pain being the usual criterion. ECG accompaniments

ABOUT THE AUTHOR

Paul Davis MB.BS (Hons), FRACP
Chief Medical Officer, RGA Australia
pdavis@rgare.com

Dr. Paul Davis brings several decades of experience as a clinical cardiologist and internal medicine consultant to his role as Chief Medical Officer, RGA, Australia. Since joining RGA in 2002, Dr. Davis has been influential in underwriting and claims management, education, medical research, and product development. Dr. Davis received his bachelor's degrees in Medicine and Surgery with Honours from Sydney University. He is a Fellow of the Royal Australasian College of Physicians (FRACP) and a member of several medical associations, including the Cardiac Society of Australia and New Zealand, the American Academy of Insurance Medicine, and the Australian Life Underwriters and Claims Association.

became supporting criteria following their description by Herrick in 1919.[15] In that era, mortality rates were of the order of 30% and treatment options were limited to weeks of bed rest. There was no material pharmacological capacity to influence prognosis and the resumption of a normal lifestyle with return to work was discouraged.

By the 1950s and 1960s myocardial infarction had become the most common cause of death in Europe and North America. The health and socioeconomic burden resulted in the establishment of dedicated coronary care units and work on pharmacological and interventional strategies that had the capacity to reduce mortality and limit infarct size. That focus saw the creation of protocols that enabled earlier discharge and resulted in reductions in mortality from 30% to 15% over the next few decades.[3]

Strategies which improved outcomes mandated reliable parameters for diagnosis. It was recognized that standardized and universally accepted definitions would provide benchmarks by which emerging treatments could be compared and judged with statistical certainty. Recognizing the need for such protocols in the clinical and research setting, the World Health Organization (WHO) published the first guideline for the definition of myocardial infarction in 1959. That definition was based on ischemic pain and ECG changes.

In 1979, WHO published a revision that allowed the detection of elevated cardiac enzymes in the circulation to be included as a third criterion although elevated enzymes were not mandated for a diagnosis. Given the limited sensitivity of the ECG in the more common non-ST elevation ECG syndromes, this revision resulted in an increase in incidence. A diagnosis was now possible in those with ischemic pain who did not satisfy ECG requirements.

Despite the benefits of including enzymes as markers of cell death, definitions remained very imperfect by today's standards. Enzymes lacked good sensitivity for damage and there was a lack of specificity because these enzymes were not absolutely cardiac-restricted. Coupled with the fact that there was no analytic standardization across various enzyme assays, levels were required to rise to twice upper reference limits (URL) to reduce false positives.

> In the 1970s and 1980s, two proteins associated with the thin actin filament (contractile proteins troponin I and troponin T) were identified and were shown to be cardiac-specific.

During the 1970s and 1980s there was research interest in the structure of actin and myosin, the two filaments in heart muscle cells responsible for cell contraction. Two proteins associated with the thin actin filament (contractile proteins troponin I and troponin T) were identified and were shown to be cardiac-specific. These proteins were undetectable in the blood of normal populations at the time and there was interest in determining if they were released into the circulation in detectable amounts following cell damage.

A protein associated with the thick myosin filament (myosin binding protein c) was also identified and also shown to be cardiac-specific. Research interest in that protein became directed towards the identification of the mutations in that protein that had become implicated in the development of cardiomyopathy. As such that protein was not pursued as a potential marker for ischemic damage at that time (Fig 1).[4]

Figure 1: Components of Human Cardiac Muscle
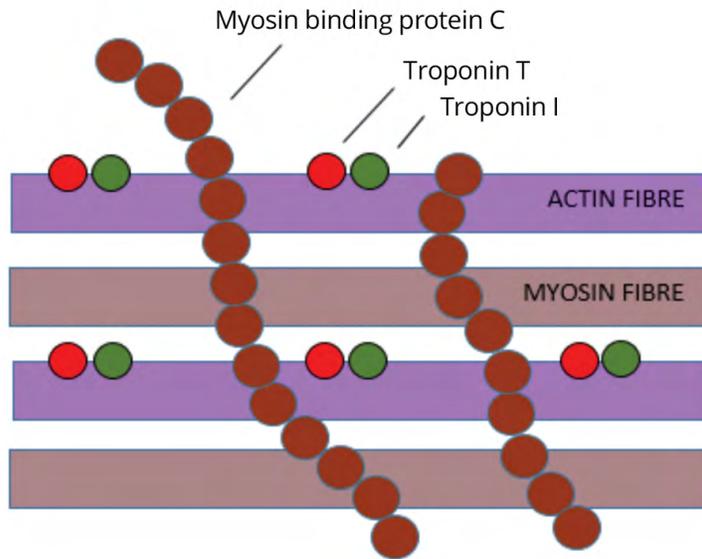
Troponin I and troponin T were able to be detected in those infarcts defined using enzyme criteria with very reliable accuracy and with some improvements in sensitivity. The high level of sensitivity coupled with the specificity benefits provided momentum for further research.

By the mid-1990s a subset of acute coronary syndromes not assigned a diagnosis of infarction on enzyme criteria but which had detectable troponins was defined. That subset was demonstrably at high risk on the basis of 30-day mortality. (Fig 2).[5]

Figure 2: 30-Day Mortality in Acute Coronary Syndromes[5]

ENZYMES	TROPONIN	MORTALITY
CKMB < 7ng/l	not detected	4.1%
CKMB < 7ng/l	detected	12.3%

Universal Definition of Myocardial Infarction

Strong clinical imperatives promoted discussions that troponins be considered the preferable markers for risk given that enzyme-based determinates of cell death did not provide acceptable prognostic triage. It was estimated that a transition from enzymes to troponins as the benchmark marker might increase the prevalence of infarction in coronary syndromes from 30% to as high as 80%.

The transition from enzymes to troponins as preferred markers was ratified in a Universal Definition of Myocardial Infarction that was published in 2000. That guideline also contained a paradigm shift in thinking with a recommendation that biomarker evidence become fundamental and central to the diagnosis. A cut point for an elevated troponin level was assigned arbitrarily at the 99th percentile for a reference population. That cut point was approximately three standard deviations (SDs) from the mean and was chosen to minimize false positives.

Guidelines recommended not only that one troponin level exceed the 99th percentile but that a typical release pattern be confirmed by the detection of rising and/or falling levels. Evidence of appropriate troponin dynamics was mandated to help confirm the clinical

context and to avoid false positives in those with chronically elevated biomarkers and non-ischemic conditions. Implementation of those guidelines provided better detection, more prompt triage to treatment and a further fall in mortality to around 3%.

Mortality rates were also influenced by the improving analytic sensitivity of markers which increased the detection of small and less immediately life threatening infarcts and with the inclusion of these cases in outcome statistics.

The Universal Definition was modified in 2007 and again in a third iteration in 2012.[6, 7] Based on etiology, five categories of infarction were described and which allowed a diagnosis outside of the traditional plaque rupture with thrombosis setting (Fig 3).

Figure 3: Types of Myocardial Infarction

TYPE	DESCRIPTOR	MECHANISM
1	Spontaneous MI	Plaque with rupture, erosion, or fissuring, causing thrombosis.
2	Secondary MI	Supply demand perfusion imbalance in coronary spasm, arrhythmias, hypotension, hypoxia, anemia, etc.
3	MI causing death without full biomarker evidence	Death in clinical context before samples could be obtained or before a rise in initial marker levels could be confirmed.
4a	MI related to coronary intervention	MI associated with angioplasty and stenting. Tropinins required to rise x5 99th percentile.
4b	MI related to stent thrombosis	Infarction with proof of acute stent thrombosis in a culprit vessel.
4c	MI related to stent restenosis	Infarction with proof of restenosis in a stent in a culprit vessel.
5	MI related to bypass grafting	MI associated with CABG. Tropinins required to rise x10 99th percentile.

Sources: References 6, 7, 8, and 9.

Since troponins were endorsed as preferred biomarkers there have been five generations of assays, and each analytic refinement has provided improvements in sensitivity for diagnosis and a capacity to detect troponins in normal populations. The emerging high sensitivity assays are required to be capable of detecting troponins in at least 50% of normal people with very high degrees of precision at the 99th percentile.

While early assay results were highly specific they were relatively insensitive. Much emphasis needs to be placed on the fact that increases in sensitivity occur at the expense of specificity. While troponins are markers of cell death they do not indicate the cause of damage and the specificity concerns for high sensitivity assays loom large.

With a diagnosis of infarction only possible when biomarkers rise as a consequence of ischemia it is imperative that clinical histories be clarified and that evidence supporting the requirement that cell death resulted from lack of blood supply be provided.

In the majority of cases where elevated levels of troponins are detected in emergency departments the discharge diagnosis is not infarction but another condition that has the capacity to damage myocytes. The causes of non-ischemic elevations of troponins can be found elsewhere.[8]

The Third Universal Definition 2012 included the following implications and recommendations:[9]

- Emphasis was placed on biomarkers as the cornerstone for diagnosis with appropriate biomarker dynamics being satisfied on serial sampling.

- The impact of troponins increasing incidence of myocardial infarction was confirmed as being between 41% (Minnesota, U.S.) and 83% (Finland).

- Advocacy for the 99th percentile for the URL was confirmed with that decision limit having the capacity to maximize detection while minimizing false positives.

- A concept of injury was introduced to emphasize that cell death was not synonymous with infarction. It was stressed that small amounts of cell necrosis may be associated with conditions including heart failure, renal failure, myocarditis, sepsis and pulmonary embolism and as a result of otherwise uneventful percutaneous procedures or coronary surgical procedures. There was a recommendation that these should be labeled non-ischemic injury and not infarction.

- The previously defined five categories of infarction were ratified. There was an endorsement that infarction be diagnosed regardless of the mechanism by which ischemia was promoted and that that infarction may occur in people with normal coronary arteries. It was recognized that given the complexities of some situations it was not always easy to discriminate between non-ischemic injury and infarction.

Conclusions and Implications for Insurers

Definitions of myocardial infarction are in flux and open to change with some questions implicit in guidelines being unanswered or open to interpretation. The following points must all be considered when developing insurance products which provide myocardial infarction benefits:

> **The Universal Definition of Myocardial Infarction, published in 2000, recommended that biomarker evidence become fundamental and central to the diagnosis.**

- The degree to which troponins might have a sensitivity deficit for defining infarction remains uncertain and other potential markers continue to be tested. The most pressing indication for continued improvements in assay sensitivities and the search for new biological signals is to enable the exclusion of infarction earlier than is currently possible with serial troponin testing. Cardiac myosin binding protein has now been tested in that context. Its abundance in the cell results in its very early appearance in the circulation following necrosis and as such it holds promise in that regard. There is no evidence that it is more sensitive for diagnosis than troponin based protocols.[14]

- Despite mandating dynamic changes in markers for a diagnosis, definitions have not quantified what constitutes a significant change for that purpose. Clinical protocols require a relative change from baseline at presentation but there is a lack of consistency in the magnitude of change required for confirmation. Based on analytical variability a change of >20% has been considered adequate but some protocols mandate higher degrees of relative change.[10]

- Absolute changes in troponin levels may prove to have better diagnostic utility than relative changes. Diagnostic and triage approaches incorporating absolute change now appear in the literature and suggested magnitudes of change have been published.

- Absolute levels, whether above or below accepted 99th percentile thresholds, carry prognostic implications. With risk being continuous for all levels of troponin it can be argued that the 99th percentile lacks biological plausibility. A clinical risk focus based on absolute levels rather than arbitrary dichotomous labeling has advantages. These notions leave open the potential for constructs of additional pathways incorporating lower biomarker thresholds for risk stratification and diagnosis in acute coronary syndromes where troponins do not reach the 99th percentile.

- There is no standardization of what constitutes a normal population for the purposes of defining biomarker reference limits. Constituents of currently defined normal populations have diverse demographic characteristics and include both high and low cardiovascular risk individuals. Troponin levels are higher in males than in females across a range of assays. Gender-specific cutoffs may be endorsed and would increase incidence rates in women while providing a prognostic benefit to those women who might be currently underdiagnosed.[11]

- The focus on biomarkers is centered on the clinical need to rule in or rule out infarction early after presentation and not on a need to document infarct size. In clinical practice troponin levels are not commonly repeated after triage with infarct size tracking most accurately with levels taken at day three or four. Recommendations exist that suggest follow up levels might be assayed for that purpose.[10]

> **Definitions of myocardial infarction are in flux and open to change with some questions implicit in guidelines being unanswered or open to interpretation.**

Author's Note: Readers are referred to "High Sensitivity Troponin Assays: Answers to Frequently Asked Questions" for a more detailed exploration of some of these points and other frequently raised matters.[13]

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UNDERSTANDING THE GENETICS OF CANCER

Abstract

Today's cancer pathology reports commonly refer to "driver mutations" that are either present in or absent from a tumor's genome. Because of this, it has become vital for insurance company medical directors, underwriters, and claims professionals to acquire at least a basic understanding of genetics and mutations as well as targeted therapies and their mechanisms. With the price of whole genome, whole exome, and other genomic sequencing continuing to drop rapidly, more complicated pathology reports that contain significant amounts of genetic information will need to be correctly interpreted.

With advanced cancers, the use of targeted therapies is not likely to impact how life or critical illness insurance policies are underwritten in the short term, but they could significantly impact the approach to claims adjudication and cost of healthcare-related products.

This article will look at how genetics is contributing to cancer development, treatment, and prognosis. It will provide a brief overview of genetics, including commonly used terms, discuss some of the more common genetic mutations, and give examples of the mutations that occur in cancer.

Introduction

The following is a terminal illness (TI) claim which will pay if death is expected within the next 12 months:

A 51-year-old male nonsmoker started afatinib (a tyrosine kinase inhibitor) four months ago for an adenocarcinoma subtype of non-small-cell lung cancer (NSCLC).

His pathology reports documented:

- Stage 4B, T3 N3 M1b disease based on PET–positive right hilum, mediastinal, and neck nodes and distant metastases in liver and bones.

- The tumor is ALK-IHC negative, ROS1-IHC negative, PD-L1 10% positive, EGFR ctDNA exon 19 deletion positive.

- First-line immunotherapy is not indicated as the level of PD-L1 is 10%. (Levels 50% or greater would support use.)

- The tumor is positive for EGFR mutation with an exon 19 deletion – hence prescribed afatinib.

This report utilizes molecular profiling of the cancer to a substantial degree. The several genetic mutations identified in the tumor may be therapeutically and prognostically relevant, and may potentially impact the assessment of the Insured's life expectancy and eligibility for benefits.

ABOUT THE AUTHOR

Dr. John J. Lefebre BSc (Hons) MD FRCPC
Medical Consultant – GST
RGA International, Toronto, Canada
jlefebre@rgare.com

Dr. Lefebre, a member of RGA's Global Medical Support team, is responsible for case consultation, product development, internal and external education, client support, and representing RGA to key industry professional organizations. A graduate of the University of Alberta, where he earned his Medical Doctor (M.D.) degree, and of the University of Toronto, where he completed his post-graduate residency with a specialty in Emergency Medicine, he has extensive clinical experience in teaching hospitals in Halifax and in Toronto. Dr. Lefebre is a member of the Canadian Life Insurance Medical Officers Association.

Genetics Review

To grasp the impact of genetics on cancer development, treatment, and prognosis, it is important for medical directors, underwriters, and claims managers to review the essentials of genetics and the cancer genome.

- The basic unit of genetic information is the double-stranded molecule deoxyribonucleic acid (DNA). DNA's building blocks are called nucleotides. Each nucleotide consists of a phosphate, a sugar, and one of four base molecules: adenine (A), cytosine (C), guanine (G), and thymine (T).

- DNA's characteristic double helix is formed by pairs of these bases. Cytosine always pairs with guanine (C:G) and adenine with thymine (A:T). Human DNA contains about three billion base pairs, which represent the entire genome and codes for 20,000 to 25,000 genes.

- The nucleotides are grouped together in three-letter code words called codons. Each codon encodes for one amino acid. Amino acids are the building blocks of proteins. This encoding occurs via messenger ribonucleic acid (mRNA) which is "transcribed" from the DNA template and the mRNA is then "translated" into an amino acid.

> **Genetic alterations can lead to the formation of driver mutations, which can serve as molecular targets of therapies.**

- Only a small portion, approximately 3% of the human genome, is translated into proteins. This means the majority of the genome is selectively repressed. The portion of the genome that codes information for protein synthesis is called the exome, meaning all the protein coding genes are found in the exome. The actual portion of exome that contains the information used for protein synthesis is call the exon.

- Introns make up the rest of the exome and are found between the exons, but the introns do not contain any protein coding information.[1]

Alterations and mutations in DNA, mRNA and/or the end product protein can make each cancer slightly different.

This article will focus only on cancers caused by DNA-based alterations and mutations.

Driver Mutations

Specific genetic mutations are thought to drive the transformation of a cell from normal growth to invasive cancer. These mutations, which can either be inherited (germline) or acquired (somatic), are known as "driver mutations."

Driver mutations within a gene lead to the formation of one or more mutant signaling proteins, which confers a selective growth advantage to the mutated cell. The advantage induces and sustains tumorigenesis (tumor development), thus promoting cancer development.[2]

The identification and presence of driver mutations occurring in multiple oncogenes (genes that can transform normal cells into tumor cells) allows the same histopathological type of cancer to be further subdivided at the molecular level, thus forming the basis of tumor heterogeneity.

Genes in cancerous cells generally contain multiple mutations. Studies have revealed approximately 140 genes that when altered by intragenic mutations can promote or drive tumorigenesis. A typical tumor will contain two to eight driver gene mutations. The rest of the mutations are alterations or "passengers" that may confer no selective growth advantage.[3]

In addition to the activating mutations of the proto-oncogenes that result in the formation of an oncogene, genetic alterations that lead to the inactivation of tumor suppressor genes have also been found. Testing for alterations and mutations in tumor suppressor genes is still not done widely due to its complexity, but there are tests that can look for altered protein expression due to inactivation of the suppressor genes.

Targeted Cancer Therapies

Targeted cancer therapies are designed to interfere with specific molecular targets involved with the growth of cancers. These therapies are meant to have no effect on normal cells and to be cytostatic (i.e., aimed at blocking tumor cell proliferation) rather than cytotoxic (i.e., aimed at killing tumor cells).

Several different targeted agents are used to treat cancers, including hormone therapies, signal transduction inhibitors, gene expression modulators, apoptosis (cell death) inducers, angiogenesis inhibitors, immunotherapies, and toxin delivery molecules.

The targeted therapies can be divided into these two classes:[4]

- Monoclonal antibody therapies, which target specific antigens on cell surfaces. The names of these agents contain the suffix "mab" (for monoclonal antibody).

- Small molecule therapies, which can penetrate the cell membrane and interfere with the activity of a certain protein inside the cell. The names of these agents ends with "-ib," indicating protein inhibitory properties.

Genetic Alterations in Cancer

Many genetic alterations occur in cancers. These alterations can lead to the formation of driver mutations, which can serve as molecular targets of therapies. Some common types of mutations are discussed below.

- **Point Mutations**
  In point mutations, also known as single nucleotide variations (SNVs), a base substitution occurs, which may or may not result in an alteration of an encoded amino acid. Testing for an SNV in a gene is one of the simpler tests to perform.

  An example of an SNV is the BRAF c.1799T>A (V600E) mutation. This is a specific mutation in the protein kinase BRAF, which is a member of the RAF family of kinases (ARAF, BRAF and CRAF [RAF1]). It is downstream of RAS in the RAS/RAF/MEK/ERK pathway and its mutation leads to uncontrolled cell proliferation. This mutation accounts for 80% to 90% of all BRAF mutations at the V600 position and occurs in 40% of all malignant melanomas.[5]

  In the V600E mutation, thymine substitutes for adenine at position c.1799, which results in the substitution of the amino acid glutamic acid for valine at position 600 in BRAF and leads to increased kinase activity.[6]

  In individuals with malignant melanoma, the BRAF V600E mutation confers increased sensitivity to targeted therapy with BRAF inhibitors. Trials of the BRAF kinase inhibitor vemurafenib have shown response rates of more than 50% in patients with

the BRAF V600E mutation who have metastatic melanoma. The problem is that resistance to treatment and tumor progression occurs in nearly all patients in the first year of therapy.[7] Studies are showing that combination therapy may be more durable than single-agent treatment.[8]

- **Gene Insertions/Deletions**

In this type of alteration, nucleotides are inserted in or deleted in the coding (exons) of the genome. These abnormalities are usually detected through whole exome sequencing, which sequences the exon rather than only a select few genes. This differs from whole genome sequencing, in which all of the nucleotides in an individual's DNA are sequenced and can determine variations in any part of the genome.

Some cancers may show both an insertion and deletion mutation. For example, NSCLC can have an EGFR (epidermal growth factor receptor) exon 19 deletion and a human epidermal growth factor receptor (HER2) exon 20 insertion. EFGR is a receptor tyrosine kinase (RTK). The exon 19 deletion occurs with a frequency of 48% in EGFR-mutated lung cancers.[9]

Driver mutation screening of NSCLC has shown that approximately 10% of U.S. patients and 35% of East Asian patients have tumor-associated mutation of the EGFR. EGFR activation drives the pathways involved in cell survival and proliferation.

In advanced NSCLC, the presence of an EGFR mutation confers a more favorable prognosis and strongly predicts for sensitivity to EGFR tyrosine kinase inhibitors (TKIs) such as erlotinib, gefitinib, afatinib, and osimertinib.[10]

The insertion mutation seen with NSCLC is related to the HER2 gene, which also belongs to the family of receptor tyrosine kinases (RTKs). In this instance, a G776(YVMA) insertion in exon 20 results in increased HER2 kinase activity, leading to increased cell survival, invasiveness, and tumorigenicity. The role of this mutation in regards to targeted therapy is being investigated.[11]

> **The cost of targeted therapy is significant and cure rates are still lower than expected.**

The presence of targetable driver mutations may result in first-line usage of targeted therapies vs. standard chemotherapy in the treatment of NSCLC. In a 2016 study conducted in France, molecular profiling of known oncogenic drivers was performed for patients with advanced NSCLC. Genetic mutations were found in about 50% of the analyses: EGFR mutations were reported in 11%, HER2 mutations in 1%, KRAS mutations in 29%, and BRAF mutations in 2%. The presence of a genetic mutation affected first-line therapy choice for 51% of patients and resulted in improved first-line progression-free survival (10 months versus 7.1 months) and overall survival (16.5 months versus 11.8 months).[12]

- **Gene Amplification**

This mutation occurs when there is an increase in the number of copies of a gene. If an oncogene is involved in the amplified region of the gene, the resulting overexpression of the oncogene can lead to tumorigenesis.

An example of an amplification mutation is HER2 overexpression in breast cancer. Amplification of the HER2-containing region of chromosome 17 (i.e., q11-12) leads
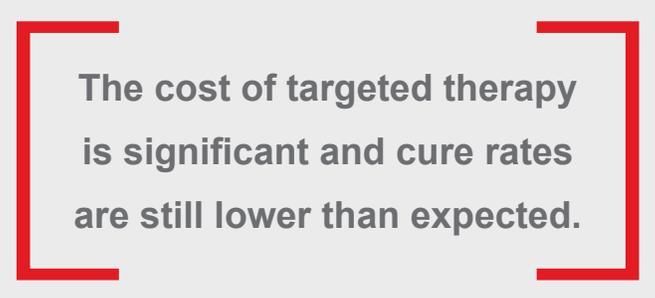
to overexpression of the HER2 oncogene, which occurs in 18% to 20% of all breast cancers. Other mechanisms can also result in HER2 gene overexpression, but gene amplification is the most common.[13]

As mentioned before, HER2 (ERBB2) encodes for one of the tyrosine kinases receptors (RTKs). Its overexpression in breast cancer is associated with higher rates of breast cancer recurrence and death. As a result, effective anti-HER2 targeted drugs, specifically monoclonal antibodies, are recommended for early and late stage breast cancer. (Specifically, trastuzumab for both early and late stage, and pertuzumab, ado-trastuzumab emtansine, and lapatinib for late stage are indicated.)

In addition to gene amplification, several other single nucleotide variations (point mutations) have been identified in 1.6% to 2.0% of breast cancers. These activating mutations appear to also drive tumorigenesis and may lead to resistance or sensitivity to some of the HER2-targeted monoclonal antibodies listed above.[14]

> **Targeted therapies could significantly impact the approach to claims adjudication and increase the cost of healthcare-related products.**

- **Gene Fusion**
  Fusion is the genetic recombination of the parts of two or more genes where regions of DNA not normally next to each other become fused together. This can result in different and/or added regulatory regions. This oncogene fusion includes at least one oncogene as one of the partners, the result of which is the translation of oncogene fusion proteins.

  The classic example of a fusion gene is the translocation that results in an abnormal chromosome 22, known as the Philadelphia (Ph) chromosome. The Ph chromosome results from a balanced translocation between chromosomes 9 and 22, denoted t(9;22) (q34.1;q11.21). This translocation of the ABL1 gene on chromosome 9q34 to chromosome 22 results in a fusion between the BCR gene and the ABL1 gene and the formation of the BCR-ABL1 leukemic oncogene. ABL1 is a tyrosine kinase and the BCR-ACL1 fusion gene leads to the unique BCR-ACL1 fusion protein, a constitutively active deregulated tyrosine kinase that leads to uncontrolled proliferation.[15] In 95% of cases, a t(9;22) (q34.1;q11.21) translocation results in the BCR-ABL1 fusion gene, which is necessary for the pathogenesis and diagnosis of chronic myeloid leukemia (CML).[16]

  Other translocations also result in the creation of the BCR-ABL1 fusion gene and may be associated with distinct leukemia phenotypes.[17]

  ABL1 kinase inhibitors are being used as targeted therapies against BCR-ABL1 positive malignancies. Imatinib was the first tyrosine kinase inhibitor (TKI) developed for CML. It works by inhibiting the activity of the oncogenic BCR-ABL1 fusion protein.[18] High rates of complete cytogenic response (no Ph chromosome cells measured) and improved survival have occurred with imatinib, but 30% to 40% of patients will develop resistance or intolerance to the drug.[19]

  Some of this resistance is due to single nucleotide variations (i.e. point mutations) in the tyrosine kinase domain of the BCR-ABL 1 fusion gene. Second generation TKIs have been developed to treat these resistant forms of CML.[20]

Financial Considerations

The cost of targeted therapy is significant and cure rates are still lower than expected. Standard chemotherapy with dacarbazine in metastatic melanoma, for example, has a median overall survival of 5.6 to 7.8 months. Vemurafenib, the BRAF kinase inhibitor used in metastatic melanoma, costs U.S. $13,000 per month and leads to a 15.9 month median survival rate. Patients for whom vemurafenib fails are often given ipilimumab, an immunomodulatory drug which costs U.S. $150,000 per course and has a relatively limited response in only 10% to 15% of patients and a median survival of 19.9 months.[21, 22] Based on this, societies and healthcare systems will need to determine how limited medical resources will be allocated and distributed as more targeted therapies are developed and made available.

Conclusion

Cancers appear to be due to the mutation of a number of genes that alter pathways responsible for cell proliferation, survival, and suppression. Each cancer appears to have numerous mutations associated with it, all of which may have an effect on the sensitivity and/or resistance to targeted molecular therapy.

Targeted therapies are not likely to have a significant impact on the underwriting of traditional life and critical illness products in the near term, especially in regard to advanced tumors. However, they could significantly impact the approach to claims adjudication (as in the terminal illness claim above) and will certainly result in a significant increase in the cost of healthcare-related products. ◼

Note: The website "My Cancer Genome" (www.mycancergenome.org) can be an invaluable reference for information on the genetic mutations provided in pathology reports.

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HEPATITIS B UPDATE

Abstract

Hepatitis B is one of the world's most prevalent infectious diseases today. The disease has been recognized for millennia, but the first actual breakthrough in understanding its etiology came more than 50 years ago, when it was discovered that the serum protein Australia Antigen (first discovered in Australian Aborigines) was in fact the surface antigen (HBsAg) of the hepatitis B virus (HBV). This discovery enabled the development of a successful hepatitis B vaccine in 1981.[1]

Although the HBV vaccine has been administered routinely at birth in the U.S. since 1991 and despite ongoing population education and awareness efforts, HBV infection remains a global health hazard. It is frequently asymptomatic, so many acutely and chronically infected patients may be unaware they have this disease and so can be the cause of significant mortality and morbidity.

The aim of this article is to update readers on advances in the understanding, treatment, and prognoses for this condition, as well as the underwriting and claims implications for life and health insurers.

About HBV: Epidemiology

The hepatitis B virus (HBV) is a DNA virus belonging to the hepadnaviridae family. It is considered to be the most complex of the five known forms of viral hepatitis (A, B, C, D, and E). HBV is also a global disease: the World Health Organization (WHO) in 2017 estimated that 325 million individuals worldwide are living with the disease's chronic form, a 25% increase from 2015's 260 million estimate. In addition, the Centers for Disease Control and Prevention (U.S.) recently stated that approximately 600,000 individuals worldwide die annually as a direct or indirect consequence of HBV infection.

The disease's highest prevalence (just over 7%) is in the Western Pacific region (including China and Taiwan) and in Africa. Eastern and Southern Europe, Southeast Asia and Japan have intermediate prevalence levels (2% to 7%), and North America has extremely low prevalence (<2%)[2] which is not surprising, as the HBV vaccine has routinely been administered to U.S. newborns for nearly three decades.

The main forms of transmission are via bodily fluids such as blood, semen, and saliva. In areas where HBV is endemic, vertical transmission (i.e., prenatal or perinatal transmission) is its dominant mode of spread. The chances of infection becoming chronic is close to 90% among infected infants, presumably because infant immune systems are immature (immune tolerance phase) whereas among older children and adults, chronicity may vary between <1% to 10%.[3] In areas of lower prevalence, the main routes for HBV transmission are unprotected sexual intercourse, intravenous drug use or, for health care workers, direct contact with bodily fluids of infected persons.[3]

ABOUT THE AUTHOR

Akhilesh Pandey
Senior Underwriter –
Research and Manual Development
RGA Global Shared Services India Pvt. Ltd.
apandey@rgare.com

Akhilesh Pandey, a Senior Underwriter with RGA Global Shared Services India Pvt. Ltd. (RGA India), develops and supports underwriting guidelines for and the administration of RGA's Global Underwriting Manual. He also trains underwriters on complex medical topics through RGA India's Academy of Continued Education, and is a member of RGA's Global Support Team. Previously, he was a Facultative Underwriter for RGA India, and before then, was an underwriter for Generali India and for Ageas India.

Clinical Manifestations

HBV infections start out as acute and progress either to resolution or to chronicity. The acute phase lasts from one to six months. During this time, infected individuals generally do not have symptoms, but are able to pass the infection to others. However, when symptomatic, individuals with acute hepatitis B can experience anorexia, nausea, low-grade fever, myalgia, changes in the ability to smell or taste, jaundice (icterus), and mild to moderate pain in the right upper quadrant of the abdomen. In rare cases (<3%) fulminant hepatitis B can develop,[5] leading to rapid liver failure, encephalopathy, coma, and death.

Those whose hepatitis B has neither spontaneously cleared in six months nor has progressed to fulminant hepatitis are considered to have progressed to chronic hepatitis B (CHB). As noted earlier, risks of chronicity will differ among infants, older children, and adults due to immune response displayed by the host and the virus's route of transmission.

Patients with chronic infection may remain infected for the rest of their lives. They are generally asymptomatic unless the infection progresses to hepatocellular carcinoma (HCC) or there is a transition from compensated cirrhosis to decompensated cirrhosis. In decompensated cirrhosis, patients may have symptoms including jaundice, ascites, edema, encephalopathy, and variceal hemorrhage.

Extrahepatic Manifestations

Extrahepatic manifestations of hepatitis B can appear both in the acute and chronic stages. They can have significant mortality and morbidity implications, but clinical prevalence of these is generally low compared to hepatic symptoms.

Notable extrahepatic manifestations include:[6]

- Polyarteritis nodosa (PAN) and other vasculitides
- Glomerulonephritis
- Hemolytic anemia
- Dermatological manifestations (e.g., purpura, oral lichen planus, urticaria, pitted keratolysis)
- Serum sickness
- Polyarthritis and polyarthralgia
- Graves' disease

Phases of Chronic Infection

HBV is not static but a very dynamic virus, hence it keeps fluctuating between different phases once chronic HBV has developed. The course of a chronic HBV infection has four phases[7]:

- *Immune tolerant phase.* This is characterized by the presence of the hepatitis B e antigen (HBeAg), high serum HBV DNA levels (>20,000 IU/ml), normal or minimally elevated ALT (alanine aminotransferase) levels, and no or minimal liver fibrosis on biopsy.

- *Immune clearance (also known as immune active or immune reactive HBeAg-positive)* phase. During this phase, the immune system is actively attacking infected liver cells. The patient is HBeAg-positive and is experiencing intermittent or persistent

elevation of ALT levels and high HBV DNA levels (although not high in comparison with those seen in the immune tolerant phase). The phase can last from weeks to years and ideally ends with HBeAg seroconversion, signaling entry into the next phase.

- *Immune control/inactive carrier phase*. This phase is characterized by a lack of HBeAg, the presence of HBsAg, persistent normal ALT levels at least three times over 12 months, and low (<2,000 IU/ml) to undetectable levels of HBV DNA.

- *Reactive/HBeAg-negative CHB (immune escape)* phase. There is always the possibility that the disease might reactivate due to mutation of the genes in the pre-core or core promoter regions of the HBV genome. In this phase, HBV DNA levels are rising despite the patient having seroconverted to anti-HBe positive (e.g., the presence of HBeAg antibodies), elevated ALT levels, viral loads of ≥2,000 IU/ml), and moderate to severe liver inflammation and fibrosis levels. In these patents, the virus is active and chronic and risk of cirrhosis rises.

The HBV Genome and Its Mutations

The HBV is a small, circular, partially double-stranded DNA genome, containing four partially overlapping open reading frames (ORFs):

- the viral core protein (C) (HBcAg)
- the polymerase/reverse transcriptase (P) (DNA polymerase)
- the surface proteins (S) (HBsAg)
- the hepatitis B virus X protein (HBx)

The general function of the X protein is not yet clearly understood, but it appears to be associated with an increased risk of developing liver cancer.[8]

The HBV genome is unique among human viral pathogens in that it replicates via a protein-primed reverse transcriptase of an RNA intermediate (i.e., pre-genomic RNA). The reverse transcriptase also lacks proofreading activity, which may explain why HBV has a reported mutation rate 10 times higher than that of other DNA viruses and why its genetic variation is so wide.

During the replication process, translation at the pre-core region results in HBeAg, and at the core region, in HBcAg. HBeAg levels are used clinically as an index for infectivity,

viral replication, severity of disease and response to treatment. HBcAg, the core antigen, indicates active viral replication (meaning the person is infectious). Mutations at these sites are considered the main causes of HBeAg-negative (Phase 4) hepatitis, as most infected individuals who are HBeAg-negative harbor mutated variants in the pre-core and core promoter regions of their HBV genome.

The most frequent mutation of the gene (e.g., mutations of the core promoter's basal core promoter section) results in an HBeAg-negative phenotype due to termination of translation, which reduces HBeAg secretion with consequent increase in viral replication. Further pre-core promoter mutation causes elimination of HBeAg production, resulting in HBeAg-negative disease.[9, 10] It has also been suggested that HBeAg proteins might modulate the patient's immune response as a tolerogen (an antigen that induces immune tolerance), thereby promoting chronicity of the HBV infection.

Additionally, there is mounting evidence that detection of such pre-core and core mutations may confirm whether a patient with no or low levels of HBeAg has HBeAg-negative disease due to the mutation is actually responding to treatment.[11, 12, 13, 14]

Many other mutations of this genome have been recognized, including several within the HBV polymerase ORF leading to antiviral drug resistance, those associated with vaccine failure (HBsAg escape mutant), or loss of HBV detection by diagnostic assays due to altered HBsAg.

A greater understanding of HBV genome mutations is likely to contribute to improved diagnostic testing and therapeutic protocols.

Diagnosis, Antiviral Therapy, Recent Advancements

Since the discovery of the Australia antigen there has been continuous improvement in HBV-related virological tools, which has made a considerable impact on the ability to screen for and diagnose HBV.

- Rapid diagnostic testing (RDT) for HBsAg has specificity close to 100% and is more convenient and is easier to perform outside of a laboratory than conventional enzyme-linked immunosorbent assays.[15]

- HBsAg assays can accurately quantify HBsAg levels which have several possible indications in clinical practice and can be used as an alternative parameter for monitoring treatment response.[16]

- Commercially available advanced molecular diagnostic tools such as real-time transcription-mediated amplification-based assays can accurately quantify HBV DNA levels, which are essential for the diagnosis and prognosis of HBV infection.[17]

Unlike in hepatitis C, complete clearance of HBV is highly unlikely due to its high mutation rate and extremely low rate of viral replication. Therefore, the goal of treatment is prevention of progressive liver disease or the development of hepatocellular carcinoma (HCC). The incidence of the latter is 15 to 20 times higher in those with chronic HBV compared with control populations.[18, 19]

Treatment guidelines are based on the recommendations of major professional organizations that are focused on the study, prevention, and cure for liver disease such as the EASL (European Association for the Study of the Liver) and the AASLD (American Association for the Study of Liver Diseases).

Treatment options focused on mutation of the genome depend on how the virus is replicating, the phase, and the patient's immune response. Current options include: [20]

- Nucleoside analogues such as lamivudine, entecavir, and telbivudine
- Nucleotide analogues such as adefovir and tenofovir disoproxil
- Pegylated interferon

Data suggests that maintained suppression of HBV replication using nucleoside and/or nucleotide analogues may reduce the worsening of liver fibrosis, thereby reducing the risk of developing cirrhosis, and prevent further disease progression (including HCC) in patients with advanced liver fibrosis or cirrhosis.[21, 22]

The main challenge with antiviral drug treatment is the emergence of drug resistance and resumption of HBV viral replication. This issue, however, may be overcome by using adjuvant therapy with low-resistance drugs (e.g., combination therapy with tenofovir and entecavir).[23]

Finally, the development of new antiviral agents and new immune therapies which restore the immune response to HBV remains a major research challenge not only to improve the efficacy of current antiviral therapy but to achieve HBsAg loss and HBV eradication.

Therefore, the approval of new treatments is largely dependent on their impact on the following surrogate markers:[24]

- Biochemical: ALT/AST levels
- Virological: HBV DNA levels, HBeAg serostatus, HBsAg serostatus
- Histological: using various histological scoring models such as the METAVIR score, which assesses the liver's level of inflammation and fibrosis, the Knodell score/HAI (histology activity index), which measures liver inflammation and scarring, or the Ishak score (a modified Knodell score)

Since the development of HBsAg loss is, as noted earlier, a rare event, it is relatively difficult to determine the therapeutic endpoint while treating HBV infection. However, the biochemical, virological, and histological surrogate markers listed above can be useful ways to measure the need for or efficacy of antiviral treatment.

Co-infection with HIV or HCV

As HIV and HBV can share similar transmission routes, up to 14% of patients with HIV are co-infected with HBV. The highest prevalence of this is in sub-Saharan Africa and Asia.[25] Mortality in these co-infected patients is 50% higher than for mono-infected individuals. [26]

Approximately 2% to 15% of HBV patients are co-infected with hepatitis C. In these patients, the hepatitis C virus can become dominant if untreated, reducing HBV levels to nearly undetectable, but once the hepatitis C has been treated and is resolved, HBV replication can increase. This co-infection can lead to more severe liver disease and an increased risk for progression to HCC.[27]

An Insurance Medicine Analysis – Mortality and Morbidity

The long-term mortality and morbidity implications of chronic HBV infection in otherwise healthy Chinese insurance applicants was reviewed in an article by Pokorski, et al. Mortality ratios of 150% to 175% and 125% to 150% were estimated for men and women respectively, suggesting that the majority of HBV cases are within insurable range. However, risk varied based on factors such as seropositivity, ALT levels, circulating HBV DNA viral loads, and degree of fibrosis or cirrhosis.[28]

In terms of morbidity, there is a significant risk of both hepatic and extrahepatic cancer, HR 2.34 (95% CI: 2.15-2.55), even after the exclusion of any co-infected patients.[29]

Although the impact of chronic HBV on the incidence of coronary artery disease or atherosclerosis appears to be insignificant, it remains under investigation.

Implications for Life Insurance and Living Benefits Risk

The continuous evolution of diagnostic tools and treatment modalities means the risk profile of those with chronic HBV infection is improving. This will provide several benefits for life insurance and living benefits applicants as well as insurance carriers.

For life insurance:

- More applicants will be insurable based only on full blood profile (e.g. serum albumin, alpha fetoprotein level, LFTs, HBV DNA viral loads).

- Non-invasive diagnostic technologies such as liver scans (e.g. Fibroscan®) can lead to earlier treatment initiation, thus improving long-term prognoses.

- Liver biopsy will continue to be an important way to assess the degree of fibrosis and the subsequent initiation of treatment. The use of biopsy in general, however, is now limited to more complex cases and therefore simpler non-invasive techniques such as Fibroscan®, USG, and others, are gaining more popularity.

- Antiviral therapy could provide more beneficial outcomes if access to these treatments was more readily available, particular in areas where chronic hepatitis B disease is endemic.

In summary, acute hepatitis B can become a chronic infection. Frequent and long-term monitoring has been shown to have a favorable impact on prognosis, thus improving insurers' ability to insure these lives.

For living benefits:

- When there is adequate treatment, fewer claims may be experienced for critical illness policies, hospital cash benefits, total and permanent disability products, and long-term care products.

- The effective prevention or early diagnosis of HBV will result in a substantial reduction in economic cost and burden on health-related services by the alleviation of chronic HBV-related disease(s).

Summary

Advances in the diagnosis and treatment of chronic HBV infection have resulted in more favorable outcomes. Although both mortality and morbidity risk may still vary, risk factors such as serostatus, circulating serum HBV DNA, and degree of fibrosis should to be taken into consideration when assessing any particular profile. Second, the cost-effectiveness of antiviral treatments and programs such as universal HBV vaccination, in adulthood as well as at birth, may have an important role in deciding the actual benefit of these advances. Hepatitis B infection, once it reaches chronicity, is less likely to resolve, but its management has improved over the past decade due to advances in diagnosis and treatment, which has resulted in significant suppression of virus activity. For those individuals with access to these advanced measures, the prognosis will be significantly improved, and will reduce its risk for both life and living benefits. ℞

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MEDICAL TEAM UPDATE

RGA welcomes Bei Zhang, M.D., M.B.A., Regional Medical Director, Asia Markets, to our Asia Pacific medical team and to our global network of medical officers. Dr. Zhang, a specialist in oncology and internal medicine, earned her medical degree from Shanghai Jiao Tong University and her MBA from The University of Hong Kong.

POLYCYTHEMIA VERA: A RESEARCHER'S VIEW

Stephen T. Oh, M.D., Ph.D., heads a research group at Washington University in St. Louis School of Medicine that is focused on the pathogenesis of myeloproliferative neoplasm (MPNs) with the goal of translating the work into improved therapies for MPN patients. His LLF-funded research, "Functional Dissection of Age-Related Differences in Disease Phenotype in Polycythemia Vera," broke important ground in the study of the genetics of this blood cancer, particularly strengthening the understanding of the distinctly different mutational profiles of younger (<45) versus older (>65) patients. In a recent interview with Daniel Zimmerman, M.D., managing director of the Longer Life Foundation and co-editor of ReFlections, Dr. Oh discussed his work, which has powerful implications for insurance medicine, as a greater understanding of the genetic mechanisms underlying these blood cancers will enable better treatment and greater patient longevity.

LLF INTERVIEW

STEPHEN T. OH
M.D., Ph.D.

*Assistant Professor,
Division of Hematology
Washington University in
St. Louis School of Medicine*

What sparked your interest in myeloproliferative neoplasms (MPNs) – specifically, polycythemia vera (PV)?

When I started my post-doctoral fellowship with Dr. Garry Nolan, Professor of Microbiology and Immunology at Stanford, I was already interested in blood cancers. It was a fascinating time: the JAK2 V617F mutation had recently been discovered as a major driver and targeted JAK2 inhibitor therapies were just starting to become available. I also worked with Dr. Jason R. Gotlib, Professor of Medicine (hematology) at Stanford University Medical Center, who is a well-known expert in MPNs, so I was able to be mentored by both.

When and why did the term "myeloproliferative disorders" change to "myeloproliferative neoplasms"?

The name was formally changed in 2008, soon after the discovery of the JAK2 mutation. The World Health Organization revised the name to signify that PV, as well as essential thrombocythemia and primary myelofibrosis, are indeed blood cancers. It also reflected the evolving understanding of the genetic basis of these conditions, signifying that the presence of the mutation is a diagnostic criterion for PV, and underscoring that the transition from these conditions to secondary acute myeloid leukemia (sAML) is from one blood cancer to another, not from a pre-cancer to a cancer state.

PV's median age of diagnosis is 61, and transitions from PV to primary myelofibrosis (MF) (bone marrow cancer) and sAML occur with similar frequency for older and younger patients. What percent of those diagnosed with PV are under age 45? Also, do older and younger age cohort patients transition at the same rate or does it differ?

Approximately 15% of PV patients are under age 45. The cumulative incidence is the same for all, but the rate of transition of PV to MF or sAML is longer for younger patients.

Is the JAK2 mutation germline or somatic? Can it be both?

The mutation is somatic, which means it is acquired at some point in the patient's lifetime. That being said, it well known that there can be a slight familial disposition. Those with a positive family history of PV are at slightly elevated risk – approximately twofold – of developing PV. However, because PV incidence is relatively low, this doubled risk does not require any special surveillance of family members.

The JAK2 mutation is present in >95% of PV patients. Why is your discovery – that other driver mutations are acquired over time – important? Also, why might it explain some of the phenotypic differences between younger and older individuals with PV?

For patients under age 45, only the JAK2 mutation is usually present, whereas older patients will present with at least one additional mutation. This may be due in part to the fact that as people age, clonal hematopoiesis of indeterminate potential (CHIP) can occur, meaning hematopoietic stem cells or other early blood cell progenitors will contribute to the formation of a genetically distinct subpopulation of blood cells. These mutations can become present in acute leukemia as well. Future functional studies on newly discovered mutations may determine if they are driver or passenger mutations, and whether they relate to the development of PV.

A small percentage of PV patients lack the JAK2 mutation. What, then, is driving their PV?

PV disease, no matter its cause, seems to operate via similar genetic pathways. We don't know yet what drives JAK2-negative PV, and there is nothing specific to guide their treatment. Interestingly, some do respond to JAK2 inhibitors.

Are you using CRISPR-Cas9 technology in your PV research?

In my lab, we're experimenting with using the technology to correct JAK2 and ASXL1 mutations (ASXL1 is one of the most frequently mutated genes in malignant myeloid diseases). CRISPR enables precise genetic engineering in human cells, which lets us to study these diseases in ways that were not possible previously. There is obvious interest in the possibility of applying this approach to the clinic. One potential limitation, however, is that for genetically modified (i.e., corrected) clones to take root once transferred back to the patient, bone marrow ablation may be required.

Could your PV research enable patient treatment to become more personalized and precise?

As our understanding matures of the impact of gene mutations and age differences, we might be able to tailor therapies for specific patients to achieve better outcomes. One avenue we are currently pursing is improving our understanding of inflammation's role. PV produces inflammatory cytokines and the inflammatory pathways might steer us to additional targeted therapies.

ReCite

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

Mid- and Long-Term Health Risks in Living Kidney Donors:
A Systematic Review and Meta-analysis
O'Keeffe LM, et al. Ann Intern Med. 2018 Feb 20.
https://annals.org/aim/article-abstract/2671305/mid-long-term-health-risks-living-kidney-donors-systematic-review

The authors of this meta-analysis reviewed 52 studies comprising more than 100,000 living kidney donors who were matched to case-controls. Donors did not demonstrate any increased relative risk for all-cause mortality, cardiovascular disease, hypertension, type 2 diabetes or adverse psychosocial health outcomes compared with controls. However, the risk of higher diastolic blood pressure, lower estimated glomerular filtration rate (eGFR), end-stage renal disease (ESRD), and pre-eclampsia (in women) was increased. Absolute risk for ESRD and preeclampsia was still relatively low.

Editor's Note: *The results of this study are reassuring as kidney donors are generally underwritten favorably for life cover. However, closer review of these individuals for living benefits may be warranted.*

Migraine and Risk of Cardiovascular Diseases: Danish Population Based Matched Cohort Study
Adelborg K, et al. BMJ. 2018 31 Jan; 360:k96.
http://dx.doi.org/10.1136/bmj.k96

This original research on a Danish population of 51,032 migraine sufferers was matched with 510,320 controls sought to determine the risk of multiple cardiovascular (CV) outcomes in the patients with migraines. After 19 years of follow-up, it was determined that migraine was associated with increased risk of myocardial infarction (aHR=1.49), ischemic and hemorrhagic stroke (aHR=2.26 and aHR=1.94, respectively), venous thromboembolism (aHR=1.59), and atrial fibrillation or flutter (aHR=1.25). The authors concluded that migraine may be an important risk factor for most CV diseases.

Editor's Note: *The association of migraine with myocardial infarction and stroke is already established. This study broadens the category of CV risk. Insurers would be well-advised to underwrite CV histories for migraine sufferers carefully, especially for living benefits products.*

Long-term Follow-up of Monoclonal Gammopathy of Undetermined Significance
Kyle R, et al. N Engl J Med. 2018 Jan 18; 378:241-9.
http://www.nejm.org/doi/full/10.1056/NEJMoa1709974

Researchers from the Mayo Clinic followed 1,384 patients with monoclonal gammopathy of undetermined significance (MGUS) from 1960 through 1994 (median period, 34.1 years) with the primary endpoint being development of multiple myeloma or another plasma cell or lymphoid disorder. Overall risk of progression (without accounting for death due to competing causes) was 36% at 35 and 40 years of age (lower at younger ages). Two additional negative risk factors identified included an abnormal serum free light-chain ratio and a high serum monoclonal M protein level. The number (0, 1, or 2) of these risk factors further stratified outcomes significantly for both IgM and non-IgM MGUS. Non-IgM generally had a more favorable prognosis than IgM MGUS.

Editor's Note: *For underwriting purposes, MGUS is frequently considered a single-risk entity. This study demonstrates that the type of MGUS (IgM vs. non-IgM) and the presence or absence of additional risk factors significantly stratifies MGUS into differential categories, some of which could be considered more favorable than others.*

Detection and Localization of Surgically Resectable Cancers with a Multi-analyte Blood Test
Cohen JD, et al. Science. 2018 Jan 18
http://science.sciencemag.org/content/early/2018/01/17/science.aar3247

This landmark paper applied a blood test consisting of circulating proteins and mutations in cell-free DNA to approximately 1,000 patients with non-metastatic, clinically detectable cancers in multiple organs. Sensitivities ranged from 69% to 98% for five cancer types (ovary, liver, stomach, pancreas, esophagus) for which no screening tests are available for average-risk individuals. The control population demonstrated a specificity of > 99%. The authors hypothesized that when weighted for actual incidence in the U.S. the sensitivity would be 55% for the eight cancer types studied.

Editor's Note: *The advent of liquid biopsies for cancers is gaining substantial traction in clinical medicine in diverse roles from screening and directing therapeutics to monitoring for recurrence. While there is certainly hype regarding this technology in the mainstream literature, it is not quite ready for prime time. Still, insurers should keep abreast of this rapidly developing technology as it is certain to impact long-term morbidity and mortality outcomes. Special attention, however, should be given to monitoring for additional impacts on existing and future insurance products, especially those with strict cancer definitions.*

NEW WEBCASTS

RGA is once again launching webcasts, with a focus on topics of interest to the underwriters, claims managers and insurance doctors who read *ReFlections*. We hope you enjoy the material in these webcasts and look forward to bringing you more in the months ahead.

Increasing Urbanization
https://www.rgare.com/knowledge-center/media/videos/increasing-urbanization
As urbanization continues to increase around the world, its effects on mortality and morbidity are increasing as well. Dr. Georgiana Pascutiu, Medical Director and member of RGA's Global Support Team, discusses urbanization's impacts and effects on a range of physical and emotional health conditions.

Thinking Inside the Box
https://www.rgare.com/knowledge-center/media/videos/thinking-inside-the-box
Dr. Eric Westhus, Data Scientists, Global Research and Data Analytics, presents a fascinating webinar on the mathematics of epidemics – understanding how compartmental models can help to calculate and clarify epidemic risk.

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