

UNDERWRITER RESOURCE

SERVING THE LIFE INSURANCE INDUSTRY

Volume 1, Issue 1
September 2007

Welcome to the first issue of the *Underwriter Resource*, published six times per year to inform, instruct and inspire the would-be, beginning and professional underwriter.

Pancreatic Cancer Screening Utilizing Tumor Markers

The incidence of carcinoma of the pancreas has markedly increased over the past several decades and is the fourth leading cause of cancer deaths in the US. It is estimated that 37,170 cases of pancreatic cancer will be diagnosed in the year 2007 and 33,370 people will die from it.

“Tumor markers are elevated in pancreatic cancer and their appropriate use may assist in reducing early cancer claims.”

Most pancreatic cancers are detected in the advanced stages and only about 20 percent are resectable at diagnosis. Long term survival is rare, most die within four to six months of diagnosis; about 5 percent will be alive at 5 years.

Cancer accounts for 35 to 40 percent of contestable claims at most life insurance companies and pancreatic cancer is frequently among them. This is mainly because current underwriting strategies for cancer screening, particularly for pancreatic cancer, are ineffective.

Even though early diagnosis of cancer is essential to improve survival, detection at any stage is adequate for risk selection and for screening out potential early claims. There is evidence in medical literature, however, that some of these cancers could be detected with the appropriate use of currently available tumor markers.

The use of tumor markers in cancer screening is not an accepted practice in clinical medicine because the markers lack the degree of sensitivity and specificity needed to detect cancer at an early curable stage.

When the goal of screening is to detect cancer at any stage with a high degree of certainty, it can be accomplished by raising the cutoff value, in other words, by raising the upper limit of normal range for the tumor marker (see Table 3). In these circumstances, sensitivity becomes less important than specificity. By raising the cutoff value, fewer cancers are detected but fewer benign disorders are not falsely labeled

Table 1. Sensitivity and Specificity of Tumor Markers for Detecting Pancreatic Cancer

Tumor Marker	Sensitivity (%)	Specificity (%)
CA19-9	81.3	75.9
CEA	39	91.4
CA 125	56.9	77.6

Source: (Ann Surg Oncol 2007; 95:142-47)

as cancer. Specificity may also be increased by using tumor markers in combination (Ann Surg Oncol 2007; 95:142-47).

Tumor markers CA 19-9, CEA and CA 125 are utilized in clinical medicine for follow-up of a variety of cancers. These markers are elevated in pancreatic cancer (see Table 1) and their appropriate use may assist in reducing early cancer claims.

Many insurance companies in Japan have been using CEA and CA 19-9 to screen for undiagnosed cancer (On The Risk 1999; 15:54-60). Even in the United States, several companies have utilized CEA as a screening test and found it effective in detecting cancers. One insurance laboratory has even demonstrated the existence of significantly higher mortality at CEA values of 10 and above, with the help of the social security death index.

CA 19-9, a high molecular weight glycoprotein, is elevated in pancreatic cancer (see Tables 1 and 2) and many gastrointestinal cancers. CA 19-9 is also elevated in benign conditions such as cirrhosis, cholestasis, cholangitis, pancreatitis, splenic cyst and giant hydronephrosis. Three to seven

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Table 2. Level of CA 19-9 in Pancreatic Cancer by Stage

Stage	Number	CA 19-9 U/ml
I	2	27.31 ± 6.56
II	5	875.45 ± 329.33
III	25	1223.43 ± 479.73
IV	97	2118.19 ± 731.36

Source: Hepatobiliary Pancreat Dis Int; 2004;3:464-68

percent of the population who have the Lewis blood type negative (Le^{a-b-}) do not synthesize CA 19-9 and for that reason would not have elevated levels even in the presence of advanced cancer.

Carcinoembryonic antigen (CEA), an oncofetal protein, is used extensively in the diagnosis and follow-up of colorectal cancers. It is also elevated in other gastrointestinal and many non gastrointestinal malignancies including breast cancer. CEA is frequently elevated in benign diseases such as ulcer disease, inflammatory bowel disease, pancreatitis and cirrhosis.

Table 3. Tumor Marker Upper Limits of Normal Ranges

Tumor Marker	Clinical Ranges	Suggested Values for Insurance Screening
CA19-9	0 - 37 U/mL	100 U/mL
CEA	0 - 5 ng/mL	10 ng/mL
CA 125	0 - 35 U/mL	100 U/mL

CA 125 is a glycoprotein that is most often associated with ovarian cancers. Elevated levels are found in other malignant tumors including non Hodgkin's lymphoma and gastrointestinal malignancies. It is also increased in pregnancy, benign gynecological disorders, congestive heart failure and cirrhosis.

Instituting a screening program using tumor markers needs careful planning. Performing a pilot study in collaboration with your insurance laboratory is the first step. This helps establish the upper limit of normal value for each marker appropriate to your risk tolerance and customer base. Table 3 provides the normal ranges used in clinical medicine and suggests cutoff values for screening the insurance population as a starting point. In cases with prior history of cancer, clinical ranges should be used.

Even with appropriately set cutoff values you will be postponing coverage for many proposed insureds who do not have cancer or for some in whom the cancer is not yet clinically evident. Therefore the success of this program depends on very precise underwriting guidelines to manage the process. Guidelines should include guidance on appropriate decisions at various marker levels, procedures for notifying the proposed insured, information on what would be considered adequate evaluation by the physician and estimates on when it would be appropriate to reconsider insurance coverage. Deviations from the guidelines should only be done in consultation with the medical director.

Cancer screening with tumor markers is not a substitute for sound underwriting practices that screen for medical problems in general. The aim of the suggested screening program is to detect some advanced cancers that are undetected with traditional underwriting. Even with the use of these tumor markers, the majority of early cancers and many advanced cancers will not be detected. Advances in medical science are needed to improve on this process. ♦

Ambulatory Blood Pressure Monitoring

The traditional technique for measuring blood pressure involves using a stethoscope and a sphygmomanometer. The measurement is done by a physician or staff nurse and one or two readings are usually obtained in a medical clinic setting.

These readings are referred to as office or **clinic blood pressure** (CBP); the measurements have been used in major clinical trials of cardiovascular outcomes as well as in clinical practice for 50 years.

In contrast, **ambulatory blood pressure monitoring** (ABPM) uses a fully automatic device that consists of a Walkman size monitor that can be worn on the belt connected to a sphygmomanometer arm cuff. The device takes a reading every 15 to 30 minutes throughout the day and night. It provides tabulated results that include a 24-hour average, a day-time average and a night-time average.

Normal blood pressure fluctuates during a 24-hour period. It drops 10 to 20 percent lower at night in normotensive and most hypertensive people and reaches its lowest level between 2 and 4 am. It rises from this lowest level to its highest level over the next three to five hours as the person transitions from sleep to wakefulness. This is referred to as the **morning surge**.

Those whose blood pressure drops less than 10 percent at night are called **non-dippers** and those with a drop of more than 20 percent are termed **extreme-dippers**. In some people, blood pressure rises at night; these are referred to as **inverted-dippers**.

Table 4. Suggested Values for Upper Limits of Normal Ambulatory Blood Pressure

	Optimal	Normal	Abnormal
Day time	<130/80	<135/85	>140/90
Night time	<115/65	<120/70	>125/75
24-hour	<125/75	<130/80	>135/85

Source: Hypertension 2005; 245: 142-61

The utility of ABPM has been validated in numerous clinical trials and found to be superior to CBP in predicting cardiovascular events and mortality. The critical values that correlate with prognosis include the 24-hour average above normal (see Table 4) and the percentage of nocturnal drop in blood pressure. The non-dippers and the inverted-dippers are at a particularly higher risk.

Ambulatory Blood Pressure Monitoring has been found to be useful in diagnosing and making decisions about the following conditions: white-coat hypertension, masked hypertension, resistant hypertension, labile hypertension, postural hypertension and pregnancy related hypertension.

White-Coat Hypertension

In 20-30 percent of those with Stage 1 (mild) hypertension, blood pressure is persistently elevated but only in the presence of a health care worker, particularly a physician. Blood pressure is not elevated when measured elsewhere, including while at work. When this phenomenon is detected in patients not taking medications, it is referred to as white-coat hypertension (WCH). These patients have normal blood pressure when measured by ABPM and have no evidence of target organ damage. Recognition of WCH is essential to avoid unnecessary therapy.

Masked Hypertension

This condition is the reverse of white coat hypertension. Masked hypertension is suspected on the basis of blood pressure readings recorded at home. The CBP is low but the ABPM shows high readings. A third of those with treated hypertension have masked hypertension. When evaluated during a five year follow-up period, their relative risk of cardiovascular events is 2.28 times that of those whose blood pressure is adequately controlled based on clinic and ambulatory readings. The prevalence of masked hypertension in the general population is 10 percent. Those with untreated masked hypertension are at risk of end-organ damage.

Resistant Hypertension

This term is applied when adequate blood pressure control cannot be achieved despite the use of appropriately combined antihypertensive therapies in the proper dosages and for

sufficient duration. Some in this group, diagnosed to have resistant hypertension, have an exaggerated white-coat effect but have normal blood pressure readings and adequate control of blood pressure when measured by ABPM. They have no evidence of target organ damage.

Labile Hypertension

All hypertension is labile, meaning likely to fluctuate. But some disorders such as pheochromocytoma may have paroxysmal hypertension. A very common cause of paroxysmal hypertension is a panic attack which is accompanied by surges in blood pressure and heart rate. ABPM is useful in diagnosing these disorders.

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Postural Hypertension

Transient hypotensive episodes causing symptoms due to hypertensive therapy or autonomic dysfunction are difficult to evaluate with standard clinic blood pressure assessments. ABPM is an effective tool for recording these events enabling appropriate diagnosis and therapy.

Pregnancy and Hypertension

Hypertension is the most common medical disorder of pregnancy and occurs in 10 to 12 percent of all pregnancies. The detection of elevated blood pressure during pregnancy is one of the major aspects of optimal antenatal care; accurate measurement of blood pressure is therefore essential. White-coat hypertension occurs in 30 percent of pregnant women. Identification of this group is crucial to avoid unnecessary hospitalization and drug therapy. Normal values specific to the pregnant population need to be used when interpreting results of ABPM in pregnancy.

Underwriting Considerations

Interpreting ABPM results requires knowledge of the diurnal (daily) variation of blood pressure, the normal ranges and the terminology used in these reports. Judgment is needed when applying ratings to the 24-hour average blood pressure as life insurance blood pressure tables are based on CBP. For instance, the upper limit of normal for 24-hour average blood pressure by ABPM is 135/85 which corresponds to 140/90 CBP. An additional factor that needs to be taken into consideration is the extent of nocturnal blood pressure drop, as non-dippers or inverted dippers are at a higher risk for cardiovascular events.

The cost of ABPM is \$100 to \$350 and it is reasonable to request this study in selected cases. For example, cases where there is disagreement about the diagnosis of hypertension, the adequacy of control, or when competitive pressures require aggressive handling may be indications for ABPM.

The use of ABPM in clinical practice will increase as its utility in managing hypertension becomes better established. A working knowledge of ABPM and interpretation of its results is an essential skill for underwriters. ♦

Monoclonal Gammopathy of Undetermined Significance

Monoclonal gammopathy of undetermined significance (MGUS) is defined by the presence of monoclonal protein in persons with no indication of multiple myeloma or other related malignant disorders. Monoclonal protein is identified by an increase in one type of immunoglobulin above the normal value. MGUS is found in approximately one percent of people 50 years or older and three percent of those more than 70 years old. (N Engl J Med. 2006; 355: 2765-70).

MGUS is usually detected through routine blood testing as an incidental finding of an elevated total protein concentration. A follow-up protein electrophoresis which shows the presence of an abnormal protein (a monoclonal spike or M protein) can further confirm the finding.

“MGUS is usually detected through routine blood testing as an incidental finding of an elevated total protein concentration.”

Further studies are necessary to ascertain this diagnosis, including:

- A complete blood count
- Serum immunofixation to determine the type and quantity of M protein
- Urine collection to determine the extent of proteinuria and urine protein electrophoresis to detect abnormal protein or light chains
- Serum creatinine and serum calcium
- Bone marrow examination
- A skeletal bone survey to evaluate for lytic bone lesions

A diagnosis of MGUS is made based on the following criteria:

- Monoclonal protein (M protein) less than 3g/dl
- Minimal-to-no light chain in the urine
- No lytic bone lesions
- No Hypercalcemia
- No renal insufficiency related to the presence of M protein
- Less than 10 percent of plasma cells in the bone marrow.

Even though patients with MGUS are asymptomatic, the diagnosis of MGUS is clinically significant because the likelihood of progression to multiple myeloma or other plasma cell malignancy is high. This rate of progression is about one percent per year and is life-long; therefore, regular follow-up is necessary. Factors that determine progression to malignant plasma cell disorders are listed in Table 5; the higher the number of high risk factors, the worse the prognosis. A decrease in the unaffected immunoglobulins does not impact prognosis.

Follow-up after the initial diagnosis usually is done in six months and every one-to-two years thereafter based on the

level of risk. A complete blood count and quantification of M protein would be required at each follow-up. A significant change in the blood count or a rise in the M protein would be cause for concern. ♦

Table 5. Factors Determining MGUS Progression to Myeloma

Risk Factors	High Risk	Low Risk
M protein	1.5 to 3.0 g/dl	<1.5 g/dl
Plasma cells less than	6 to 9%	≤5%
Ratio of free kappa light chains to free lambda light chains	<0.26 or >1.65	0.26 to 1.65
Type of monoclonal protein (IgD and IgE are rare)	IgA or IGM	IgG

Source: New England Journal of Medicine. 2002; 346: 564-69

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Understanding Immunoglobulins

Immunoglobulins are antibodies; proteins that protect against infection. Each immunoglobulin is formed by combining two heavy and two light chains of amino acids. There are five types of *heavy chains* (gamma, alpha, mu, delta and epsilon) and two types of *light chains* (kappa and lambda). Each type of immunoglobulin may have only one type of heavy chain but may have either light chain. They are named based on the type of heavy chain used in its production, for example, IgG, IgA, IgM, IgD, or IgE.

Under normal conditions, the appropriate amounts of heavy and light chains are produced to manufacture immunoglobulins. In plasma cell disorders, the production of these chains is abnormal, resulting in an imbalance between heavy and light chains. The light chains are small molecules and are excreted in the urine. They are detected in the urine as *Bence Jones protein* or as an abnormal spike on the urine protein electrophoresis.

Monoclonal gammopathy is an increase in one type of immunoglobulin and is usually seen in disorders of plasma cells.

Polyclonal gammopathy is an increase in more than one type of the immunoglobulin and is seen in liver diseases, collagen vascular disorders and chronic infections.