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Generation of a New Cystatin C–Based Estimating Equation for Glomerular Filtration Rate by Use of 7 Assays Standardized to the International Calibrator

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Guest: Dr. Anders Grubb is Professor of Clinical Chemistry and in the Department of Laboratory Medicine, University Hospital of Lund, Sweden.

Bob Barrett: This is a podcast from *Clinical Chemistry* sponsored by the Department of Laboratory Medicine at Boston Children's Hospital. I am Bob Barrett.

Estimating Glomerular Filtration Rate or GFR is important for the detection and monitoring of impairment of renal function for safety in the use of potentially nephrotoxic pharmaceuticals and radiographic contrast media, and for administration of correct dosage of drugs cleared by the kidneys. Even though it is not ideal, serum creatinine is widely used as a marker for calculating Glomerular Filtration Rates.

A paper in the July 2014 issue of *Clinical Chemistry* described a new simple equation for estimation of GFR compromising measurement of plasma cystatin C and knowing the age of a subject. This multicenter study examined over 4,000 individuals to develop the new equation.

Dr. Anders Grubb was lead author of that paper. He is a Professor of Clinical Chemistry and in the Department of Laboratory Medicine, University Hospital of Lund, Sweden, and Dr. Grubb is our guest in today's podcast.

Doctor, why is it important to know the kidney function of a patient?

Dr. Anders Grubb: Presently the two most common blood tests are the hemoglobin concentration and the serum creatinine concentration. Since the serum concentration of creatinine is used as a marker for kidney function this emphasizes the importance of knowing the kidney function of a patient.

The reason that it is important to know the function, or more specifically the Glomerular Filtration Rate, is that it is essential for the detection and monitoring of impairment of renal function for safety in the use of potentially nephrotoxic medicines and radiographic contrast media, and for administration of correct dosage of medicines cleared by the kidneys.

Bob Barrett: Why is serum creatinine problematic as a marker of kidney function?

Dr. Anders Grubb: The serum concentration of creatinine is not only influenced by GFR (Glomerular Filtration Rate), but also by many other factors including muscle mass, amount of ingested meat, and varying medicine influenced to a blood secretion of creatinine. To improve the situation so-called creatinine-based GFR estimating equations are used to partially compensate for the influence of muscle mass on the creatinine concentration. But one major problem is that the average muscle mass differs for males and females and for different ethnic groups or races.

The use of creatinine-based equations therefore requires knowledge of both the sex, defined as male or female, and race of a patient. Race factors have been suggested for among others, Black, Hispanic, Asian, Chinese, African-American, White; White or other to exclude African-Americans, Korean, Japanese, and Afro-American populations. But race is a very vague and ill-defined biological property, and to connect a certain race to a patient might be ethically problematic and it's not allowed in many countries, for example in Sweden.

In addition the sex of a patient in all the cases be defined as male or female and in several countries, for example, Germany, more than two sexes are acknowledged.

Another drawback associated with the use of creatinine-based GFR estimating equations is that all presented equations with one exception requires specialized equations for children, arbitrarily defined as people below 18 years of age. This is of course due to the varying muscle mass of growing children.

Bob Barrett: Serum cystatin C is less problematic than serum creatinine as a marker of kidney function, why is that?

Dr. Anders Grubb: That is because influence of other factors than GFR on the cystatin C concentration is much lower and therefore less complex cystatin C-based GFR estimating equations can be used. For example, the race of a patient does not significantly influence the cystatin C concentration, and shown in the recent article in *Clinical Chemistry* neither does the sex of a patient. Therefore cystatin C-based GFR estimating equations do not require vague and ill-defined terms like race and sex.

As the serum cystatin C concentration is not significantly associated with the muscle mass of a patient, the same substance cystatin C-based GFR estimating equation can usually be used both for children and adults.

In contrast of serum creatinine, serum cystatin C is not influenced by ingestion of meat or medicines influencing the kidney tubular secretion.

As a matter of fact the so-called renal disease reserve defined as the increase in EFR after ingestion of meat and measured by invasive clearance techniques, for example renal inulin clearance, can be simply determined by measuring the serum cystatin C concentration before and after the intake of the meat.

Bob Barrett: But we all know that no method is perfect, so are there problems with the use of serum cystatin C as a marker of GFR?

Dr. Anders Grubb: Yes, because the cost of a cystatin C test is higher than that of the creatinine test. In our laboratory we charge $1.50 for an enzymatically based test of serum creatinine and $4 for a test of serum cystatin C. We do not use assay-based tests of serum creatinine as they often produced erroneous results.

Another disadvantage of serum cystatin C as a marker of GFR is that hydrolysis of glucocorticoids will increase the synthesis of cystatin C serum substance and does produce an increase in serum cystatin C and then erroneously low estimate of GFR.

Bob Barrett: Doctor, why did you involve so many diagnostic companies and clinical chemists in the production of your results reported in that recent article in *Clinical Chemistry*?

Dr. Anders Grubb: One problem connected with a use of both cystatin C and creatinine-based GFR estimating equations is that because no international acknowledged calibrators have previously been available a very large number of equations have been published. This has caused confusion about which equations to use and about the diagnostic performance of different equations used at different laboratories.

In an effort to improve the situation for cystatin C, IFCC and the standardization authority of the European Commission established a working group for the production of an international cystatin-C calibrator with me as the chairman.

Such a calibrator was recently produced but to be able to generate a truly assay-independent cystatin C-based GFR estimating equation, the availability of a calibrator is not sufficient. It must also be assured that it is implemented in similar and optimal way in the cystatin C assays provided by the major diagnostic companies. It was with great satisfaction that I noted that all coworkers of all companies involved, worked altruistically together in order to produce

the best possible diagnostic tool for estimation of GFR to the benefit of all patients.

Bob Barrett: Well finally, doctor, what is the best way to estimate the Glomerular Filtration Rate?

Dr. Anders Grubb: Although in my evaluation cystatin C-based GFR estimating equations generally show a diagnostic performance superior to that of creatinine-based equations, they do not provide the best GFR estimate.

For it has been shown in many investigations that the mean of cystatin C and creatinine-based estimate represents the very best estimate, at least for adults.

Comparison of the cystatin C and creatinine-based estimates also allows a check of the reliability of the mean estimate. The closer the estimates are, the better and the more secure the estimate. This procedure for superior estimation of GFR has been used in my hospital for several years and is described at the www.egfr.se in several languages, and this site also provides tools for implementation of this strategy.

Bob Barrett: Dr. Anders Grubb is Professor of Clinical Chemistry and in the Department of Laboratory Medicine, University Hospital of Lund, Sweden. He has been our guest in this podcast from *Clinical Chemistry* on eGFR based on creatinine.

I'm Bob Barrett. Thanks for listening!