While the use of laboratory testing for life insurance underwriting has been in practice for many years, there has been a dramatic increase over the last decades. With this increase comes the introduction of new tests and concepts that can be incorporated in the underwriting process. The following article offers a primer on the current concepts used in laboratory screening and an overview of three relatively new tests.

At John Hancock, we have seen a dramatic increase in the usage of laboratory testing for life insurance underwriting across the industry. Some of the factors that have contributed to this increase include:

• Onset of HIV with its high mortality and attendant risk of anti-selection
• Increasing concern for lifestyle-related conditions, such as alcohol and drug abuse
• Nicotine misrepresentation
• Popularity of advanced-age marketing where medical impairments are the norm
• Ability to provide multiple test results using auto-analyzers at a relatively low cost
• Continued advances in the availability, protective value and pricing of screening tests such as those featuring mortality analysis of old (alcohol markers, HbA1c, etc.) and newer tests such as p-BNP, CEA, risk scores, etc.
The Mechanics of Laboratory Screening
To really understand the use of laboratory testing in insurance underwriting, there must be a simplified grasp of the concepts involved in laboratory screening.

a Normal Range
There are essentially two types of tests used in laboratory screening: Binary Tests and Continuous Tests.

Binary Tests – These tests provide “Yes/No” answers, with no external range of values for the underwriter to compare with. These tests are reported as Negative/Positive, with an internal threshold that must be reached before the test becomes positive. Examples of some binary tests include pregnancy tests and CDT tests for alcohol excess.

Continuous Tests – These tests have results reported through a range of values that is unique to the specific servicing laboratory, which also arbitrarily selects cutoff limits. Frequently, 95% of the population fit within this constructed normal range, leaving 5% of the population outside the so-called “normal” range. An example of this type of continuous test is serum albumin. Ninety-five percent of the population should fall within the normal published range, while 2.5% will be below and 2.5% above this range.

Normal ranges can have significant variability based on many factors such as age, pregnancy and build. Importantly, underwriters must not lose sight of the concept of a normal value for a particular individual. For instance, an individual might normally have hemoglobin of 17 g/dl (normal range 14–18 g/dl). If the same individual was later noted to have hemoglobin of 14 g/dl, this might be an indication of blood loss, despite the hemoglobin being within the normal range. We often garner what is normal for a particular individual from serial blood work available in Attending Physicians’ Statements (APSs).

Finally, the concept of “regression to the mean” can be very helpful in underwriting when considering test results. This term implies that if a blood test is found to be outside the normal range solely on the basis of statistical chance (and not due to disease), on retesting the value should return — or at least draw closer — to the normal range. This produces a logical rationale for retesting some applicants when abnormal results arise that do not seem in accord with the overall clinical picture.

b The Impact of Multiple Testing
While multiple auto-analyzer blood sampling provides both accurate and reliable results, there is an inherent statistical source of error. The error lies in the statistical assumption that is made to define the normal range — i.e., that 5% of the normal population falls outside the 95% normal range and is considered abnormal. Multiply by the number of tests done, and the following table illustrates the impact:

<table>
<thead>
<tr>
<th>Number of Tests</th>
<th>Probability of All Test Results in Normal Range*</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>74%</td>
</tr>
<tr>
<td>12</td>
<td>54%</td>
</tr>
<tr>
<td>20</td>
<td>36%</td>
</tr>
</tbody>
</table>

*Assumption is that each test is independent of the others.

The greater the number of tests performed, the greater the chance that some will have values that fall outside the normal range on a purely statistical basis. This could easily result in mislabeling applicants unless the underwriter considers all factors and aspects of a particular case — so called “whole case underwriting.”

c Sensitivity/Specificity
Sensitivity and specificity are two terms that are used when evaluating tests.

Sensitivity is defined as the probability that an individual with disease will have an abnormal test result. Screening tests must be very sensitive, as sensitivity offers the ability to detect disease — something we do not want to miss in any possible applicant.

Specificity is defined as the probability that a normal individual will have a normal test result. Confirmatory tests must be very specific because specificity reflects the ability to detect normal, and not mislabel applicants with “disease.”

d Predictive Accuracy
Test parameters that include sensitivity and specificity are calculated based upon utilizing populations where we already know whether the disease is present or not. In a screened population, we may know the prevalence of disease, but we do not know which particular individuals actually have the disease. Predictive accuracy takes us into the realm of
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Clinical Situation

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Insurance Situation

XXX1 is similar to clinical medicine, (i.e., advance the time of diagnosis), but not to affect therapy. It provides prognostic information. XXX2 is really not a screening test because clinical disease is already present, but allows for the detection of anti-selection.

Innovations in Laboratory Medicine

The following outlines three relatively new tests and the information they reveal.

p-BNP

Brain natriuretic peptide (p-BNP) is a 32-amino-acid polypeptide secreted by the ventricles of the heart in response to excessive stretching. It was originally identified in extracts of pig brain (hence the name), although in humans it is produced mainly in the cardiac ventricles.

This test is designed to provide added protection against the risk of undiagnosed or incipient Congestive Heart Failure (CHF), which is not uncommon in older individuals. Additional protective information is also provided for other impairments, such as coronary risks and valve disorders.

There is difficulty in providing mortality ratings for specific p-BNP values in various clinical conditions given the early nature of the clinical literature, and sometimes many of the conditions are incipient or undiscovered. Elevated p-BNP values are very common in atrial fibrillation. Echocardiogram (ECHO) findings are especially valuable in deciding which elevated p-BNP values are significant.

Some unfavorable ECHO parameters associated with elevated p-BNP include:

- Low ejection fraction (systolic heart failure)
- Generalized hypokinesis/wall motion abnormalities (coronary disease/cardiomyopathy)
- Left ventricular dilation (early sign of failing heart)
- Moderate/severe left ventricular hypertrophy (LVH)
- More than grade 1 diastolic dysfunction (diastolic heart failure)
- Moderate or severe valve disorders

CDT

Carbohydrate deficient transferrin (CDT) is an alcohol marker. Alcohol-related mortality is common in the form of cirrhosis, GI bleeding, diabetes mellitus and/or traumatic death. Daily alcohol use of more than four drinks for men and more than three drinks for women is associated with increased risk.

A recent study of CDT suggested that positive results had mortality in the 150% to 350% range for ages 20–59 years.¹ Alcohol excess is also associated with smoking, elevated HDL cholesterol, and elevated GGT. Underwriters use these associations to get a better predictive accuracy from a positive CDT test.
CEA

Carcinoembryonic antigen (CEA) was first discovered in the 1960s in Montreal by Drs. Phil Gold and Sam Freedman.\(^2\) Clinical medicine began to find a role for the test with a radioimmunoassay for circulating CEA.\(^3\) Unfortunately, it was early in its history, and misleadingly labeled as the definitive test for bowel cancer, despite warnings to the contrary.

CEA is a glycoprotein that normally circulates in the blood at low levels. It has higher values in smokers, but the upper limit of normal is <5 ng/ml (i.e., 95% of population has a lower level).

CEA levels can be elevated in:

- Malignancy
- Benign tumors
- Inflammation
  - Peptic ulcer
  - Diverticulitis
  - Pancreatitis
  - Inflammatory bowel disease
- Cirrhosis
- Biliary obstruction
- Renal failure
- Hypothyroidism
- Fibrocystic breast disease

Traditionally, CEA has been utilized for detecting tumor recurrence and prognosis with respect to diagnosed tumors (colon, stomach, pancreas, lung, breast). CEA has not been previously recommended as a screening tool for the general population because of low sensitivity and specificity for malignancy in low prevalence populations. Also CEA levels often do not rise until the malignancy is already quite advanced (e.g., sensitivity of only 28% in Stage 1 colon cancer, 14–29% localized gastric cancer, and 15% early stage breast cancer.)

In the past, insurance populations have represented a group that CEA screening was not well suited for, since the issue of test specificity (specifically getting a positive CEA in an applicant without disease — also called a false positive) would arouse unnecessary concern and more invasive testing in many applicants.

There have been a number of recent mortality studies, however, that show CEA seems to have significant mortality predictive value in insurance applicants.\(^4\)

Many companies seem to be experiencing increasing cancer claims, and with the above mortality study backing, there has been a resurgence in pursuing tumor markers, more specifically, CEA as a screening lab test.

In the above studies, it has been shown that mortality increases as CEA ranges increase. As an example, one study showed that all-cause mortality for a CEA >10 ng/ml was close to 3,000% at duration 0–1 years, and still 650% at duration 6–7 years.

The following are possible benefits for use of this test:

- Currently, there are very few tools for screening insurance applicants for occult cancer. Cancer claims are clearly on the rise and of great concern. Adopting a CEA test might help improve this picture.
- The test is well known throughout clinical medicine. It would not be difficult in rationalizing decisions to applicants and MDs.
- Detecting an elevated level might actually save lives by leading to an earlier diagnosis of cancer when results are provided to the applicant and attending MDs.

Going Forward: Testing When It Makes Sense

John Hancock continually stays abreast of advancements in laboratory testing to help refine our mortality assessments and at the same time be easy to use and cost effective. Please see page 6 for details on factors we consider as we research tests, as well as some case studies that show how tests are used by our underwriters to assess a proposed insured’s risk.


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