

CYSTATIN C

A Promising Test for Insurance Screening

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EXECUTIVE SUMMARY

This review of the world literature on cystatin C, a novel marker for renal impairment, encompasses all relevant studies published up to the end of November, 2008. It was undertaken to contribute to essential efforts aimed at replacing conventional screening practices, most notably the deployment of chest x-rays, treadmill stress tests and resting ECGs. For a variety of reasons, these entities are no longer appropriate choices for routine use in underwriting.

This literature review demonstrates clearly that cystatin C is superior to creatinine and creatinine-based eGFR equations as an indicator of mild-to-moderate impairment of kidney function. It further reveals that cystatin C is an independent

marker for the risk of cardiovascular disease, potentially synergistic with NT-proBNP as a screening duo at older ages. Moreover, cystatin C may confer additional risk assessment advantages in terms of premature physical frailty, early cognitive impairment and assessing the severity of liver disease.

There do not appear to be any significant impediments to the deployment of cystatin C in risk appraisal. Therefore, in consideration of the foregoing, it is this author's opinion that cystatin C should now be further evaluated for deployment as both a screening and reflexive test in mortality and morbidity risk underwriting.

FORWARD

In 21st century mortality and morbidity risk appraisal, we are in the midst of an ongoing and profound shift toward screening tools that accommodate these clear mandates of senior insurance company management:

- Lower business acquisition costs.
- Reduce application-to-issue cycle time.
- Enhance customer-friendliness, consistent with the "financial services" concept.

In order for these challenging goals to be achieved, we must make key changes in how we underwrite risks. One of these is to consider viable alternatives to certain traditional risk screening practices.

The driver of this transformation of risk appraisal is teleunderwriting. Wide embrace of teleunderwriting has greatly facilitated the realization of all three of the above-mentioned mandates.

Nevertheless, it is clear that further enhancements are necessary, working synergistically with teleunderwriting.

Several of these are already in use in the United States:

- Pharmacy (Rx) profiles
- Motor vehicle records
- MIB reports
- Screening with novel laboratory tests such as NT-proBNP

One of the obstacles to modernization of underwriting is the continued use of three slow, costly, cumbersome, client-unfriendly and highly subjective screening modalities carried over from the 20th century: chest x-rays, treadmill stress tests and resting electrocardiograms. These obsolete tests need to be replaced by screening alternatives that do not have these formidable drawbacks.

Several novel screening tests are already being deployed by progressive insurers toward this end, most notably NT-proBNP and hemoglobin A1c. What is needed now is to further embellish this tandem of CV markers with one or more additional

tests which compliment them by providing additional independent and additive protective value.

Such tests must be affordable, and easily done in conjunction with screening blood profiles and sufficiently studied in research, epidemiological and clinical contexts, such that their value can be readily ascertained. Ideally, such tests would not only bring added value in terms of screening for circulatory disease but also afford additional advantages in other ways directly linked to excess mortality and morbidity, most notably in older aged patients.

Earlier this year, after reviewing a number of studies on the novel kidney marker cystatin C, I recognized its potential and thus the need for a comprehensive review of the medical literature. Regrettably, the time commitment necessary to accomplish this imposing task was far beyond the scope of what is feasible on a pro bono basis.

Therefore, I approached Roche Diagnostics, offering to undertake this project if the company would provide sufficient funding to compensate me for my time as well as the expense of obtaining copies of published studies. I made it clear that my work, despite their financial support, would not be subject to oversight,

editing or any other type of influence on their part, thus assuring my uncompromised independence in this undertaking.

When Roche agreed to proceed and accepted these conditions, I embarked upon this project. In its wake, it is now clear to me that cystatin C offers enormous potential as a companion screening test with NT-proBNP for older age insurance applicants. The importance of this cannot be overstated as this is the fastest growing market for U.S. life insurers.

In the concluding portion of this paper, I offer my thoughts and recommendations regarding cystatin C in mortality and morbidity underwriting.

It is my hope that this research will motivate industry laboratories to work with proactive clients to further assess the merits of cystatin C in carefully-designed studies that optimize our knowledge of its relationships to as many related factors as possible, including NT-proBNP and other commonly-used screening tests.

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December 4, 2009

BACKGROUND

"The prevalence of chronic kidney disease and end-stage renal disease is increasing worldwide with the aging of the world population and a global epidemic of type 2 diabetes"

Janice SC Chew, et al
Christchurch, New Zealand
Clinical Biochemistry Review
29(2008):47

"The measurement of serum cystatin C-concentration as a simple measure of kidney function is rapidly gaining in popularity"

J. Aprestgård, et al
Karolinska University Hospital, Stockholm
Atherosclerosis
199(2008):397

"Cystatin C has emerged as a more accurate estimator of glomerular filtrate rate than creatinine and demonstrates a linear association with cardiovascular disease."

**James A. de Lemos, MD and
Donald M. Lloyd-Jones, MD**
University of Texas SW Medical Center, Dallas
The New England Journal of Medicine
358(2008):2173[editorial]

"[Cystatin C] is emerging as a strong risk marker for cardiovascular morbidity and mortality, as well as overall mortality"

Anna Köttgen, MD, MPH, et al
Johns Hopkins University Medical School
American Journal of Kidney Diseases
51(2008):385

What is cystatin C?

A protein associated with vascular damage, produced by all nucleated cells at a constant rate, freely filtered by the glomerular membrane and metabolized but not secreted in the proximal renal tubule.

When was cystatin C identified?

It was first isolated in 1961, in CSF and serum, and dubbed "gamma-trace protein". The amino acid sequence was determined 20 years later and its current name bestowed in 1984. [Chew, Massey]

Is cystatin C the only cystatin?

No.

At least 10 cystatins have been identified and designated with letters, as well as two others called "kininogens". Cystatin C is unique among them because it is produced by all nucleated cells. To our knowledge, the others are not used in any clinical context at this time. [Filler]

What does cystatin C do?

"Its functions include involvement in extracellular proteolysis, modulation of the immune system, and anti-bacterial and antiviral activities."

Michael G Shlipak, MD, et al.
Annals of Internal Medicine
145(2006):237

In which mediums can cystatin C be effectively measured?

Serum, plasma, urine, saliva, CSF, seminal plasma, amniotic fluid, tears and breast milk. [Filler]

This paper will focus solely on blood testing of cystatin C.

Which analytical and related laboratory factors influence cystatin C?

- Day-to-day variation is small (3.1% in a cohort of diabetic patients). [Hoek]
- Week-to-week variation is also modest (4.55%), which is significantly lower than creatinine [Bandaranayake]
- Cystatin C can be tested at any time of the day, fasting or post-prandial [Larsson]
- Its concentration is stable in stored serum [Perkins]
- It is not affected by muscle mass, hemolysis, diet, hyperbilirubinemia, lipemia, rheumatoid factors, hemoglobin or serum protein [Chu, IX, Roche Diagnostics]

What is the heritability of cystatin C?

Multivariate-adjusted heritability was found to be 0.35 in a study of 3,241 subjects. [Parikh]

What is the normal range for cystatin C?

There are a number of cystatin C assays and normal ranges differ among them.

The current "expected values" for the Roche cystatin C assay are:

Age range	Expected values
20-50 years old	0.56-0.90 mg/L
51-70 years old	0.58-1.09 mg/L

What is the prevalence of elevated cystatin C in the general population?

Based on "elevated" cystatin C, defined as ≥ 1.09 mg/L, Muntner and his Mt. Sinai School of Medicine colleagues pegged it at 8.1% overall, 9.2% in males and 7.0% in females, based on an assessment of 6951 subjects, ages 20-59, in the NHANES III Study.

Does cystatin C rise with age?

Yes.

Köttgen and her colleagues reported these mean values in their 2008 study:

Mean cystatin C (mg/L)	Age range (years)			
	12-19	20-39	40-59	≥60
Males	0.89	0.85	0.90	1.13
Females	0.79	0.78	0.84	1.11

Finney et al found that mean values increased significantly with increasing age over age 60.

C appears to become the rule rather than the exception."

Carter acknowledged that at a mean age of 86, 92% of his study subjects had cystatin C readings above the conventional normal range and Shlipak observed that "...by the 9th decade of life, "abnormal" cystatin

We would need to adjust our underwriting guidelines to accommodate these findings. Hopefully, forthcoming industry studies will provide sufficient information to accomplish this.

Does cystatin C differ by gender?

- Moran et al reported no significant difference in the percentage of his subjects who were male in the 2nd through 5th quintiles of cystatin C, in a cohort of 4, 971 subjects at mean age 62.
- Fried et al showed that, in subjects ages 70-79, the percentage of females was 64% of all subjects in the lowest cystatin C quartile, as compared to 47% in the 3rd quintile and 41% in the highest quintile.
- Ognibene et al found that significant univariate differences in gender did not persist after multivariate analysis.

Drugs specifically shown to have no influence on cystatin C include tacrolimus, cyclosporine, mycophenolate mofetil, fosinopril, ramipril, enalapril and losartan [Foster, Xu]

Vitamin B supplementation (in this case, to manage homocystine levels) also has no significant effect. [Potter]

de Boer reported that 30% of females in the lowest cystatin C quintile were taking unopposed estrogen as compared to 22% in the 4th and 20% in the highest quintile. Similar relative effects were reported for progestins.

On balance, any gender differences in cystatin C would be easily adjusted for when setting underwriting guidelines.

At this writing, it appears that the influence of Rx on cystatin C will be insignificant in an underwriting context.

Is cystatin C affected by any prescription medications?

Not much has been published as yet in this regard.

The only drugs shown in some but not all studies to influence cystatin C levels are corticosteroids, and these only in larger doses. [Abbink, Cimerman, Filler, Fried, Zhu]

CYSTATIN C AND THE KIDNEY

"Individuals with moderate and mildly decreased renal function are at increased risk for chronic kidney disease and cardiovascular disease."

Laura Pucci et al
University of Pisa
Clinical Chemistry
53(2007):480

How do experts perceive cystatin C as a kidney function test?

"Serum cystatin C can be used as a simple, sensitive and relatively robust screening test to detect renal insufficiency, requiring a single blood sample. . ."

Edmund J. Lamb
Department of Clinical Biochemistry
Kent and Canterbury Hospital, UK
Clinica Chimica Acta
334(2003):25

What is seen as the #1 clinical role of cystatin C in a kidney function context?

"Perhaps the most promising use of cystatin C will be as a marker for preclinical or early kidney disease, among persons with creatinine-based eGFR in the 'normal range' but elevated cystatin C."

Michael G. Shlipak, MD, MPH
VA Medical Center, San Francisco
American Journal of Kidney Diseases
51(2008):358[editorial]

What will drive clinical use of cystatin C?

Whether or not it enhances medical decision making and hence the capacity of physicians to treat their patients. . .

. . . which could be a slow process of embrace because of half a century of using creatinine in this context!

Clinical deployment of cystatin C should not be a factor in how this test is used in underwriting. It raises no apparent RED FLAG issues akin to those associated with genetic tests, tumor marker tests not used clinically to screen patients and so on.

CYSTATIN C AND CREATININE

"A large portion of older persons with impaired renal function are not diagnosed if clinicians rely solely on normal serum creatinine as evidence of normal renal function."

Sandra V. Giannelli MD, et al
Journal of the American Geriatric Society
 55(2007):816

"Serum creatinine is a biomarker that has been used to screen for kidney disease for almost 80 years. By definition, it has a high specificity in the diagnosis of kidney disease because its levels are the basis for our definition of kidney disease, but its sensitivity is clearly lacking in many common clinical scenarios. For the detection of reduced eGFR, [cystatin C] has been shown to have a higher sensitivity and a higher negative predictive value than serum creatinine, both important characteristics to consider in the evaluation of any screening test."

Ian Wu and Chirag R. Parikh
 Section of Nephrology
 Yale University Medical School
Clinical Journal of the American Society of Nephrology
 3(2008):1895

What are the significant drawbacks to creatinine, as compared to cystatin C?

- It is not standardized. [Stevens and Levey]
- It is not generated at a constant rate. [Stevens and Levey]
- Its concentrations change significantly at ages 1-50. [Grubb]
- It is greatly influenced by muscle mass, a major limiting factor when underwriting elderly applicants. [Chew, Ichihara]
- It is impacted by dietary choices (which we do not measure in underwriting). [Chew]
- A subject with significant change in serum creatinine will often fall within the stated reference range because it is insensitive to significant changes in GFR at older ages [Lamb]
- It does not efficiently demarcate mild renal impairment [Chew]

From an underwriting perspective, the greatest concern where creatinine is concerned is best summed up as follows:

"As elderly patients often have low muscle mass and poor nutrition, serum creatinine may remain in the normal 'blind' range despite decreasing GFR and therefore renal impairment may go unrecognized."

Janice SC Shew
 Op. Cit.

Do cystatin C and creatinine correlate well on a univariate basis?

Yes, across quintiles of ostensibly healthy subjects [Moran]:

Cystatin C quintiles (mg/L)				
≤ 0.74	0.75-0.82	0.83-0.90	0.91-1.02	≥ 1.03
Creatinine (mg/dL)				
0.83+0.15	0.90+0.15	0.94+0.17	0.98+0.17	1.17+0.56

Does cystatin C have a superior correlation with creatinine clearance?

Yes [Koenig, Knight]

Hojs et al also showed that cystatin C has a significantly greater diagnostic accuracy than calculated creatinine clearance at GFR cutoffs consistent with mild-to-moderate renal impairment.

Is cystatin C a better choice than creatinine, overall, as a screening test for kidney impairment?

Yes, based on a 2002 meta-analysis of 46 studies. [Dharnidharka]

Why do a few studies, nevertheless, report that they have equivalent value?

"Such discrepancies may be attributable at least in part for intraassay variations for creatinine and cystatin C measurements related to differences in assay techniques."

Laura Pucci et al
Op. Cit.

In what context do the advantages of cystatin C over creatinine become most apparent?

Cystatin C begins to increase as GFR falls below 80, as compared to GFR of 40 and below affecting creatinine significantly. [Finney, Lamb]

How do cystatin C and creatinine compare in terms of GFR determined by "gold standard" methods such as iothalamate, inulin, EDTA clearance, etc.?

According to the director of the renal lab at Mayo Clinic, Cystatin C correlates more closely in nearly all published studies [Larson] This statement is affirmed by Italian clinical chemists studying cystatin C reference values, and many others as well. [Ognibene, Tidman, Ustundag, White, Zhu]

Which test is more efficient at detecting mild-to-moderate diabetic nephropathy?

Cystatin C, based on many studies including some that measured GFR by one of the "gold standard." methods. [Aksun, Buysschaert, Harmoinen, Lee, Maclsaac, Mojiminiyi, Mussap, Perlemoine, Premaratne, Shimizu, Uslu, Willems, Xia, Yang]

Does cystatin C have a stronger correlation with cardiovascular disease?

"Several recent reports have indicated that cystatin C may be a better predictor of adverse CV events and all-cause mortality than either serum creatinine or creatinine-based estimating equations."

Ernesto L. Schifflin, MD, PhD, FRSC, FRCPC, et al
McGill University Medical School, Montreal
Circulation
116(2007):85

Brinkman et al found that the impact of creatinine as a CV marker "disappeared after the inclusion of cystatin C".

Cystatin C has also been shown to be significantly superior to creatinine in terms of identifying increased risk of adversity in these additional CV contexts:

- Diastolic dysfunction in children with known kidney disease [Mitsnefes]
- Early renal insufficiency in hypertensives [Bicik]
- Aortic stiffness [Song]
- Angiographically-significant coronary artery disease [Cho]
- Renal impairment in patients undergoing cardiac catheterization [Artunc]

Has cystatin C been shown to be superior to creatinine in other clinical settings?

Yes:

- Rapid decline in GFR in acute renal failure [Hergert-Rosenthal]
- Early decline in GFR in intensive care unit patients [Bagshaw]
- Renal dysfunction in anorexia nervosa [Delanaye]
- Early renal impairment in spinal cord injury [Jenkins]
- Kidney damage in HIV-1 [Odden and Scherzer]
- Renal disease in cirrhosis [Gerbes, Randers]
- Renal function status of live kidney donors [Gourishankar]
- Early renal damage in Fabry disease [Ferlozzi]
- Contrast-induced nephropathy [Kato, Kim]
- Kidney damage due to cancer chemotherapy [Benöhr, Hoppe]

- Renal damage from digitalis toxicity [Hallberg]
- Diagnosis of renal impairment in children [Narvaez-Sanchez, Zaffanello]
- Renal damage in children due to UT malformations [Corrao]
- Monitoring renal function in pediatric cancer patients [Lankisch]

What is the next step in studying the relationship between cystatin C and creatinine in the context of known or suspected renal disease?

"A critical next step in CKD [chronic kidney disease] patients will be to extend longitudinally the comparisons of cystatin C and creatinine with measured GFR to compare their value for monitoring changes in kidney function."

Michael G. Shlipak, MD, MPH
Op Cit.

CYSTATIN C AND GLOMERULAR FILTRATION RATE (GFR)

What advantage does serum cystatin C have over conventional methods of estimated (e) GFR?

"Cystatin C captures an association of preclinical impairments of kidney function that cannot be detected using eGFR."

David Singh, et al
University of California-San Francisco
School of Medicine
Nephrology, Dialysis and Transplantation
12(2007):1087

What are the implications of this consistent finding?

"Cystatin C, when properly used, should markedly improve GFR estimates in patients with moderately-advanced stage of CKD" ... which, of course, is the population of greatest interest to us in most risk appraisal contexts!

O. Bakoush et al
University Hospital of Lund, Sweden
Clinical Nephrology
68(2008):331

Has cystatin C been shown to be superior - as a marker for mild-to-moderate renal impairment - to the main methods of calculating e-GFR (Cockcroft-Gault and MDRD)?

Yes, consistently [Coll, Hojs and Bevc, Jonsson, Moran, Parikh, Pucci, Ozer, Toffaletti, White]

Does cystatin C enjoy a significant advantage over creatinine in terms of correlation with conventional eGFR calculations?

Yes

In this study of nondiabetics with mild-to-moderate renal impairment, Malyszko and her colleagues showed that cystatin C readings are superior indicators of mild-to-moderate renal impairment based on e-GFR.

Malyszko
Renal Failure
30(2008):625

	Healthy volunteers	eGFR 60-69	eGFR 30-59
Creatinine (mg/dL)	0.77+0.18	1.03+0.19	1.47+0.87
Cystatin C (mg/L)	0.81+0.19	1.24+0.47	1.96+1.28

The driver here is the relative impact of the typical creatinine normal range used in underwriting vs. the likely range we would use with cystatin C.

<p>At what stage of renal impairment does cystatin C lose its advantages over conventional eGFR methods?</p> <p>Severe impairment (eGFR < 15). [Sjöström, Martin]</p> <p>Is cystatin C a reliable marker for mild-to-moderate renal impairment in the</p>	<p>elderly?</p> <p>Yes [Odden, O'Hare, Sarnak, Törner]</p> <p>Do cystatin C-based eGFR equations provide more accurate assessment of GFR than creatinine-based methods, based on comparisons with "gold standard" GFR determinations?</p> <p>Yes, consistently [Chudleigh, Grubb, Ledoux, Stevens, Zahran]</p>
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	Cystatin C-based eGFR			
	90	75	60	45
Serum cystatin C (mg/L)	0.88	1.02	1.23	1.57

CYSTATIN C AND CARDIOVASCULAR DISEASE

How does cystatin C relate to CV risk factors overall?

"Cystatin C is a useful clinical marker that provides complementary information to the established risk determinants."

Aude Servais, MD, et al
Pitié Salpêtrière Hospital, Paris
The American Journal of Medicine
 121(2008):426

"The mechanisms behind these associations [cystatin C and CV disease] are unclear but do not appear to involve common risk factors such as hypertension, BMI or smoking."

Anders Larsson, et al
Uppsala University Hospital, Sweden
International Journal of Cardiology
 125(2008):263

How does cystatin C correlate with weight-related parameters?

In a new study, Muntner and his associates looked at the association between cystatin C and BMI using NHANES III data:

- 9.2% of all males had elevated cystatin C based on their criteria; however, 14% of stage 1 obese subjects (BMI 30-34.9) and 13.2% with stage II obesity (BM 35-39.9) had elevated levels.
- Among female subjects, 7% overall had elevated cystatin C, which increased to 8% and 14% respectively in stages I and II obesity.
- In their study, the percentage of cystatin C levels declined between BMI 18.5 and 22.5; then, it rose sharply until it peaked and flattened out around BMI 35.

de Boerer et al at UC-SF assessed the relationship between BMI and cystatin C in the Multi-Ethnic Study of Atherosclerosis (MESA), involving 6,814 subjects from six American communities. They found that BMI

	Cystatin C quintile				
	1	2	3	4	5
Cystatin C (mg/L)	0.07-0.72	0.73-0.79	0.80-0.87	0.88-0.96	0.97-2.32
BMI	26.8_±5.1	27.2_±4.9	27.9_±5.2	29.1_±5.7	29.6_±5.9

How is the relationship between BMI and cystatin C best characterized in the elderly?

U-shaped, in the largest study we found where BMI levels were sufficiently fractionated to isolate the “underweight” group from the rest.

Wasén, Isoaho and coworkers reported, in a cohort of 1,260 elderly residents of rural municipality in Finland, that BMI < 20 in both genders was steeply U-shaped, with mean volumes at BMI < 20 and ≥ 35 being essentially identical.

The highest median cystatin C reading was found in males with BMI < 20, followed by females with similarly low BMI determinations.

In other studies where the lowest BMI subset was not considered separately, researchers reported the following:

- Wang and his associates found no differences in mean BMI in quartiles of BMI in 408 Australian subjects, age 60 and over.
- Djoussé et al reported essentially the same thing in 440-person subset, mean age 73, from the Physician’s Health Study.

- Sundelöf and his Swedish coworkers found the same in a study of 1914 subjects mean age 71.
- In addition, O’Hare and colleagues found similar results in the Cardiovascular Healthy Study.

Clearly, BMI is not going to be a significant factor impeding the use of cystatin C in underwriting.

Does cystatin C reflect adverse patterns of adiposity?

Yes, in terms of central (visceral) vs. peripheral adiposity. [Ichihara, Young]

For example, in the Framingham Offspring Study, subjects with normal cystatin C readings had a mean waist circumference of 98.2 centimeters as compared to 106 cm in those with a high cystatin C level.

[Parikh]

It must also be mentioned that cystatin C appears to be closely associated with a novel marker for risk in obese subjects, etc. This marker, adiponectin, may work its way into clinical testing in the near future.

[Graziani]

CYSTATIN C: ASSOCIATIONS WITH SMOKING, ALCOHOL USE AND EXERCISE

Is cystatin C influenced by cigarette smoking?

To a degree, in some but not all studies.

- Muntner, Mann et al found 50% more cigarette smokers in the 4th quartile of cystatin C as compared to the 1st and 2nd quartiles. In this study, the association between smoking and cystatin C was actually greater in former smokers than current smokers among male subjects.
- Moran reported a 20% greater probability of being an "ever" or "current" smoker in the highest quintile of cystatin C. Notably, for "current" smokers, the percentage did not change significantly between the 2nd and 5th quintiles.
- Galteau looked at both smoking and drinking in 1,233 healthy individuals and found no significant differences in mean cystatin C on the basis of being a "drinking smoker" as compared to a "non-drinking smoker".
- Knight studied smokers by cystatin C quintile and there was no difference between the 4th and 5th quintiles, and only a minimal one when these were compared to the 2nd and 3rd quintiles. Only the 1st quintile had a significantly smaller percentage of cigarette smokers.
- Among patients with known CAD, Singh found no significance attributable to current smoking in terms of cystatin C quartiles.
- In the Women's Health Initiative Study – the largest where smoking has been related to cystatin C levels – the correlation was U-shaped, with over 50% more smokers in the 2nd and 3rd quartiles than in the 4th quartile.

We found additional 6 studies where cigarette smoking was contrasted to cystatin C readings and in all of them the relationship was insignificant. [Deo, Djoussé, O'Hare, Shlipak and Fyr, Yaffe]

We could go on, but the point has been made: current cigarette smoking – at least without regard to aggregate level of consumption – exerts a very modest effect at most, and will not significantly influence the use of cystatin C in an underwriting context.

Is there any association between aggregate level of cigarette use - defined as "pack-years" of smoking - and cystatin C?

Yes...and this is important because most insurers do not take steps to assess "pack-years" (despite being well-positioned to do so!).

- In the MESA Study, mean "pack-years" was nearly twice as high in the top cystatin C quartile. [Kestenbaum]
- Ichihara et al reported similar results.

Further studies may show that cystatin C adds value in terms of degree of smoking exposure. This would be advantageous in terms of its aggregate impact on risk appraisal.

Is alcohol intake associated with cystatin C?

Yes, alcohol intake is inverse to cystatin C...but the extent of this relationship has yet to be adequately elucidated. [Ichihara, LaCroix, Singh]

Is cystatin C affected by level of exercise vs. being sedentary?

It would appear that it is not.

Baxmann separated subjects into three groups: sedentary, mild regular exercise and moderate-to-intense regular exercise. On this basis, cystatin C was insignificant between the three subsets whereas creatinine was – as anticipated – higher in those with a high level of regular exercise.

CYSTATIN C, BLOOD PRESSURE AND LIPIDS

Is cystatin C associated with blood pressure?

Yes.

In the PREVEND Study, the prevalence of hypertension increased across quintiles of cystatin C. [Knight] Far less relative change in percentage of subjects with high blood pressure was seen across quintiles of cystatin C in the MESA Study. [de Boer]

Therefore, there is a significant univariate correlation between hypertension and cystatin C.

Is there also an increased prevalence of hypertension associated with higher cystatin C readings in persons age 65 and over?

Yes, in 3 studies, once again on a univariate basis. [Deo, Sarnak, Shlipak and Fyr]

Is cystatin C an independent marker for the risk of future hypertension?

"We found higher cystatin C levels to be associated with a greater incidence of hypertension independent of known risk factors. We found no evidence of a synergistic relationship between cystatin C and the urinary albumin-creatinine ratio on the risk for incident hypertension."

Bryan Kestenbaum, MD, MS, et al
The Multi-Ethnic Study on Atherosclerosis
Archives of Internal Medicine
148(2008):501

In this study, subjects had a 31% greater risk of developing hypertension, after adjusting for known risk factors. This included subjects whose baseline readings were < 120/80. Creatinine did not exhibit this relationship.

Have there been any findings relating cystatin C to the risk of preeclampsia?

Yes, 3 studies and all of them confirmed that high cystatin C is a significant risk factor for this hypertension-mediated, potentially life-threatening complication of pregnancy [Franceschini, Kristensen, Strevens]

Is cystatin C associated with increased pulse pressure (PP) in the elderly?

Yes, on a linear basis and mainly through its association with lower diastolic reading (an established marker for arterial stiffness). [Parikh, Peralta]

Is cystatin C associated with end-organ damage in hypertension other than as directly related to renal dysfunction?

Yes.

Watanabe and his colleagues found that cystatin C was directly associated with left ventricular mass index and carotid intima-media thickness in patients diagnosed with essential hypertension.

Are there associations between various blood lipid parameters and cystatin C in persons with normal and minimally abnormal eGFR?

"Greater serum cystatin C was associated with unfavorable lipid and lipoprotein abnormalities among a diverse, community-dwelling population with eGFR \geq 60..."

Ian H. de Boer, et al
Multi-Ethnic Study of Atherosclerosis
Clinic Journal of the American Society of Nephrology
3(2008):125

In the PREVENT Study [Knight]:

	Cystatin C quintile				
	1	2	3	4	5
% with hyperlipidemic profiles	17%	21%	25%	38%	36%

What is the relationship between cystatin C and total cholesterol (TC)?

Significantly inverse [de Boer, Deo, Parikh, Sarnak, Shlipak and Fyr, Sundelöf]

This is important to us because of the well-established association between low/falling cholesterol and physical frailty at older ages. [Brescianini]

Does this differ with LDL-C?

Parikh et al reported lower total LDL-C levels in subjects with "high" cystatin C. However, de Boer and colleagues found that each 0.2 mg/L increase in cystatin C was associated with a 24 nmol/L higher concentration of small LDL-C particles, even after multivariate adjustment.

This is notable because small, dense LDL-C is the LDL-C component most consistently associated with atherosclerosis. [Mudd]

How does cystatin C correlate with HDL-C?

Significantly inversely: the higher the cystatin C, the lower the HDL-C [de Boer, Kestenbaum, Muntner and Mann].

Is cystatin C independent of the TC:HDL-C ratio as a predictor of CV risk?

Yes. [Muntner]

What about triglycerides?

de Boer found that triglycerides increased through quintiles of cystatin C. However, the ranges for the mean levels were quite broad and the mean value in the highest quintile, 140 mg/dL, was not at the threshold typically associated with debiting triglycerides in mortality and morbidity risk underwriting.

Have any other associations been shown between lipid markers and cystatin C?

Yes.

- Koenig, Twardella and associates found that cystatin C was strongly and positively correlated with levels of lipoprotein-associated phospholipase A-2 (Lp-PLA-2). This is an emerging marker for atherosclerotic disease as well as circulatory events in patients with known CAD. Unfortunately, it does not appear adaptable for practical use in risk appraisal [Roberts, personal communication]
- Studies have also shown associations between cystatin C and apolipoprotein A1 as well as the apo B/A1 ratio. [Florvall, Samouilidou]

CYSTATIN C, DIABETES AND THE METABOLIC SYNDROME

Is cystatin C an independent marker for the presence of type 2 diabetes?

No. [Fried, Larsson, Muntner, Parikh]

Does cystatin C correlate with increased risk of prediabetes?

It would appear that it does.

Donahue et al, in the Western New York Health Study involving 1,455 subjects, reported that normoglycemic subjects in the top cystatin C quartile were 3.3-fold more likely to become prediabetic over 6 years of followup than those in the four lower quintiles, after adjustment for known risk factors.

de Boer had similar findings with regard to IFG (impaired fasting glucose).

Does cystatin C help to differentiate between "good" vs. "poor" control in diabetics?

Yes, in 3 small studies. [Maraldi, Sartore, Uslu]

Is cystatin C a marker for early diabetic nephropathy?

Yes.

Earlier, we established that it is superior to creatinine in this capacity.

In addition, there are now a number of studies which affirm that cystatin C is particularly valuable in detecting stage 2 and stage 3 nephropathy in both normotensive and hypertensive type I and type II diabetics. [Costacou, Kimura, Rigalleau, Satoh].

Could cystatin C be an underwriting asset as a predictor of progression from early diabetic hyperfiltration (GFR > 120) through stages of decline of GFR?

"Together with testing for microalbuminuria, clinical protocols using cystatin C to diagnose early renal function decline and track responses to therapeutic interventions should be developed."

Bruce A. Perkins, et al

Joslin Diabetes Center, Boston

Journal of the American Society of Nephrology
18(2007):1353

Abundant additional evidence supports this role for cystatin C [Ogawa, Hutchinson, Perkins, Pucci, Uslu]

Is cystatin C an independent marker for CV disease in known diabetics?

Yes.

Larsson found that "men with both diabetes and CVD had significantly increased levels of cystatin C alone compared to men with diabetes alone ($p < 0.001$) or men without diabetes ($p = 0.003$)".

Niccoli and his coworkers stated that "...the association between Cys-C and CAD severity-extent was independent of risk factors, including diabetes which is a known strong predictor of atherosclerotic burden".

What is the metabolic syndrome?

A grouping of 5 distinct risk parameters associated with increased risk of atherosclerotic disease.

Is cystatin C associated with this syndrome?

Yes. And, mean cystatin C increases in proportion to the number of metabolic syndrome components present. [Demircan, Servais]

CYSTATIN C AND NOVEL MARKERS FOR CV RISK

Note: the relationship between cystatin C and NT-proBNP is the most important to underwriting if these tests are used together to screen for circulatory disease risk. Therefore, we have deferred discussion of this relationship to the final portion of this report.

What is C-reactive protein (CRP)?

CRP is a well-established marker for inflammation and CV risk. Its use – in the form designated high-sensitivity CRP (hs-CRP) – was considered by insurers but putative drawbacks severely reined in its use in underwriting.

Is cystatin C linked to CRP (C-reactive protein)?

Yes. There is a positive relationship between cystatin C and CRP in middle- and older-aged individuals [Johnston, Keller, Knight, Koenig, Luc, Shlipak and Fyr, Wang]

Is cystatin C also related to other markers of inflammation?

Yes...with the caveat that it does not appear that inflammation is itself a mechanism directly accounting for cystatin C elevation. [Arpegård, Niccoli, Ogawa, Sjöström]

These markers include interleukin 6 (IL-6) and tumor necrosis factor [Keller, Luc], and their direct use in underwriting is not feasible.

Unlike cystatin C, eGFR has no correlation with these markers in subjects with eGFR \geq 60. [Singh]

Is there a correlation between a history of arthritis and cystatin C?

No – and we mention this because of the expected association between active arthritis and elevation of most inflammatory markers. [Fried].

Does cystatin C relate to severe periodontal disease?

Yes. In one study, cystatin C does did correlate with periodontal disease, a recognized risk factor for CV disease and events [Chu]

Is there an association between hyperfibrinogenemia and cystatin C?

Yes – cystatin C has consistently been shown to be significantly associated with elevated fibrinogen levels [Keller, O'Hare, Sarnak, Singh].

Fibrinogen, one hastens to add, is a marker for increased risk of CV events which we theoretically could...but do not...use in underwriting at this time. [Fibrinogen Studies Collaboration]

Is cystatin C related to blood levels of homocysteine?

Yes, consistently and significantly. [Lewerin, Ramel, Wang]

Like hs-CRP, homocysteine is an established risk factor for atherosclerotic disease which we have not been able to adapt for use in underwriting. [Nilsson]

The strong associations between cystatin C and IL-6, TNF, fibrinogen and homocysteine can only enhance its value in underwriting.

CYSTATIN C AND CARDIOVASCULAR DIAGNOSTIC TESTING

Which elements of CV screening and diagnostic testing have been shown to have a significant association with cystatin C?

- Significant parameters on treadmill stress testing

"We found that greater cystatin C levels were associated independently with decreased exercise capacity and HRR [heart rate recovery] in patients with CHD. We found that cystatin C had more linear associations with poor exercise capacity and HHR than creatine-based measures."

David McManus
Heart and Soul Study
American Journal of Kidney Diseases
49(2007):365

- Modest association with the extent of coronary artery calcifications on CT scans. [Maahs, Parikh and Hwang]
- Increased LV mass, wall thickness and end diastolic volume, as well as decreased LV ejection fraction. [Patel, Singh]
- Presence of LVH and diastolic dysfunction [Ix and Shlipak, Moran]

Is cystatin C associated with increased intima-media thickness (IMT) in the carotid arteries?

Yes, in 4 studies, which included diabetic and hypertensive subjects [Naour, Sarnak, Sohn, Skalska] However, there was one study of subjects in the Seychelles where neither cystatin C nor creatinine had any association with IMT. [Rodondi]

Has cystatin C been studied in context with impaired endothelial function?

Yes.

Potter and her Australian associates evaluated 173 stroke patients and found that cystatin C was an independent marker for impaired flow-mediated arterial dilation (FMD), a widely-recognized marker for endothelial impairment.

CYSTATIN C AND CIRCULATORY DISEASE

"In this large nationally-representative sample of U.S. adults without traditional markers of kidney diseases, higher serum cystatin C was associated with a progressively increased CVD prevalence."

"... the association between higher cystatin C and CVD was strong, graded and independent of cigarette smoking, overweight and obesity, hypertension, diabetes mellitus, total and HDL-C cholesterol, and detectable and increased C-reactive protein"

Paul Muntner, PhD et al
NHANES III
The American Journal of Cardiology
102(2008):54

These observations are particularly important because they affirm that cystatin C is independent of other major CV risk factors. In other words, the univariate

associations between cystatin C and some of these factors, cited previously, do not compromise its value as an underwriting screening asset.

Are patients with elevated cystatin C more likely to have a history of CV disease than those whose cystatin C is normal?

Yes.

- In the Framingham Offspring Study, 25.7 % of persons with high cystatin C had prevalent CV disease, as compared to only 9.5% of those whose cystatin C was deemed to be normal. [Parikh]
- In the Health, Aging and Body Composition Study of 2,135 persons ages 70 to 79, the percentage with established coronary disease increased in a linear manner from 11.6% to 21.8% across quartiles of cystatin C. [Fried]

- A similar pattern was found in the Cardiovascular Health Study involving 4,025 elderly patients. Those in the 5th quintile (cystatin C \geq 1.28 mg/L) had almost twice the prevalence of diagnosed coronary disease as those in the 1st and 2nd quartiles and 23% higher prevalence as compared to the 4th quartiles (1.11 to 1.27 mg/L). [O'Hare]
- Nilsson et al in Sweden revealed that their patients with vascular disease were 5.4-fold more likely to have elevated cystatin C when compared to patients free of CVD.

Is there an association between cystatin C and extent of angiographic CAD?

Yes.

Koenig reported a linear and significant relationship between the number of involved vessels and the share of subjects in the highest cystatin C quintile.

In a smaller cohort, Niccoli described a strong trend toward the same association based on cystatin C tertile.

Can this analogy be extended to a history of MI?

Absolutely.

In the Physicians' Health Study and the Health, Aging and Body Composition Study, there was a significantly greater prevalence of prior MI among patients in the top tertile of cystatin C. [Deo, Djoussé]

Does cystatin C also link congestive heart failure and cerebrovascular disease?

Yes.

For CHF, this was found in 3 major studies; in one, for both diastolic and systolic failure. [Djoussé, Fried, Moran]

Fried et al reported twice the prevalence of prior stroke in subjects in the 4th quartile of cystatin C compared to those in the 3rd tertile.

Is there a connection between cystatin C and peripheral arterial disease (PAD)?

Yes, again.

- Fung et al at Stanford reported that, after adjusting for age, smoking, diabetes and other CV risk factors, elevated cystatin C was linked to a 2.6-fold increased risk of having clinically-evident PAD.
- Arpegård et al in Sweden documented similar results.
- Wilson et al were able to implicate cystatin C in PAD based on proteomic profiling studies.

Do these findings also extend to asymptomatic PAD based on ankle:brachial index (ABI)?

Yes, and we will start here by acknowledging that ABI – also referred to as ankle:arm index (AAI) – is well established as the premier screening predictor of PAD.

Below-normal (< 0.09) results and, more recently, markedly elevated ratios (≥ 1.24) have been implicated in excess morbidity and mortality as well as increased risks of both cognitive impairments and premature physical frailty. [Menke, O'Hare and Katz, Price]

We found 2 studies where cystatin C was correlated with low ABI measurements:

- In the Cardiovascular Health Study, subjects in the top quartile of cystatin C had a 50% greater prevalence of low ABI than those in the 3rd quartile and 2.5 times the probability of the two lowest quartiles. [Sarnak]
- In the Health, Body and Aging study, the top quartile of cystatin C had 35% higher risk of prevalent PAD than subjects in any other quartile. [Fried]

Fried and her associates looked at the risks of needing surgical intervention for PAD in terms of cystatin C level. When cystatin C was > 1.27 mg/L, this risk jumped 2.9-fold as compared to lower cystatin DC levels.

Does deep venous thrombosis (DVT) affect cystatin C?

No. [Wattanakit]

Cystatin C and Other Disorders

CYSTATIN C, FRAILITY AND COGNITIVE FUNCTION

Is there a relationship between cystatin C and premature functional impairment (frailty) in the elderly?

Yes.

- Based on a functional index assessed by questionnaire, Wasén et al found a linear association between impaired function and cystatin C, with the risk 7-fold greater in the highest quintile and over 3 times higher in the 5th quintile as compared to the 4th quintile. Neither creatinine nor eGFR were of significance in this study.
- Fried et al reported that degree of overall functional limitation was significantly greater in the 4th quartile of cystatin C, as well as the extent of reduced gait speed.
- Using a 10-item rating scale known by the acronym RAND, LaCroix and her colleagues in the Women's Health Observational Study discovered a steeply inverse relationship between a high (favorable) and low (impaired) RAND score and quartiles of cystatin C.
- Odden and associates in the HABC Study documented associations between high cystatin C and poorer performance on the 400-m walk as well as diminished lower extremity performance and strength associated with higher cystatin C.
- In the Osteoporotic Fractures in Men Study, subjects in the highest cystatin C quartile (≥ 1.26 mg/L) had significantly reduced leg strength [Ishani]

Is high cystatin C also a factor in bone marrow density, hip fracture and falls in the elderly?

- On the matter of falls, Schwartz and her associates found a 50% increased risk of falling per 0.38 mg/L increase in cystatin C.
- Two studies found a correlation between cystatin C and decreased BMD. [Fried and Shlipak, Ishani]
- Two studies show that cystatin C is a significant risk factor for hip fracture [Fried and Biggs, LaCroix]

Considering the broad impact of cystatin C in these key domains of physical frailty, this test should be evaluated further as an underwriting marker for this dominant mortality risk factor at ages 70 and above.

Is cystatin C also associated with the risk of dementia?

Yes. However, the evidence becomes a bit more challenging to sort out.

Does cystatin C have a pathophysiologic link to the brain lesions associated with Alzheimer dementia?

Yes.

Mare and his colleagues report that cystatin C is an amyloidogenic protein, co-occurring with beta-amyloid (a primary marker for AD) in the walls of cerebral arterioles of AD patients.

Has cystatin C been found to have a relationship with the risk of cognitive impairment?

Yes – however, the nature of that relationship is uncertain given conflicting study results.

Sundelöf and his Swedish colleagues followed 1,914 subjects, age 70 or 77, for 11.3 years.

- During that interval, the risk of AD was inverse to cystatin C tertile.
- Among 70 year olds, those in the lowest 1/3rd of cystatin C had a 2-fold increased risk of being diagnosed with AD ($p = 0.01$). In the 77 year old cohort, the AD risk as 3.4-fold raised in the lowest cystatin C tertile. ($p = 0.007$)
- It is interesting, in light of these findings, that plasma levels of beta-amyloid proteins 40 and 42 both increased by tertile in age 70 cohort. In the age 77 cohort, the mean level of beta-amyloid 40 was substantially higher in the 3rd cystatin C tertile whereas beta-amyloid 42 was unchanged across all three tertiles.

Chuo et al in Taiwan also found a modestly-significant ($p < 0.05$) association between higher cystatin C and a reduced risk of late-onset AD.

On the other hand...

In the Cardiovascular Healthy Study involving 2,140 subjects age 65 and over,

- Subjects in the top quartile of cystatin C had twice the prospective incidence of cognitive impairment as individuals in all three other quartiles. [Sarnak]
- Higher cystatin C was associated with progression from normal cognitive status to cognitive impairment and from MCI (mild cognitive impairment) to dementia. However, there was no association between cystatin C and either going from normal to MCI or remaining with stable MCI (vs. progression to overt dementia). [Lopez]

In the Health ABC Study of 3,033 subjects, ages 70 to 79 [Yaffe]

- Cystatin C > 1.25 mg/L was associated with a 2-fold multivariate-adjusted risk of cognitive impairment based on the Modified MMSE Examination.
- There was also a 50% higher risk of impaired cognition based on the DSST (Digital Symbol Substitution Test) for dementia among those whose cystatin C was > 1.25 mg/dL.

How do we explain these differences?

As several authors point out, additional studies are needed to establish the nature of the relationship between general cognitive function, the main types of dementia and relative levels of cystatin C.

Cystatin C's relationship to Alzheimer dementia may be much different than it is to vascular dementia and possibly other non-AD mechanisms of dementia as well.

All things considered, the weight of evidence linking elevated cystatin C to physical functioning problems impairment carries more weight from a risk appraisal perspective than the conflicting findings related to cognitive impairment.

Has cystatin C been linked to any other impairment of aging?

Other than cancer – which we will cover on the next page – the only one strongly impacted by aging is cataract formation. University of Wisconsin School of Medicine investigators found that cystatin C was a significant predictor of cortical and posterior subcapsular – but not nuclear – cataracts. [Knutson]

Considering the strong association between oxidative stress and cataracts, it could be instructive to see how this test relates to gamma-glutamyltransferase (GGT) and given the extensive use of GGT in insurance screening, this determination should be readily attainable from industry laboratory data.

CYSTATIN C AND THYROID FUNCTION

Is cystatin C influenced by thyroid status?

Yes.

Two studies show that both hyper- and hypofunction of the thyroid gland are associated with significance elevations of cystatin C. [Manetti, Wiesli]

Two caveats are important here:

- The magnitude of thyroid dysfunction associated with on cystatin C in these two small studies will not impact how cystatin C is used in underwriting.

- Studies have shown that subclinical hypothyroidism – the far more prevalent state of asymptomatic thyroid abnormality – is itself associated with a 50% increase in extra mortality at ages 75 and over, as well as greater risks of pathological cardiac changes and the development of congestive heart failure [Ochs, Rodondi and Bauer]

CYSTATIN C AND CANCER

How do cystatin C levels relate to the presence/risk of cancer?

"There are contradictory data concerning the possible influence of malignant diseases on the serum concentration of cystatin C; however, most authors have the opinion that malignant processes do not influence serum cystatin C concentration."

Radovan Hojs, et al
Maribor, Slovenia
Renal Failure
30(2008):181

Nakai et al compared patients with various cancers to those free of malignancy and concluded that while cystatin C was somewhat higher in the former, the result was not statistically significant in their underpowered study of 352 subjects, of whom only 83 had a known malignant neoplasm.

What has been cited to date as regards Cystatin C in specific kinds of cancer?

- Kos et al found that increased cystatin C predicted for disease progression in melanoma and colorectal cancer.

- Strojan concluded that cystatin C could be a tumor marker for invasive behavior in head and neck carcinoma based on their study of patients with both laryngeal and non-laryngeal primaries.
- Tumminello et al reported that cystatin C was associated with breast cancer as well as osteoblastic activity in patients with prostate cancer.
- Mulaomerovi described cystatin C as a potential marker for relapse in non-Hodgkin B-cell lymphoma.
- Nishikawa documented a relationship between cystatin C and invasive behavior on ovarian neoplasms.
- Tokyo did not find an association between cystatin C and progression of primary bladder carcinoma.

Given the foregoing, one can say that the value of cystatin C in regard to possible cancer mortality and morbidity remains to be clearly defined.

CYSTATIN C AND LIVER DISEASE

"... it was reasonable to say that serum cystatin C concentration was closely related to the progression of liver diseases and chronic liver inflammation, but not affected by HBV or HCV infection or tumor size. This has suggested that cystatin C may be feasible, at least to a certain extent, in routine monitoring for liver function."

Shu-Chen Chu, et al
Taichung, Taiwan
Clinica Chimica Acta
241(2004):133

In their study, these Taiwanese investigators found significantly greater cystatin C levels in patients with hepatic disease overall, as well as in those with cirrhosis and liver carcinoma.

Is there further evidence of a role for cystatin C in liver disease assessment?

Yes.

- Russian researchers reported elevated cystatin C associated with chronic hepatitis C as well as liver cirrhosis. [Korolenko]
- Chen et al found a linear relationship between cystatin C and matrix metalloproteinase-2 activity, and then between MMP-2 and severity of liver disease. We know that MMP-2 levels equate to those of serum hyaluronate, a proven marker for advanced fibrosis and liver cirrhosis. [Murawaki]
- Japanese investigators discovered a strong correlation between cystatin C and stage of liver disease in subjects with various chronic liver diseases. Cystatin C was also a marker for liver cancer in this context. [Takeuchi]

Is cystatin C associated with the magnitude of ALT?

Yes, in patients with known chronic liver disease. [Chu]. However, there is no apparent connection between cystatin C and liver enzymes in the general population. [Ognibene]

CYSTATIN C, HEALTH OUTCOMES AND MORTALITY

Does cystatin C correlate with patients' perceptions of their own health?

Yes.

- Ishani et al found a 3-fold greater incidence of personal health rated "fair/poor" versus more favorable assessments in a cohort of 404 older males, which was marginally significant in this small study population.
- LaCroix and her colleagues questioned 93,676 women, ages 40 to 79 on this point. There was no difference in the percentage who rated their health "fair to poor". However, those in the highest cystatin C quartile were far less likely to describe their health as "excellent to very good" and were apt to choose "good" instead.

Is there evidence of extra mortality risk independently attributable to elevated cystatin C?

Yes.

- Fried and Katz found that, after full adjustment for 13 mortality-related factors (7 of which we cannot routinely use in underwriting), persons in the highest quartile of cystatin C had a 2-fold greater ($p < 0.001$) risk of CV mortality than those in the 3rd quartiles. For non-CV mortality, 4th quartile cystatin C was also a highly significant predictor of death.
- Menon et al found cystatin C to be a significant indicator of mortality in patients with chronic kidney disease. In this context, it was notably superior to both creatinine and e-GFR.
- In patients with GFR > 60 , followed an average of 9.3 years, high cystatin C was associated with over a 2-fold higher overall mortality and 2.5-fold greater CV mortality. Creatinine was not significant to risk in this study. [Shlipak and Katz]

Does this relationship between cystatin C and excess mortality extend specifically to general elderly populations?

Yes.

In a 2006 report from the Health, Aging and Body Composition Study, Shlipak and Fyr reported:

- High cystatin C (≥ 1.19 mg/L) was found to be significantly associated with 2.7-fold higher mortality as compared to low readings after adjusting for 16 cofactors including several key ones which we do not have the capacity to use.
- The difference between the "medium" level cystatin C and those with high readings was also significantly different both prior to and after adjustment.

A 2008 follow-up and expanded 2008 report on the Health ABC Study by Deo et al added these findings:

- High cystatin C (≥ 1.19 mg/L) significantly outperformed creatinine in terms of mortality.
- It was linked to over 3-fold greater CV mortality than in those with "low" levels and 40%+ greater risk that in the middle range cystatin C cohort ($p < 0.001$).
- In those patients free of any prior circulatory events, high cystatin C was as potent in its impact as it was in subjects with a history of such events.

Shinkai and his Tokyo coworkers followed 1,034 non-disabled persons age 65 and over for a mean 7.9 years and cystatin C in the highest tertile was associated with twice the mortality of the 1st tertile and almost 70% greater death rate than the middle tertile.

Does cystatin C have mortality risk significance in persons with known CAD?

Yes.

- A brand new study, reported at the annual American Heart Association meeting, found that increasing cystatin C by one quartile resulted in a 2.3-fold greater risk of future CV death. This study involved 2,082 persons with known CV disease but no or only very mild renal impairment, followed for 3.7 years. [Keller and Messow]
- When Koenig, Twardella and their University of Ulm coworkers followed 1,033 patients with known CAD, those with cystatin C > 1.24 mg/L (their 5th quintile) had a dramatic increase in fatal and nonfatal CV events as compared to subjects in all four lower quintiles.

- Ix followed 990 patients with proven coronary disease for 37 months and, once again, there was an abrupt increase in all-cause mortality, CV events and incident heart failure in the top cystatin C quartile.
- Wiviott et al in Boston tracked 3,754 patients who survived acute coronary syndrome (ACS) events for 2 years and found that the risk of one of two endpoints – death or developing congestive heart failure – increased linearly across cystatin C quintiles and was dramatically higher in the 5th quintile.
- Eggers and her Swedish colleagues reported that cystatin C ≥ 1.28 mg/L was the most useful marker to distinguish those at risk for adverse outcomes following acute chest pain episodes.
- Jernberg et al discovered that elevated cystatin C was a marker for not only post-ACS mortality but also in patients who presented with presumptive ACS but received another diagnosis.
- Garcia-Acuna et al in Spain found that cystatin C was a marker for adverse post-MI outcomes and recommended that it be evaluated for use on this basis in patient care.
- McNeilly reported that when patients were followed a mean of 515 days after cardiac surgery, cystatin C in the 4th quartile was strongly predictive of interim death.

- Deo and Katz have just reported that cystatin C is a predictive indicator of risk of cardiac sudden death after following 5,157 older persons for 11.2 years.

Do these event and mortality implications extend to other forms of circulatory disease?

Yes.

- Tang et al reported a significantly increased risk of adverse events in patients with heart failure at a cut-off of 1.23 mg/L for cystatin C.
- Similar findings in heart failure patients were reported by Arimoto and his coworkers, Ilva and colleagues and Mitsuke et al in their respective studies.
- Ni et al reported that elevated cystatin C was “independently associated with both ischemic and hemorrhagic stroke in Chinese subjects” and that their stroke patients with the lowest cystatin C levels also had the lowest risks of death and new events.

Clearly, a growing literature is emerging related to the highly significant association between elevated cystatin C and adverse circulatory events as well as CV and all-cause mortality across a wide spectrum of middle-aged and older subjects.

CYSTATIN C AND NT-PROBNP

Is cystatin C associated with NT-proBNP?

Yes, but independently so, in a detailed laboratory assessment of cardiac and renal function markers involving in 815 healthy subjects, ages 46-75. [Johnston]

Magnusson et al found that they were also independently related to the risk of diabetes.

Are they also independent predictors of adverse outcomes?

Yes, in all but one study.

In these studies, they were independent markers:

- CV events in the 979-subject Heart and Soul Study [Shlipak and Ix]
- Hospitalization for or worsening of congestive heart failure in 367 consecutive patients [Naruse]
- Mortality in 480 subjects with acute heart failure [Lassus]

They were both significant markers but not independently so in a cohort of patients on admission who were subsequently diagnosed with ACS. In this group, 89% of patients with cystatin C \geq 125 mg/L had an NT-proBNP reading \geq ng/L. [Jernberg]

In another study of ACS patients, BNP (the other prominently used natriuretic peptide heart marker which largely correlates closely with NT-proBNP) was independently linked to adverse outcomes after adjusting for cystatin C levels.

Have any studies used cystatin C and NT-proBNP together to take advantage of their synergistic relationship?

Yes.

A team of European cardiologists followed 555 patients with CHF and found that combining the predictive power of cystatin C and NT-proBNP was "...superior to separate assessment of these markers." [Rozentryt]

Why is it important that the contributions of cystatin C and NT-proBNP be synergistic rather than redundant to one another?

Because this assures optimized pay-off from their use in insurance screening.

Clearly, what evidence we have to date supports the argument that cystatin C and NT-proBNP, reflecting different biological mechanisms, are independent markers suitable for use together in mortality and morbidity risk underwriting.

CONCLUSIONS AND RECOMMENDATIONS

This comprehensive review of the global research, clinical and epidemiological literature demonstrates that cystatin C has significant potential for use in mortality and morbidity risk underwriting.

There are no apparent barriers in terms of specimen collection and handling, laboratory analysis or affordability contraindicating the use of cystatin C in underwriting.

The main value of cystatin C appears to be as a routine screening test at ages 55 and over. Its greatest relative impact will be realized in elderly applicants, where the widely-appreciated drawbacks to screening with creatinine currently result in significant numbers of false-negatives in applicants with risk-significant renal impairment.

In addition to screening, cystatin C should be considered for use as the reflexive test of choice in these scenarios:

1. Resolving the underwriting significance of equivocal findings involving creatinine, BUN and eGFR.
2. Assessing the risk of diabetic and hypertensive nephropathy in applicants with longstanding disease, poor control and/or proteinuria and other kidney-related findings.
3. Gauging the degree of current renal impairment in applicants with a history of any type of kidney disease.

Given the clear superiority of cystatin C over creatinine as a marker for mild-to-moderate renal impairment, cystatin C results should take precedence over creatinine results in this context.

Cystatin C has substantial value as a marker for cardiovascular disease risk, independent of and synergistic with that conferred by NT-proBNP. It may also have value in the context of the assessing the severity of chronic liver disease.

Cystatin C may contribute significantly to screening for the risk of premature physical frailty, especially when used in conjunction with objective frailty tests, certain laboratory tests and medical history factors.

The following recommendations are offered for consideration by chief underwriting and medical officers, as well as executives of laboratories serving the insurance industry

1. Industry laboratories should initiate studies on their own and, where possible, with clients, assessing the efficacy of cystatin C as a potential underwriting asset. These studies should be carefully designed to maximize their contribution to our understanding of this test. Among the considerations to be explored are the relationship between cystatin C and NT-proBNP, HbA1c, GGT, low cholesterol, creatinine, microalbumin, hepatitis B and C, and all other tests related to the risk of circulatory and renal impairment.
2. The potential for replacing creatinine-based eGFR equations with a formula based on cystatin C should be evaluated.
3. In order to further clarify the relationship between cystatin C and the two most significant parameters of premature aging, insurance screening test outcomes for cognitive dysfunction and physical frailty should be correlated with cystatin C results.
4. The potential for combining cystatin C with NT-proBNP and, perhaps, HbA1c as an alternative to current use of treadmill stress tests and, potentially, resting ECGs should be carefully studied, bearing in mind the evidence cited here, findings in industry studies and whatever is reported henceforth in the medical literature.
5. All future studies and reports in the literature related to cystatin C as a potential insurance screening test should be carefully tracked and reported upon for industry consumption. This underwriter will do his best to accomplish this task, reporting on his findings in JournalScan™, Hot Notes™ and other appropriate venues.

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