APPENDIX B

**Jackson Heart Study Manuscript Proposal Form**

**Please read JHS Publications & Presentations Guidelines before completing this proposal form.**

**JHS P #**

**Date of Submission: \_\_\_ (mm/dd/yyyy) Date of Approval: \_\_\_ (mm/dd/yyyyy)**

**PART I. OUTLINE OF PAPER**

**1.  Title Information**

a. Proposal Title: Effects of Serum Creatinine Calibration on Estimated Glomular Filtration Rate and CKD determination in African Americans: The Jackson Heart Study

b. Abbreviated Title: Serum Creatinine Calibration and CKD

c. Suggested key words:  Serum Creatinine Calibration, eGFR, CKD-EPI, Deming Regression

**2.**   **Lead Author Name:**Wei Wang

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**3.**   **Co-authors, Contact Information, and Responsibilities:** (Proposed co-authors,

Email address and/or telephone numbers and proposed responsibilities.  Examples of responsibilities include design and concept of study, statistical analysis, data acquisition, methodological expertise, funding acquisition, literature review. Also indicate specific writing assignments including: introduction methods, results, discussion, preparation of tables and figures. Items not assigned to a co-author are assumed to be the responsibility of the lead author. Corresponding author should also be identified if it is not to be the lead author.)

|  |  |  |
| --- | --- | --- |
| **Name** | **Contact Information** | **Responsibilities** |
| Michael Griswold | MGriswold@umc.edu | Conception and design, methodological expertise, statistical expertise |
| Adolfo Correa | ACorrea@umc.edu | methodological expertise, interpretation of data, critical revision of manuscript, supervision |
| Bessie Young | youngb@u.washington.edu | methodological expertise, interpretation of data, critical revision of manuscript |
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| Ronit Katz | rkatz@u.washington.edu | methodological expertise, interpretation of data, critical revision of manuscript |
|  |  |  |

**4.**   **Non-JHS Lead Authors:** Non JHS Lead authors are required to have a JHS co-author and primary contact person (indicate with an asterisk). Non-JHS Lead Authors are encouraged to visit the JHS Website

<http://jhs.jsums.edu/jhsinfo> or [www.nhlbi.nih.gov/about/jackson/](http://www.nhlbi.nih.gov/about/jackson/)

for information on JHS investigators. The JHS Steering Committee may nominate additional authors if special expertise for interpreting JHS data is needed)

**5**. **Brief Overview**: In 250 words maximum, provide a brief overview of the proposal including the nature of the problem to be addressed, scientific relevance, objectives/aims, research question/hypotheses, and methods/analytical plan. This overview will be posted on the internal JHS website.

The calibration of serum creatinine (SCr) values to Isotope Dilution Mass Spectroscopy (IDMS)-calibrated creatinine is considered to be essential for valid use of the new Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation in order to accurately calculate the estimated glomerular filtration rate (eGFR). Using a more general population, the CKD-EPI equation derived different coefficients for the same 4 variables used in the Modification of Diet in Renal Disease (MDRD) Study equation but has been shown to estimate GFR more accurately than the MDRD study equation.

We aim to (1) determine the optimal IDMS traceable SCr calibration equation under different modeling approaches (2) assess differences in CKD prevalence (defined by eGFR less than 60 ml/min/1.73 m2) across combinations of calibration approaches (no calibration & IDMS) and eGFR equations (MDRD & CKD-EPI) using Visit 1 measurements of Jackson Heart Study participants (N=5,210).

To determine calibration equations, a three-way data splitting strategy combined with both pure-validation and cross-validation approaches will be applied to JHS Visit 1 calibration samples (N=206) to select the optimal calibration model, estimate true error and assess performance of final selected calibration equation.

**6.**   **Background/Rationale (**Include the relevance of this proposal to African Americans

and justify the need for the JHS cohort to answer the research question):

Glomerular filtration rate (GFR) is used in the diagnosis of chronic kidney disease (CKD) and is an independent predictor of all-cause and cardiovascular mortality and kidney failure in a wide range of populations. Clinical guidelines recommend reporting estimated GFR (eGFR) when SCr level is measured [1, 2]. The CKD-EPI equation using four variables — age, sex, race and IDMS traceable SCr measurements- has been recently proposed and showed to estimate measured GFR more accurately than the MDRD study equation [3, 4]. Because, IDMS traceable SCr measurements are not available among Jackson Heart Study participants in Visit 1, there is a need to determine a calibration equation using 206 calibration samples and then apply this calibration equation to current SCr measurements to achieve IDMS traceable SCr values used for GFR estimation with CKD-EPI equation. Performing the calibration will enhance the ability of other investigators in Jackson Heart Study to validly estimate kidney function in their studies.

**7.**   **Research Hypotheses:**

We hypothesize that specific regression model will provide an excellent calibration equation to calibrate local laboratory serum creatinine measurements and achieve IDMS traceable creatinine values used for GFR estimation with CKD-EPI equation.

To evaluate this hypotheses, we will compare alternative modeling techniques including linear, Deming (errors in variables), piecewise linear and quadratic regression models using three validation methods (pure training/validation samples, ten-fold cross-validation and leave-one-out cross validation) to determine the optimal calibration equation of current SCr measurements of Jackson Heart Study V1.

In addition, we will compare cross-sectional CKD-EPI and MDRD equation calculated eGFRs as well as dichotomized CKD determinations (using eGFR < 60 ml/min/1.73 m2 as a threshold) across non-calibrated and IDMS-calibrated visit 1 SCr.

**8.**   **Data:** (Visits and variables to be used, sample inclusions/exclusions)

* Please see the attached Variable Request Table (Excel Workbook)
  + CKD001 Wang - JHS proposal variable list Feb 06 2014.xlsx

**9.**   **Brief Statistical Analysis Plan and Methods:**(Including power calculations, if necessary.)

For calibration samples, we will calculate summary statistics for the original SCr, IDMS traceable measurements and also the difference (IDMS - original). Extreme outliers (difference > 3 SDs from the mean) will be excluded under the premise that these outliers will not contribute useful information to the calibration because they are believed to be caused by sample evaporation, insufficient sample mixing or other handling issues, rather than differences between SCr assays [5, 6]. Three-way data splits strategy will be used in which the data (200 subjects) will be divided into three mutually exclusive datasets: a training data set, a validation dataset and a test data set to select appropriate calibration equation, estimate true error and also assess performance of final selected calibration equation [7]. We will split the whole data set as 25% for test data (50 subjects) [8] for model performance assessment, and employ holdout method, 10-fold cross validation and leave-one-out cross validation to further split training and validation data set for model selection and true error estimation. Four potential calibration models will be considered, simple linear regression, quadratic regression, piecewise linear regression and Deming regression. The final selected calibration equation will be applied to the test data set, and the predicted and measured IDMS traceable SCr values will be compared with paired t-test and the agreement will be assessed with concordance correlation coefficient statistics. The data will be further depicted using scatterplots and Bland-Altman plots.

The selected calibration equation will be applied to SCr measurements of 5,210 subjects from Jackson Heart Study V1 to estimate the GFRs. CKD prevalence based on eGFR calculated by CKD-EPI equation and MDRD Study equation using IDMS traceable SCr measurements will be compared with McNemar’s test, and we will also compare CKD prevalence based on eGFR calculated by CKD-EPI equation using IDMS traceable and non-calibrated SCr measurements with McNemar’s test.

**10.**  **References:** (Maximum 15)

1. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease. Am J Kidney Dis. 2002 39(2)(suppl 1):S1-S266.
2. Early identification and management of chronic kidney disease: summary of NICE guidance. Crowe E, Halpin D, Stevens P, Guideline Development Group. BMJ. 2008 Sep 29; 337:a1530.
3. Comparison of risk prediction using the CKD-EPI equation and the MDRD study equation for estimated glomerular filtration rate. [Matsushita K](http://www.ncbi.nlm.nih.gov/pubmed?term=Matsushita%20K%5BAuthor%5D&cauthor=true&cauthor_uid=22570462), [Mahmoodi BK](http://www.ncbi.nlm.nih.gov/pubmed?term=Mahmoodi%20BK%5BAuthor%5D&cauthor=true&cauthor_uid=22570462), [Woodward M](http://www.ncbi.nlm.nih.gov/pubmed?term=Woodward%20M%5BAuthor%5D&cauthor=true&cauthor_uid=22570462), [Emberson JR](http://www.ncbi.nlm.nih.gov/pubmed?term=Emberson%20JR%5BAuthor%5D&cauthor=true&cauthor_uid=22570462), [Jafar TH](http://www.ncbi.nlm.nih.gov/pubmed?term=Jafar%20TH%5BAuthor%5D&cauthor=true&cauthor_uid=22570462), [Jee SH](http://www.ncbi.nlm.nih.gov/pubmed?term=Jee%20SH%5BAuthor%5D&cauthor=true&cauthor_uid=22570462), [Polkinghorne KR](http://www.ncbi.nlm.nih.gov/pubmed?term=Polkinghorne%20KR%5BAuthor%5D&cauthor=true&cauthor_uid=22570462), [Shankar A](http://www.ncbi.nlm.nih.gov/pubmed?term=Shankar%20A%5BAuthor%5D&cauthor=true&cauthor_uid=22570462), [Smith DH](http://www.ncbi.nlm.nih.gov/pubmed?term=Smith%20DH%5BAuthor%5D&cauthor=true&cauthor_uid=22570462), [Tonelli M](http://www.ncbi.nlm.nih.gov/pubmed?term=Tonelli%20M%5BAuthor%5D&cauthor=true&cauthor_uid=22570462), [Warnock DG](http://www.ncbi.nlm.nih.gov/pubmed?term=Warnock%20DG%5BAuthor%5D&cauthor=true&cauthor_uid=22570462), [Wen CP](http://www.ncbi.nlm.nih.gov/pubmed?term=Wen%20CP%5BAuthor%5D&cauthor=true&cauthor_uid=22570462), [Coresh J](http://www.ncbi.nlm.nih.gov/pubmed?term=Coresh%20J%5BAuthor%5D&cauthor=true&cauthor_uid=22570462), [Gansevoort RT](http://www.ncbi.nlm.nih.gov/pubmed?term=Gansevoort%20RT%5BAuthor%5D&cauthor=true&cauthor_uid=22570462), [Hemmelgarn BR](http://www.ncbi.nlm.nih.gov/pubmed?term=Hemmelgarn%20BR%5BAuthor%5D&cauthor=true&cauthor_uid=22570462), [Levey AS](http://www.ncbi.nlm.nih.gov/pubmed?term=Levey%20AS%5BAuthor%5D&cauthor=true&cauthor_uid=22570462); [Chronic Kidney Disease Prognosis Consortium](http://www.ncbi.nlm.nih.gov/pubmed?term=Chronic%20Kidney%20Disease%20Prognosis%20Consortium%5BCorporate%20Author%5D). [JAMA.](http://www.ncbi.nlm.nih.gov/pubmed/22570462) 2012 May 9;307(18):1941-51.
4. The CKD-EPI equation incorporating both cystatin C and creatinine best predicts individual risk: a cohort study in 444 patients with chronic kidney disease. [Rogacev KS](http://www.ncbi.nlm.nih.gov/pubmed?term=Rogacev%20KS%5BAuthor%5D&cauthor=true&cauthor_uid=24166454), [Pickering JW](http://www.ncbi.nlm.nih.gov/pubmed?term=Pickering%20JW%5BAuthor%5D&cauthor=true&cauthor_uid=24166454), [Seiler S](http://www.ncbi.nlm.nih.gov/pubmed?term=Seiler%20S%5BAuthor%5D&cauthor=true&cauthor_uid=24166454), [Zawada AM](http://www.ncbi.nlm.nih.gov/pubmed?term=Zawada%20AM%5BAuthor%5D&cauthor=true&cauthor_uid=24166454), [Emrich I](http://www.ncbi.nlm.nih.gov/pubmed?term=Emrich%20I%5BAuthor%5D&cauthor=true&cauthor_uid=24166454), [Fliser D](http://www.ncbi.nlm.nih.gov/pubmed?term=Fliser%20D%5BAuthor%5D&cauthor=true&cauthor_uid=24166454), [Heine GH](http://www.ncbi.nlm.nih.gov/pubmed?term=Heine%20GH%5BAuthor%5D&cauthor=true&cauthor_uid=24166454). [Nephrol Dial Transplant.](http://www.ncbi.nlm.nih.gov/pubmed/?term=the+ckd-epi+equation+incorporating+both+cystatin+c+and+creatinine+best+predicts) 2013 Oct 28.
5. [Standardization of serum creatinine and estimated GFR in the Kidney Early Evaluation Program (KEEP).](http://www.ncbi.nlm.nih.gov/pubmed/18359411) Stevens LA, Stoycheff N. Am J Kidney Dis. 2008 Apr;51:S77-82.
6. [Calibration of serum creatinine in the National Health and Nutrition Examination Surveys (NHANES) 1988-1994, 1999-2004.](http://www.ncbi.nlm.nih.gov/pubmed/18037092) Selvin E, Manzi J, Stevens LA, Van Lente F, Lacher DA, Levey AS, Coresh J. Am J Kidney Dis. 2007 Dec;50(6):918-26.
7. Pattern recognition and neural networks. Ripley BD, Cambridge: Cambridge University Press, ISBN 0-521-46086-7, 1996.
8. The Elements of Statistical Learning. Hastie, T., Tibshirani, R., and Friedman, J. New York: Springer-Verlag, 2001.

# PART II.  AUTHOR CONTRIBUTIONS

**11.**  Have all co-authors reviewed and approved this document?   X    Yes (Required)

**12.**  Does the lead author (or designee) agree to present findings at a JHS Colloquium**?**

or Seminar?    X   Yes (required)

# PART III.  ADDITIONAL INFORMATION

# 13. Is this manuscript proposal based on an Ancillary Study? \_\_\_\_\_ Yes \_\_X\_\_ No

# If yes, please provide the ASC # .

**14.**  **Type of Study:**

\_ X     Full Cohort                   Family Study           Sub-Study

\_      Ancillary Study           Case Control           Other (list):

**15.**  **Type of Data:**

\_\_    Longitudinal       X   Cross-Sectional         Other (list):

**16.**  **Location of Statistical Analysis:**

\_X     Central (by Jackson Heart Study Staff)

\_      Local (list site)

**17.** **Genetic Information:**

**a.** Do you propose use of data from a participant’s DNA?       Yes (see b)   X    No

**b**.   If yes, for a primary aim or secondary aim of JHS? (Please check one or both)

       Primary Aim (heart, vascular disease)       Secondary Aim (other conditions)

**18.**  **Conflict of Interest**

**a.** Are these analyses to involve a for-profit corporation?  \_\_\_\_\_Yes \_\_X\_\_No

**b**. Do you or any member of your Writing Group intend to patent any process, or

aspect of outcome from these analyses?  \_\_\_\_\_\_Yes    \_\_\_X\_\_\_\_No

**19.**  **Data Sharing Agreement**

Has the Lead Author and any co-authors who will have direct access to JHS

data signed the JHS Data Sharing Agreement?     \_\_X\_\_\_Yes (Required)

**20.**  **JHS Manuscript Overlap**

The Lead Author is responsible for reviewing the manuscript list on the JHS website http://jhs.jsums.edu/jhsinfo, listing the JHS manuscripts / manuscript proposals that are similar to the one he/she is proposing and justifying the differences and similarities. The lead author is encouraged to contact lead authors of the most related manuscript proposals for comments on the new proposal or collaboration.

**a**. Similar manuscripts / proposals : \_\_X\_\_\_No  \_\_\_\_\_\_Yes

**b**. If “yes”, list MS # title and Lead Author below)

**21. Manuscript Completion**

It is expected that the manuscript will be completed in less than one year. The manuscript proposal will expire if no manuscript is submitted for JHS review at the end of one year from the date of approval. If additional time is needed after one year, the Lead Author should request an extension from the Publications and Presentations Subcommittee.