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Cystatin C: Transforming cognitive and frailty screening

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The multivariate-adjusted impact of elevated cystatin C on mortality was clearly demonstrated[1]:

	Hazard ratios all-cause mortality
All ages	1.72
< Age 65	1.60
≥ Age 65	2.04

Underwriting executives and their medical director colleagues have been challenged by life insurer senior management to accomplish three major goals:

1. Control new business acquisition costs,
2. Substantially reduce application-to-issue cycle time and
3. Make insurance buying as convenient and customer-friendly as possible.

Where these goals are concerned, the older-age market presents its own unique challenges. Most insurers currently use one or more cognitive and/or physical function tests, typically for individuals aged 70 and older.

For the most part, the cumbersome and time-consuming resources presently relied upon for these purposes rouse the ire of both producers and their clients. Replacing such things as clock drawing, delayed word recall, walking speed and timed-get-up-and-go with a far more convenient alternative would constitute a major step forward.

Because blood profiles are routinely required at these older ages, adding an additional laboratory test component would be the easiest solution to this problem.

Now there is robust evidence that we have the blood test needed to get this accomplished. That test is cystatin C.

BACKGROUND

Cystatin C is produced by all tissues and found in all bodily fluids. It was initially regarded as a kidney test offering a substantial advantage over creatinine because it is not affected by aging-mediated loss of skeletal muscle mass.

The impact of cystatin C in renal function, as well as cardiovascular disease, has been well explained from a life underwriting perspective.

In 2015, a meta-analysis was conducted with nine general population-based studies that encompassed 38,854 individuals. The multivariate-adjusted impact of elevated cystatin C on mortality was clearly demonstrated.[1] (See chart to the left.)

We also know that the risk impact of cystatin C is largely independent of that reflected by NT-proBNP. This is important given the widespread use of NT-proBNP in life insurance screening.[2]

Based on this evidence, we need to shift our focus to cystatin C as a viable alternative marker for cognitive function and physical frailty.

COGNITIVE FUNCTION

Serum cystatin C has an important role in predicting the transition from mild cognitive impairment (MCI) to dementia, which indicates that the level of cystatin C plays an important part in the prediction of cognitive decline.

Wei Wei Chen, MD, et al
European Review for Medical and Pharmacological Sciences
10(2015):2957

Several major studies have explored this relationship. In a study with 2,104 healthy subjects with a mean age of 74, cystatin C correlated significantly with the odds of developing cognitive impairment (CI) over 4.3 years of follow-up[3]:

Cystatin C quartile (range)	% Developing CI
1 (≤ 0.90)	4.5%
2 (0.91-1.01)	5.4%
3 (1.02-1.15)	5.3%
4 (≥ 1.16)	10.5%

In an 11-year follow-up of 6,184 elders, cystatin C ≥ 1.24 predicted cognitive decline even after adjustment for inflammatory markers. Its impact was equivalent to that of shorter telomere length.[4]

Data from the National Health and Nutrition Examination Survey (NHANES) study revealed that cystatin C – but not creatinine – was a significant predictor of cognitive impairment based on the widely used Digit Symbol Substitution Test (DSST).[5]

After seven years of follow up, elderly subjects, who were enrolled in the Health ABC study and had a higher cystatin C baseline reading, showed greater cognitive decline and a higher incidence of cognitive impairment based on both the Mini-Mental Status Examination (MMSE) and the DSST.[6]

Three studies found that high cystatin C was a marker for the presence and severity of brain white matter lesions; even, in one case, after adjusting for apolipoprotein E genotype screening marker for Alzheimer disease risk. [7,8,9]

The weight of evidence to date reveals that cystatin C affords us an opportunity to effectively screen for early cognitive impairment without imposing the customer-unfriendly methods currently used by many insurers.

PHYSICAL DECLINE

Cystatin C was consistently associated with functional declines independent of other biomarkers.

Anne B. Newman, MD, et al
University of Pittsburgh Graduate School of Public Health
International Journal of Epidemiology
45(2016):1135

In her study, Newman included cystatin C as one of five biomarkers for mobility limitation and activities of daily living (ADL) difficulties, along with carotid intima-media thickness, fasting glucose, pulmonary function testing and brain MRI.

Fried found that subjects in the 4th cystatin C quartile (≥ 1.13) had a 40% greater likelihood of meeting widely recognized frailty diagnostic criteria, as compared to those individuals in the 1st cystatin C quartile.[10]

In a cohort of 1,332 community-dwelling females with a mean age of 77, the odds of having multiple ADL impairments increased dramatically between the 1st (27.8%) and 4th (45.6%) cystatin C quartiles.[11]

Hart reported a significant association between all five frailties criteria used in an analysis of 1,602 males, mean age 74, participating in the Osteoporotic Fractures in Men study.[12] These findings were adjusted for all of the usual risk factors including creatinine:

	Odds ratio: 4th vs. 1st quintile
Shrinking	2.31
Weakness	1.32
Exhaustion	1.91
Slowness	1.65
Decreased activity	1.89

At least another dozen studies have underscored the aforementioned investigations in terms of the impact of elevated cystatin C as a predictor of physical decline.

Note: for more in-depth information about these and all insurability-related aspects of cystatin C, please see 2016 review of the medical literature accessed at: http://insureintell.com/sites/default/files/CystatinC_HGeorge_2016.pdf

CONCLUSIONS

There is now abundant evidence that cystatin C is a more than adequate replacement for the various cumbersome cognitive and physical function tests insurers currently impose on elderly applicants.

We no longer need to rely upon the imprecise and often difficult-to-analyze findings from those procedures.

Cystatin C affords us the powerful advantage of an objective test for which we can readily set consistent and non-ambiguous criteria to distinguish degrees of excess risk.

In addition, by screening with cystatin C we also realize the payoff from its well-demonstrated impact as a marker for all-cause mortality.

Cystatin C is a reliable approach to cognitive and frailty screening that is most compatible with the underwriting-related objectives of senior life insurer management.

ABOUT THE AUTHOR

Hank George, FALU, CLU, FLMI, has been involved in life underwriting for almost 45 years. After 14 years with ExamOne, he became self-employed as a writer, speaker and educator. Hank has authored over 700 articles and research papers and made in excess of 1,000 presentations worldwide. His work had a major impact on the widespread embrace of underwriting assets such as Rx records and NT-proBNP. Hank publishes the monthly e-magazine Hot Notes with 5,000 readers in 52 countries and also manages three underwriting study groups. He may be reached at hank@hankgeorge.com and www.hankgeorgeinc.com.

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