New Medical Markers in Life Insurance Underwriting

Sponsored by

Association of Home Office Underwriters
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Background

Milliman was engaged by the Society of Actuaries (SOA) to conduct research identifying laboratory tests that are not widely used in the life insurance industry but could have potential benefits for use in the life insurance underwriting process. This report presents the results of the research.

The primary objective of this research was to identify and provide information on laboratory tests for consideration in the underwriting process for life insurance coverages and to objectively determine the cost and benefit of each test. The goal of this research was to provide information that can be used by each life insurance company to help it determine whether or not to incorporate these additional markers into its underwriting process. Specific recommendations will not be made on any marker as each company has its own unique circumstances that must be considered.

Note that throughout this report, the terms “marker” and “test” are used interchangeably. Both are considered to have the same meaning in this report.

This project was sponsored by the Association of Home Office Underwriters (AHOU), the Canadian Institute of Underwriters (CIU), and the SOA’s Committee on Life Insurance Research, Product Development Section and Reinsurance Section. The researchers would like to acknowledge the following individuals who participated on the project oversight group (POG) and provided guidance and feedback critical to the success of the project:

Jean-Marc Fix, FSA, MAAA, chair
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The researchers would also like to thank the three major laboratories — Clinical Reference Laboratories Inc. (CRL), Heritage Labs Inc. and Quest Diagnostics Inc./Exam*One* (Quest) — for their input and insight into the various aspects of the markers most likely to be used by the life insurance industry. The researchers would also like to thank the three laboratories for their peer review of the report. While others at each of the laboratories provided assistance, the researchers would specifically like to acknowledge the help of Dr. Robert “Bob” Stout of CRL, Dr. David Winsemius of Heritage Labs and Betsy Sears of Quest.

Executive Summary

Milliman was engaged by the Society of Actuaries (SOA) to conduct research identifying laboratory tests that are not widely used in the life insurance industry but could have potential use in the life insurance underwriting process. The medical markers of interest were those that met the criteria of i) currently available but not widely used and ii) applicable to life insurance underwriting (i.e., being a good indicator of all-cause mortality).

Representatives from the three main U.S. laboratories, Clinical Reference Laboratory Inc., Heritage Labs, Inc. and Quest Diagnostics Inc./Exam*One*, were interviewed to help determine the potential markers to review. The medical markers analyzed in this report include:

- Apolipoprotein A-1 and B (Apo A-1 and B)
- Complete blood count (CBC)/red cell distribution width (RDW)
- Cystatin C
- Hemoglobin
- Hemoglobin A1c
- Microalbumin
- Amino-terminal pro B-type natriuretic peptide (NT-proBNP)
- Oxidized low density lipoprotein (oxidized LDL)
- Phospholipase A2 (Lp-PLA2)
- Tumor necrosis factor-alpha (TNF-alpha)
- Troponins I and T

A methodology was developed to review the cost and benefit of each marker, which is described in this report so the reader can use it in independent research. The Internet was researched to find clinical studies that provided mortality data on the markers.

The elements considered in determining the cost of these new tests were:

- Laboratory charges to administer the test
- Underwriter training costs
- Underwriter time costs
- Cost of an attending physician statement (APS)
- Cost of additional not takens

The benefit was determined as the mortality savings.

For most ages where the test is relevant and where blood testing is routinely conducted, the addition of each of the markers appears to be cost-justified at a face amount level of $100,000,

the most typical level in the industry where blood and urine testing begins. Table 53 shows more details on the results of this analysis for each marker.

A spreadsheet was developed to facilitate the review of each marker and allow the readers to do their own sensitivity analysis.

Milliman is not recommending or rejecting any of these markers for use. Instead, the goal was to provide independent research and to provide enough information for each company to make their own informed decision as to whether or not to implement these or any other new markers.

Introduction

This report is divided into a number of sections and subsections. The report begins with a brief history of current laboratory testing and then explains the methodologies used. This is followed with some other thoughts and considerations on the cost and benefit analysis. Next, there is a section that provides definitions and the medical terms introduced by the markers studied. The main section of the report provides an explanation of each marker and an analysis and the considerations for the cost and benefit of each marker. Next, other information provided by the laboratories, not previously covered, is described. The next section covers some recent developments the project oversight group (POG) became aware of in working on this project that the reader may find of interest. The report concludes with some observations, caveats and limitations of the work.

History and Markers Selected for Study

In the late 1980s, the life insurance industry began to worry about a possible AIDS epidemic. In response, the industry began to blood test insurance applicants for the HIV virus. The industry, with the laboratories' help and encouragement, realized that since they now had to draw blood to test for HIV, they could use the blood draw for additional tests that could help in the quantification of mortality at a small incremental cost. This additional testing included medical markers such as lipid panels. This led to the creation of preferred underwriting, as it is known today. While preferred underwriting has evolved over time, most of the same medical markers initially implemented are still used today (e.g., cholesterol, alcohol and drug markers).

Today, vendors and life insurance companies continue to look to gain a competitive advantage. Some are doing this through studying ways to improve mortality experience while others are looking at new ways of attracting customers. Recent mortality research has involved looking at the traditional underwriting factors differently. The labs, some outside vendors and some reinsurers have taken this approach. Others have begun looking at other information, such as consumer data, in an attempt to gain additional insights into mortality. Yet another approach, and the one this report deals with, is to look at new medical markers for additional and hopefully better ways to predict mortality.

In researching the new medical markers discussed in this report, the researchers interviewed representatives from the three main U.S. laboratories, Clinical Reference Laboratory Inc. (CRL), Quest Diagnostics Inc./Exam*One* (Quest) and Heritage Labs Inc. The researchers would like to thank the laboratories for the time spent, their helpful and insightful comments, some additional written materials they provided and their peer review of this document.

The medical markers of interest were those that met the criteria of i) currently available but not widely used and ii) applicable to life insurance underwriting (i.e., being a good indicator of

mortality). The discussions with each of the three labs included the following general topic list for each medical marker the laboratory presented:

- The name of the test or marker
- A description of the marker
- What the marker is designed to detect
- Whether the new marker replaces or supplements current tests and whether new or supplemental information is provided by the marker
- Primary and secondary uses of the results of the test
- How the sample(s) are collected and limitations related to the viability of the sample
- Stability, reproducibility, sensitivity and specificity of the test
- Mortality information available related to the condition(s) identified by the test
- Cost of the marker
- Current and anticipated utilization by the life insurance industry

The full set of questions asked can be found in Appendix A. Each lab was provided with an advance copy of these questions to better help them prepare for the interview.

The researchers compiled the information the laboratories provided and did further Internet research to provide the reader with a better understanding of each test, along with the cost and benefit associated with each test. The POG also helped estimate some of the typical costs associated with each test.

Methodology

There are different approaches and factors involved with evaluating whether or not to introduce a new medical marker. The approach used in this report is to evaluate the cost and benefit of each new marker. There are many elements to consider when evaluating both the cost and benefit of the new marker. Some of these elements are objective and some subjective. Best judgment was used in making certain assumptions. The POG and other industry professionals were also helpful in setting those assumptions.

Cost

There are many elements that go into determining the cost of using each of these new tests. The following is a list of the elements considered. Specific values used for each individual marker are explained in the Medical Markers section.

- Laboratory charges to administer the test
- Underwriter training costs
- Underwriter time costs
- Cost of an attending physician statement (APS)
- Cost of additional not takens

The rest of this section will describe each of these costs in more detail.

- Laboratory charges to administer the test
    - These costs exclude the cost of the blood draw.
    - The cost will vary laboratory to laboratory and client to client. The laboratories generally have a certain “average” cost they charge most clients. Their best clients will pay less than this average cost while companies that do not provide much business to the laboratory will pay more.
    - The cost of the test will also vary if it is used on a reflex basis vs. if it is used routinely on applicants. Routinely does not necessarily mean the test is used on every applicant, but rather on every applicant that meets the pre-assigned criteria (e.g., 50 and older). A reflex test is one ordered only for applicants that have certain readings on another test. Hemoglobin A1c, one of the tests being reported on, is a good example. It can be ordered only when glucose levels from another test are out of line. In this case, this would be a reflex test. Or, it could be ordered on, for example, all applicants 35 and older. This would be considered a routine test.
    - The cost used in the calculations is the average cost from the laboratory assuming the test is used on a routine basis.

- Underwriter training costs
    - Some tests are generally understood by the underwriter and require little additional training while others may be new or require some more specialized training to understand the nuances of the results. The latter example would require more training time than the former.
    - The training costs need to be amortized to spread them over each applicant. They also need to be spread over time as the training would not be needed each and every year. The assumptions made were to amortize the cost straight line over five years and that 500 applications were reviewed per year.
- Underwriting time costs
    - While the focus is on the underwriter time costs in this report, there could also be medical director costs involved as well. For this report, medical director costs were indirectly covered by adding a little extra time to the underwriter's time where a medical director may also be involved.
    - The underwriter time costs involve an assumption for the time spent on an initial review of the results, ordering an APS when necessary, reviewing the APS results and explaining a decline in coverage, when necessary.
    - An average salary, including benefits, was assumed to determine the cost associated with the time spent. It was assumed an average base salary of $75,000 with an additional 35 percent of this salary for employee benefits was appropriate. A 40-hour workweek for this work was also assumed. With these assumptions, the average annual salary with benefits will be $101,250. This translates into an hourly rate of $48.68 and a rate per minute of $0.81.
    - Another assumption needed for this calculation is the percentage of the time a new medical marker will be the only trigger for ordering an APS. This assumption varies by marker.
- Cost of an APS
    - This represents the cost of the APS itself. The time cost of ordering an APS and reviewing the results from the APS is covered elsewhere. It was assumed the average cost of an APS is $50.
    - Note that an APS may not be needed for all markers, primarily due to the presence of other confirmatory tests already being done.
- Cost of additional not takens
    - There is an increased cost due to increased number of declines, not takens and free looks. This cost varies by marker.

One assumption made in this report was that the new marker did not replace any existing marker. If this is not the case, the mortality savings from the test to be discontinued should be considered as a cost for this marker. This cost would hopefully be more than made up for through the additional mortality savings on the new marker.

Another factor not considered in this analysis was the sensitivity and specificity of the new tests. It is recommended the reader consider this issue before implementing a new marker. While it is

desirable to have high sensitivity and specificity scores, it is generally assumed the sensitivity score is high (i.e., the disease is found by the marker when one has it) or the test would not be used. Assuming that is the case, it is now important to set the cutoff level high enough (or low enough when low readings represent poorer results) such that very few false negatives will slip through. In other words, it is desirable to minimize the times someone is rated or declined because the marker indicated they had a disease when in fact they did not have it. If these "false negatives" were to happen, the company could lose credibility, despite having an otherwise potentially good new marker.

Benefit

To determine the "benefit" of the cost/benefit analysis, the mortality savings due to the introduction of the new test was estimated. The general process used is explained below. Each marker presented its own challenges in following this approach, as the mortality data available was limited and in different formats. Despite this, a consistent approach was used. The following are the steps taken and assumptions made.

1. Find a study with prevalence and mortality data related to marker.
2. Use the mean and standard deviation to determine the average substandard reading.
3. Determine the average non-substandard reading.
4. Use the hazard ratios and the readings from steps 2 and 3 to determine the excess mortality between the substandard and non-substandard groups.
5. Determine the mortality savings.

The rest of this section describes these steps in more detail and several other considerations.

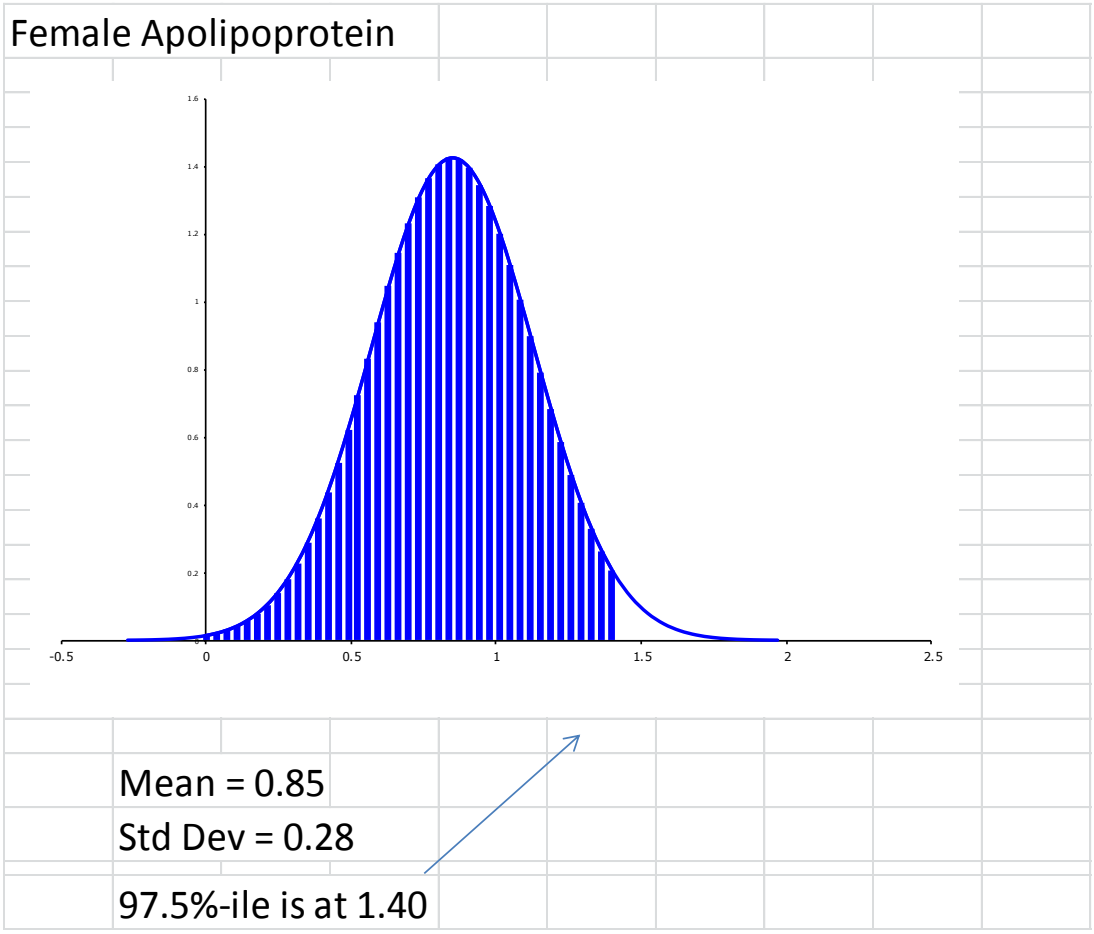
1. Find a study with prevalence and mortality data related to marker. This involves finding one or more studies that provide prevalence and mortality data regarding the specific marker. Note that this data is likely to vary not just study by study, but also based on the impairment the marker is designed to catch. Ideally, the prevalence data has a mean and standard deviation and mortality data expressed either as a hazard or odds ratio. Sometimes, the mean and standard deviation and the hazard ratios were expressed over the full spectrum of readings and sometimes these were broken into quintiles or some other smaller groupings. Sometimes, the mean and/or standard deviation needed to be derived and in other cases the mortality data was sufficient to use directly.

   The studies were found to diverge from the ideal in other ways, including:
   - Some studies were from the United States and some were foreign.
   - The study periods and participation rules for the study participants varied considerably.
   - While the preference was to have either healthy or a mix of healthy and unhealthy lives in the study, in some cases, only studies with all impaired

participants were found. In these cases, this would not be representative of a population applying for insurance.
    - While the first choice was for an all-cause mortality study, in a number of instances, studies that focused on specific causes (e.g., incidence and/or death from myocardial infarction) were all that could be found.
    - While the studies are summarized to some extent in the report, it is suggested the reader refer to the full study to better understand the nuances. This is particularly important if this report is to be utilized to determine which new markers to incorporate into the underwriting process as different interpretations of the same study can be made.

2. Use the mean and standard deviation to determine the average substandard reading. There were a number of assumptions that went into this.
    - A normal distribution of the data was assumed. Though most of the study data did not represent a normal distribution, it was close enough for this to be a reasonable assumption.
    - The worst 5 percent of the distribution of readings from each marker is considered substandard. This is a reasonable assumption based on industry averages.
    - While the researchers have seen J- and U-shaped curves with some current medical markers, none of the studies found and used mentioned this. Therefore, without specific data on these shapes, this was not incorporated into any of the calculations. Except for hemoglobin, all substandard business was considered to be fully in the high reading end of the distribution. For hemoglobin, the low reading end of the distribution was considered substandard. The reader may consider fine-tuning the benefit results for J- and U-shaped curves, where appropriate. In general, the reader should do their own due diligence on all assumptions to make sure they are appropriate for their own situation.
    - The average substandard reading was considered to be at the 97.5 percentile (87.5 percentile of the fifth quintile when that was available). These percentiles were chosen because it was assumed the average substandard reading was in the middle of the 5 percent substandard range (i.e., at 2.5 percent). While this is not accurate, it is also not an unreasonable assumption.
    - The following graph is an example of how the 97.5 percentile was derived.

Graph 1. Example of Normal Curve Calculation



3. Determine the average non-substandard reading. This can be done using the following formula, where X represents the average non-substandard reading.

    - 95% x X + 5% x Substandard Reading = Mean Reading for the population

4. Use the hazard ratios and the readings from steps 2 and 3 to determine the excess mortality between the substandard and non-substandard groups. Dividing the substandard hazard ratio by the non-substandard hazard ratio quantified the initial amount of extra mortality that could be expected from risks associated with the substandard reading when these values were given. However, for some markers, the extra mortality associated with each standard deviation was the only mortality data provided. In these cases, the number of standard deviations between the average substandard and average standard readings was determined and then the extra mortality per standard deviation was used to determine the initial mortality savings estimate.

5. Determine the mortality savings.
    - The standard mortality assumption was assumed to be 94 percent of the SOA 2008 Valuation Basic Table (VBT) composite (i.e., combined smoking status) age last birthday (ALB) tables. Ninety-four percent was chosen to be applied to the 2008 VBT because that was the overall percentage found in the most recent SOA (2005-07) study. It was also assumed mortality in any one year would be capped at 750 deaths per 1,000 and, beginning at age 105, mortality would grade back to the 2008 VBT rates by age 120.
    - Different male and female rates were used when available and different prevalence was used when given.
    - Examples are provided using an age in the study age range. In the Other Laboratory Information section of this report, additional ages are provided within the range of ages for which the laboratories suggested this marker could be used.
    - An average size of $100,000 was used to determine the cost effectiveness of each marker. Often, a lower face amount was also reviewed. In the summary section, the face amount to the nearest $5,000 that could be cost-justified for a male age 70 was also provided.
    - An assumption was made as to how much of the mortality savings would be uniquely identified by the marker. This is a subjective assumption and one difficult to quantify. This assumption can have a material impact on the overall results of the analysis.
    - A discount rate of 5 percent was used to calculate the present value of the cost of insurance to derive the mortality savings.
    - An Excel spreadsheet has been developed to calculate the mortality savings based on the input described above. The spreadsheet is called the Medical Marker_Mortality Benefit Calculator_11.21.2011.xlsm (Calculator) and is described more fully in Appendix B.

One item not estimated, but that would add to the mortality savings, is the amount of mortality savings received from ordering an APS and finding something beyond what this marker intended to cover. The reader can make an assumption for how often this occurs and how much extra savings there will be. This factor was not used because it was not considered to have a large amount of extra savings.

Another item not estimated was the savings attained if a current test was replaced by a new marker. The added savings would include the cost of the current test since it was no longer used and the additional mortality savings that would be uniquely found by the new marker. The mortality savings would likely be larger than that assumed below since the assumption below included only savings uniquely found with the new marker, which often times was limited due to the continued use of one or more current markers. There would also be an added cost of the mortality savings no longer received from the current

marker. This was not considered because an assumption was made that the new markers would be introduced without eliminating any of the current markers.

A consideration not typically taken into account in this report was whether different population segments (e.g., differences by age) had different prevalence because this information was not typically provided by the studies.

Another consideration was the sentinel effect. With the technology and information available today, potential insurance applicants may learn about a company doing some additional testing for a particular impairment or condition. If that applicant is aware of this and they have the particular impairment or condition, they may desire to seek coverage elsewhere. While this routinely occurs to a limited extent, the mortality savings per applicant would not be impacted because the company would lose this applicant whether through their individual action of going to another company or through the new marker weeding them out in the selection process.

While not part of the benefit calculation, the final step is to compare the male and female mortality savings at the face amounts mentioned above to the cost for the marker.

Cost and Benefit Considerations

The cost and benefit determinations were challenging to complete and certain portions of the determinations were subjective. It is recommended the reader thoroughly review the literature in addition to the calculations to make a determination of whether or not to introduce a new marker. It is also recommended readers have a conversation with their laboratory to get the laboratory's opinion on a particular marker as well as to determine the cost for the reader's specific company.

A few caveats are in order:

- The results for each marker are based on the assumptions discussed in that section. Any deviations from these assumptions will produce different results.
- The analysis is often based on one study. Other studies may produce different results.
- Results will vary by age. The impact by applicant age can be reviewed with the spreadsheet provided.

It is also important to understand that other factors should be considered in determining whether or not to implement a particular test or marker that go beyond the cost and mortality savings associated with the test itself. One such consideration is that when there is widespread use of a particular test in the industry, and unless there is another way to determine the potential impairment the test reveals, one could be selected against by not implementing the test. In this situation, it is not necessarily a matter of the mortality savings from the test, but rather the additional mortality that will be experienced in the book of business by not having implemented the test. Also note this extra mortality will likely grow over time by inaction.

Glossary

In this report, the reader will encounter terminology typically used by the medical laboratories and physicians. The hope is to not only provide the reader with an understanding of the medical markers being studied in this report, but to also acquaint the reader with some of the other medical terminology introduced in the Medical Marker section and that may be needed to better understand the markers and testing in general. The definitions provided below are in alphabetical order to make it easier for the reader to refer back as needed. They include:

- Blood Serum
- Cytokine
- Glycation
- Hazard Ratio
- Odds Ratio
- Reagent
- Relative Risk
- Risk profile/score
- Sensitivity
- Specificity
- Symbols

Blood Serum

The clear yellowish fluid that remains from blood plasma after clotting factors (as fibrinogen and prothrombin) have been removed by clot formation.[1]

Blood serum is described because this is a specific type of blood draw needed to evaluate certain markers. This is the "pure" portion of the blood needed for certain blood tests.

Cytokine

One of a large group of low-molecular-weight proteins secreted by various cell types and involved in cell-to-cell communication, coordinating antibody and T cell immune interactions, and amplifying immune reactivity. Cytokines include colony-stimulating factors, interferons, interleukins and lymphokines, which are secreted by lymphocytes.[2]

[1] *Merriam-Webster Online*, s.v. "blood serum," accessed December 8, 2011, http://www.merriam-webster.com/dictionary/blood%20serum.
[2] *Mosby's Medical Dictionary*, 8th ed., s.v. "cytokine."

Glycation

The result of the bonding of a protein or lipid molecule with a sugar molecule, such as fructose or glucose, without the controlling action of an enzyme.[3]

Hazard Ratio

Hazard ratios are commonly used when presenting results in clinical trials involving survival data, and allow hypothesis testing. The hazard ratio is calculated from hazard rates, the conditional instantaneous event rate calculated as a function of time. To understand this, it helps to look at an example. If a group of 1,000 patients are given a treatment, and, in month 1, 20 die, the hazard rate for month 1 is 20/1,000 or .0200. If in month 2, 20 more die, the hazard rate for month 2 is 20/980, or .0204 and so on. In this case, the hazard rate is the number of patients dying divided by the number still alive at the start of that interval. By looking at the hazard rate over small increments of time (giving an approximation of the instantaneous event rate), it is possible to compare the rate with the rate occurring in another group of patients being given an alternative treatment, ideally within a randomized controlled trial. At different points in time, the ratio of the hazard rates can be calculated. If the *pattern* of events is similar in each group, it can be assumed this ratio remains constant. Thus, the hazard ratio is the ratio of the hazard rates, that is, a ratio of the rate at which patients in the two groups are experiencing events. To understand this further, for example, a ratio of 1 corresponds to equal treatments; a hazard ratio of 2 implies that at any time, twice as many patients in the active group are having an event proportionately compared with the comparator group. A ratio of 0.5 means that half as many patients in the active group have an event at any point in time compared with placebo, again proportionately.[4]

Odds Ratio

Ratio of the odds, not the percentages. In statistics, the odds of an event occurring is the probability of the event divided by the probability of an event not occurring. The odds ratio is used to compare the odds of something occurring to two different groups. The odds ratio is the ratio of the odds for the first group and the odds for the second group. The formula is:

$$\frac{p / (1 - p)}{q / (1 - q)}$$

where p is the probability for the first group and q is the probability for the second group.[5]

[3] *http://encyclopedia.thefreedictionary.com/glycation*. Accessed December 15,2011
[4] Duerden, "What are Hazard Ratios?"
[5] Goldin, "Odds Ratios."

Reagent

A substance or compound added to a system to bring about a chemical reaction. It can also be used to see if it causes a reaction. This is important because in the medical markers, a reagent is often added to blood to determine the reaction of the protein being studied.

Relative Risk

The ratio of the probabilities of two events. If p is the probability of the first event and q is the probability of the second, then the relative risk is p / q.

This is what is being referred to when researchers say, for example, that smokers' risk of developing coronary heart disease is two to four times that of nonsmokers. The risk of developing heart disease for smokers is relative to the same risk for nonsmokers. Mathematically, this means the probability for a smoker will be two to four times the probability for a nonsmoker. If the risk of dying from coronary heart disease is 20 percent for a nonsmoker, the risk of dying from this disease for a smoker is between 40 percent and 80 percent.[6]

Risk Profile/Score

A proprietary scoring system compiled of many, generally hundreds of, test results on applicants over a period of time. Death records are obtained from the Social Security Death Master Index so the different tests can be studied with respect to their predictability of mortality. The risk scoring has been developed independently and differently by each of the laboratories.

Sensitivity

The probability a test indicates a person has a disease or impairment when they actually have that disease or impairment. When evaluating a test, the higher the sensitivity the better.

[6] Ibid**.**

Specificity

The probability a test indicates a person does not have a disease or impairment when they actually do not have that disease or impairment. Like sensitivity, when evaluating a test, the higher the specificity the better.

Symbols

The following are measurement symbols used with the markers studied.

Table 1. Table of Measurement Symbols

Symbol	Measurement
L	Liter
dL	Deciliter
mL	Milliliter
g or gm	Gram
mg	Milligram
µg	Microgram
pg	Picogram
µmol	Micromole
µ	The mean of a distribution
Ơ	The standard deviation of a distribution

Medical Markers

The medical markers are listed in alphabetical order. The discussion of each marker will begin with a description of the marker in both technical and nontechnical terms. The Glossary section may be referred to for a better understanding of the marker. The description is followed by the analysis of the cost and then the analysis of the benefit for each of the markers. The markers studied are:

- Apolipoprotein A-1 and B (Apo A-1 and B)
- Complete blood count (CBC)/red cell distribution width (RDW)
- Cystatin C
- Hemoglobin
- Hemoglobin A1c
- Microalbumin
- Amino-terminal pro B-type natriuretic peptide (NT-proBNP)
- Oxidized low density lipoprotein (oxidized LDL)
- Phospholipase A2 (Lp-PLA2)
- Tumor necrosis factor-alpha (TNF-alpha)
- Troponins I and T

As stated at the beginning of this report, the intent of this section is to provide the reader with the tools to determine whether the test is appropriate for their individual situation. The intent is not to make any specific recommendations. The information discussed below is a compilation of the results of the interviews with the three labs and independent research. It is intended for a life insurance audience.

Apolipoprotein A-1 and Apolipoprotein B (Apo A-1 and Apo B)

Apolipoproteins are proteins that bind to lipids (such as cholesterol) in the blood to form lipoproteins. The function of lipoprotein particles is to transport lipids (fats, such as cholesterol) around the body in the blood.[7] Apo B is the primary lipoprotein in LDL (low density lipoprotein or *bad* cholesterol) while Apo A-1 is a major component of lipoprotein in the HDL (high density lipoprotein or *good* cholesterol). Apo A-1 is a major component of HDL and helps clear cholesterol from the arteries.

Apo B on the LDL particle is responsible for delivering cholesterol to the cells. There is considerable evidence that Apo B is a better indicator of heart disease than LDL or total cholesterol because LDL is typically only estimated by formula. However, primarily for historic reasons, cholesterol, and more specifically, LDL-cholesterol, remains the primary lipid tests for the risk factor of atherosclerosis.[8]

The ratio of Apo B to Apo A-1 has been shown to be a better indicator of cardiovascular disease than either Apo A-1 or Apo B alone.[9] Note that this is a different relationship between the markers than the traditional total cholesterol to HDL ratio used today.

Cost
The average laboratory cost for both the Apo A-1 and Apo B tests is approximately $15.

Another cost to consider is the underwriter's time to learn about the marker. As these tests are similar to the cholesterol tests, the time it takes to learn about these markers is assumed to be negligible.

It is assumed it takes about one minute for the underwriter to evaluate an applicant's test results based on this marker. However, as there may be some uncertainty initially about the marker, it is assumed it would take another minute to review the cholesterol results as well for confirmation. This would happen in about 10 percent of the cases. The cost per minute used is $0.81 as explained on page 8. Therefore, the 1.1 (1 + 1 x 10%) minutes of review for this marker adds $0.89 to the cost of this test.

An initial verification of adverse test results can be completed through the traditional lipid panel as described above. However, there will be times where an APS would be needed to make a final decision. It is assumed this would happen in about 5 percent of the cases. When an APS is needed, it would take an underwriter about 10 minutes to order an APS and about 15 minutes to

[7] *http://encyclopedia.thefreedictionary.com/lipoprotein, accessed December 15, 2011*
http://en.wikipedia.org/wiki/Apolipoproteins.
[8] *http://encyclopedia.thefreedictionary.com/apolipoprotein+B, accessed December 15, 2011*
[9] Van der Steeg, Boekholdt, et al. "Role of the Apolipoprotein B." 640-48.

review the results from an APS. Therefore, the extra time spent would be 1.25 (25 x 5%) minutes on average per applicant. Using the same salary information, the cost would be $1.01. It is estimated the cost of an APS is $50. So the cost per applicant would be $2.50 (50 x 5%).

The underwriter will need to explain why the rating came in as it did due to this new marker, especially if it produces a different result than the more traditional cholesterol measurement. This is assumed to happen in 1 percent of the cases and that it would take about 10 minutes of the underwriter's time to explain on average. The additional cost here is estimated to be $0.08.

The total estimated cost of this test is $19.48 ($15.00 + $0.89 + $1.01 + $2.50 + $0.08). Assuming 5 percent of the cases are declined or not taken, and spreading this cost over all applicants, the final cost estimate for this marker is $20.50 ($19.48 / 0.95). For simplicity, a cost of $21 is assumed.

It is assumed there will be continued availability and use of the traditional lipid panel analysis. Because of continued use of the lipid panel analysis, mortality savings lost if the apolipoprotein test were to replace the lipid panel analysis was not factored in.

The Apo costs are summarized in Table 2 below.

Table 2. Apolipoprotein Costs

Item	Cost
A) Laboratory cost	15.00
B) Training time	0.00
C) Review of marker	0.89
D) Ordering an APS	0.40
E) Cost of APS	2.50
F) Review of APS results	0.61
G) Communication of negative results due to marker	0.08
H) Subtotal (sum of A through G)	19.48
I) Percentage of declines and not takens	5%
J) Total cost (H / [1 – I])	20.50
Total cost used (J rounded up to next dollar)	**$21**

Benefit

There are several articles available that include information on the mortality associated with Apo A-1 and Apo B levels but most focused solely on the cardiovascular impact. A couple of general observations from these studies were that Apo A-1 and Apo B were better predictors of mortality than the more traditional lipids (HDL and LDL cholesterol) and that the ratio of Apo B to Apo A-1 was a better predictor of mortality than either Apo A-1 or Apo B alone. These studies also indicated that the ratio of Apo A-1 to Apo B appeared to be the best measure. As just mentioned, most of these studies looked as much at the predictability of stroke and cardiovascular events as fatality. They also tend to focus on stroke and cardiovascular-related fatalities rather than all-cause mortality.

The study used for the analysis below examined the relationship between lipoprotein components and risk of myocardial infarctions and is referred to as the Apolipoprotein MOrtality RISk study (AMORIS)".[10] This analysis studies fatal myocardial infarctions. Although the preference would have been for an all-cause mortality study and this study did not have it, it was used because it seemed to be the best study available. Since this marker is meant to predict cardiovascular events, an adjustment can be made to the final result to account for all-cause mortality.

The study included subjects who submitted blood samples during medical checkups and at outpatient clinics between 1985 and 1996 who did not have an acute myocardial infarction (AMI). Some of the characteristics of the study include:

Table 3. Apolipoprotein Mortality Risk Study

Study period	1985-2002
Number of participants	149,121
Number of deaths	2,293 (1.5%)
Requirements	No previous AMI
Ages	Men: mean 49.4, standard deviation 11.1; women: mean 52.7, standard deviation 12.5
Follow up	Mean 11.8 years, range 7 to 17 years
Location	Stockholm, Sweden

The mean and standard deviation of the results are used to define a normal curve. While the underlying data is not necessarily normally distributed, it is assumed to be close enough to produce reasonable results. Since the results were split between males and females, separate normal curves for males and females were calculated.

This analysis uses the Apo B-to-Apo A-1 ratio (Apo ratio) rather than the individual components because the authors concluded that this ratio provided greater predictive value. It was assumed that all substandard business would be generated from the highest values because there was no discussion of a J- or U-shaped curve in the article. However, there is other data that shows a J- or U-shaped curve for cholesterol. It is recommended the reader research this point further.

Table 4 shows the mean and standard deviation for the Apo ratio.

Table 4. Apolipoprotein Mean and Standard Deviation

	Male	Female
Mean	1.00	0.85
Standard deviation	0.29	0.28

[10] Holme, et al. "Relationships Between Lipoprotein Components." 30-38.

As mentioned above, the top 5 percent of the total population was considered to be substandard. Further, it was assumed the average reading for the substandard population was in the middle of this 5 percent or at 2.5 percent. Using the mean and standard deviation of the distribution, the Apo ratios corresponding to the 97.5 percentiles were as follows:

Table 5. Apolipoprotein Ratios for 97.5 Percentiles

	Male	Female
Average substandard	1.57	1.40
Average non-substandard	0.97	0.82

The next step is to determine the average non-substandard Apo ratio readings. These are derived from the total population mean value in Table 4 and the substandard value in Table 5.

$$\underline{Male: 95\% \times X + 5\% \times 1.57 = 1.00}$$
$$\underline{Female: 95\% \times X + 5\% \times 1.40 = 0.85}$$

For males, X = 0.97 and for females, X = 0.82, the non-substandard Apo ratio readings.

The next step is to use the hazard ratios provided in the study to convert the Apo ratio values into a mortality assumption to determine the ratio of mortality in the substandard class to the average mortality of all others.

For males, the mean non-substandard Apo ratio was 0.97 and the mean substandard Apo ratio was 1.57. The difference between these is 0.60. Per the study, the age-adjusted hazard ratio for fatalities for each standard deviation of the Apo ratio for males was 1.51 or 51 percent extra mortality. The corresponding standard deviation was 0.29. Therefore, the extra mortality expected for a male substandard was 106 percent more than that for a male standard based on the formula below.

$$\underline{Male: (0.60 \,/\, 0.29) \times 51\% = 106\%}$$

Similarly, for females, the mean standard Apo ratio was 0.82, the mean substandard Apo ratio was 1.40 and the difference was 0.58. The age-adjusted hazard ratio for fatalities for each standard deviation was 1.39 or 39 percent extra mortality. The corresponding standard deviation was 0.28. Therefore, the extra mortality, as calculated below, for a female substandard was 81 percent more than that for a female standard.

$$\underline{Female: (0.58 \,/\, 0.28) \times 39\% = 81\%}$$

Table 6 summarizes the results.

Table 6. Apolipoprotein Mortality Savings Calculation

Item	Male	Female
A) Non-substandard risk	0.97	0.82
B) Substandard risk	1.57	1.40
C) B – A	0.60	0.58
D) Non-substandard standard deviation	0.29	0.28
E) C / D	2.069	2.071
F) Age-adjusted hazard ratio per one standard deviation	1.51	1.39
G) (F – 1) x E	1.06	0.81
H) Proportion of the distribution assumed substandard	**5%**	**5%**
I) G x H	**0.053**	**0.0405**
Additional mortality exhibited by substandard risks	**5.3%**	**4.1%**

To estimate how much of the extra mortality would be determined uniquely by this marker primarily depends on whether the current cholesterol tests are retained or discontinued. It was assumed the tests will be continued until companies became more comfortable with the Apo ratio. With cholesterol still being tested, it is assumed the Apo ratio will uniquely find 5 percent of the substandard cases.

The final assumption needed is for the underlying mortality. It was decided to use mortality assumption described on page 14.

Assuming an average face amount of $100,000, the above assumptions, and using the Calculator, the mortality savings for a male and female age 50 would be $22 and $16, respectively. The cost of the test was determined to be $21. This means this test would be cost-justified at $100,000 for age 50 males, but not for age 50 females. Age 50 females would require a face amount of about $135,000 before the mortality savings would exceed the $21 cost of the test. Note that results will vary by age. In this case, for females, a $100,000 face amount would be cost-justified for ages beginning somewhere between 60 and 70.

This is one of the places where a new marker may be most likely to replace a current marker. Eliminating the lipid panel analysis would influence the cost-benefit analysis of Apo ratios. If the lipid panel analysis is discontinued, more substandard risks will be uniquely identified by the Apo ratio and the savings of no longer doing the other test could be figured into the savings; however, the cost of the Apo ratio test should be increased by the lost mortality savings from using the lipid panel analysis. However, as stated above, replacement of markers is not being considered in this report.

Complete Blood Count (CBC)/Red Cell Distribution Width (RDW)

While this blood test is primarily used in clinical practice, some components have been used by the life insurance industry and others are being reviewed for potential use as valuable mortality predictors. One such component, which will be described in more detail below, is the red cell distribution width. This is a new marker for identifying conditions, such as anemia, that can be a leading indicator for an increased risk of mortality.

Standard components of a complete blood count test include:[11]

- White blood cell count (WBC). This is the number of white blood cells, also known as leukocytes, in a volume of blood. In an infection, white blood cells attack the foreign entity in the body (e.g., the bacteria, virus or some other organism). The number of white blood cells rises with an infection. White blood cells are larger than red blood cells in size, but fewer in number. Health insurers have used the white blood cell count to determine other abnormalities (i.e., a high white blood cell count is indicative of some type of infection).
- White blood cell differential count. There are many different types, shapes and sizes of white blood cells, each playing a different role in protecting the body. The white blood cells used in the differential count are granulocytes (neutrophils, eosinophils and basophils) and agranulocytes (lymphocytes and monocytes).
- Red blood cell count. This is the number of blood red cells in a volume of blood. Red blood cells are more common than white blood cells and serve the purpose of carrying oxygen from the lungs to the rest of the body and carrying carbon dioxide back to the lungs to be exhaled.
- Hematocrit. This is the ratio of the volume of red blood cells to the volume of the whole blood. This ratio varies by gender. Hemocrit has been used by the life insurance industry to check for anemia. A low hematocrit reading signals potential anemia, which is a leading indicator of cancer, iron deficiency and blood loss, among other things. A high hematocrit reading could be indicative of dehydration.
- Hemoglobin. This test represents the amount of hemoglobin in the volume of blood. Hemoglobin is the protein molecule within red blood cells that carries the oxygen to the cells and carbon dioxide from the cells and gives blood cells their red color.
- Mean corpuscular volume. This is the average volume of a red blood cell. It is calculated from the hematocrit and the red blood cell count.

[11] See *LabtestsOnline.org*, s.v. "complete blood count," accessed December 9, 2011, http://labtestsonline.org/understanding/analytes/cbc/tab/glance; *WebMD.com*, s.v. "complete blood count (CBC)," accessed December 9, 2011, http://www.webmd.com/a-to-z-guides/complete-blood-count-cbc; *MedicineNet.com*, s.v. "complete blood count (CBC)," accessed December 9, 2011, http://www.medicinenet.com/complete_blood_count/article.htm.

- Mean corpuscular hemoglobin. This is the average amount of hemoglobin in the average red blood cell. It is derived from the measurement of hemoglobin and the red blood cell count.
- Mean corpuscular hemoglobin concentration. This is the average concentration of hemoglobin in a given volume of red blood cells. It is derived from the hemoglobin measurement and hematocrit.
- Red cell distribution width (RDW). This is the measurement of the variability of red blood cell size and shape and is a nonspecific marker. As mentioned above, this component of the CBC is being reviewed as a potential predictor of mortality. It has been found that the larger the variety of sizes of red blood cells, the higher the all-cause mortality risk.
- Platelet count. This is the number of platelets in a volume of blood. Platelets are the smallest type of blood cell and are the component of blood cells that help in blood clotting.
- Mean platelet volume. This is the average size of the platelets in a volume of blood.

For purposes of this study, it is assumed the marker of interest obtained from the CBC is the red cell distribution width (RDW).

Cost
Despite the focus on only the red cell distribution width, the entire CBC panel would need to be purchased. The cost of a CBC is approximately $10.

One hour of training is the estimate of the time needed for underwriters to learn about this new test. The cost for this training is $48.60 based on the salary information described on page 8. Spreading this cost over an amortization period of five years and over 500 applications per year results in a per applicant cost of $0.02.

It is estimated it would take about two minutes for the underwriter to analyze the results for this marker. This adds $1.62 to the cost.

An APS is likely to be ordered due to positive results from this test since the test is a nonspecific marker and an investigation of the cause of the positive results would be needed. It is assumed this would happen in 5 percent of the cases and it would take an underwriter 10 minutes to order an APS and 15 minutes to review it when received. The time cost would be $1.01 based on the same salary information and 1.25 minutes (25 x 5%). The cost for an APS is assumed to be $50. Therefore, the per-applicant cost for the APS would be $2.50 (50 x 5%).

As this marker is new and unique, it is estimated that in 2 percent of the cases, the underwriter may need to take 15 minutes to explain the test to someone receiving an unfavorable rating due to this test. This adds $0.24 to the cost.

The total cost of the test would therefore be $15.39 ($10.00 + $0.02 + $1.62 + $1.01 + $2.50 + $0.24). Assuming 5 percent declines and not takens and spreading the cost over only the

applicants, the cost comes to $16.20 ($15.39 / 0.95). For simplicity, $17 is assumed to be the cost for this analysis.

The RDW costs are summarized in Table 7 below.

Table 7. Red Cell Distribution Width Costs

Item	Cost
A) Laboratory cost	10.00
B) Training time	0.02
C) Review of marker	1.62
D) Ordering an APS	0.40
E) Cost of APS	2.50
F) Review of APS results	0.61
G) Communication of negative results due to marker	0.24
H) Subtotal (sum of A through G)	15.39
I) Percentage of declines and not takens	5%
J) Total cost (H / [1 – I])	16.20
Total cost used (J rounded up to next dollar)	**$17**

Benefit

There are several articles regarding mortality and red cell distribution width. Two studies were chosen that focused on the general population rather than those with populations of people with acute heart failure. The studies chosen both drew information from the third National Health and Nutrition Examination Survey, Centers for Disease Control and Prevention (NHANES III). Further information about these studies is shown in Table 8. The two studies are distinguished below by number of participants —16K[12] and 8K[13]).

[12] Perlstein, et al. “Red Blood Cell Distribution Width.” 588-94.
[13] Patel, et al. “Red Blood Cell Distribution Width.” 515-23.

Table 8. NHANES III Studies

16K study	
Study period	1988-2000
Number of participants	15,852
Number of deaths	2,629 (16.6%)
Requirements	A stratified, multistage sample design was used to produce a nationally representative sample of the noninstitutionalized U.S. civilian population.
Ages	Mean ranged from 39.7 in quintile 1 to 54.1 in quintile 5
Follow up	Mean 8.7 years, survey was 1988-94 and mortality observed through 2000
Location	U.S.
8K study	
Study period	1988-2000
Number of participants	8,175
Number of deaths	2,428 (29.7%)
Requirements	A stratified, multistage sample design was used to produce a nationally representative sample of the noninstitutionalized U.S. civilian population.
Ages	45+, mean ranged from 58.3 in quintile 1 to 65.7 in quintile 5
Follow up	Median 7.9 years, maximum 12.1 years, survey was 1988-94 and mortality observed through 2000
Location	U.S.

Both studies had data split into quintiles. While the data may not be normally distributed, a normal distribution was assumed for simplicity. The 16K study had more data allowing for the determination of the normal curve for the fifth quintile, while for the 8K study, the normal curve needed to be determined over the entire data set.

The extra data provided in the 16K study was the interquartile range within each quintile. The standard deviation was calculated in the 16K study from this data and both the mean and standard deviation were calculated in the 8K study.

As just mentioned, the 16K study provided interquartile ranges for each quintile. The interquartile range represents the middle 50 percent of the quintile. Using a normal distribution assumption, this implies the middle value is the mean. Therefore, for this study, the mean of the fifth quintile was 14.525 percent (the average of 14.00 percent and 15.05 percent). Next, the standard deviation for the fifth quintile needed to be determined for this study and it was calculated as follows:

$$15.05\% = 14.525\% + 0.675\, x\, \sigma$$

Therefore, 15.05 percent represents the 75th percentile of the fifth quintile as provided in the report, 14.525 percent is the mean as just determined and 0.675 is the probability distribution for a normal curve at the 75th percentile. O' is the standard deviation, and solving the equation above produces a standard deviation in the fifth quintile of 0.778 percent (0.00778) for the 16K study.

For the 8K study, both the mean and standard deviation needed to be solved for. Here, the standard deviation was solved for first as follows:

$$\underline{14.05 = \mu + 0.842\ x\ O'}$$

$$\underline{13.40 = \mu + 0.253\ x\ O'}$$

Subtracting the second equation from the first equation produces:

$$\underline{0.65 = 0.589\ x\ O'}$$

Therefore, the standard deviation is equal to 1.104 for this study. Next, the overall mean was solved for. Substituting the standard deviation into the first equation produces:

$$\underline{14.05 = \mu + 0.842\ x\ 1.104}$$

Solving for the mean, 13.12 is the result for the 8K study.

Table 9 summarizes the mean and standard deviation for the two studies.

Table 9. RDW Mean and Standard Deviation

	16K study: 5th quintile results	8K study: overall results
Mean	14.525%	13.12%
Standard deviation	0.778	1.104

All of the studies reviewed confirmed that mortality increases with increasing variability of red cell distribution width. Increasing variability of red cell distribution width corresponds to a higher percentage measurement. Therefore, only one side of the curve needs to be utilized. To determine the average substandard red cell distribution width, the top 5 percent of the total population is assumed to be substandard and the middle of this (2.5 percent) to be the average. For the 16K study, only the fifth quintile is considered, so the 87.5 percentile within the fifth quintile is what needs to be looked at. For the 8K study, the full study was considered so the 97.5 percentile is used.

Using the normal curve as described above, the average substandard red cell distribution width percentages were determined and are shown in Table 10.

Table 10. Average Substandard RDW Percentages

16K study	15.42%
8K study	15.28%

The next step is to determine the average non-substandard red cell distribution width percentage. These were derived from the total population mean value in Table 9 and the substandard values in Table 10.

$$\underline{16K\ study}: 95\% \times X + 5\% \times 15.42\% = 14.525\%$$
$$\underline{8K\ study}: 95\% \times X + 5\% \times 15.28\% = 13.12\%$$

For the 16K study, X = 14.48%, and for the 8K study, X = 13.01%.

The next step is to use the hazard ratios provided to convert the red cell distribution percentages into a mortality assumption to determine the extra mortality in the substandard class over that in the non-substandard class.

For the 16K study, the difference between the substandard and non-substandard red cell distribution percentages is 0.94 percent (15.42% – 14.48%), and 0.94 percent represents 1.21 (0.94% / 0.778%) standard deviations. The adjusted hazard ratio from the study was 1.23 for each standard deviation. Therefore, the extra mortality in the substandard group over the non-substandard group is 27.83 percent (1.21 x [1.23 – 1]).

For the 8K study, the difference between the substandard and non-substandard red cell distribution percentages is 2.27 percent (15.28% – 13.01%). In this study, it was found that mortality increased by 22 percent for each 1 percent increment of red cell distribution width percentage. Therefore, the extra mortality in the substandard group over the non-substandard group is 49.94 percent (2.27% x 22%).

To come up with one extra mortality assumption, the individual results were averaged using the number of lives in the study as a weight.

Table 11. RDW Mortality Savings Calculation

Item	16K study	8K study
A) Non-substandard risk	14.48%	13.01%
B) Substandard risk	15.42%	15.28%
C) B – A	0.94%	2.27%
D) Non-substandard standard deviation	0.778%	
D1) Percent increase in mortality per 1% increment		22%
E) C / D; (C / .01) x D1	1.21	49.94%
F) Age-adjusted hazard ratio per one standard deviation	1.23	
G) (F – 1) x E	.2783	
H) Number of lives in each study	15,582	8,175
I) Weighted average additional mortality	34.43%	
J) Proportion of the distribution assumed substandard	5%	
K) I x J	1.722%	
Weighted average additional mortality	**1.7%**	

Assuming this is a unique marker, an estimate of 90 percent of the extra mortality findings from this marker could be attributed to the marker.

The same underlying mortality, as described on page 14, is assumed to be the normal mortality assumption.

Assuming an average face amount of $100,000, the above assumptions, and using the Calculator, the mortality savings for a male and female age 60 would be $163 and $150, respectively. At $25,000, the mortality savings for male and female 60-year-olds would be $41 and $37. This means the $17 cost for the red cell distribution width test is justified for a face amount as low as $25,000 for a 60-year-old applicant due to the mortality savings one could expect from this test.

This marker is unique and appears to be both effective and cost-justified, so it is possible this marker may be adopted, possibly even ahead of some of the other more well-known markers. Neither this nor any other marker is being endorsed. Rather, some observations are being provided for the reader.

Cystatin C

Cystatin C is a blood serum measure of renal (kidney) function and elevated levels are associated with cardiovascular diseases such as myocardial infarction, stroke, heart failure and peripheral arterial disease, and the risk of death. In the life insurance industry, cystatin C is typically used with older age applicants or when there is a known kidney dysfunction. Other conditions that can affect serum cystatin C levels are cancer, some thyroid diseases and possibly some medications.

Often when assessing the underwriting status of an older age applicant, a serum creatinine test will be ordered as part of the underwriting process or will be reviewed when such a test is part of the attending physician's statement. Creatine is a compound made primarily in the liver and then transported to the muscles, where it is used as an energy source for muscle activity. Once in the muscle, some of the creatine is spontaneously converted to creatinine. The creatinine is subsequently filtered by the kidney. The amount of both creatine and creatinine depend on muscle mass, so men usually have higher levels than women. Creatinine levels relate to both muscle mass and to kidney function. As people age, muscle mass decreases, lowering creatinine, and the kidneys tend to function less effectively, raising creatinine levels. The result is little detectible net change in the creatinine test result.

Cystatin C is a protein produced by most cells in the body. It is removed from the body by the kidneys. If the kidneys are not functioning well, levels of cystatin C will rise. Cystatin C is not influenced by muscle mass conditions and therefore is a more independent marker specific to kidney dysfunction. Cystatin C can correct a falsely low value from a serum creatinine test.[14] It appears to be independent of age, sex and lean muscle mass.[15]

The test itself is conducted on blood serum in the laboratory using a reagent (see the Glossary section for a definition of both blood serum and reagent). Currently, the cystatin C test is ordered as a supplement to the creatinine test, primarily on older age applicants. The primary reason for its development is the expansion of the senior age demographic. It is also currently used in long-term care underwriting.

Cost
The current average cost for cystatin C is about $10.

Another cost to consider is the underwriter's time to learn about the marker. It is estimated it would take the underwriter about one hour to learn about this test. Like before, this is spread over five years and 500 policies. Using the salary information on page 8, the additional cost per applicant would be $0.02 ($48.60 / 5 / 500).

[14] *LabTestsOnline.org*, s.v. "cystatin C," accessed December 15, 2011, http://labtestsonline.org/understanding/analytes/cystatin-c/tab/test.
[15] Shlipak, et al. "Cystatin C and the Risk of Death." 2049-60.

It is assumed it would take an underwriter about five minutes to evaluate this marker. It is also assumed an APS is needed in about 5 percent of the cases and that it would take the underwriter another five minutes to order an APS and 15 minutes to evaluate it once received. Using the same salary information, this would result in an extra cost of $4.86 for the underwriter's time.

It is assumed the cost of an APS will average $50. If an APS is ordered in 5 percent of the cases, this would add another $2.50.

Assuming 5 percent of these cases result in a decline and it takes 15 minutes on average to provide the decline notice and sometimes respond to follow up, this would add $0.61 to the cost.

The total cost would be $17.99 ($10.00 + $0.02 + $4.86 + $2.50 + $0.61). Assuming a rate of declines and not takens of 5 percent, the final cost per insured would be $18.94 ($17.99 / 0.95). For simplicity, a total cost of $19 is assumed for this marker.

Another potential cost would be the mortality savings lost if this test were to replace the creatinine test; however, it is assumed cystatin C will be used in addition to the creatinine test rather than instead of it.

The cystatin C costs are summarized in Table 12 below.

Table 12. Cystatin C Costs

Item	Cost
A) Laboratory cost	10.00
B) Training time	0.02
C) Review of marker	4.05
D) Ordering an APS	0.20
E) Cost of APS	2.50
F) Review of APS results	0.61
G) Communication of negative results due to marker	0.61
H) Subtotal (sum of A through G)	17.99
I) Percentage of declines and not takens	5%
J) Total cost (H / [1 – I])	18.94
Total cost used (J rounded up to next dollar)	**$19**

Benefit

There were a number of articles on the mortality associated with cystatin C. Two scientific studies — one from the New England Journal of Medicine (NEJM)[16] and one from the American Society of Nephrology (ASN)[17] — were chosen because they provide good mortality results for the general population.

Higher cystatin C levels were directly associated with a higher risk of death from all causes. Demonstration of this conclusion was portrayed in the studies using hazard ratios (see the Glossary section for a definition of hazard ratios). The mortality events in successive quintiles were compared back to the first quintile, which carried a hazard ratio of 1.00. Note that in one study, the fifth quintile was subdivided into thirds, designated 5a, 5b and 5c.

In each of these studies, creatinine was also reviewed. However, it was concluded that cystatin C is a stronger predictor of all-cause mortality (and cardiovascular events) in the elderly than is creatinine. In fact, while creatinine showed mortality to be J-shaped curve with only the last quintile demonstrating higher mortality, cystatin C showed a linear relationship to the risk of death from all causes.

While analysis was also completed in these studies on cardiovascular and stroke mortality, only all-cause mortality was analyzed as that is the most important measure for this review of the benefit of using cystatin C as a medical marker used in life insurance underwriting.

As the focus is solely on the analysis of mortality results, it is recommended the reader review the actual studies for an in-depth understanding of the results and the limitations and caveats noted therein.

Both studies were performed on population-based cohorts of elderly adults, although one study selected participants on the basis of preserved physical function. Some of the characteristics of the studies include:

[16] Ibid.
[17] Shlipak, et al. “Cystatin C and Mortality Risk.” 254-61.

Table 13. Cystatin C Studies

New England Journal of Medicine (NEJM) study	
Study period	1992-2001
Number of participants	4,637
Number of deaths	1,316 (28%)
Requirements	Age 65+, Medicare eligible, not institutionalized and expected to remain that way for three or more years, must be able to provide own written consent
Ages	Quintile 1: 73 ± 4 years; Quintile 5: 78 ± 6 years
Follow up	Median 7.4 years, maximum 8.1 years
Location	Forsyth County, N.C.; Sacramento County, Calif.; Washington County, Md.; Pittsburgh, Pa.
American Society of Nephrology (ASN) study	
Study period	1997-2004
Number of participants	3,075
Number of deaths	557 (18%)
Requirements	Age 70-79, Medicare eligible, highly functional
Ages	Quintile 1: 73.0 ± 2.8 years; Quintile 5: 74.3 ± 2.9 years
Follow up	Six years
Location	Memphis, Tenn.; Pittsburgh, Pa.

Both studies parsed the cohorts into quintiles of cystatin C measurements, though the quintiles in the two studies had slightly different break points.

The first thing looked at was the mean and standard deviation of the fifth quintile for cystatin C in each study to create a normal distribution. While the data in the quintile may not follow a normal distribution, it is close enough to one to produce reasonable results. Note that since the whole cystatin C curve is linear, as mentioned above, Quintile 1 is not needed for the calculation since there is no indication of a J- or U-shaped curve. Table 14 shows the mean and standard deviation for the fifth quintile for both of the studies.

Table 14. Cystatin C (mg/L) Mean and Standard Deviation

	NEJM	ASN
	Quintile 5	Quintile 5
Mean	1.61	1.48
Standard deviation	0.48	0.52

As with the other markers, the top 5 percent of the total population is assumed to be substandard. Further, it is assumed the average is in the middle of this 5 percent or at 2.5 percent. Since quintiles are being used, the top 2.5 percent of the entire population is found in quintile 5 (top 20 percent). Therefore, the ratio (.025 / .20) or 12.5 percent is used to determine the cystatin C level at which substandard begins. For this step in the process, one only needs to

be concerned with cystatin C readings at and beyond the 87.5 percentile (100 – 12.5) of the normal curve representing the fifth quintile. Using the mean and standard deviation of the distribution for the fifth quintile, the cystatin C readings corresponding to the 87.5 percentile is as follows:

Table 15. Average Substandard Cystatin C (mg/L) Percentages

	NEJM	ASN
Average substandard	2.16	2.08

The next step is to determine the average non-substandard cystatin C readings. These are derived from the mean quintile values, the total population mean value and the substandard values just calculated.

$$\underline{NEJM: 95\% \times X\ (\text{mg/L}) + 5\% \times 2.16\ (\text{mg/L}) = 1.12\ (\text{mg/L})}$$
$$\underline{ASN: 95\% \times X (\text{mg/L}) + 5\% \times 2.08\ (\text{mg/L}) = 1.04\ (\text{mg/L})}$$

For NEJM, *X* = 1.07 (mg/L). For ASN, *X* = 0.99 (mg/L). Table 16 below provides detail.

Table 16. Mean Cystatin C Readings

	NEJM							
	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	Mean total population[18]	Mean non-substandard	Mean substandard
Cystatin C (mg/L)	0.81	0.95	1.05	1.18	1.61	1.12	1.07	2.16
	ASN							
	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	Mean total population	Mean non-substandard	Mean substandard
Cystatin C (mg/L)	0.75	0.88	0.99	1.10	1.48	1.04	.99	2.08

The next step is to use the hazard ratios provided to convert the cystatin C values into a mortality assumption to determine the ratio of mortality in the substandard class to the average mortality of all others.

For the New England study, the mean non-substandard cystatin C value of 1.07 mg/L falls in the Quintile 3 range of 1.00 to 1.10 mg/L. This corresponds to an adjusted hazard ratio[19] of 1.00 to 1.53. Since 1.07 mg/L falls 80 percent of the way between 1.00 and 1.10 mg/L, the hazard ratio,

[18] Arithmetic average of all five quintile values.
[19] Adjusted for age, sex and a variety of presence or absence of conditions and diseases.

which is 80 percent of the way between 1.00 and 1.53, is 1.42 (1.21 + 80% x [1.53 – 1.00]). To determine the corresponding adjusted hazard ratio for the substandard class, the Quintile 5 (including 5a, 5b and 5c) range is 1.34 to 3.27. Remember, the average is 87.5 percent of the way toward the end of this quintile. Therefore, the adjusted hazard ratio for the substandard class is 3.03 (1.34 + 87.5% x [3.27 – 1.34]). Therefore, the ratio of substandard to standard mortality is 2.13 (3.03 / 1.42) or 113 percent extra mortality in the substandard class.

For the ASN study, the mean non-substandard cystatin C value of 0.99 mg/L falls in the Quintile 3 range of 0.94 to 1.03. This corresponds to an adjusted hazard ratio of 1.17 to 2.30; 0.99 mg/L falls half way between 0.94 and 1.03. Therefore, the hazard ratio at the midpoint of 1.17 and 2.30 is 1.74 (1.17 + 50% x [2.30 – 1.17]). To determine the corresponding hazard ratio for the substandard class, the Quintile 5 range is 1.95 to 3.70. Remember, the average is 87.5 percent of the way toward the end of this quintile. Therefore, the hazard ratio for the substandard class is 3.48 (1.95 + 87.5% x [3.70 – 1.95]). The ratio of substandard to non-substandard mortality is 2.00 (3.48 / 1.74) or 100 percent extra mortality in the substandard class.

The weighted average of this extra mortality between the two studies, based on the population of the studies, is 108 percent ([113 x 4,637 + 100 x 3,044] / [4,637 + 3,044]).

Table 17. Cystatin C Mortality Savings Calculation

Item	NEJM	AJS
A) Hazard ratio non-substandard risk	1.42	1.74
B) Hazard ratio substandard risk	3.03	3.48
C) B / A	213%	200%
D) [C – 100%]; extra mortality	113%	100%
E) Number of lives in study	4,637	3,044
F) Weighted average extra mortality	108%	
G) Proportion of the distribution assumed substandard	5%	
H) E x F	5.4%	
Additional mortality exhibited by substandard risks	**5.4%**	

There is now enough information to determine the mortality savings for implementing the cystatin C test. As before, normal mortality is assumed to be as described on page 14.

It is assumed creatinine tests will continue to be used and 40 percent of the findings will be uniquely found by cystatin C.

Based on these assumptions, a $100,000 average policy size, and using the Calculator, the mortality savings for a 70-year-old male and female would be $272 and $260, respectively. For a $10,000 policy, the mortality savings for a 70-year-old male and female would be $27 and $26, respectively, still greater than the estimated cost of $19.

Note that the savings will vary by age and are typically lower at the younger ages. Also, if cystatin C were to replace the creatinine test, the mortality savings found for kidney disease would go up, but this would be balanced by the mortality savings lost from not doing the creatinine test. This loss of mortality savings should be considered an added cost.

Hemoglobin (also spelled haemoglobin and abbreviated Hb or Hgb)

Hemoglobin is a protein in the red blood cells that transports oxygen from the lungs to the rest of the body, where it releases the oxygen for cell use and collects carbon dioxide to bring back to the lungs. Hemoglobin readings can reveal physiological diseases. Low levels of hemoglobin can indicate anemia, a condition in which the body is not getting enough oxygen, causing fatigue and weakness. Common causes of anemia include iron deficiency, cirrhosis of the liver, kidney disease and bone marrow failures. A low hemoglobin level can also be considered an indicator for other conditions and diseases, such as cancer. In other people, a low hemoglobin value can be a sign of poor nutrition. Particularly in senior populations, low hemoglobin may be indicative of an undiagnosed malignancy.

The hemoglobin test is typically used for older ages. Normal ranges for hemoglobin vary, but in general are:[20]

Male	13.8 to 17.2 gm/dL
Female	12.1 to 15.1 gm/dL

Cost

There is a cost of approximately $10 for the hemoglobin test. Hemoglobin is part of the CBC, and it is assumed the full CBC needs to be ordered to receive the hemoglobin analysis. Note that if the red blood cell distribution test and hemoglobin were both adopted for use in underwriting, the cost of the CBC would be shared among these tests and any other CBC test utilized. For the purposes of this report, it is assumed this marker is independent of the others in deriving the cost.

Another cost to consider is the underwriter's time to learn about the marker. While it is assumed most underwriters are familiar with this test, a 30-minute refresher may be necessary. Assuming the salary information on page 8, a five-year amortization and 500 applicants per year, the per applicant cost for underwriter training is $0.01.

It will take about one minute to evaluate an individual's test result if the values are normal, but will take 10 minutes for further evaluation if there are readings outside the normal range. It is assumed 10 percent of the cases would have abnormal readings. Therefore, the average evaluation time is about two minutes (1 x 0.90 + 10 x 0.10). The underwriter's time cost for evaluating the risk for this marker is $1.62.

An unfavorable hemoglobin measure may lead to an APS and evaluation of those results. It is assumed an APS is ordered in some of the cases (10 percent of the cases) and it will take an underwriter an extra five minutes to order the APS and 15 minutes to evaluate the results. This

[20] *MedlinePlus.org*, s.v. "hemoglobin," accessed December 15, 2011, http://www.nlm.nih.gov/medlineplus/ency/article/003645.htm.

would result in an extra $1.62 of the underwriter's time and an extra $5 ($50 APS cost x 10 percent of the cases) for the APS cost.

Since an unfavorable hemoglobin measure may be caused by a variety of issues, it may be a bit more difficult for the underwriter to explain an unfavorable rating due to hemoglobin. It is assumed it will take 20 minutes on average for this call. It is also assumed this would occur in about 1 percent of the cases. The additional cost for this would be $0.16.

Therefore, the estimated cost of this test would be $18.41 ($10.00 + $0.01 + $1.62 + $1.62 + $5.00 + $0.16). Assuming 5 percent of the cases were declined or not taken, and the cost is spread over all insureds, the final cost estimate for this marker is $19.38 ($18.41 / 0.95). For simplicity, a total cost of $20 for this marker is used.

The hemoglobin costs are summarized in Table 18 below.

Table 18. Hemoglobin Costs

Item	Cost
A) Laboratory cost	10.00
B) Training time	0.01
C) Review of marker	1.62
D) Ordering an APS	0.40
E) Cost of APS	5.00
F) Review of APS results	1.22
G) Communication of negative results due to marker	0.16
H) Subtotal (sum of A through G)	18.41
I) Percentage of declines and not takens	5%
J) Total cost (H / [1 – I])	19.38
Total cost used (J rounded up to next dollar)	**$20**

Benefit

There were a number of articles on hemoglobin and its relationship to mortality; however, they typically focused on impaired lives. These studies reveal there is an increased risk of death associated with lower-than-average levels of hemoglobin while there is no increased risk or mortality associated with higher-than-average levels of hemoglobin. Also noted in the studies is that the variability among an individual's hemoglobin readings is generally more predictive than the actual hemoglobin reading level itself. Leveraging hemoglobin variability as an indicator of health risk poses a problem for use in life insurance underwriting unless prior readings can be reliably obtained. For the purposes of this report, the focus is on the absolute level of hemoglobin in the blood and how it influences mortality.

Data used in this analysis is from research referred to as the Fresenius Medical Care Study.[21] For the reader interested in further research on hemoglobin, there are two additional studies.[22]

[21] Ofsthun et al. "The Effects of Higher Hemoglobin Levels." 1908-14.

Fresenius Medical Care North America is a dialysis provider that treats end-stage renal dialysis patients throughout the United States and maintains an extensive database of patient information. The purpose of the Fresenius study was to evaluate the association of hemoglobin level with mortality, among other things. Details of the study are shown in Table 19.

Table 19. Fresenius Medical Care Study

Study period	1998-2000
Number of participants	44,550
Number of deaths	3,975 (9%)
Requirements	Hemodialysis patients with end-stage renal disease (ESRD) in Fresenius Medical Care North America facilities for six consecutive months between July 1, 1998, and June 30, 2000
Ages	Mean 59.73, standard deviation 15.3
Follow up	Six months following initial six-month stay
Location	Fresenius Medical Care North America, more than 900 facilities across U.S.

Assuming a normal distribution, the first step is to determine the mean and standard deviation so an estimate can be made of the substandard reading. In the study, the population was categorized into six hemoglobin reading levels: <9 g/dL, 9 to <10 g/dL, 10 to <11 g/dL, 11 to <12 g/dL, 12 to <13 g/dL, and ≥13 g/dL. These categories and corresponding mean hemoglobin values are shown in Table 20.

Table 20. Fresenius Study Hemoglobin (g/dL) Reading Levels

	<9	9 to <10	10 to <11	11 to <12	12 to <13	≥13	All
Mean hemoglobin	8.36	9.59	10.57	11.47	12.36	13.64	11.00

As the standard deviation was not provided, it had to be solved for.

The study data suggests the risk of death is inversely associated with hemoglobin levels. In a true normal distribution, it would not matter where on the curve the standard deviation was calculated. However, the data is not exactly normally distributed. Therefore, the calculation of the standard deviation was performed on the lower end of the readings range, assuming a normal distribution within that range.

For the six groups provided, the mean is 11 g/dL. From Table 17, the value at the 16.67 percentile (the first category of readings, or the bottom 16.67 percent of the population) is 9. From a standard normal distribution, the x-value corresponding to 16.67 percentile is -0.966. Therefore, the standard deviation was solved for using the following formula:

[22] See Carson, et al., “Mortality and Morbidity,” 812-18, and Gilbertson, et al., “Hemoglobin Level Variability,” 133-38.

$$9\ (\text{g/dL}) = 11\ (\text{g/dL}) - 0.966\ X\ \sigma$$

From this equation, the standard deviation is 2.07 g/dL. Table 21 shows the mean and standard deviation.

Table 21. Hemoglobin (g/dL) Mean and Standard Deviation

Fresenius Study	
Mean	11
Standard deviation	2.07

It is assumed that 5 percent of the total population with the lowest hemoglobin readings is substandard and the average substandard is in the middle of this 5 percent or at 2.5 percent.

Given the distribution parameters above, the average substandard hemoglobin reading is 6.94 g/dL. To calculate the average non-substandard hemoglobin reading, the following formula is used:

$$95\% \times X\ (\text{g/dL}) + 5\% \times 6.94\ (\text{mg/L}) = 11\ (\text{g/dL})$$

Solving for X, the average non-substandard hemoglobin reading is 11.21. The averages are summarized in Table 22.

Table 22. Average Substandard and Non-substandard Hemoglobin (g/dL) Readings

Substandard	6.94
Non-substandard	11.21

The next step is to determine the extra mortality associated with the substandard group. Hazard ratio information is provided in the study. Per the study, for each movement down of 1 g/dL, there is an increase in hazard ratio of 0.3 (or 30 percent) from the non-substandard level. Therefore, the extra mortality is calculated as follows:

$$Extra\ mortality = (11.21 - 6.94) \times 30\%$$

The extra mortality for those with substandard hemoglobin readings when compared to those with non-substandard hemoglobin readings is 6.4 percent.

Table 23. Hemoglobin Mortality Savings Calculation

Item	Mortality savings
A) Non-substandard risk	11.21
B) Substandard risk	6.94
C) B – A	4.27
D) Hazard ratio increase per -1 g/dL change in hemoglobin reading	30%
E) [C / 1] x 30%; additional mortality	1.28
F) Proportion of the distribution assumed substandard	5%
G) E x F	.064
Additional mortality exhibited by substandard risks	**6.4%**

It is assumed normal mortality is as described on page 14.

It is also assumed this marker is solely responsible for identifying 70 percent of the excess mortality. Each applicant situation is different, however, and it is possible an APS may have already been ordered for another reason or other related issues are found through other markers.

Based on these assumptions, a $100,000 average policy size, and using the Calculator, the mortality savings for a 60-year-old male and female would be $472 and $434, respectively. The savings is greater than the estimated cost of $20 and is so at age 60 for policy sizes as low as $5,000.

Hemoglobin A1c (formal name: hemoglobin A1c or glycated hemoglobin)
The best way to measure blood glucose levels over time is the glycated hemoglobin A1C test. This blood test, given by a physician, reflects average blood sugar control over three months.[23]

Hemoglobin is a protein in the red blood cells that transfers oxygen to tissues and removes carbon dioxide for transfer to the lungs. The predominant form of hemoglobin is called hemoglobin A. As glucose enters the blood stream, it spontaneously binds to hemoglobin A. This compound is said to be glycated. Higher amounts of glycated hemoglobin reflect higher levels of glucose in the blood. The glycated hemoglobin lasts the life span of a red blood cell, about 120 days. The A1C test serves as a marker for the average amount of glucose in the blood over the last two to three months. It does this by calculating the ratio of glycated hemoglobin to total hemoglobin.

Currently, A1c is used to monitor diabetic control. The American Diabetes Association (ADA) recommends A1c testing at least twice a year for those with diabetes. In addition, the ADA has recently added A1c as a diagnosis marker for diabetes.

The A1c test itself is not new. Historically, it has been used to monitor diabetic control in known diabetics. It wasn't until about six years ago that this test was believed to be able to be used for more than reflex purposes. It is now thought, at least for life insurance purposes, that A1c can be used for nondiabetics to determine the ability of the body to utilize glucose and help predict those more likely to get diabetes. It is also thought that A1c should be used as a "primary test" due to a pilot study indicating some diabetes risks were missed with normal markers.

Cost
The average hemoglobin A1c test cost is $10.

Most underwriters know about and understand the hemoglobin A1c test so it is assumed training costs would be negligible. It is assumed it takes about one minute for the underwriter to evaluate this marker. However, poor readings that do not result in a decline or postpone may cause the underwriter to order an APS. This is assumed to occur in about 10 percent of the cases and takes about 10 minutes to order the results and 15 minutes to evaluate it. Therefore, the extra cost for an underwriter's time would be $2.84 (3.5 minutes on average and using the salary from page 8). The cost of the APS is about $5 (10% x $50).

Extra time should not be needed by the underwriter to explain the reason for any poor ratings for the hemoglobin A1c because this information is referred to the physician, who is very familiar with the test.

Therefore, the estimated cost of this test would be $17.84 ($10.00 + $2.84 + $5.00). If 5 percent of the cases were assumed to be declined or not taken, and the cost was spread over all

[23] http://www.mayoclinic.org/news2009-mchi/5174.html, accessed December 15, 2011

insureds, the final cost estimate for this marker would be $18.73 ($17.84 / 0.95). For simplicity, $19 is assumed as the total cost for this marker.

The hemoglobin A1c costs are summarized in Table 24 below.

Table 24. Hemoglobin A1c Costs

Item	Cost
A) Laboratory cost	10.00
B) Training time	0.00
C) Review of marker	0.81
D) Ordering an APS	0.81
E) Cost of APS	5.00
F) Review of APS results	1.22
G) Communication of negative results due to marker	0.00
H) Subtotal (sum of A through G)	17.84
I) Percentage of declines and not takens	5%
J) Total cost (H / [1 – I])	18.73
Total cost used (J rounded up to next dollar)	**$19**

Benefit

There were a number of good articles on hemoglobin A1c. Two good articles were not used but are recommended for the readers.[24] These articles were not used because they were written by Clinical Reference Laboratory and it was desired to maintain independence in evaluating the mortality results for a marker. The articles are geared for application to life insurance underwriting and provide a good analysis by age group.

Two other good articles[25] were not chosen because these studies dealt solely with impaired lives. The study used[26] is part of the larger European Prospective Investigation into Cancer in Norfolk (EPIC-Norfolk). This is a study on a general population, not an impaired population. Further details on the Norfolk A1c study are shown in Table 25.

[24] See Stout, et al., “Relationship of Hemoglobin A1c,” 174-81, and Dolan, et al., “Hemoglobin A1c and Mortality.”
[25] See Menon, et al., “Glycosylated Hemoglobin,” 3411-17, and Aguilar, et al., “Relationship of Hemoglobin A1C,” 422-48.
[26] Khaw, et al. “Association of Hemoglobin A1.” 413-20.

Table 25. Norfolk Study

Study period	1995-2003
Number of participants	10,232 (4,662 men and 5,570 women)
Number of deaths	521 (5%)
Requirements	Norfolk residents who had their hemoglobin A1c and other cardiovascular risk factors assessed from 1995 to 1997
Ages	40-79
Follow up	To 2003
Location	Norfolk, U.K.

The first step is to estimate the average A1c level of individuals considered to exhibit substandard mortality. It was assumed the 5 percent of the population with the highest A1c readings to be substandard. While this study showed worse mortality as the A1c levels increased, other studies have shown some worse mortality results at the lowest readings. That said, the highest readings had much worse mortality experience than the lowest so it was assumed this is one sided.

Data is provided for males and females separately. Study participants with the highest readings (mean of 8.0 percent ± 1.9 percent standard deviation) were categorized together as people with known diabetes. Participants with known diabetes represent 2.4 percent ([160 + 83] / [4,662 + 5,570]) of the overall population. This was derived from the individual male and female population figures. To complete the assumed 5 percent population considered substandard, an additional 2.6 percent of the worst risks of the population are needed. These individuals would have high A1c readings but have not been clinically diagnosed as diabetic.

The study provided a mean of 5.3 percent ± 0.7 percent standard deviation for nondiabetic study participants. Assuming a normal distribution and the middle of the remainder representing the average, the average remainder readings were calculated. With 2.6 percent remaining, the middle or 1.3 percent (98.7 percentile) reading is 6.86 percent. Combining these to determine the overall substandard, gives the following formula:

$$\underline{Substandard\ A1c}: (\ 2.4\% \times 8\% + 2.6\% \times 6.86\%\ ) / 5\%$$

The substandard A1c reading is 7.41 percent. The non-substandard reading can then be determined by the following formula:

$$\underline{Male\ Nonsubstandard\ A1c}: 95\% \times 5.3\% + 5\% \times 7.41\%$$

Therefore, the non-substandard A1c reading is 5.41 percent. Table 26 summarizes the results.

Table 26. Average Hemoglobin A1c Percentages

Substandard	7.41%
Non-substandard	5.41%

The next step is to determine the extra mortality of the substandard group. From the study, the age-adjusted relative risk ratios show that for each 1 percent increase in A1c, mortality increases by 24 percent for men and 28 percent for women. Therefore, the following formulas show the extra mortality for the substandard individuals.

$$\underline{Male\ extra\ morality}\text{: } (7.41\% - 5.41\%) \times 24\%$$
$$\underline{Female\ extra\ morality}\text{: } (7.41\% - 5.41\%) \times 28\%$$

The extra mortality for those with substandard A1c readings over those with non-substandard A1c readings is 48 percent for males and 56 percent for females.

Table 27. Hemoglobin A1c Mortality Savings Calculation

Item	Male	Female
A) Non-substandard risk	5.41	5.41
B) Substandard risk	7.41	7.41
C) B – A	2.00	2.00
D) Mortality increase per 1% increase in hemoglobin A1c reading	24%	28%
E) D x C; additional mortality	.48	.56
F) Proportion of the distribution assumed substandard	5%	5%
G) E x F	.024	.028
Additional mortality exhibited by substandard risks	**2.4%**	**2.8%**

Normal mortality was again assumed to be described on page 14.

It was assumed this marker is solely responsible for identifying 50 percent of the excess mortality, as there are other ways to discover higher glucose levels.

Based on these assumptions, a $100,000 average policy size, and using the Calculator, the mortality savings for a 60-year-male and female would be $128 and $137, respectively. The savings is greater than the estimated cost of $19, for policy sizes as low as $15,000.

As of the writing of this report, more companies are using the A1c as a routine marker at ages 35 to 40 and up, where until recently A1c had primarily been used as a reflex test.

Microalbumin

Albumin, an important protein found in blood, is almost entirely retained in blood as it passes through healthy kidneys. Although most normal people do not lose any albumin into their urine, labs usually accept that a concentration of albumin of < 3mg/dL measured from a spot urine sample is within normal limits. Albumin amounts greater than this can be associated with disease states such as diabetic nephropathy or hypertension. Some basic terminology for this condition (expressed in concentration in a spot urine sample) is:

Normoalbuminuria 0 – 3 mg/dL
Microalbuminuria 3 – 30 mg/dL
Macroalbuminuria > 30 mg/dL

Albuminuria can also be expressed as a ratio between urinary albumin and urinary creatinine. This is done to compensate for variations in urine concentration due to patient dehydration or deliberate adulteration of a specimen by dilution with water. This ratio may be called by various terms such as the albumin/creatinine ratio, or the microalbumin/ creatinine ratio. The most common units for this ratio are mg (albumin)/gm (creatinine) or mg/mmol. Using these units, *micro*albuminuria occurs between levels of 30 mg albumin/gm creatinine and 300 mg albumin/gm creatinine (or 3.5 to 35 mg/mmol).

Proteinuria is a more general term used when there is protein, of which albumin is only one of several types, in the urine.

Cost
There is a laboratory cost of approximately $10 for microalbumin. It is assumed for this analysis the test is used on all applicants. If the test is used solely as a reflex test, the laboratory cost would likely increase some, but the percentage of applicants for which the test would be used would decrease materially.

Another cost to consider is the underwriter's time to learn about the marker. As many underwriters are familiar with the marker, 30 minutes of training time is assumed to be needed. Using the salary information on page 8, amortization over five years and 500 applications per year, the cost would be $0.01 per applicant.

It is assumed it would take an underwriter about two minutes to evaluate this marker, possibly in conjunction with the hemoglobin A1c. Assuming the same salary information, the cost for the underwriter evaluation would be $1.62.

For adverse readings, an underwriter may request two additional urine specimens. These may either confirm the abnormalities or reveal no microalbuminuria in the new specimens. It is assumed this would be needed in 10 percent of the cases. It should be noted this percentage is likely to vary by age, being lower for the younger ages and higher for the older ages. It is also

assumed it would take 10 minutes to order the new specimens and 15 minutes to review the results. The average cost for the new tests will be higher than the $10 assumed for the microalbuminuria test because the urine test is needed for just this test so the cost can no longer be spread over multiple tests. The average cost for a urine specimen is $45. Therefore, the added test cost would be $9 ($90 x 10%). The added time cost would be $2.03 (25 x 10% x $0.81).

It is assumed an explanation of the microalbumin test results will be needed in about 5 percent of the cases and it would take an underwriter 10 minutes to explain negative ratings as a result of microalbumin. This adds another $0.41 to the cost.

The total estimated cost for this test would be $21.45 ($10.00 + $0.01 + $2.03 + $9.00 + $0.41). It was assumed 5 percent of the cases were declined or not taken. The final cost estimate spread over all insureds is $22.58 ($21.45 / 0.95). For simplicity, a total cost of $23 for this marker is assumed.

Another potential cost would be the mortality savings lost if this test were to replace the hemoglobin A1c test. However, these tests are performed independently and it is assumed one would not replace the other.

The microalbumin costs are summarized in Table 28 below.

Table 28. Microalbumin Costs

Item	Cost
A) Laboratory cost	10.00
B) Training time	0.01
C) Review of marker	1.62
D) Ordering new specimens	0.81
E) Cost of new specimens	9.00
F) Review of results from new specimens	1.22
G) Communication of negative results due to marker	0.41
H) Subtotal (sum of A through G)	21.45
I) Percentage of declines and not takens	5%
J) Total cost (H / [1 – I])	22.58
Total cost used (J rounded up to next dollar)	**$23**

Benefit

There are several articles relating to microalbumin and mortality. Two studies[27] — one examining long-duration diabetes and the other older-onset diabetes — were used because these were the best studies found. Details about each of the studies are shown in Table 29.

Table 29. Microalbumin Studies

Long-duration study	
Study period	1995-2000
Number of participants	190
Number of deaths	37 (19%), 25 were cardiovascular deaths (2/3 of deaths)
Requirements	Patients with type 1 diabetes for at least 30 years
Ages	33-83
Follow up	Five years
Location	U.K.
Older-onset study	
Study period	1984-96
Number of participants	840
Number of deaths	364 cardiovascular deaths (43%)
Requirements	Persons with older-onset diabetes mellitus who provided urine samples in a 1984-86 examination of a population-based study of diabetic people
Ages	Mean 67.9, standard deviation 11.0
Follow up	12 years
Location	11-county area in southern Wisconsin

The first step is to estimate the average microalbumin level of individuals considered to exhibit substandard mortality. Unlike the other markers discussed so far, normal readings have no or minimal traces of protein in the urine. Therefore, those with normoalbuminuric readings can be considered non-substandard and those with microalbuminuria and those with worse cases of proteinuria can be considered substandard. For this report, only those with microalbuminuria substandard were considered. Note that all the lives in these two studies are clinically diagnosed diabetics. In the long-duration study, 66 percent of the lives were normoalbuminuric and 22 percent microalbuminuric. Sixty-six percent was considered non-substandard and the 22 percent substandard. In the older-onset study, 55 percent of the lives were normoalbuminuric and are considered non-substandard and 25 percent were microalbuminuric and are considered substandard.

Because the makeup of the population between substandard and non-substandard is known, the readings determination can be skipped. The next step would be the hazard ratio calculation to determine the excess mortality of the substandard over the non-substandard group. With

[27] See Allen and Walker, “Microalbuminuria and Mortality,” 2389-91, and Valmadrid et al., “The Risk of Cardiovascular Disease Mortality,” 1093-1100.

respect to specific readings, the laboratory can provide information as to whether an applicant has microalbuminuria.

For the long-duration study, 11 percent of the non-substandard group (defined as normoalbuminuric) died while 26 percent of the substandard group (defined as microalbuminuric) died over the study period. This implies extra mortality of 136 percent (0.26 / 0.11 – 1) for the substandard over the non-substandard lives.

In the older-onset study, those with microalbuminuria had a 1.84 relative risk ratio, implying 84 percent extra mortality over the non-substandard group. While this result may seem more reasonable, the normal weighting scheme is applied to determine the extra mortality to use:

$$[136\% \times (125 + 42) + 84\% \times (460 + 208)] / [125 + 42 + 460 + 208]$$

Note that 125 and 42 in the above equation are the normoalbuminuric and microalbuminuric count from the long-duration study and 460 and 208 are the same values for the older-onset study. The weighted average extra mortality from the formula above is 94 percent.

Table 30. Microalbumin Mortality Savings Calculation

Item	Long-duration study	Older-onset study
A) Non-substandard risk (percentage dying)	11%	
B) Substandard risk (percentage dying)	26%	
C) (B / A) – 1	136%	
D) From older-onset study, additional mortality of substandard		84%
E) Number of lives for weighting	167	668
F) Weighted average additional mortality	94.4%	
G) Proportion of the distribution assumed substandard	5%	
H) F x G	.0472	
Additional mortality exhibited by substandard risks	**4.7%**	

It is assumed this marker is solely responsible for identifying 25 percent of the excess mortality as there are other ways to discover higher glucose levels.

Normal mortality is assumed to be as described on page 14.

Based on these assumptions, a $100,000 average policy size and using the Calculator, the mortality savings for a 60-year-old male and female would be $125 and $115, respectively. The savings is greater than the estimated cost of $23, even for policy sizes as low as $20,000.

Microalbumin is currently used as a reflex test, if at all. The assumptions made here were based on it becoming a routine test.

NT-proBNP (formal name: amino-terminal pro B-type natriuretic peptide)
This test measures the concentration of NT-proBNP in the blood and is used as a marker for congestive heart failure. It can also differentiate between heart failure and other problems, such as lung disease. This accuracy is even more important in the emergency hospital setting than the life insurance situation. High levels of NT-proBNP (and BNP as will be explained below) are indicative of heart failure or similarly poor conditions for the individual tested. This test can also be used as an indicator for pulmonary disease and poor renal function.

It should be noted that NT-proBNP (and BNP) levels generally decrease when one is taking drugs for a heart condition, such as angiotensin-converting enzyme (ACE) inhibitors, beta blockers and diuretics. On the other hand, the levels increase with age and increase if the person has kidney disease.

ProBNP is a precursor protein for the active hormone BNP (brain natriuretic peptides). In the body, BNP helps regulate blood volume and is an indicator of how hard the heart must work in pumping blood throughout the body. Both BNP and NT-proBNP are produced mainly in the heart's left ventricle, the main pumping chamber, in response to ventricular wall stretch, dilation and pressure overload. When the heart works harder, the concentrations of BNP and NT-proBNP can increase significantly. These two markers may be used to help identify heart failure and quantify its severity. The reason NT-proBNP is used for life insurance purposes rather than BNP is that it is a more stable marker than BNP and lasts longer. BNP is typically the marker used in emergency room settings.[28]

Cost
The cost of the NT-proBNP test is approximately $25.

Another cost to consider is the underwriter's time to learn about the marker. While most underwriters are familiar with the NT-proBNP test, it is assumed they all need to go through a training session to make sure they are familiar with all of the nuances of the test. The training is estimated to take one hour. Based on the salary information on page 8, an amortization period of five years and 500 new applicants per year, the cost would be $0.02.

It is assumed it will take an underwriter two minutes to evaluate a normal case and 15 minutes to evaluate an abnormal test. The percentage of abnormal tests varies greatly by age, with many more abnormal cases being found for older individuals. As it is assumed this test is going to be used primarily at the older ages, it will also be assumed that readings requiring more in-depth analysis will be needed in 10 percent of all cases. Using the same salary information, the 3.3 minutes (2 x 0.90 + 15 x 0.10) translates into a cost of $2.67.

[28] *LabTestsOnline.org*, s.v. "BNP and NT-proBNP," accessed December 15, 2011, http://www.labtestsonline.org/understanding /analytes/bnp/tab/sample.html.

It is assumed an APS may be needed in 10 percent of the cases. It is also assumed it would take the underwriter 10 minutes to order the APS and 15 minutes to review the results. Therefore, the underwriter's time will be 2.5 minutes (10% x [10 + 15]) at a cost of $2.03. The cost for the APS would be about $5 (10 percent of $50).

It is assumed the underwriter will need to spend 10 minutes explaining adverse actions in 5 percent of the cases. This cost is $0.41.

Therefore, the estimated total cost for this test is $35.13 ($25.00 + $0.02 + $2.67 + $2.03 + $5.00 + $0.41). If 5 percent of the cases were declined or not taken and the cost was spread over all insureds, the final cost estimate for this marker would be $36.98 ($35.13 / 0.95). For simplicity, $37 is assumed as the total cost for this marker.

Another potential cost would be the mortality savings lost if this test were to replace the stress test. Some in the industry believe that it should while most are not convinced and continue to use both.

The NT-proBNP costs are summarized in Table 31 below.

Table 31. NT-proBNP Costs

Item	Cost
A) Laboratory cost	25.00
B) Training time	0.02
C) Review of marker	2.67
D) Ordering an APS	0.81
E) Cost of APS	5.00
F) Review of APS results	1.22
G) Communication of negative results due to marker	0.41
H) Subtotal (sum of A through G)	35.13
I) Percentage of declines and not takens	5%
J) Total cost (H / [1 – I])	36.98
Total cost used (J rounded up to next dollar)	**$37**

Benefit

Many research articles were found that focused on NT-proBNP and its relation to mortality. Though not used in this analysis because the authors are associated with the laboratories on which this analysis relied, the reader is encouraged to review this additional material.[29]

The article chosen for analysis examines biomarkers for heart failure.[30] More information on this study is provided in Table 32.

[29] See Winsemius, "The Potential for NTproBNP," 1-10; Winsemius, "New Results Regarding NTproBNP," 1-5; and Illango, "Utilizing NT-ProBNP," 182-91.
[30] McKie, et al. "Amino-Terminal Pro-B-Type Natriuretic Peptide." 874-80.

Table 32. NT-proBNP Study

Study period	1997-2004
Number of participants	1,991
Number of deaths	106 (5%)
Requirements	Randomly selected age 45+ residents of Olmsted County, Minnesota, who did not have heart or renal failure; this was part of the Rochester Epidemiology Project
Ages	45+
Follow up	Mean and median 5.6 years; followed until the earlier of death and November 1, 2004
Location	Olmsted County, Minnesota.

The first step is to determine the average substandard NT-proBNP (pg/mL) reading. While a mean and standard deviation were provided in the study, they appeared to be skewed and could not be used with our normal distribution assumption. Therefore, the mean and standard deviation of the assumed normal distribution were derived based on the key percentiles given (i.e., each third of the distribution) using the following formulas:

$$36.7\ (\text{pg/mL}) = \mu - 0.431 \times \sigma$$
$$109\ (\text{pg/mL}) = \mu + 0.431 \times \sigma$$

The amounts 36.7 and 109 were provided in the report as the upper and lower one-third values and 0.431 are the probabilities from the standard normal distribution for 33.33 percent and 66.67 percent. Subtracting the first from the second, one can solve for σ, the standard deviation. The standard deviation is 83.87 (pg/mL). Solving for μ, the mean, is 72.85 (pg/mL). The mean and standard deviation are shown in Table 33.

Table 33. NT-proBNP (pg/mL) Mean and Standard Deviation

Mean	72.85
Standard deviation	83.87

Using the mean and standard deviation just derived, the average substandard NT-proBNP (pg/mL) reading is determined. Assume substandard represents the worst 5 percent and that the average is in the middle at 2.5 percent. Assuming a normal distribution, the 97.5 percentile, and using the values above, the average substandard NT-proBNP reading is 237.23 (pg/mL).

To determine the average non-substandard NT-proBNP (pg/mL) reading, use the following formula:

$$95\% \times X\ (\text{pg/mL}) + 5\% \times 237.23\ (\text{pg/mL}) = 72.85\ (\text{pg/mL})$$

Solving this equation, the average non-substandard NT-proBNP reading is 64.20 (pg/mL). The results are summarized in Table 34.

Table 34. NT-proBNP (pg/mL) Average Substandard and Non-substandard Readings

Substandard	237.23
Non-substandard	64.20

The next step is to determine the extra mortality associated with the substandard NT-proBNP (pg/mL) readings. The study indicated an extra 63 percent increase in mortality for each standard deviation. The difference between substandard and non-substandard readings is 173.03 (pg/mL) [237.23 (pg/mL) – 64.20 (pg/mL)]; 173.03 (pg/mL) represents 2.06 standard deviations [173.03 (pg/mL) / 83.87 (pg/mL)]. Therefore, the extra mortality expected for substandard NT-proBNP (pg/mL) readings over non-substandard ones would be 130 percent.

Table 35. NT-proBNP Mortality Savings Calculation

Item	Mortality savings
A) Non-substandard risk	64.20
B) Substandard risk	237.23
C) (B – A)	173.03
D) C / standard deviation (C / 83.87)	2.06
E) Increase in mortality per each standard deviation	63%
F) D x E	1.30
G) Proportion of the distribution assumed substandard	5%
H) F x G	.065
Additional mortality exhibited by substandard risks	**6.5%**

Because NT-proBNP reveals some cardiovascular risk cases that today's traditional underwriting does not, assume this marker is solely responsible for identifying 50 percent of the excess mortality of the substandard cases.

The underlying mortality assumption used is as described on page 14.

One item not discussed here is that there is a big difference in prevalence and mortality savings by age with NT-proBNP. The average age in the study was 62. For the calculations below, age 60 is assumed. However, there may be a somewhat reduced impact at younger ages and a significantly larger impact at older ages. The reader is referred back to the laboratory studies to better determine the age range and cost/benefit appropriate for this marker.

Based on these assumptions, a $100,000 average policy size and using the Calculator, the mortality savings for a 60-year-old male and female would be $344 and $316, respectively. The total cost of this marker is estimated at $37, and it appears cost-justified down to $15,000 for age 60. This test is likely not cost-justified at all ages and other studies can be referenced to determine the age (and face amount) at which this test should be considered.

Oxidized LDL (full name: oxidized low density lipoprotein)

This test measures the oxidized LDL in the blood. LDL oxidizes when free radicals in the blood damage the existing LDL cholesterol. LDL is also more likely to oxidize when there is extra LDL, due to genetics or diet, and when there are not enough antioxidants to eliminate the free radicals. Diet, exercise, smoking cessation and good diabetes control can also help avoid the oxidizing of LDL.

Oxidized LDL goes directly into the inner lining of the arteries and causes plaque to form, accelerating a number of health conditions. Some of the potentially serious conditions include jumpstarting atherosclerosis, inhibiting nitric oxide production by blood vessel cells and disrupting the operation of white blood cells. Therefore, this test may be used as an indicator of increased risk of mortality from heart disease.

Cost
There is a laboratory cost of approximately $20 for the oxidized LDL test. This is in addition to the usual LDL and HDL cholesterol screens.

While underwriters are very familiar with HDL and LDL cholesterol, many are not as familiar with the oxidized LDL test. Therefore, it would be expected that an hour of training would be needed to bring underwriters up-to-speed on how to appropriately use and interpret the results of an oxidized LDL test. Based on the salary information on page 8, spreading the training cost over a five-year period and assuming 500 applicants per year, the underwriter's training cost per applicant would be $0.02.

It is assumed it will take the underwriter two minutes to evaluate the initial results of this marker. Based on the same salary information, the extra cost would be $1.62. In cases with poor results, it is assumed it will take the underwriter an additional 30 minutes, 10 to order an APS and 20 to review the results. It is assumed this will occur in about 5 percent of the cases. Based on the same salary information, the APS processing cost is $1.22. The extra cost for the APS itself would be $2.50 ($50 x .05).

It is assumed it would take an underwriter 10 minutes to explain the results and that this will be needed in 2 percent of the cases. This adds $0.16 to the cost.

Therefore, the estimated cost for this test would be $25.52 ($20.00 + $0.02 + $1.62 + $1.22 + $2.50 + $0.16). Assuming 5 percent of the cases were declined or not taken, and spreading the cost over all insureds, the final cost estimate for this marker is $26.86 ($25.52 / 0.95). For simplicity, a total cost of $27 is assumed for this test.

It is possible, but not likely, this could replace the cholesterol test. If it did, the mortality savings lost from no longer using the cholesterol test would need to be factored into the cost for this test.

The oxidized LDL costs are summarized in Table 36 below.

Table 36. Oxidized LDL Costs

Item	Cost
A) Laboratory cost	20.00
B) Training time	0.02
C) Review of marker	1.62
D) Ordering an APS	0.41
E) Cost of APS	2.50
F) Review of APS results	0.81
G) Communication of negative results due to marker	0.16
H) Subtotal (sum of A through G)	25.52
I) Percentage of declines and not takens	5%
J) Total cost (H / [1 – I])	26.86
Total cost used (J rounded up to next dollar)	**$27**

Benefit

The oxidized LDL studies referenced for this analysis were designed to determine if oxidized LDL was a predictor of metabolic syndrome, coronary artery disease and diabetes, but not increased mortality risk. One study, which focused on metabolic disorder, began with a cohort of healthier individuals. Healthier individuals are more likely to seek insurance, so this study became the basis for the mortality benefit analysis. Those with metabolic syndrome are more likely to develop coronary disease and thus exhibit higher mortality risk. Therefore, by inference, it is reasonable to assume that those with the worst oxidized LDL readings are the substandard lives.

The study used examines oxidized LDL and myocardial infarction.[31] Characteristics of the study are shown in Table 37.

[31] Holvoet, et al. “The Metabolic Syndrome.” 1068-73.

Table 37. Oxidized LDL Study

Study period	1997-2002
Number of participants	3,033 total, 1,886 without metabolic syndrome
Number of events	656 events, 238 among healthier group; events were considered coronary death or overnight hospitalization in an acute care hospital for myocardial infarction, angina, coronary angioplasty or artery bypass surgery, or chronic heart failure
Requirements	No lower extremity functional limitation; study targeted best functioning 40-60% of the older population; well-functioning was determined by self-report and defined as no difficulty in walking one quarter mile or going up 10 steps without resting reported on two separate occasions
Ages	70-79
Follow up	Entered study March 1997 and June 1998, follow up every six months from entry
Location	Memphis, Tennesse; Pittsburgh, Pennsylvania

While the data in the study may not be normally distributed, like other markers, it was assumed close enough to a normal distribution to produce reasonable results. The results were presented in two categories: those with metabolic syndrome and those without. The total population is considered for this analysis as it is likely individuals from both cohorts would apply for insurance.

Results for oxidized LDL, similar to cholesterol, may produce a J-shaped curve; however, there is not sufficient data in this study to review this. Therefore, the highest values were assumed to represent the substandard risks. Specifically, the 5 percent of the total population with the highest readings represent substandard risks. The average is in the middle of this 5 percent or at 2.5 percent. Using the mean and standard deviation of the distribution, the oxidized LDL mg/dl corresponding to the 97.5 percentile was found.

Table 38 shows the mean and standard deviation for the oxidized LDL study and the estimate of the substandard oxidized LDL mg/dl from the description above.

Table 38. Oxidized LDL (mg/dl) Mean, Standard Deviation and Substandard Readings

Mean	1.32
Standard deviation	0.74
Substandard	2.77

The next step is to determine the average non-substandard oxidized LDL reading. This is derived from the mean values, the total population mean value and the substandard value above, and determined from the following formula:

$$\underline{95\% \times X + 5\% \times 2.77 = 1.32}$$

X = 1.24, the non-substandard oxidized LDL mg/dl.

To determine the extra mortality, the hazard ratios for the substandard and non-substandard oxidized LDL need to be compared. In this study, the ratios are called the odds ratios; these are similar to hazard ratios. The odds ratios were split into quintiles. The substandard oxidized LDL of 2.77 is in the fifth quintile. In fact, at the 97.5 percentile, it is 12.5 percent from the highest value of the fifth quintile. Odds ratios in the fifth quintile range are 1.00 to 3.49; therefore, the 87.5 percentile is 3.18.

For the non-substandard oxidized LDL of 1.24, based on the same normal distribution, the 1.24 value corresponds to the 45.7 percentile of the total population distribution. The 1.24 oxidized LDL measurement is in the third quintile and would correspond to the 28.5 ([45.7 – 40] / 20) percentile of the third quintile. With a range of 0.88 to 3.10 for odds ratios in the third quintile, the odds ratio for the non-substandard oxidized LDL is 1.51.

Therefore, the mortality ratio between the substandard and non-substandard is 2.10 (3.18 / 1.51) and the extra mortality for the oxidized LDL is 110 percent.

Table 39. Oxidized LDL Mortality Savings Calculation

Item	
A) Hazard ratio non-substandard risk	1.51
B) Hazard ratio substandard risk	3.18
C) B / A	210%
D) [C – 100%]; extra mortality	110%
E) Proportion of the distribution assumed substandard	5%
F) D x E	5.5%
Additional mortality exhibited by substandard risks	**5.5%**

To determine the mortality savings for oxidized LDL, it is assumed this marker is solely responsible for identifying 15 percent of the extra mortality. The estimate is low because, while oxidized LDL is considered a better marker than LDL cholesterol, in the majority of cases, mortality savings will be found by some other form of cholesterol measure. Current measures of cholesterol are not likely to be discontinued in the near term.

The underlying mortality assumption used is as described on page 14. Based on this, the above assumptions and using the Calculator, the mortality savings for oxidized LDL for a 70-year-old male and female at an average policy size of $100,000 is $105 and $100, respectively. Given the estimated cost of $27 for the oxidized LDL test, this marker may be cost efficient for policy sizes as low as $40,000 at age 70.

Phospholipase A2 (full name: lipoprotein-associated phospholipase A2, also known as Lp-PLA2)

This test measures the amount of an enzyme called lipoprotein-associated phospholipase A2 in blood. It is used to predict a cardiac event or stroke. It is also used to help assess the risk of coronary artery disease. Often called the PLAC test, the enzyme it measures is one bound to the lipoprotein particles. Lipoprotein particles are the vehicles that drive cholesterol around the body and into the walls of an artery causing atherosclerosis.[32] If one has elevated Lp-PLA2 levels, one is twice as likely to suffer an ischemic stroke as similar individuals without such elevation.

Cost
The cost for this test is approximately $20.

It is assumed training will be needed for this new marker and estimate one hour as a reasonable training period. Assuming salary information provided on page 8, the cost is spread over five years and there are 500 new applicants per year, the underwriter's cost per applicant is $0.02.

It is assumed it would take about two minutes to evaluate the results for this test, and if unfavorable, another 10 minutes to review other cardiovascular risk measures. It is also assumed that unfavorable results occur about 10 percent of the time in the elderly population, where this test would be focused. Therefore, based on the same salary information, the cost for the underwriter's time is $2.43 based on three minutes (2 + 10 x 0.10) of time on average. Since other cardiovascular risk measures are considered to be readily available, it is assumed an APS would not need to be ordered.

It is estimated the underwriter will need to spend about 10 minutes on average explaining unfavorable results of this test and this would happen in about 5 percent of the cases. Using the same salary information, the cost for this would be an extra $0.41.

The total cost for this test would therefore be $22.86 ($20.00 + $0.02 + $2.43 + $0.41). It is assumed 5 percent of the cases are declined or not taken and, spreading this cost over all insureds, the final cost estimate for this marker is $24.06 ($22.86 / 0.95). For simplicity, a total cost for this marker of $25 is assumed.

Note there are a number of cardiovascular risk markers currently used in underwriting. If it was decided to stop using any of those tests due to the use of the phospholipase A2 marker, the mortality savings from the replaced test(s) should be included as a cost in this analysis, but there would also likely be additional morality savings associated with this marker that would increase its benefit.

[32] Richman, "Cholesterol Management 101."

The phospholipase A2 costs are summarized in Table 40 below.

Table 40. Phospholipase A2 Costs

Item	Cost
A) Laboratory cost	20.00
B) Training time	0.02
C) Review of marker	2.43
D) Ordering an APS	0.00
E) Cost of APS	0.00
F) Review of APS results	0.00
G) Communication of negative results due to marker	0.41
H) Subtotal (sum of A through G)	22.86
I) Percentage of declines and not takens	5%
J) Total cost (H / [1 – I])	24.06
Total cost used (J rounded up to next dollar)	**$25**

Benefit

Two studies are used in this analysis. The first[33] — the Bruneck study — is a prospective, population-based survey initiated in 1990. The study primarily looked at incident cardiovascular disease (CVD). CVD includes cardiovascular death, myocardial infarction, stroke and transient ischemic attack. Further details about the Lp-PLA2 study are shown in Table 41.

The second[34] — the Ludwigshafen Risk and Cardiovascular Health (LURIC) Study — is an ongoing prospective hospital-based cohort study investigating environmental, bio-chemical and genetic risk factors for coronary artery disease (CAD).

Lp-PLA2 was found to be significantly related to incident cardiovascular disease and cardiovascular death but not to non-cardiovascular deaths. The marker was also associated with metabolic syndrome. It showed highly significant positive associations with LDL-C and Apo B-100 and an inverse association with HDL-C.

[33] Tsimikas, et al. “Lipoprotein-associated Phospholipase A2 Activity.” 107-15.
[34] Winkler, et al. “Lipoprotein-associated Phospholipase A2.” 1440-47.

Table 41. Lp-PLA2 Studies

Bruneck study	
Study period	1990-2005
Number of participants	765
Number of deaths	Unknown; number of CVD 82
Requirements	Sex- and age-stratified random sample of all inhabitants of Bruneck, Italy; started with 125 men and women in their fifth to eight decades each (1,000 total)
Ages	45-84 in 1995
Follow up	Study was initiated in 1990 and follow-ups were done in 1995-2005
Location	Bruneck, Italy
LURIC study	
Study period	Unknown
Number of participants	3,232; 719 of these without angiographically confirmed CAD
Number of deaths	501
Requirements	Undergo angiography at Ludwigshafen General Hospital
Ages	45-74
Follow up	Median 5.5 years; range 0.1 to 7.2 years
Location	Ludwigshafen, Germany

The first step is to try to determine the Lp-PLA2 (µmol/min/L) substandard reading. The Bruneck study provided Lp-PLA2 (µmol/min/L) readings split between males and females. Table 42 shows the mean and standard deviation of the Lp-PLA2 (µmol/min/L) readings split between males and females.

Table 42. Bruneck Study Lp-PLA2 (µmol/min/L) Mean and Standard Deviation

	Males	Females
Mean	817	749
Standard deviation	205	179

The highest 5 percent of the readings for the total population are assumed substandard. Further, it is assumed the average is in the middle of this 5 percent or at 2.5 percent. While it is possible that Lp-PLA2 could produce a J-shaped curve, there is insufficient data in the study to determine this. Therefore, this analysis considers a one-sided substandard distribution.

Using the mean and standard deviation above and assuming a normal distribution, the average substandard Lp-PLA2 (µmol/min/L) readings are determined for males and females. Table 43 shows the results.

Table 43. Bruneck Study Average Substandard Lp-PLA2 (µmol/min/L) Readings

Male	Female
1219	1100

The next step is to determine the average non-substandard Lp-PLA2 (µmol/min/L) readings. These are determined by the following formulas:

$$\underline{Male: 95\% \times X \text{ (µmol/min/L)} + 5\% \times 1219 \text{ (µmol/min/L)} = 817 \text{ (µmol/min/L)}}$$
$$\underline{Female: 95\% \times X \text{(µmol/min/L)} + 5\% \times 1100 \text{ (µmol/min/L)} = 749 \text{ (µmol/min/L)}}$$

For males, *X* = 796 (µmol/min/L) and for females, *X* = 730 (µmol/min/L). Table 44 shows the results.

Table 44. Bruneck Study Average Non-substandard Lp-PLA2 (µmol/min/L) Readings

Male	Female
796	730

The next step is to use the hazard ratios provided to convert the Lp-PLA2 (µmol/min/L) readings into a mortality assumption to determine the ratio of mortality in the substandard class to the average non-substandard mortality. This will be used to determine the extra mortality due to the substandard business.

As the Bruneck study did not provide the Lp-PLA2 (µmol/min/L) readings corresponding to the hazard ratios, the LURIC study was looked to for this information. The hazard ratios were used from the LURIC study for cardiac mortality adjusted for age, sex, body mass index, smoking, diabetes, hypertension, use of lipid-lowering drugs, use of aspirin and/or other antiplatelet agents, LDL-C, HDL-C, logTG and presence of angiographic CAD.

The Lp-PLA2 (µmol/min/L) readings of 510 to 1247 correspond to hazard ratios based on the adjustments just described of 1.52 to 3.35. For the male substandard Lp-PLA2 (µmol/min/L) reading of 1219, this is in the 96.2 percentile, calculated as (1219 – 510) / (1247 – 510). Therefore, the hazard ratio would be 3.28, calculated as 0.962 x (3.35 – 1.52) + 1.52. For the male non-substandard Lp-PLA2 (µmol/min/L) reading of 796, this is in the 38.8 percentile, calculated as (796 – 510) / (1247 – 510). Therefore, the hazard ratio would be 2.23, calculated as 0.388 x (3.35 – 1.52) + 1.52. The ratio of the male substandard and non-substandard hazard ratios is 147 percent (3.28 / 2.23), and the extra mortality associated with the substandard risks is 47 percent (147 – 100).

Performing the same calculations for females results in a substandard Lp-PLA2 (µmol/min/L) percentile of 80.1, calculated as (1100 – 510) / (1247 – 510) and hazard ratio of 2.98, calculated

as 0.801 x (3.35 – 1.52) + 1.52. For the female non-substandard Lp-PLA2 (µmol/min/L) percentile the result was 29.9, calculated as (730 – 510) / (1247 – 510) and hazard ratio of 2.07, calculated as 0.299 x (3.35 – 1.52) + 1.52. The ratio of the female substandard and non-substandard hazard ratios is 144 percent (2.98 / 2.07), and the extra mortality associated with the substandard risks is 44 percent (144 – 100).

Table 45. Phospholipase A2 Mortality Savings Calculation

Item	Male	Female
A) Hazard ratio non-substandard risk	2.23	2.07
B) Hazard ratio substandard risk	3.28	2.98
C) B / A	147%	144%
D) [C – 100%]; extra mortality	47%	44%
E) F x 0.05, where 5% represents the proportion of the distribution assumed substandard	5%	5%
F) D x E	2.35%	2.20%
Additional mortality exhibited by substandard risks	**2.4%**	**2.2%**

The underlying mortality used is as described on page 14. In many cases, the excess mortality may be found by other tests. As a result, it is assumed this marker is solely responsible for identifying 15 percent of the excess mortality. Should the cholesterol test be eliminated, this percentage would increase; however, the mortality savings loss from the elimination of the cholesterol test should be factored into an increased cost for this test.

Based on these assumptions, a $100,000 average policy size and using the Calculator, the mortality savings for a 60-year-old male and female would be $39 and $32, respectively. With the estimated cost of $25, this test would be considered cost-justified for amounts beginning at $100,000, depending on the age and gender of the applicant.

TNF-alpha (full: tumor necrosis factor-alpha, also known as TNF; TNF-alpha; TNFA; TNFSF2)

TNF-alpha is a protein manufactured by white blood cells to stimulate and activate the immune system in response to infection or cancer. Overproduction of TNF-alpha can lead to disease where the immune system acts against healthy tissue.[35]

Cost
The average cost for TNF-alpha is about $3.

The underwriter may need more than the usual amount of time to learn about this marker due to it not being stable and that its results may vary depending on the situation. The training is assumed to take two hours. Based on the salary information on page 8, dividing the cost over five years and assuming 500 applicants per year, the cost is $0.04.

It will take the underwriter about two minutes to review the result if it is in the normal range. If it is outside the normal range, it will take the underwriter an additional 30 minutes to review, meanwhile consulting with other possible sources. An APS is likely not necessary as other sources would be consulted for unfavorable readings. It is estimated this extra review will be required in about 20 percent of the cases. Therefore, the cost of the underwriter's evaluation time is $6.48 based on eight minutes (2 + 30 x 20 percent) on average.

It is unlikely there will be very many negative actions taken due to this marker alone; however, when one is taken it will take the underwriter about 20 minutes to explain. It is estimated this will occur in 0.5 percent of the cases. The cost for the underwriter's time is an additional $0.08.

In total, the estimated cost of the test is $9.60 ($3.00 + $0.04 + $6.48 + $.08). If 5 percent of the cases are declined or not taken and this cost is spread over all insureds, the final cost estimate for this marker is $10.11 ($9.60 / 0.95). For simplicity, the total cost of the test is assumed to be $11.

It is not anticipated that this test will be replacing any others.

The TNF-alpha costs are summarized in Table 46 below.

[35] *About.com*, s.v. "TNF alpha," accessed December 9, 2011, http://psoriasis.about.com/od/glossary/g/TNFalpha.htm.

Table 46. TNF-alpha Costs

Item	Cost
A) Laboratory cost	3.00
B) Training time	0.04
C) Review of marker	6.48
D) Ordering an APS	0.00
E) Cost of APS	0.00
F) Review of APS results	0.00
G) Communication of negative results due to marker	0.08
H) Subtotal (sum of A through G)	9.60
I) Percentage of declines and not takens	5%
J) Total cost (H / [1 – I])	10.11
Total cost used (J rounded up to next dollar)	**$11**

Benefit

Several articles were found relating studies of TNF-alpha, but only a couple had mortality data and only one[36] had mortality data that could be used. This was an all-cause mortality study that found TNF-alpha was predictive of mortality in men but not women and its predictive value was independent of other traditional risk factors for death (blood pressure, smoking, fitness, etc.). The study also found that a history of cardiovascular disease, malignant neoplasm, diabetes or chronic pulmonary disease is not associated with increased TNF-alpha and TNF-alpha was not impacted by an intake of anti-inflammatory drugs.

The study was of both TNF-alpha and interleukin-6 and concluded that while both markers produced independent results, interleukin-6 may have been the better predictor of all-cause mortality. The reader may want to look further into interleukin-6 as another possible marker for predicting death in the elderly population.

Other characteristics of the study are shown in Table 47.

Table 47. TNF-alpha Study

Study period	1995-2001
Number of participants	333
Number of deaths	133
Requirements	Initial survey was of 50-year-olds in 1964 in the location below with follow-ups every five to 10 years. More people were added at age 70 and 75 so there were initially 362 people; 29 were removed from this study because they had an acute illness that could trigger temporary increases in TNF-alpha. Therefore, the study began with 333 healthy 80-year-olds, none of which had dementia.
Ages	80 (only those born in 1914)
Follow up	Six years
Location	Seven municipalities around Glostrup University Hospital, Denmark

[36] Bruunsgaard, et al. “Predicting Death.” 24-31.

The first step is to determine the TNF-alpha (pg/ml) substandard reading. This is done by assuming a normal distribution and the worst 5 percent in this distribution are substandard. From the article, while there were no specific numbers, it did not appear that the mortality would form a J- or U-shaped curve. Therefore, it is assumed the average was in the middle of that 5 percent, at 2.5 percent.

The study provided the median, the 25th percentile and 75th percentile values. From this, one can solve for the standard deviation. Consistent with a normal distribution, assume the median is equal to the mean since the study did not provide the mean. TNF-alpha did not prove predictive for women, so this analysis is based on data for men. The standard deviation is calculated using the following formula:

$$\underline{Males: 5.0\ (\text{pg/ml}) = 4.1\ (\text{pg/ml})\ + 0.675\ \times\ \sigma}$$

The standard deviation (σ) is 1.33 and all of these values are shown in Table 48.

Table 48. TNF-alpha (pg/ml) Readings for Males

Median	4.1
25th percentile	3.1
75th percentile	5.0
Standard deviation	1.33

Using the data in Table 48 and assuming a normal distribution, the average substandard TNF-alpha (pg/ml) reading was determined as 6.71.

The next step is to determine the average non-substandard TNF-alpha (pg/ml) reading. This is determined by the following formula:

$$\underline{Males: 95\%\ \times\ X\ (\text{pg/ml})\ + 5\%\ l\ 6.71\ (\text{pg/ml}) = 4.1\ (\text{pg/ml})}$$

The resulting non-substandard TNF-alpha (pg/ml) reading is 3.96 (pg/ml).

The next step is to convert the TNF-alpha (pg/ml) reading into a hazard ratio to determine the ratio of mortality in the substandard class to the average non-substandard mortality. This will be used to determine the extra mortality due to the substandard business.

The study provided an adjusted (for physical exercise and body mass index) male risk of dying of 15 percent for each pg/ml of TNF-alpha. Therefore, the estimate of the difference in mortality between substandard and non-substandard is calculated as follows:

$$\underline{[6.71\ (\text{pg/ml}) - 3.96\ (\text{pg/ml})]\ \times\ 15\% = 41\%}$$

The estimate of the extra mortality from the substandard business is 41 percent.

Table 49. TNF-alpha Mortality Savings Calculation

Item	Male
A) Non-substandard risk	3.96
B) Substandard risk	6.71
C) B – A	2.75
D) [C x 15%], where 15% is extra mortality per each pg/ml TNF-alpha	41%
E) Proportion of the distribution assumed substandard	5%
F) D x E	2.05%
Additional mortality exhibited by substandard risks	**2.1%**

This marker is assumed solely responsible for identifying 75 percent of the excess mortality. This is a higher percentage than for other markers because the article frequently talked about the independence of this marker relative to many other risks for death.

The final assumption for the calculation is the mortality assumption. The same underlying mortality assumption as described on page 14 is used.

Based on these assumptions, a $100,000 average policy size and using the Calculator, the mortality savings for an 80-year-old male would be $205. Based on the estimated cost of $11 and the mortality savings for an 80-year-old male, this marker could be cost-justified down to $10,000.

Note that the unadjusted hazard ratio was 2 percent per pg/ml, rather than the 15 percent used above. If the risk is applied, the extra mortality on substandard over non-substandard reduces to 0.3 percent and the mortality savings for an 80-year-old male with a $100,000 policy reduces to $30, still above the $11 cost of the test, meaning the test would again be cost-justified at $100,000.

Note also that there wouldn't be any mortality savings for females so the test, if used, should only be performed on males. Finally, this test was based on age 80. Therefore, results may differ at other ages and possibly even be insignificant at some younger ages.

Troponins I and T (full name: troponin I; troponin T)

Elevations of troponin I and troponin T may indicate previous heart attack or damage to the heart. A troponin I or troponin T assay is sometimes recommended clinically for those with chest pain. If there is chest pain or angina, but low troponin levels, this indicates no heart damage has been done. Troponin levels are normally very low, so even slight elevations may indicate some degree of damage to the heart. Significantly elevated troponin concentrations are indicative of a heart attack or some other form of heart damage. Troponin values can remain high for one to two weeks after a heart attack.

The test is not affected by damage to other muscles, so injections, accidents and drugs that impact muscle do not impact troponin levels. Troponin levels may rise following strenuous exercise; however, without other signs or symptoms of heart disease, this is not a medical issue.

Troponin is specific is to the heart and is a protein released by dying heart cells. Cardiac troponin consists of three proteins, troponin T, troponin I and troponin C. Commercial tests exist only for the detection of troponins I and T. Because troponin provides an earlier indication of myocardial infarction, it is considered a better marker for myocardial infarction than creatine kinase-MB, at least in a hospital setting. Newer tests are able to detect and measure troponin levels in a patient with chest pains when they first arrive at the hospital, speeding diagnosis and saving lives.[37]

For life insurance purposes, one of the benefits of using troponin is its ability to identify potential heart and renal failure.[38]

Cost
The cost for troponins I and T is approximately $25.[39]

It is estimated it would take about an hour for an underwriter to learn about troponin I and troponin T. Assuming the salary information on page 8, an amortization period of five years and 500 applicants per year, the cost would be $0.02.

It is assumed it would generally take an underwriter about two minutes to review the case if the reading was normal and about 20 minutes to review the case if the marker is elevated. At the older ages, the marker is estimated to be elevated in 6 percent of the cases. In about a third of these 6 percent, it is assumed an APS will need to be ordered, which will add another 25 minutes to this time, 10 to order the APS and 15 to review the results. Therefore, based on the same salary information, the estimate of the cost of the underwriter's time would be $2.90 based

[37] New England Journal of Medicine 2009; 361:868-87, August 27, 2009 "Sensitive Troponin I Assay in Early Diagnosis of Acute Myocardial Infarction."
[38] Roongsritong, Warraich, and Bradley. "Common Causes of Troponin Elevations." 1877-84.
[39] Fonarow. "Cardian Toponin-1 Assay."

on 3.58 minutes on average (2 x 0.94 + 20 x 0.04 + 45 x 0.02). The cost of the APS would add $1 (6% x 33% x $50).

This marker can identify pretty severe cases in which the condition is likely to be known to the applicant. Knowledge of this condition is estimated to be present in 0.5 percent of the cases. It is assumed the marker requires 10 additional minutes of underwriter time to explain the rating. In the case of false positives due to heavy exercise, the underwriter would check other sources to confirm the issue before making a final negative decision. The cost of the time it would take the underwriter to explain the rating (or decline) would be $0.04.

The estimated total cost for this test would be $28.96 ($25.00 + $0.02 +$2.90 + $1.00 + $0.04). If it is assumed 5 percent of the cases were declined or not taken and this cost was spread over all insureds, the final cost estimate for this marker is $30.48 ($28.98 / 0.95). A cost of $31 is assumed for this marker.

It is assumed this marker would not replace any other tests.

The troponin costs are summarized in Table 50 below.

Table 50. Troponin Costs

Item	**Cost**
A) Laboratory cost	25.00
B) Training time	0.02
C) Review of marker	2.50
D) Ordering an APS	0.16
E) Cost of APS	1.00
F) Review of APS results	0.24
G) Communication of negative results due to marker	0.04
H) Subtotal (sum of A through G)	28.96
I) Percentage of declines and not takens	5%
J) Total cost (H / [1 – I])	30.48
Total cost used (J rounded up to next dollar)	**$31**

Benefit

Two studies — one examining acute heart failure (AHF)[40] and the other dealing with end-stage renal disease (ESRD)[41] — were found that are used for the analysis of troponin I and troponin T. In each of the studies, all-cause mortality is observed. However, in both studies, troponin I and troponin T measures are obtained from people who generally had some type of serious impairment. Those impairments are acute heart failure, chronic obstructive pulmonary disease and end-stage renal disease. The lack of healthy individuals in these studies may not be an

[40] Ilva et al. “Clinical Significance of Cardiac Troponins.” 772-79.
[41] Apple, et al. “Predictive Value of Cardiac Troponin.” 2941-45.

issue because, like microalbumin, absence of troponin or trace readings is considered normal and any other reading is considered adverse.

There are numerous assays for troponin I, but only one assay for troponin T. Therefore, if troponin I is to be used as a marker, the troponin I assay needs to demonstrate superior performance. In one study, troponin I showed to be more predictive; however, it was stated that the reason for this was the better assay collected for troponin I.

Further details about the studies are shown in Table 51.

Table 51. Troponin I and Troponin T Studies

AHF study	
Study period	2004-09
Number of participants	364
Number of deaths	68 (18.7%) after six months
Requirements	Patients hospitalized with AHF in 14 hospitals in Finland between February and May 2004 (620); those with acute coronary syndrome (ACS) were excluded (198); those with missing blood samples were also excluded (58)
Ages	Mean 74.8, standard deviation 10.9
Follow up	Six months, one year, five years
Location	Finland
ESRD study	
Study period	Beginning 1998. End period unknown.
Number of participants	733
Number of deaths	192 deaths occurring during 1,052 patient-years of follow up
Requirements	Treated by chronic intermittent hemodialysis for at least 30 days (Monday, Wednesday and Friday or Tuesday, Thursday and Saturday) by metro outpatient dialysis units of DaVita (formerly Total Renal Care) from April 1998 to March 1999
Ages	Mean 62, range 18 to 93
Follow up	One, two and three years
Location	Minneapolis and St. Paul, Minnesota

For this marker, as with the others, the objective is to determine the mortality differential between these groups so the mortality savings can be assessed relative to the cost of the marker.

As stated above, troponin I and troponin T (µg/L) readings are either negative or positive. Negative readings will be considered the non-substandard group and positive readings will be split into non-substandard and substandard. This is because there is an increasingly higher mortality rate as more troponin I and troponin T is released.

For the AHF study, 51.1 percent had positive troponin I (µg/L) readings and 29.7 percent had positive troponin T (µg/L) readings. The positive readings were split into two groups. It was assumed the substandard lives represent the worst of the two positive groups and the two groups were split evenly. The non-substandard group six-month mortality was calculated to be 15.87 percent for troponin I and 16.49 percent for troponin T, using the following formulas:

$$\underline{Troponin\ I}: [48.9\% \times 13.5\% + (51.1\% / 2) \times 20.4\%] / [48.9\% + (51.1\% / 2)]$$
$$\underline{Troponin\ T}: [70.3\% \times 14.1\% + (29.7\% / 2) \times 27.8\%] / [70.3\% + (29.7\% / 2)]$$

The six-month mortality for the substandard group is 26.9 percent for troponin I and 31.5 percent for troponin T. Therefore, the difference in mortality between the non-substandard and the substandard would be 70 percent (26.9% / 15.87% – 1) for troponin I and 91 percent (31.5% / 16.49% – 1) for troponin T.

For the ESRD study, 132 of the 733 troponin T (µg/L) readings were negative [not greater than .04 (µg/L)]. This represents 18 percent. For troponin T, this study was divided into three positive groups, with the two-year mortality being 26 percent, 39 percent and 47 percent with each successively higher group vs. 8.4 percent for the group with negative readings. This study used unhealthy lives from the start, as a result, the worst two groups were assumed to both be substandard and it was assumed that all three groups were split evenly.

To calculate the extra mortality for troponin T, first determine the non-substandard and substandard values. The non-substandard mortality is calculated as follows:

$$\underline{Troponin\ T}: [18\% \times 8.4\% + (82\% / 3) \times 26\%] / [18\% + (82\% / 3)]$$

Therefore, the non-substandard mortality is 19.01 percent. The substandard mortality is 44 percent (the average of 39 percent and 47 percent). The difference in mortality between non-substandard and substandard for troponin T is 131 percent (44% / 19.01% – 1).

For troponin I, the two-year mortality rates given were for negative troponin I levels (30 percent) and positive troponin I levels (52 percent). Assume an extra mortality of 73 percent (52% / 30% – 1) for troponin I.

Using a weighted average between the studies, the mortality savings is for troponin I is 72 percent and 118 percent for troponin T. This is calculated by the formulas below.

$$\underline{Troponin\ I}: [(70\% \times 364) + (73\% \times 733)] / [364 + 733]$$
$$\underline{Troponin\ T}: [(91\% \times 364) + (131\% \times 733)] / [364 + 733]$$

Table 52 summarizes the mortality savings results.

Table 52. Troponin I and Troponin T Mortality Savings Calculation

Item	Troponin I	Troponin T
A) AHF study	70%	91%
B) ESRD study	73%	131%
C) Weighted average	72%	118%
D) Proportion of the distribution assumed substandard	5%	5%
E) C x D	3.6%	5.9%
Additional mortality exhibited by substandard risks	**3.6%**	**5.9%**

The final assumption for the calculation is the mortality assumption. The same underlying mortality assumption as described on page 14 is used. It is also assumed this marker is solely responsible for identifying 25 percent of the excess mortality. The reason for this percentage is that there was discussion in one of the articles that both cystatin C and NT-proBNP were found to be elevated when troponin was elevated.

Based on these assumptions, a $100,000 average policy size and using the Calculator, the mortality savings for a 70-year-old male and female would be $114 and $109, respectively, for troponin I and $187 and $178, respectively, for troponin T. For a $30,000 policy, the mortality savings for a 70-year-old male and female would be $34 and $33, respectively, for troponin I. For a $20,000 policy, the mortality savings for a 70-year-old male and female would be $37 and $36, respectively, for troponin T. Therefore, savings is greater than the estimated cost of $31, for face amounts as low as $30,000 for troponin I and $20,000 for troponin T.

Summary of Results

Table 53 provides a summary of the results just discussed. If there is a difference by gender, male values are used. If two studies were used, the results of the larger study were used for the readings and the combined study results were used for the mortality.

The table shows the purpose of the marker, the ages the laboratories recommended the testing to be done at, and the average substandard and non-substandard reading expressed in the units specific to each marker. It also shows the net mortality savings, the cost for the marker and an estimate of the minimum face amount level that would be cost-justified (to the nearest $5,000 that is cost-justified), with both mortality-related values being calculated for a male age 70.

The summary shows that, for male age 70, all of the markers studied are cost-justified at a face amount level of $100,000, the most typical level in the industry where blood and urine testing begins.

Table 53. Summary of Results

Marker	Primary purpose	Ages recommended by labs for testing	Average substandard reading	Average non-substandard reading	Net mortality savings (based on male age 70 and $100,000 face amount)	Cost for marker	Face amount to near $5,000 where benefit > cost (for male age 70)
Apo A-1 and B	Cardio	40+	1.57 (ratio)	0.97 (ratio)	$33.70	$21	$65,000
Red cell distribution width	All cause	60+	15.42%	14.48%	$193.44	$17	$10,000
Cystatin C	Kidney	55+	2.16 mg/L	1.07 mg/L	$272.29	$19	$10,000
Hemoglobin	Anemia, more	65+	6.94 g/dL	11.21 g/dL	$558.76	$20	$5,000
Hemoglobin A1c	Glucose	35+	7.41%	5.41%	$151.95	$19	$15,000
Microalbumin	Kidney	35+	-	-	$148.80	$23	$20,000
NT-proBNP	Cardio	60+	237.23 pg/ml	64.20 pg/ml	$407.64	$37	$10,000
Oxidized LDL	Cardio	45+ (males), 55+ (females)	2.77 mg/dl	1.24 mg/dl	$104.65	$27	$30,000
Phospholipase A2	Cardio	45+	1219 µmol/min/L	796 µmol/min/L	$45.77	$25	$55,000
TNF-alpha	Immune system	50+	6.71 pg/ml	3.96 mg/ml	$199.09	$11	$10,000
Troponin I and troponin T	Cardio	55+ (males), 65+ (females)	- µg/L	- µg/L	I: $114.13 T: $186.54	$31	I: $30,000 T: $20,000

Other Laboratory Information

The laboratories provided some other information not yet discussed in the report. The labs provided the specimen source (blood, urine, etc.) needed for each of the markers as well as whether there were any stability issues with the draw. Table 54 provides this information.

Table 54. Marker Source and Stability Issues

Marker	Source	Stability issues?
Apo A-1 and B	Whole blood	No
Red cell distribution width	Whole blood	Analytes stable Time and handling can affect specimen
Cystatin C	Serum blood	No
Hemoglobin	Whole blood (purple tops)	Analytes stable Time and handling can affect specimen
Hemoglobin A1c	Whole blood	Analytes stable Time and handling can affect specimen
Microalbumin	Urine	No
NT-proBNP	Serum blood	Analytes stable
Oxidized LDL	Whole blood	No
Phospholipase A2	Whole blood	Yes, sample must be received refrigerated or frozen
TNF-alpha	Whole blood	Yes, sample must be received frozen
Troponin I and T	Whole blood	Yes, sample must be received frozen

There were no regulatory issues on the markers reviewed.

If a new marker produces an adverse result, the company must be sure it is accurate and very careful in their message as to why the applicant was rated or declined, especially if this may be the first time the applicant is learning about the disease or impairment.

Additional Observations

Apo A-1 and B, oxidized LDL and Lp-PLA2 are all lipid measures that could and probably should replace the current less accurate cholesterol markers. That said, it is unlikely all three would be adopted by the industry and it is difficult to say which one or ones would be more likely to be adopted. The one exception to this might be if the cost were further reduced from that described above and there was a "package deal" offered by the lab for implementing them all. Assuming this is not the case, this is one time where being a first adopter may put a company at a competitive disadvantage if all later adopters move in a different direction. It is recommended the reader talk to the lab(s) used and find out from them which they think is the most likely to be adopted. The labs are likely to be the primary drivers of these new markers.

Likewise, a number of the new markers described in this report relate to cardiovascular risk factors. While it is believed more than one of these markers is likely to be adopted by the industry, it is not believed they all will be and it is unknown which will be. Again, it is recommended the lab(s) be talked to before deciding to move forward with one of these markers.

When using clinical studies as was done in this report to determine the mortality savings of the various markers, it should be understood that clinical studies differ from traditional life insurance experience studies in a number of ways, some of which could cause a mis-estimation of the value of the test (in either direction). Some of these differences include:

- People in the clinical studies may or may not be insurable.
- People in the clinical studies are often more homogeneous (e.g., they may all be from the same town).
- Sample sizes are often small and may not be credible.
- Distributions by age, gender, etc. may not be representative of the insurance population.
- Studies are often performed over a very short period of time; this may or may not reflect mortality experience over a longer period of time, which is of interest to the life insurance actuary.
- Measurement of exposure may be different than traditional actuarial methods.
- There are often a very limited number of studies so confirmation of the results may not be possible.

Also, readings at the time of the study may be different than what they are today. This could be due to what is considered new and different normal cutoff readings or due to a change in instrumentation. The point here is that the reader must make certain the study used in this report is still relevant as things change over time.

For some tests, there could be an issue with different quality of the assays, whether serum is needed, or the length of time the result is stable for. It is believed the labs are aware of all of

these issues and do a good job avoiding these potential pitfalls in the analysis of the results. However, it is pointed out so the reader is aware of them.

Recent Developments – Other Potential Markers

During the course of the work on this project, other developments were discovered. The reader might be interested in some of these. The items briefly described in this section are:

- Risk profile/score
- Other potential markers
- BioSignia
- Aviir
- Telomere Health

Risk profile/score

Each of the laboratories has completed extensive statistical analysis of their data and has developed a unique risk profile/scoring technique. The risk profiles are described in the Glossary section of this report. As of the writing of this report, each of the labs has begun to market its new tools for risk assessment.

Other potential markers

When the laboratories were interviewed, a list of many potential markers to study was developed. Those considered, but that did make the list of 11, include the following. Also included is the condition the marker is used to test for.

- Aldosterone; renal function
- Alpha-1 and beta-2 microglobulin; kidney function
- Alpha-fetoprotein; fetus test for later cancer
- CDT (carbohydrate-deficient transferrin); alcohol abuse
- CEA (carcinoembryonic antigen); cancer
- CRP (C-reactive protein); nonspecific inflammatory marker
- EtG (ethyl glucuronide); alcohol abuse
- Fibrinogen; cardiovascular
- HIV 4
- Homocysteine; cardiovascular
- Hyaluronic acid; hepatitis C
- Methamphetimine; drug abuse
- Pre-PSA marker; cancer
- Triumph[42]; cardiovascular

[42] Provided by Clinical Reference Laboratory

BioSignia

BioSignia has taken the traditional information collected in the preferred underwriting process and analyzed it using its own research to create a better predictor of mortality.[43]

Aviir

Aviir has developed a cardiovascular risk predictor (called TruRisk) using a number of different cardiovascular markers drawn from the blood that is supposed to be a better risk predictor than other cardiovascular markers.[44]

Telome Health

Telomere Health, Inc. has developed a technique to measure the length of telomeres, which they claim is a better measure of life expectancy than any other tool available today.[45]

Telomeres are found at the end of every chromosome. Telomeres protect the chromosomes. With each cell division, the telomere shortens. The cell will die when there is no more telomere.

[43] www.biosignia.com
[44] www.aviir.com
[45] www.telomehealth.com

Limitations of Data and Analysis

The data and other information provided to us as well as found on the Internet was relied upon. There were no detailed audits or reviews of the data and other information for reasonableness and consistency performed. If the underlying data or other information is inaccurate or incomplete, the results of this analysis may likewise be inaccurate or incomplete.

At times, interpretations of the data were necessary. There are generally multiple ways to interpret the same data. It is recommended readers do their own thorough analysis before making any decisions on whether to proceed with the use of any new medical marker. Also, as stated in the report, it is recommended readers thoroughly review the references provided (and others) for a more thorough understanding of the different aspects of the markers provided in this report.

Final Remarks

There are many potential new medical markers that could be incorporated into life insurance underwriting. Eleven of these are described in detail in this report and others are mentioned toward the end of the report.

As stated in the report, the goal was not to make a recommendation as to which markers to use, but rather to provide an independent analysis of the markers selected to be studied and, more importantly, to give the reader a basis for studying the 11 chosen markers or any other future markers. New or different studies may produce different results so readers must use caution in their decision as to whether to introduce a new marker. Another caution is that the results may only be indicative for a certain segment of the population (e.g., age or those with a certain impairment).

What may be appropriate for one company may not be appropriate for another company, as there is more to consider in making a decision than just the cost and benefit. For example, if all other companies are using a particular marker, the company not using it may be selected against so the poor mortality experience resulting from the anti-selection may outweigh any other cost/benefit analysis.

Finally, the authors recommend discussing the issue with the reader's laboratory or laboratories to make a more informed decision.

The authors would like to thank the SOA for the opportunity to provide this research and to the POG, the laboratories and all others who helped complete this analysis and report.

Appendix A

Milliman

Society of Actuaries
New Medical Markers Research Project
Questions for Laboratories
Interviewers – Al Klein, Karen Rudolph

Introduction

Thank you for taking the time to meet with us. As you know, we are conducting research for the Society of Actuaries on new medical markers. We would like to discuss any tests/markers currently available or that will soon be available (within the next 6-12 months). We are interested in tests/markers that you think are of value to life insurance companies for helping to predict mortality, that are either not widely used today by the life insurance industry or not used at all. You may currently perform this test for other lab work you do or you may be aware of it and not currently use it yourself. One example of a test that may meet our definition is nt-ProBNP. This is a test that has been around, but we don't believe is widely used yet by the life insurance industry; this test could be included if you agree that it is still not widely used.

We would like to better understand these tests/markers and get any additional resource information you are aware of about the specific tests/markers we discuss.

We will be interviewing the three major US laboratories that handle life insurance lab work.

If there are any tests that you feel are proprietary, we would also like to learn about these, however, we will only publish something about them if at least two of the three laboratories indicate they are working on them. Otherwise, we will just mention that there are x number of proprietary tests that are currently being evaluated that we cannot disclose at this time.

We will set up an initial call for two hours to discuss these issues through the questions below. If we need additional time, we will schedule another call at the end of the initial call.

We believe the resulting report, based on our discussions with you will be a benefit to the whole life insurance industry, as well as potentially getting you more business! Thank you for your help!

Questions for each new medical marker/test

1. Please name and describe any new medical test/marker that you are currently aware of. For our purposes, new is defined as currently available and not yet widely used by the life insurance

industry or about to be available within the next 6-12 months. If in doubt, please include the test/marker.

2. What is the source of the test/marker (i.e., blood, urine, saliva, other)?

3. Will this test/marker replace any current test(s)/marker(s), and if so, which one(s)?

4. Will this test/marker bring new information to the evaluation process or supplement a current test/marker? If a supplement, which test/marker will it supplement and what extra will the new test/marker bring not already covered by the original test/marker?

5. What is the primary use/benefit of this test?

6. Are there any secondary uses/benefits of this test? If so, please describe.

7. Are there any downsides or risks related to using this test?

8. Are there any regulatory issues or do you anticipate any regulatory issues related to this test? If so, please explain.

9. How stable is the collection for this test? Are there any sensitivities with respect to heat, time between collection and receipt in the lab or any other issues?

10. Does the collection need to be sent back to the lab or can it be analyzed in the field?

11. Are the results from this test reproducible?

12. Do you have data on the sensitivity and specificity of the tests?

13. Do you have any mortality information related to this test? If not, please comment on the efficacy of the test.

14. Do you have any resources for more information on this test?

15. Have you done internal research on this test/marker or do you rely on outside studies?

16. We realize the cost structure for tests/markers varies depending on the client and a number of other factors. Please provide the cost range for this test, even if it is a wide range. If you do not know yet, please provide an estimate.

17. If we were to do a cost/benefit analysis on this test, would there be a specific cost you would suggest using, and if so, what would it be?

18. What percentage of your life insurance clients use this test/marker today?

19. What percentage of your life insurance clients do you expect to use this test/marker in 5 years (from today)?

20. Is there anything else we should know about this test?

21. Do you believe this test/marker to be proprietary? If so, when would you estimate that we would be able to discuss it?

<u>Other Questions</u>

1. What is the average and/or range of the percentage of your life insurance clients that use the currently popular life insurance tests/markers? We would like to use this as a baseline for your answer to question 18 and 19 above.

2. Please rank what you think are the three most important tests/markers mentioned above and explain why they are so important.

3. Where do you get your ideas for new tests/markers?

4. How do you go about analyzing a new test/marker?

5. Are there any more tests/markers not mentioned above that you are aware of, even if they might be more than one year away? If so, please explain.

6. Are there any plans for recalibration of any current machines and/or "normal" readings for current tests/markers?

7. Is there anything else that you would like to say that would help the readers of our report?

8. Is it OK to mention your name as a contributor to our report?

Thank you for your answers. Is it OK if we call to follow up with any questions we might have?

Appendix B

Medical Marker Mortality Calculator

The Medical Marker Mortality Calculator (Calculator) workbook uses input regarding the extra mortality (expressed as a percentage of substandard mortality over non-substandard mortality) together with various other input items described in the report to derive a mortality savings (i.e., mortality benefit) expressed in dollars and cents. This appendix and example will lead the reader through the use of the Mortality Benefit Calculator.

Note that the workbook file is not protected or locked. Changes made to formulas on sheets beyond the "Input and Results" tab will impact the underlying calculations and the authors are not responsible for the validity of calculated results under these circumstances.

Overview

As it is used in this report, quantifying the mortality savings or benefit involves taking the difference between two estimates of mortality cost, call these A and B. The first estimate, A, is a present value of projected mortality rates, or costs of insurance, that reflect the additional mortality presented by those risks to whom the marker is targeted. In the analysis for Apolipoprotein, the extra mortality exhibited by substandard risks to whom the Apolipoprotein marker is targeted is 5.3 percent for males. This implies these male risks will exhibit 105.3 percent of non-substandard male mortality.

The second estimate, B, is the present value of projected mortality rates, or costs of insurance, that would develop from non-substandard risks. In the Calculator, non-substandard risks are assumed to exhibit 94 percent of the 2008 VBT ALB Male or Female mortality table.

In both cases, present values are taken at 5 percent interest.

Table B1 – Mortality Benefit Calculator Description and Use

Sheet Name	Description and Use
Input and Results	Input fields and result fields are here. For Apolipoprotein, begin with inserting the extra mortality of 5.3% (for males) into the yellow shaded area under the area marked "Item 1." This input can vary by age. All ages should be completed. Item 2 is the finder factor. Input should represent the estimate of the percentage of substandard risks that are solely found (or uniquely found) by the marker. For Apolipoprotein, the percentage is 5% and should be entered in the yellow shaded area under Item 2. Item 3 is the policy size to use in the analysis. This analysis uses a $100,000 policy size as its baseline. The user can modify the policy size as appropriate for the situation. Item 4 is the scalar against the VBT used to represent standard

	mortality. For this analysis, 94% is the assumed scalar. The user can modify this factor as appropriate for the situation in the orange shaded box under Item 4. Item 5 is the interest discount rate used in calculating the A and B values described above. The user can modify this factor as appropriate for the situation in the orange shaded box under Item 5. After completing the input variables and pressing the "Recalculate" button, the results can be found in the blue box on this tab. A sample of the blue "Results Here" box is shown below.
Interim	This sheet holds the scalars generated by the input tab for use in later sheets. It also holds the results of the macro, which in turn end up in the "Results Here" section of the Input and Results sheet.
M 2008 VBT ALB	2008 VBT ALB Male mortality rates
F 2008 VBT ALB	2008 VBT ALB Female mortality rates
M Stand	The underlying non-substandard mortality rates for males
F Stand	The underlying non-substandard mortality rates for females
M Mod	The substandard mortality rates for males, according to the specified input
F Mod	The substandard mortality rates for females, according to the specified input

Results

For the sample case of Apolipoprotein, the results field should appear as shown below. For a male age 50, the mortality savings or mortality benefit of the marker is $22.03 or $22 as reported in the analysis.

RESULTS HERE		
Mortality Benefit of Marker		
Age	Male	Female
30	$ 11.41	$ 10.13
40	$ 16.16	$ 14.71
50	$ 22.03	$ 20.21
60	$ 28.37	$ 26.08
70	$ 33.70	$ 32.16
80	$ 34.78	$ 35.28
90	$ 32.20	$ 34.03

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