U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

BIOMARKER QUALIFICATION

Biomarker Name	Total Kidney Volume (TKV)
Context of Use*	Baseline TKV can be applied as a prognostic biomarker for clinical trial enrichment in Autosomal Dominant Polycystic Kidney Disease (ADPKD)
Submitter	Polycystic Kidney Disease Outcomes Consortium
Briefing Documents Date(s)	March 20, 2014
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Keywords: Enrichment, Prognostic

***Qualification of Total Kidney Volume (TKV) as a prognostic biomarker for the following Proposed Context of Use:**

- **General Area**

Clinical trial enrichment in Autosomal Dominant Polycystic Kidney Disease (ADPKD)

- **Target Population for Use**

Patients with ADPKD

- **Stage of drug development for use**

All clinical stages of ADPKD drug development, including proof of concept, dose-ranging, and confirmatory clinical trials

- **Intended application**

Baseline TKV can be applied as a prognostic biomarker that, in combination with patient age and baseline estimated Glomerular Filtration Rate (eGFR), can be used to help identify those ADPKD patients who are at the greatest risk for a substantial decline in renal function defined as (1) 30% worsening of eGFR, (2) 57% worsening of eGFR (equivalent to doubling of serum creatinine), or (3) End-Stage Renal Disease (ESRD, defined as dialysis or transplant). This biomarker will be used as an inclusion criterion in clinical trials to identify patients likely to show a clinically relevant decline in kidney function during the duration of the trial. Data are provided showing the calculated risk of each of these outcomes of declining renal function depending on age, total kidney volume, and baseline eGFR. Tables will be used by clinical trial researchers to determine the inclusion criteria to help select patients who are likely to reach the clinical endpoint of interest within a timeframe practical for the trial. These criteria include the optimum age, TKV, and eGFR for selecting subjects to be enrolled in the clinical trial.

Documents Reviewed:

- PKDOC FDA Submission Cover Letter 3-20-2014.pdf
- PKDOC_FDA-EMA_Final_Briefing_Book_(03-20-2014)_FINAL.pdf
- PKDOC_Briefing_Book_Appendices_(3-20-2014)_FINAL.pdf
- PKDOC_Briefing_Book_Appendices_(3-20-2014)_FINAL (2).pdf

Table of Contents

I. Qualification Executive Summary

Baseline Total Kidney Volume (TKV) can be used to help predict the rate of confirmed 30% decline in estimated Glomular Filtration Rate (eGFR) in clinical trials of patients with Autosomal Dominant Polycystic Kidney Disease (ADPKD). GFR was estimated by the Modification of Diet in Renal Disease (MDRD) equation. The datasets submitted seem to support this context of use that TKV as a prognostic biomarker can be used for clinical trial enrichment in ADPKD patients. A modeling approach is used to estimate the event rate or predict the event risk at different time points based on baseline age, eGFR, with and without TKV. Including TKV in the model provides a seemingly modest improvement over the best model using age and eGFR alone in terms of predictive performance on event risk based on estimation of a time to event concordance measure that is free of study-specific censoring distributions. This was observed internally (by cross validation) using the submitter’s dataset. FDA performed an independent validation using a separate dataset available internally that further supported the predictive performance and the draft qualification of the prognostic biomarker. For the endpoints of 57% decline in eGFR and ESRD, the number of events within 5 years is too small to make any conclusions.

II. Overview and Timelines of the CDER Biomarker Qualification Submission

Submission History:
1/3/2012: PKDOC submits Letter of Intent to FDA
2/1/2012: PKDOC receives official acceptance of Letter of Intent and submission into the Biomarker Qualification Program.
9/24/2012: PKDOC submits the initial Briefing Book to the FDA.
3/21/2014: PKDOC submits final Briefing Book, appendices, and datasets to the FDA.
7/8/2014: PKDOC submits additional datasets requested by FDA after the initial submission (all longitudinal eGFR measurements and patients' registry identification).

There are several important statistical topics that are important to evaluate to address the proposed context of use. First, how to characterize the joint distribution of baseline covariates in the submitter’s dataset? Second, how to generate the best base model based on the known science recommending the prognostic variables to include before considering another prognostic variable and the existing data? Third, how to evaluate the predictive performances of the “best” models with or without the new prognostic variable (in this case, it is TKV)? Fourth, how to use the model and this assumed distribution of covariates to predict the event risk or the event rate in a future trial?

Regarding the assessment of predictive performance using the estimated event rate, it should be noted that the true event rate at any time is unknown and hence it is not possible to determine whether any estimated event rate is close to the true event rate or not. If two approaches give similar estimated event rates at all time points, then the two approaches provide similar predictive performances. Otherwise, it can be said that the two approaches provide different event rate estimates. The C-statistic proposed by Uno et al assesses the predictive performance with the probability of directional concordance between the event risk predicted by a time-to-event model (e.g., Cox regression model) and the true time to event. The higher the directional concordance probability the better the predictiveness is in comparing the C-statistic between the models. In this review, both estimated event rate and Uno C-statistic for predictive performance of the event risk will be explored.

III. Assessment of Biomarker Regarding Its Context(s) of Use Statement

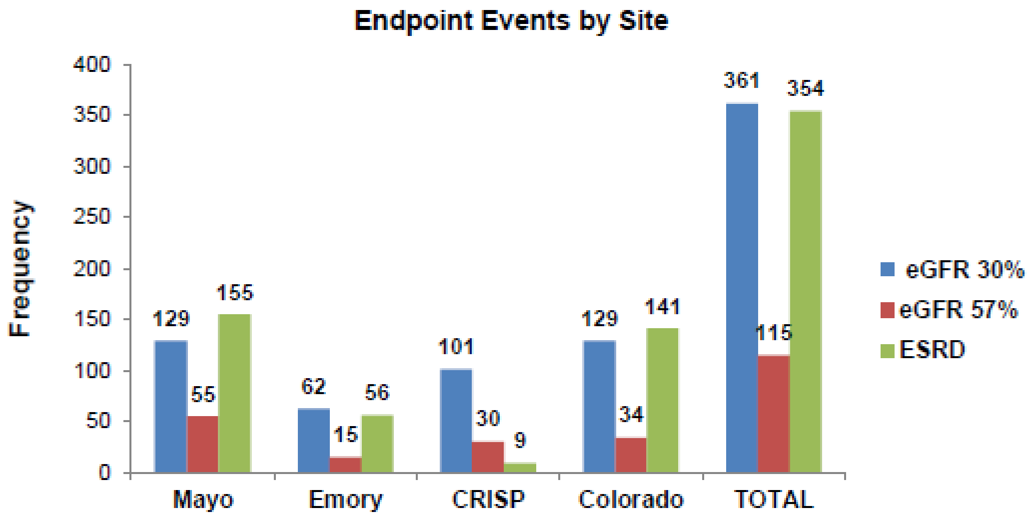
The submission includes the datasets from 5 observational registries of patients with ADPKD. These are individually known as the Emory University, Mayo Clinic, University of Colorado, CRISP I, and CRISP II registries. Some of the characteristics of the data are summarized in Table 1 and Figure 1 below. In Figure 1, the sum of the number of events in the different registries does not equal the total number of events because some patients were included in more than one registry.

Table 1. Characteristics by Imaging Population

Characteristic	At Least One Image (n=2355)		
	At Least One Image (n=2355)	Only One Image (n=1173)	Two or More Images[1] (n=1182)
Age at Study Entry (Years), *mean* ± *SD*	35.37 ± 16.28	39.31 ± 15.74	31.45 ± 15.86
Year of Study Entry, *mean* ± *SD*	1995 ± 11.67	1997 ± 11.08	1993 ± 11.87
Sex (Male), *n (%)*	933 (39.62)	479 (40.84)	454 (38.41)
Death			
Count, *n (%)*	145 (6.16)	90 (7.67)	55 (4.65)
Age at Death, *mean* ± *SD*	62.33 ± 14.50	62.55 ± 13.37	61.97 ± 16.30
End Stage Renal Disease (ESRD)			
Count, *n (%)*	546 (23.18)	309 (26.34)	237 (20.05)
Age at ESRD, *mean* ± *SD*	52.27 ± 10.57	52.28 ± 10.48	52.27 ± 10.70

[1]Two or more renal images at least 6 months apart
Source: Table 1 of Briefing Document

Figure 1. Number of Endpoints (by registry cohort)



Source: Figure 22 of Briefing Document

There are many reasons to be skeptical about the relevance of this data to predicting event rates in a clinical trial. It's not possible to know what differences these things make, if any, nor how to adjust things to try to compensate for these differences. These reasons include:

a) Differences in the sampling mechanism. The population was not a random sample from the population of people with diagnoses of ADPKD. In some cases, family members were recruited based on genotyping although they did not necessarily have a diagnosis. In addition, the people recruited for a clinical trial are not a random sample from the population.

b) In a clinical trial, baseline eGFR will often be calculated as an average of two or more values taken within a short time (one or two weeks) before randomization or first dose of study drug. This is done in part because of a moderate level of within subject variability. The average is more reliable. In this dataset, only one baseline value was used and it could have been measured many months (up to a year) after the defined time 0 (the time of the baseline TKV measurement).

c) Because an event cannot occur unless a measurement is observed, the timing and frequency of serum creatinine measurements can affect the event rate. In a clinical trial, serum creatinine measurements are taken at defined time points such as every 3 months or every 4 months. Although missing data is inevitable, there is an expectation that most people will follow that schedule. In this dataset, they were taken haphazardly whenever chosen by the subject or physician. In some case, measurements were taken every day for many days in a row; in other cases there were gaps of a year or more between measurements.

d) In a clinical trial, the endpoint of confirmed 30% change from baseline would usually need to be confirmed by the very next subsequent measurement. If the qualifying and confirmatory measurement were not consecutive, then an event does not count. However, in this dataset, events could count even when the qualifying and confirmatory events are years apart with many non-confirmatory measurements in between.

e) In a clinical, an event of confirmed 30% worsening of eGFR would also include more severe endpoints including need for initiation of dialysis or transplant. In this dataset, subjects with these more severe events were censored at the time of the event.

According to Figure 4 of the Briefing Document, there were 2610 total subjects in the combined datasets. 2355 of these subjects had at least one TKV measured. Of these 2355 patients, 1140 of these subjects had a baseline eGFR and at least two eGFR measurements post-baseline. These 1140 subjects were used by the applicant to develop their model. Of these 1140 subjects, 361 had events of 30% decline in eGFR. This dataset was used by the applicant to fit a Cox proportional hazards model. The coefficients of that model are contained in Table 21 of the Briefing Document and copied below in Table 2.

Table 2. Applicant's Final Multivariate Cox Model Including Interaction Terms for the Probability of a 30% Worsening of eGFR (1140 patients with 361 events)

Parameters	coef	exp(Coefficient)	se(Coefficient)	z	P-Value
Prognostic Factors					
Ln Baseline TKV	2. 755094	15.723	0.367392	7.5	6.40E-14
Baseline Age	0.26031	1.297	0.043426	5.99	2.00E-09
Baseline eGFR	0.096056	1.101	0.016639	5.77	7.80E-09
Interaction Terms					
TKV:Age	-0.02905	0.971	0.005861	-4.96	7.20E-07
eGFR:Age	-0.00079	0.999	0.00014	-5.65	1.60E-08
eGFR:TKV	-0.00994	0.990	0.002633	-3.77	0.00016

(Source: Table 21 of Briefing Document).

When we looked at the patient characteristics in the dataset, we saw that there were patients who were less than 12 years old and others had starting eGFR less than 25 mL/min per 1.73 m^2. Patients with these characteristics are unlikely to be included in clinical trials and their data may not be useful for the purpose of predicting event rates in future clinical trials. After discussing this issue with the applicant, we mutually decided that it would be best to remove those patients from the dataset in our analysis. That left us with 925 subjects with 300 events for our analysis.

First, we want to describe the distribution of the baseline covariates in our dataset or 925 subjects. Table 3 shows the sample means, standard deviations, and correlations.

Table 3. Summary statistics for dataset with n=925 subjects

Covariate	Mean	St. Dev.	Corr. w/ TKV	Corr. w/ log(TKV)	Corr. w/ eGFR	Corr. w/ log(eGFR)
Age	39.423	13.394	0.25114	0.29305	-0.64007	-0.63517
TKV	1308.9	1103.7		0.88251	-0.39954	-0.44726
log(TKV)	6.9357	0.67019			-0.48040	-0.51154
eGFR	73.417	30.193				0.95688
log(eGFR)	4.2139	0.41219				

We will try to describe the best fitting normal distribution so that in a future trial, the baseline covariates can be assumed to have a similar distribution truncated at the lower limits and upper limits set by the inclusion criteria in that trial. The maximum likelihood estimates are shown in Table 4. See Appendices A-C for an explanation of how the maximum likelihood estimates of the truncated multivariate normal distribution were found and also how the marginal distributions were found.

Table 4. Maximum likelihood estimates of multivariate normal distribution parameters for baseline covariates

Covariate	Mean	Covariance w/ Age	Covariance w/ log(TKV)	Covariance w/ log(eGFR)
Age	38.582	220.73	3.4075	-4.5065
log(TKV)	6.9276		0.46848	-0.16303
log(eGFR)	4.2237			0.19770

Figures 2-4 show the estimated density functions for each covariate and the density from the marginal distribution of the truncated multivariate normal distribution. Note that none of the variables actually have a normal distribution. This can be seen from the skewness and kurtosis in the figures (the sample values are shown plus or minus 1.96 times the estimated standard error). In addition, the marginal distributions from the truncated multivariate normal distribution also do not appear to fit the data very well. Despite that, people may still want to use this truncated multivariate normal approximation and we don't have any better suggestion.

Figure 2. Density of baseline Age

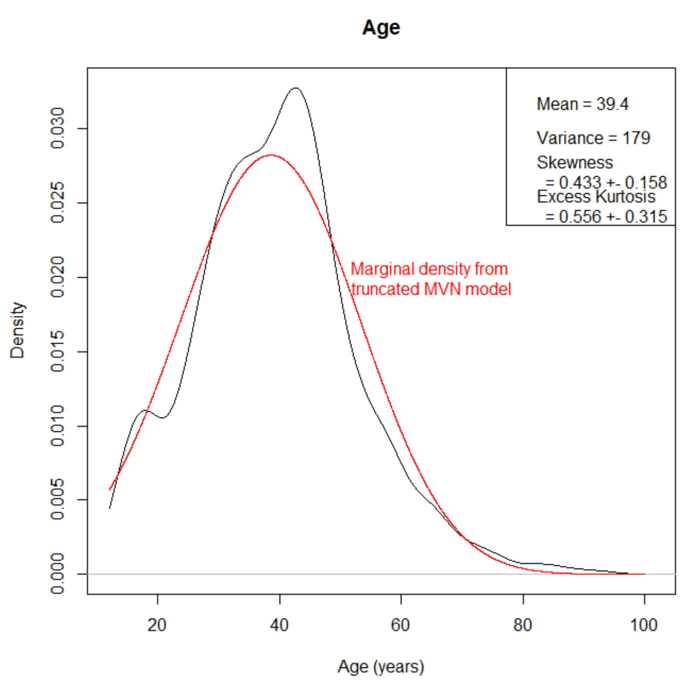


Figure 3. Density of baseline log(TKV)

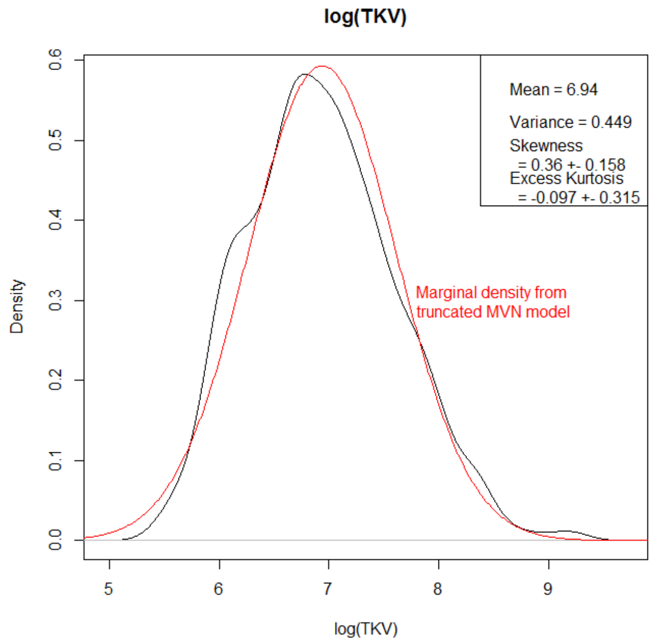
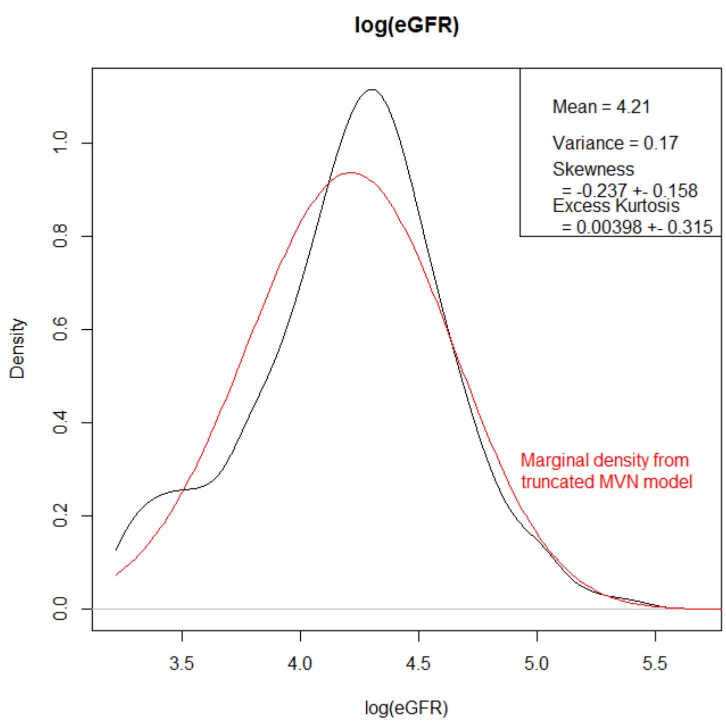


Figure 4. Density of baseline log(eGFR)

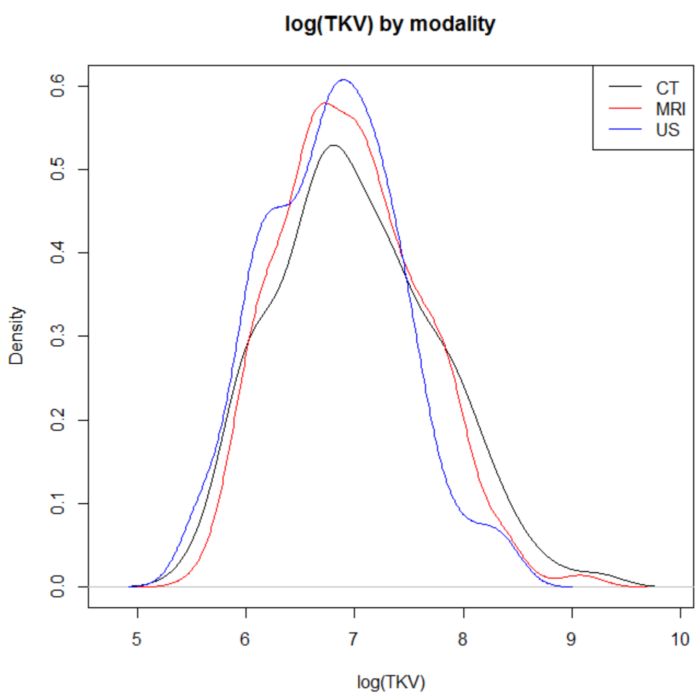


The distribution of baseline log(TKV) is different across the 3 different modalities. If a person has an MRI measurement, then they are included in the MRI stratum. Otherwise, if they have a CT measurement, then they are included in the CT stratum. The remaining have only a US measurement and are included in that stratum. Table 5 shows the summary statistics for log(TKV) for the 3 modalities. The US mean differs from both the CT and MRI means (two sample t-test) and the CT variance is significantly larger than the MRI variance (Snedecor's F-test). Differences between strata in the distribution of log(TKV) may be due to differences in the actual measurement process or may be due to different underlying characteristics of the people in those stratum. The estimated densities of log(TKV) for each stratum are shown in Figure 5.

Table 5. Summary statistics for baseline log(TKV) by modality

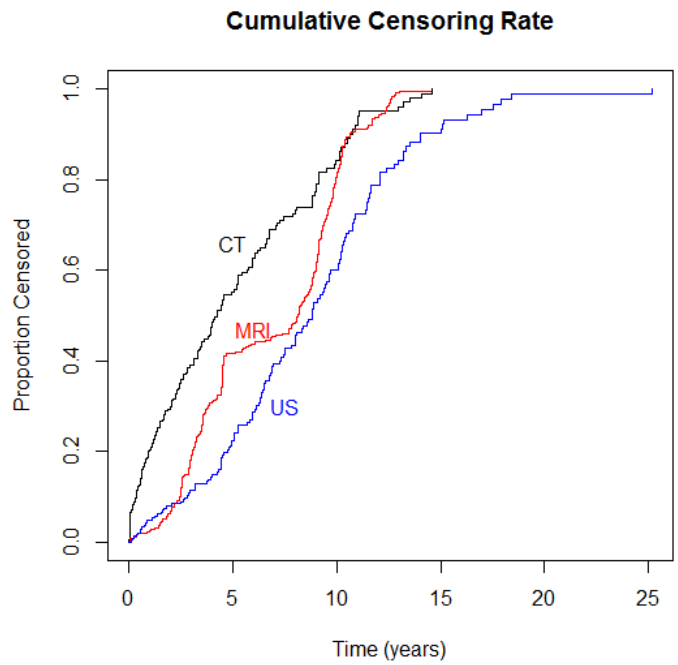
Modality	Sample size	Mean	St. Dev.
CT	245	7.014	0.7375
MRI	430	6.968	0.6466
US	250	6.804	0.6230

Figure 5. Density of log(TKV) by modality



The reverse Kaplan-Meier estimates (Altman et al 1995) of the followup time are shown in Figure 6. The median duration of followup was about 8.0 and 8.8 years in the MRI and US strata, but about 4.2 years in the CT stratum.

Figure 6. Kaplan-Meier estimates of Censoring distributions by modality



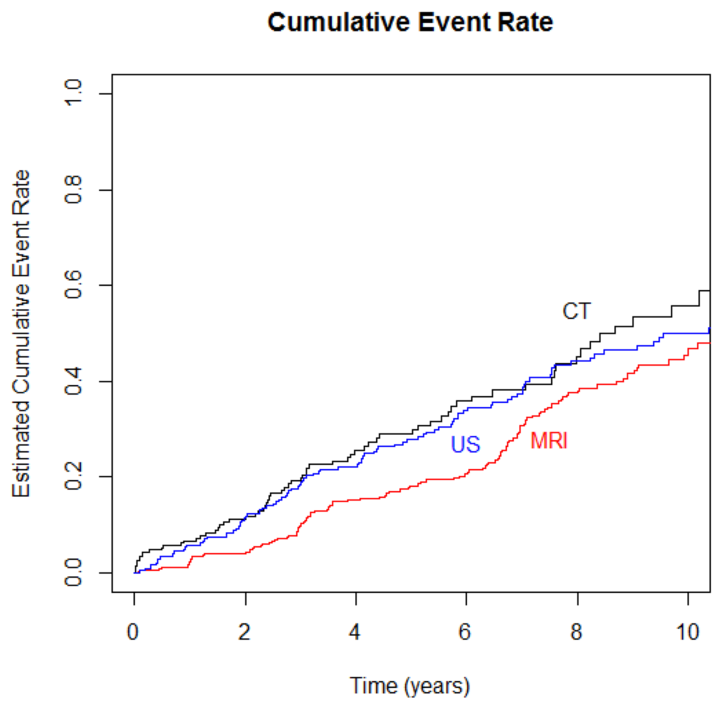
The total number of events was 300. The number of events by modality is shown in Table 6. Many of the events occurred after 5 years and the event rate seemed to be higher in the US stratum compared to the other two strata. The estimated cumulative event rates by modality are shown in Figure 7. These Kaplan-Meier estimates are not adjusted for any covariates. In addition, the log-likelihood from the Cox proportional hazards model without stratification (with no covariates) is –1830.4, but improves to –1510.4 when including the stratification factor. It appears that stratification by modality is needed.

Table 6. Number of events (confirmed 30% decline in eGFR, submitter's definition) by time period and modality

	MRI	CT	US
Number of Subjects	430	245	250
Number of Events by end of Year 1	9	15	14
Number of Events by end of Year 2	17	23	27
Number of Events by end of Year 3	39	36	43
Number of Events by end of Year 4	56	45	51
Number of Events by end of Year 5 (%)[1]	64 (15%)	49(20%)	63(25%)
Number of Events After Year 5 (%)[1]	62 (14%)	21 (9%)	41(16%)
Number of events by study end (%)[1]	126 (29%)	70 (29%)	104 (42%)

[1]Percent out of the total of 300 events.

Figure 7. Kaplan-Meier estimated cumulative event rates by modality



We next searched for the best fitting model using the covariates Age, baseline eGFR (on the original scale of mL/min per 1.73 m^2 or the log transformation) and the two-way interaction. There were 8 models considered: no covariates, Age, eGFR, Age+eGFR, Age+eGFR+Age:eGFR, log(eGFR), Age+log(eGFR), Age+log(eGFR)+Age:log(eGFR). All models included a stratification factor for TKV modality. We used the AIC criteria to select the best model. The best fitting model included terms for Age, log(eGFR) and the two way interaction. The estimated coefficients are shown in Table 7. The concordance (Uno's C statistic) is 0.598 and the likelihood ratio test statistic is 35.4. The C statistic is derived from a linear predictor that uses the coefficients in the table together with a constant term that depends on the modality stratum. These constant terms are –3.4652 (US), –3.3374 (MRI), and –3.5518 (CT).

Table 7. Coefficients from model including covariates Age and log(eGFR)

Term	Coefficient
Age	0.17331
log(eGFR)	0.87168
Age:log(eGFR)	-0.043517

The estimated covariance matrix for the coefficients and the survival curve, $S_0(t)$, for each stratum and the estimated standard error of $\log(-\log(S_0(t)))$ for the model with coefficients in Table 7 are shown in Appendix D. The estimates and standard errors are for a patient with all values of the covariates in the model equal to 0. The estimates for a patient with different values of these covariates can be found from the information in the Appendix (examples will be shown later in this review). The martingale and deviance residuals did not show a gross lack of fit of this model (see Figure 8 and

Figure 9). The size of the individual's Martingale residual indicates model accuracy. However, in the single event setting such as Cox's model, the Martingale residuals are heavily skewed and this skewness distorts the appearance of a standard residual plot. The deviance transform symmetrizes the Martingale residuals and helps to alleviate this problem. Note that the deviance residual suggests that a few individuals with large negative Martingale residuals who look like outliers in the Martingale plot, are probably not outliers shown in the deviance residual plots.

Figure 8. Martingale residuals vs. linear predictor plot for model from Table 7

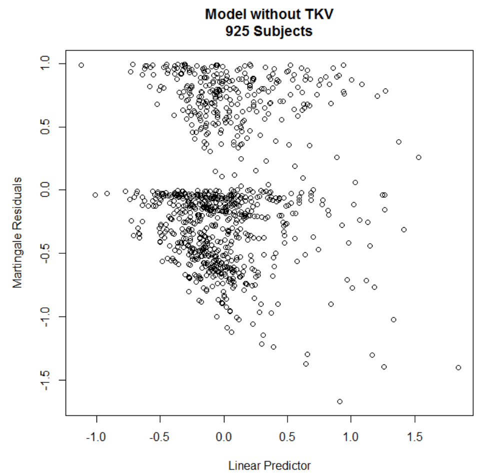
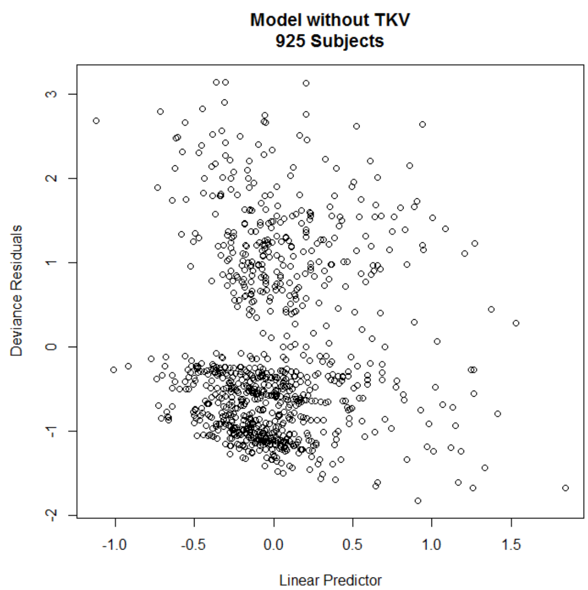


Figure 9. Deviance residuals vs. linear predictor plot for model from Table 7



Then, we searched for the best fitting model including any of those covariates in addition to log(TKV). Now, there were 23 models considered: 1 model with log(TKV), 6 models with log(TKV) with one other covariate with or without the 2-way interaction, 8 models with log(TKV), Age, eGFR and all the possible ways of including 2-way interactions, 8 models with log(TKV), Age, log(eGFR) and all the possible ways of including 2-way interactions. The best model included log(TKV), Age, eGFR and all the two-way interactions. The estimated coefficients are shown in Table 8. The concordance (Uno's C statistic) is 0.686 and the likelihood ratio test statistic is 127.1. The constant terms used to calculate the linear predictor for the C statistic are –21.941 (US), –22.041 (MRI), and –22.134 (CT). The improvement in the AIC for this model over the model without log(TKV) from Table 7 was about 86 (= 127.1 – 35.4 – 6). This is a substantial improvement in the AIC. The estimated covariance matrix and the estimates of $S_0(t)$ and the standard errors are in Appendix E. The martingale and deviance residuals from this model are shown in Figure 10 and Figure 11.

Table 8. Coefficients from model including covariates Age, eGFR, and log(TKV)

Term	Coefficient
log(TKV)	2.8323
Age	0.23802
eGFR	0.11326
log(TKV):Age	-0.027187
Age:eGFR	-6.0368×10^{-4}
log(TKV):eGFR	-0.012429

Figure 10. Martingale residuals vs. linear predictor plot for model from Table 8

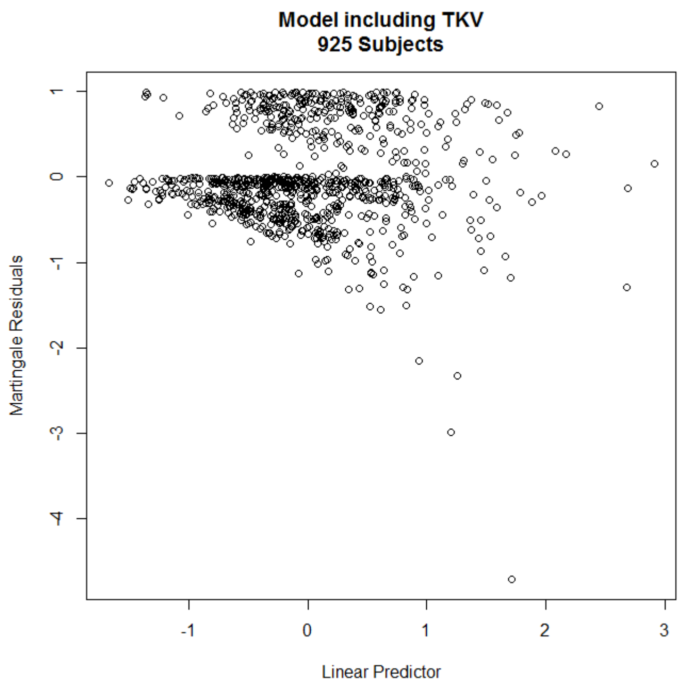
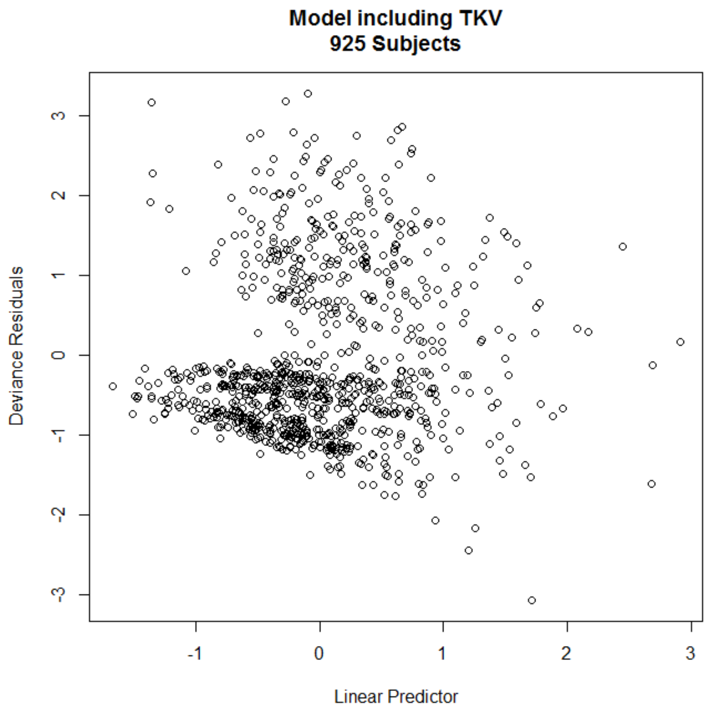


Figure 11. Deviance residuals vs. linear predictor plot for model from Table 8



The values of the C statistics at different time points are shown in Table 9. The estimated value of Uno's C statistic truncated at different time points was found using the R package SurvC1. The standard error was found by resampling (100 resampled datasets) and the p-value was found from this standard error assuming the difference in C statistics was approximately normal. The C-statistic considered here provides a global assessment of a fitted survival model for the continuous event time that consistently estimates a conventional concordance measure and is free of study-specific censoring distributions. From Table 9, it appears that there is an improvement of a fitted survival model including log(TKV) as compared to not including log(TKV) based on the C-statistics using the submitter's pooled dataset. Although C-statistics are commonly used for quantifying the predictability of working models, it has been argued that the C-statistic is less sensitive in capturing overall added values from a new marker on top of conventional predictor. The argument is used and emphasized when the added value of a new marker cannot be shown. However, when the C-statistic shows visible improvements from a model with log(TKV) as compared to a model without TKV at all time points, it seems to suggest that the model including log(TKV) appears to be sensitive in capturing overall added values from use of log(TKV) on top of a model without TKV, see the p-value column in Table 9.

Table 9 C statistics for each model at different time points.

Time (years)	C no TKV	C with log(TKV)	p-value
1	0.424	0.617	0.002
2	0.493	0.660	0.0002
3	0.599	0.698	0.0008
5	0.617	0.703	0.0001
Maximum	0.598	0.686	0.002

In order to see how well this procedure would perform in predicting an independent dataset, we performed cross-validation using the submitter's dataset. We also used a clinical trial data that is available internally as a test set.

We first look at the comparisons between the clinical trial dataset available internally and what would be predicted from these models.

Let $\Lambda(t; \boldsymbol{x}) = -\log\{S(t; \boldsymbol{x})\}$ be the cumulative hazard function for a set of covariates $\boldsymbol{x}$
Then, $\Lambda(t; \boldsymbol{x}) = e^{\boldsymbol{x}'\beta}\Lambda(t; 0)$ and $\log\{\Lambda(t; x)\} = \boldsymbol{x}'\beta + \log\{\Lambda(t; 0)\}$. We have estimates of β and $\zeta(t) = \log\{\Lambda(t; 0)\}$ in the Appendix (Appendix D or E). Let $\hat{\Sigma}$ be the estimated covariance matrix of $\begin{bmatrix}\hat{\beta} \\ \hat{\zeta}\end{bmatrix}$, also in the Appendix . For a given set of covariates, $\boldsymbol{x}$, the estimate of $\log\{\Lambda(t; x)\}$ is $[\boldsymbol{x}' \quad 1]\begin{bmatrix}\hat{\beta} \\ \hat{\zeta}\end{bmatrix}$ and the estimated variance of this estimate of $\log\{\Lambda(t; \boldsymbol{x})\}$ is $[\boldsymbol{x}' \quad 1]\hat{\Sigma}\begin{bmatrix}\boldsymbol{x} \\ 1\end{bmatrix}$.

If we knew β and ζ, the expected number of events for the placebo arm is

$$ED = h(\boldsymbol{\beta}, \zeta) = \sum_{i=1}^{n_{Test}} \{1 - S(t_i; \boldsymbol{x}_i)\} = \sum_{i=1}^{n_{Test}} \left\{1 - \exp\left\{-\exp\left\{[\boldsymbol{x}_i' \quad 1]\begin{bmatrix}\beta \\ \zeta\end{bmatrix}\right\}\right\}\right\}$$

The estimate for this expected number of events is

$$h(\hat{\boldsymbol{\beta}}, \hat{\zeta}) = \sum_{i=1}^{n_{Test}} \left\{1 - exp\left\{-exp\left\{[\boldsymbol{x}_i' \quad 1]\begin{bmatrix}\hat{\boldsymbol{\beta}} \\ \hat{\zeta}\end{bmatrix}\right\}\right\}\right\}$$

To find its estimated variance, we will use the Delta method. First, we find

$$\frac{\partial}{\partial \beta_j} \sum_{i=1}^{n_{Test}} \left\{1 - exp\left\{-exp\left\{[\boldsymbol{x}_i' \quad 1]\begin{bmatrix}\boldsymbol{\beta} \\ \zeta\end{bmatrix}\right\}\right\}\right\}$$
$$= \sum_{i=1}^{n_{Test}} \boldsymbol{x}_{i(j)} exp\left\{[\boldsymbol{x}_i' \quad 1]\begin{bmatrix}\boldsymbol{\beta} \\ \zeta\end{bmatrix} - exp\left\{[\boldsymbol{x}_i' \quad 1]\begin{bmatrix}\boldsymbol{\beta} \\ \zeta\end{bmatrix}\right\}\right\}$$
$$= \sum_{i=1}^{n_{Test}} \boldsymbol{x}_{i(j)} \Lambda(t; \boldsymbol{x}) S(t; \boldsymbol{x}_i)$$

and

$$\frac{\partial}{\partial \zeta} \sum_{i=1}^{n_{Test}} \left\{1 - exp\left\{-exp\left\{[\boldsymbol{x}_i' \quad 1]\begin{bmatrix}\boldsymbol{\beta} \\ \zeta\end{bmatrix}\right\}\right\}\right\}$$

$$= \sum_{i=1}^{n} \Lambda(t;\boldsymbol{x}) S(t;\boldsymbol{x}_i)$$

The estimated variance of $h(\widehat{\boldsymbol{\beta}},\hat{\zeta})$ is $\nabla h(\widehat{\boldsymbol{\beta}},\hat{\zeta})'\widehat{\boldsymbol{\Sigma}}\ \nabla h(\widehat{\boldsymbol{\beta}},\hat{\zeta})$.

We used cross-validation to assess the predictive ability of the modeling process. The submitter's dataset was randomly split into 5 mutually exclusive subsets of approximately the same size (925/5=181 subjects per subset). The first four subsets were combined, the best models with and without log(TKV) were found for this pooled set of 724 subjects. Next, this model was used to predict the results in the fifth subset. The C-statistic were found as well as the event rates at years 2, 3, and 5 and then compared with the observed event rate in that subset. The entire process was done 5 times to allow each combination of 4 subsets to be pooled together to be the training set and each subset to be the test set.

Table 10 and Table 11 show the estimated event rates and C-statistics for each iteration at different time points. The Tables show that either model predicts the actual event rates about as well as the other. For the C-statistics, in nearly all the iterations and time points, the model with log(TKV) was better.

Table 10. Cross-validation estimated event rates and Kaplan-Meier estimated event rates at different time points

CV Iteration	Time (Years)	Kaplan-Meier Estimate	Estimated using no TKV model	Estimated using log(TKV)
1	2	0.085	0.070	0.066
1	3	0.137	0.138	0.133
1	5	0.226	0.226	0.219
2	2	0.064	0.081	0.093
2	3	0.136	0.149	0.168
2	5	0.235	0.238	0.260
3	2	0.092	0.073	0.074
3	3	0.163	0.138	0.144
3	5	0.252	0.228	0.240
4	2	0.053	0.084	0.081
4	3	0.140	0.143	0.140
4	5	0.233	0.233	0.226
5	2	0.093	0.079	0.083
5	3	0.146	0.154	0.164
5	5	0.218	0.252	0.269

Table 11. Cross-validation C-statistics at different time points

CV Iteration	Time (Years)	C no TKV	C with log(TKV)	p-value
1	2	0.331	0.529	<0.001
1	3	0.481	0.603	0.003
1	5	0.464	0.579	<0.001
2	2	0.453	0.719	<0.001
2	3	0.596	0.765	<0.001
2	5	0.628	0.757	<0.001
3	2	0.607	0.688	<0.001
3	3	0.582	0.703	0.001
3	5	0.617	0.705	<0.001
4	2	0.371	0.498	<0.001
4	3	0.640	0.635	0.720
4	5	0.673	0.689	0.583
5	2	0.491	0.683	<0.001
5	3	0.577	0.668	<0.001
5	5	0.585	0.662	0.001

The Briefing Document includes a table (Table 49) that shows the predicted probabilities of 30% decline based on the submitter's model and some other assumptions. This table is copied here as Table 12.We cannot determine what, if any, value this table would have for designing a future clinical trial. First, it is unclear what distribution for the covariates is assumed other than having a lower or upper bound. For example, the first column represents the subgroup with TKV<1 L, Age<40 and eGFR $\geq$ 50 mL/min per 1.73 m^2. What is the lower bound on TKV for the subgroup? Is the distribution assumed uniform between that lower bound and the upper bound of 1L? What correlation is assumed between the 3 covariates? Second, there are no standard errors for the estimates. Third, it is not clear what model the estimates are obtained from or how one could obtain the corresponding estimates if they wanted to change something (e.g. change <40 years to <50 years). We could not find any description of these issues in the submitted documents.

Table 12. Submitter's Trial Enrichment Example - Tabular Presentation of Predicted Probabilities of a 30% Worsening of eGFR According to Pre-Specified Baseline Age, Baseline TKV and Baseline eGFR Cut-Offs

Follow-Up Times (Years)	Probabilities of Avoiding 30% Worsening of eGFR							
	TKV < 1 L				TKV ≥ 1 L			
	Age: < 40 years		Age: ≥ 40 years		Age: < 40 years		Age: ≥ 40 years	
	eGFR ≥ 50 mL/min	eGFR < 50 mL/min	eGFR ≥ 50 mL/min	eGFR < 50 mL/min	eGFR ≥ 50 mL/min	eGFR < 50 mL/min	eGFR ≥ 50 mL/min	eGFR < 50 mL/min
1	0.991	0.992	0.992	0.991	0.984	0.982	0.985	0.979
2	0.980	0.980	0.981	0.979	0.963	0.959	0.966	0.953
3	0.950	0.949	0.951	0.947	0.907	**0.899**	0.915	**0.884**
4	0.917	0.916	0.918	0.913	0.852	0.839	0.863	0.815
5	0.887	0.888	0.889	0.884	**0.805**	0.789	0.818	**0.757**

Source: Table 49 of Briefing Document.

We made a similar table (Table 13) that shows estimates in these 8 subgroups defined by the same cutoffs of age, TKV, and eGFR. The estimates and standard errors in this table come from the model in Table 8 and Appendix E. To define the distribution of the covariates assumed to find the estimates, we used the observed covariate values in the dataset from that subgroup. We do not know exactly why the predictions in Table 12 are in some cases very different from those in

Table 13 because there was not a clear explanation of where those numbers in Table 12 came from. The Kaplan-Meier estimates in those subgroups are shown in Table 14. With the exception of the subgroup in the second column, the predictions in

Table 13 appear to be closer to the Kaplan-Meier estimates than the prediction in Table 12 are. The Kaplan-Meier estimates for the subgroup in column 2 may be very unreliable because the sample size was only n=4. From Table 15, it appears that for the subgroup with baseline TKV ≥ 1 L, age effect does not seem to play a role in those subjects whose baseline eGFR is less than 50 mL/min per 1.73 m^2 regarding the predicted probabilities of not having confirmed 30% decline in eGFR. In contrast, for the subgroup with baseline TKV < 1L, age appears to affect the predicted probabilities of not having confirmed 30% decline in eGFR in those subjects whose baseline eGFR is less than 50 mL/min per 1.73 m^2 subgroup. This observation is not seen from Table 14.

Table 13. Predicted probabilities of not having confirmed 30% decline in eGFR in subgroups defined by Baseline Age, Baseline TKV and Baseline eGFR using the model from Appendix E. Estimated standard errors in parentheses

Followup Time (Years)	Predicted probability of not having a confirmed 30% decline in eGFR							
	TKV < 1 L				TKV ≥ 1 L			
	Age < 40 years		Age ≥ 40 years		Age < 40 years		Age ≥ 40 years	
	eGFR ≥ 50 mL/min per 1.73 m^2	eGFR < 50 mL/min per 1.73 m^2	eGFR ≥ 50 mL/min per 1.73 m^2	eGFR < 50 mL/min per 1.73 m^2	eGFR ≥ 50 mL/min per 1.73 m^2	eGFR < 50 mL/min per 1.73 m^2	eGFR ≥ 50 mL/min per 1.73 m^2	eGFR < 50 mL/min per 1.73 m^2
1	0.971 (0.005)	0.982 (0.004)	0.977 (0.005)	0.954 (0.015)	0.960 (0.008)	0.916 (0.020)	0.961 (0.007)	0.914 (0.014)
2	0.944 (0.008)	0.965 (0.007)	0.958 (0.008)	0.919 (0.024)	0.922 (0.012)	0.851 (0.026)	0.928 (0.010)	0.851 (0.021)
3	0.895 (0.010)	0.938 (0.011)	0.916 (0.013)	0.853 (0.038)	0.846 (0.016)	0.735 (0.034)	0.858 (0.016)	0.730 (0.035)
4	0.860 (0.012)	0.920 (0.015)	0.879 (0.016)	0.803 (0.045)	0.787 (0.020)	0.654 (0.039)	0.800 (0.020)	0.640 (0.043)
5	0.828 (0.013)	0.897 (0.017)	0.854 (0.018)	0.765 (0.052)	0.738 (0.022)	0.594 (0.043)	0.758 (0.023)	0.581 (0.048)

Table 14. Kaplan-Meier estimates of probabilities of not having confirmed 30% decline in eGFR in subgroups defined by Baseline Age, Baseline TKV and Baseline eGFR

Followup Time (Years)	Predicted probability of not having a confirmed 30% decline in eGFR							
	TKV < 1 L				TKV ≥ 1 L			
	Age < 40 years		Age ≥ 40 years		Age < 40 years		Age ≥ 40 years	
	eGFR ≥ 50 mL/min per 1.73 m^2 (n=275)	eGFR < 50 mL/min per 1.73 m^2 (n=4)	eGFR ≥ 50 mL/min per 1.73 m^2 (n=159)	eGFR < 50 mL/min per 1.73 m^2 (n=28)	eGFR ≥ 50 mL/min per 1.73 m^2 (n=168)	eGFR < 50 mL/min per 1.73 m^2 (n=28)	eGFR ≥ 50 mL/min per 1.73 m^2 (n=128)	eGFR < 50 mL/min per 1.73 m^2 (n=135)
1	0.967	1.000	0.941	0.927	0.969	1.000	0.942	0.951
2	0.944	1.000	0.919	0.927	0.931	0.918	0.925	0.859
3	0.902	0.779	0.904	0.832	0.905	0.696	0.874	0.634
4	0.880	0.779	0.895	0.770	0.853	0.651	0.785	0.508
5	0.846	0.558	0.884	0.624	0.786	0.575	0.785	0.455

Finally, we will consider a hypothetical example to illustrate how to design a randomized controlled trial using these models. In this example, we will assume equal (1:1) allocation to experimental drug or placebo and all subjects are followed for exactly 3 years (no censoring or loss to follow-up), two-sided α=0.05, and desired power of 90%. We will assume a proportional hazards model so that the hazard rate in the experimental arm is proportional to the hazard rate in the control arm; the postulated hazard ratio is 0.7. Let r_0 be the event rate in the placebo group. The formula for the total number of subjects needed for the trial (N) is

$$N = 2\frac{\left(\Phi^{-1}(0.025) + \Phi^{-1}(0.1)\right)^2 \left(\frac{1}{1-(1-r_0)^{0.7}} + \frac{1}{r_0}\right)}{(\log 0.7)^2}$$

We will use the models to estimate r_0.

First, assume that the entry criteria will be subjects with age between 20 and 50 years and eGFR greater than 50 mL/min per 1.73 m^2. TKV will be measured at baseline by MRI, but will not be used as an exclusion criterion. One way to approximate the distribution of the subjects' age, baseline eGFR, and TKV is to start with the multivariate normal distribution with parameters from Table 4 and to find the distribution of truncated based on the entry criteria (see Appendix C).

Using the simpler model (Appendix D), the estimated event rate is 0.0905 with a standard error of 0.0140. Using the model with log(TKV) in Appendix E, the estimated event rate is 0.0803 with a standard error of 0.0126. Clearly, the estimates are virtually indistinguishable (less than one standard error apart). Using the first point estimate, the number of subjects needed is $N = 4400$ rounded to the nearest 10. If the trial uses this many subjects, the estimate of the number of events that will be observed is about 340; that is, 199≈2200*0.0905 in the control group and 141≈2200*(1-(1-0.0905)$^{0.7}$) in the treatment group. The best advice we can give is to monitor the event rate in a blinded way and continue to enroll subjects in order to ensure that 340 events will be observed. If 4400 subjects are enrolled, a confidence interval for the expected number of events is (236, 445). An approximate prediction interval for the observed number of events can be found by noticing that, conditional on r_0, the number of events in the two groups are independent and Binomial with rates r_0 and $1-(1-r_0)^{0.7}$. So, the prediction interval can be found from the quantiles of the distribution of the sum of these two Binomial random variables. In this case, the prediction interval would be (233, 452). It turns out that the prediction interval is not much wider than the confidence interval for the expected number of events. This is because the variability in the number of events conditional on r_0 is small in comparison to the uncertainty about r_0 itself. We note that the projected number of subjects needed for enrichment may vary depending on the likely hazard ratio an experimental treatment over the control is expected to exhibit and the necessary assumptions considered including, but, are not limited to, accrual rate and censoring distribution in future clinical trials that may be pursued by individual drug development programs.

The final comment we want to make about this example is in regards to using TKV limits as an exclusion criteria. Suppose we used TKV>1 L as an inclusion criteria in addition to the earlier exclusion criteria for age and baseline eGFR. Only 43% of the subjects who meet the criteria for age and eGFR will also qualify based on TKV. The expected event rate in the control group in this enriched population will now be 0.110 with a standard error of 0.017 and a confidence interval of (0.0760, 0.144) using the model with log(TKV). In comparison, using the model without log(TKV) the expected event rate would be 0.0935 with a standard error of 0.0145 and a confidence interval of (0.065 , 0.122). It is difficult to say whether the treatment effect will be the same in the enriched population.

Returning again to the other endpoints (confirmed 57% decline in eGFR and ESRD). In Figure 1, the number of events of these two types was 115 and 354 respectively. However, when we counted the number of events in the population with eGFR>=25 and Age>12 (the 925 subjects we used for the analysis of 30% decline endpoint), we counted 99 events for the 57% decline in eGFR endpoint and 152 events for the ESRD endpoint. For both of these endpoints, the number of events within the first 5 years was 34 (not the same subjects, just coincidentally the same number). To be included in this analysis set of 925 subjects, a subject had to have a baseline eGFR and at least 2 post-baseline eGFR. The ESRD event can occur without any eGFR measurements (because dialysis or transplant can occur without any eGFR measured), so the analysis population for the ESRD endpoint could be enlarged. For this larger ESRD analysis population, the number of people who could be used for the analysis (were >12 years old and had baseline eGFR>=25 and a baseline TKV) was 1358 subjects. The total number of events in that population was 182, of which 47 occurred during the first 5 years and only 12 events in the first 3 years. Of the 47 subjects with an ESRD event in the first 5 years, 12 were from the MRI stratum, 21 were from the CT stratum and 14 were from the US stratum. Since a clinical trial is not likely to have more than 5 years of followup, we think the numbers of events within 5 years for these two endpoints is too small to be of any value for predicting event rates in a clinical trial.

IV. Summary and Conclusion

Through modeling approaches, models developed are described to predict event rates and event risks in future trials using the submitted data. Models using age and baseline eGFR alone appeared to be about as useful as models including baseline TKV in terms of predicting event rate. By and large, there appears to be a substantial improvement on predictive performance of event risk (based on a concordance measure for time-to-event data) of a fitted survival model including log(TKV) as compared to not including log(TKV) based on the C-statistics using either the submitter's registry data in model development (with cross validation) or in a clinical trial data that is available internally as independent validation. However, there are reasons [see (a)-(e) listed on pages 5-6] to have doubts about whether the event rates in a clinical trial would be similar to what would be predicted by these models with or without TKV. For the endpoints of 57% decline in eGFR and ESRD, the number of events within 5 years is too small to make any conclusions.

V. List of References

Altman, D. G., et al. "Review of survival analyses published in cancer journals." *British Journal of Cancer* 72.2 (1995): 511.

Uno, Hajime, et al. "On the C-statistics for evaluating overall adequacy of risk prediction procedures with censored survival data." *Statistics in medicine* 30.10 (2011): 1105-1117.

VI. Appendix

A. Derivation of maximum likelihood estimates from a truncated normal distribution

Suppose $x_1, \dots, x_n$ is a random sample from a normal distribution with mean μ and variance σ^2 but has been truncated such that values less than a are removed from the sample. For our purposes, this is the only kind of truncation we are concerned about (truncation below), but the cases of truncation of above or truncation both above and below can be handled similarly. The likelihood is

$$\prod_{i=1}^{n} \frac{\frac{1}{\sigma}\phi\left(\frac{x_i-\mu}{\sigma}\right)}{1-\Phi\left(\frac{a-\mu}{\sigma}\right)}$$

The log-likelihood is

$$-n\log\left\{\sigma\sqrt{2\pi}\left\{1-\Phi\left(\frac{a-\mu}{\sigma}\right)\right\}\right\} - \frac{1}{2\sigma^2}\sum_{i=1}^{n}(x_i-\mu)^2$$
$$= -n\log\{\sqrt{2\pi}\} - n\log\left\{\sigma\left\{1-\Phi\left(\frac{a-\mu}{\sigma}\right)\right\}\right\} - \frac{\sum_{i=1}^{n} x_i{}^2 - 2\mu\sum_{i=1}^{n} x_i + n\mu^2}{2\sigma^2}$$
$$= -n\log\{\sqrt{2\pi}\} - n\log\left\{\sigma\left\{1-\Phi\left(\frac{a-\mu}{\sigma}\right)\right\}\right\} - \frac{(n-1)S^2 + n(\bar{X}-\mu)^2}{2\sigma^2}$$

The sample mean, $\bar{X}$, and sample variance, $S^2 = \frac{1}{n-1}\sum_{i=1}^{n}(x_i-\bar{X})^2$, are complete and sufficient statistics for μ and σ^2.

B. Derivation of maximum likelihood estimates from a truncated multivariate normal distribution

For the multivariate normal distribution (dimension *d*), let $\boldsymbol{x}_1, \dots, \boldsymbol{x}_n$ be a random sample from a multivariate normal distribution with mean $\boldsymbol{\mu}$ and covariance matrix $\boldsymbol{\Sigma}$ but has been truncated such that values less than $\boldsymbol{a}$ are removed from the sample (in the sense that if any coordinate of the vector $\boldsymbol{x}$ is less than the corresponding coordinate of $\boldsymbol{a}$, then the random vector is not in the sample). The likelihood is

$$\prod_{i=1}^{n} \frac{f(\boldsymbol{x}_i; \boldsymbol{\mu}, \boldsymbol{\Sigma})}{k(\boldsymbol{\mu}, \boldsymbol{\Sigma})}$$

where k is the probability that a random variable from the multivariate normal distribution with mean $\boldsymbol{\mu}$ and covariance matrix $\boldsymbol{\Sigma}$ will have all coordinates larger than the corresponding coordinate of $\boldsymbol{a}$. The log-likelihood is

$$-n \log\left\{|\boldsymbol{\Sigma}|^{1/2}(2\pi)^{d/2}k(\boldsymbol{\mu}, \boldsymbol{\Sigma})\right\} - \frac{1}{2} tr\left[\boldsymbol{\Sigma}^{-1}\{(n-1)\widehat{\boldsymbol{\Sigma}} + n(\overline{\boldsymbol{x}} - \boldsymbol{\mu})(\overline{\boldsymbol{x}} - \boldsymbol{\mu})'\}\right]$$

where the sample mean, $\boldsymbol{\mu}$, and the sample covariance matrix, $\widehat{\boldsymbol{\Sigma}} = \frac{1}{n-1}\sum_{i=1}^{n}(\boldsymbol{x}_i - \boldsymbol{\mu})(\boldsymbol{x}_i - \boldsymbol{\mu})'$ are complete and sufficient statistics for $\boldsymbol{\mu}$ and $\boldsymbol{\Sigma}$.

C. Marginal distribution of the components of the truncated multivariate normal distribution

We will consider the case d=3 where $\boldsymbol{\mu}' = (38.5821, 6.92763, 4.22367)$, $\boldsymbol{a}' = (12, -\infty, \log(25))$ and $\boldsymbol{\Sigma} = \begin{pmatrix} 220.73 & 3.4075 & -4.5065 \\ 3.4075 & 0.46848 & -0.16303 \\ -4.5065 & -0.16303 & 0.19770 \end{pmatrix}$.

The joint density is

$$f(x_1, x_2, x_3) = \frac{|\boldsymbol{\Sigma}|^{-1/2}(2\pi)^{-d/2}}{k(\boldsymbol{\mu}, \boldsymbol{\Sigma})} exp\left(-\frac{1}{2}(\boldsymbol{x} - \boldsymbol{\mu})'\boldsymbol{\Sigma}^{-1}(\boldsymbol{x} - \boldsymbol{\mu})\right)$$

for $x_1 > 12$ and $x_3 > log(25)$

where $k(\boldsymbol{\mu}, \boldsymbol{\Sigma})$

$$= \int_{12}^{\infty}\int_{-\infty}^{\infty}\int_{log(25)}^{\infty} |\boldsymbol{\Sigma}|^{-1/2}(2\pi)^{-d/2} exp\left(-\frac{1}{2}(\boldsymbol{x} - \boldsymbol{\mu})'\boldsymbol{\Sigma}^{-1}(\boldsymbol{x} - \boldsymbol{\mu})\right) dx_3\, dx_2\, dx_1 \approx 0.951294.$$

We start by finding an exact expression for the marginal density of x_1.

The marginal density of (x_1, x_3) is

$$\int_{-\infty}^{\infty} f(x_1, x_2, x_3)dx_2 = \frac{|\boldsymbol{\Sigma}_1|^{-1/2}(2\pi)^{-1}}{k(\boldsymbol{\mu}, \boldsymbol{\Sigma})} exp\left(-\frac{1}{2}\left(\begin{pmatrix} x_1 \\ x_3 \end{pmatrix} - \begin{pmatrix} \mu_1 \\ \mu_3 \end{pmatrix}\right)'\boldsymbol{\Sigma}_1^{-1}\left(\begin{pmatrix} x_1 \\ x_3 \end{pmatrix} - \begin{pmatrix} \mu_1 \\ \mu_3 \end{pmatrix}\right)\right)$$

where $\boldsymbol{\Sigma}_1 = \begin{pmatrix} 220.73 & -4.5065 \\ -4.5065 & 0.19770 \end{pmatrix}$.

The marginal density of x_1 is

$$\int_{log(25)}^{\infty}\int_{-\infty}^{\infty} f(x_1, x_2, x_3)dx_2\, dx_3 = \frac{1}{k(\boldsymbol{\mu}, \boldsymbol{\Sigma})\sqrt{220.73}}\,\phi\left(\frac{x_1 - \mu_1}{\sqrt{220.73}}\right)\Phi\left(\frac{x_1 - \left(\mu_1 + \frac{(log(25) - \mu_3)220.73}{-4.5065}\right)}{\frac{220.73\sqrt{0.1977}}{-4.5065}\sqrt{1 - \frac{4.5065^2}{220.73 \times 0.1977}}}\right)$$ for

$x_1 > 12$.

Similarly, the marginal density of x_3 is

$$\int_{12}^{\infty} \int_{-\infty}^{\infty} f(x_1, x_2, x_3) dx_2\, dx_1 = \frac{1}{k(\mu, \Sigma)\sqrt{0.1977}} \phi\left(\frac{x_3 - \mu_3}{\sqrt{0.1977}}\right) \Phi\left(\frac{x_3 - \left(\mu_3 + \frac{(12-\mu_1)0.1977}{-4.5065}\right)}{\frac{0.1977\sqrt{220.78}}{-4.5065}\sqrt{1 - \frac{4.5065^2}{220.78 \times 0.1977}}}\right) \text{ for}$$

$x_3 > log(25)$.

The marginal density of x_2 can be found by numerical integration.

D. Estimated parameters for survival curves for model in Table 7 after standardizing covariates

This is a different representation of the same model (a different parameterization). The covariates have been standardized first by subtracting the sample mean and dividing by the sample standard deviation.

$\hat{\boldsymbol{\beta}}$

log(eGFR)	Age	log(eGFR):Age
-0.3478579	-0.1348302	-0.2402465

Estimated $Var(\hat{\boldsymbol{\beta}})$

	log(eGFR)	Age	log(eGFR):Age
log(eGFR)	0.0068095608	0.0044755400	0.0004506525
Age	0.0044755400	0.0067357705	0.0006593714
log(eGFR):Age	0.0004506525	0.0006593714	0.0025091766

Estimated parameters for survival curves for model in Table 7 (after standardizing covariates).

t (days)	Estimated log(Λ(t;**0**))	$\hat{\Sigma}_{1,4}$	$\hat{\Sigma}_{2,4}$	$\hat{\Sigma}_{3,4}$	$\hat{\Sigma}_{4,4}$
CT modality					
4	-5.9000337	3.054360e-03	-0.0009383070	0.0034337697	1.00870711
5	-5.2055564	3.060997e-03	-0.0009420836	0.0034360207	0.50873406
7	-4.7975998	3.055317e-03	-0.0009478533	0.0034354332	0.34206905
16	-4.4907296	3.019581e-03	-0.0009465508	0.0033914671	0.25880849
18	-4.2536347	2.999765e-03	-0.0009433376	0.0033691193	0.20875233
19	-4.0617242	2.990148e-03	-0.0009394446	0.0033562668	0.17533043
34	-3.8989210	3.000637e-03	-0.0009129779	0.0033436586	0.15143894
35	-3.7579315	3.008978e-03	-0.0008892645	0.0033309361	0.13349966
52	-3.6336160	3.017457e-03	-0.0008707125	0.0033231070	0.11955285
56	-3.5225774	3.022644e-03	-0.0008579447	0.0033180140	0.10839602
100	-3.4200474	3.038256e-03	-0.0008327921	0.0033129899	0.09928226
179	-3.3231003	3.057569e-03	-0.0008002891	0.0033033102	0.09170856
189	-3.2337001	3.063829e-03	-0.0007791530	0.0032917259	0.08527619
305	-3.1465575	3.082597e-03	-0.0007520684	0.0032857974	0.07985944
324	-3.0659295	3.102951e-03	-0.0007251651	0.0032825434	0.07514294
407	-2.9888419	3.125982e-03	-0.0006974286	0.0032825936	0.07104896
436	-2.9157939	3.147672e-03	-0.0006757423	0.0032823884	0.06744305
469	-2.8465870	3.163325e-03	-0.0006600272	0.0032846670	0.06423842
530	-2.7794692	3.171893e-03	-0.0006468520	0.0032785539	0.06136527
553	-2.7140721	3.176245e-03	-0.0006315218	0.0032606105	0.05876103

564	-2.6518382	3.173580e-03	-0.0006213145	0.0032414806	0.05637689
584	-2.5925843	3.173814e-03	-0.0006169665	0.0032219133	0.05420322
625	-2.5357949	3.170593e-03	-0.0006168478	0.0032073384	0.05222170
736	-2.4801051	3.160537e-03	-0.0006215126	0.0031960074	0.05042595
798	-2.4255051	3.142254e-03	-0.0006349319	0.0031867932	0.04879307
814	-2.3733752	3.129494e-03	-0.0006436932	0.0031799667	0.04727352
854	-2.3225531	3.116532e-03	-0.0006526194	0.0031756290	0.04587719
864	-2.2734442	3.108960e-03	-0.0006547103	0.0031706456	0.04457046
870	-2.2263227	3.102270e-03	-0.0006564533	0.0031666227	0.04334293
875	-2.1809664	3.097147e-03	-0.0006563780	0.0031629001	0.04218749
891	-2.1371969	3.087520e-03	-0.0006610204	0.0031610205	0.04110333
897	-2.0937013	3.078030e-03	-0.0006612828	0.0031489419	0.04006949
967	-2.0505367	3.066925e-03	-0.0006659331	0.0031392509	0.03912138
987	-2.0090047	3.058168e-03	-0.0006692485	0.0031310061	0.03821973
1019	-1.9680963	3.048323e-03	-0.0006733007	0.0031240668	0.03737717
1030	-1.9280170	3.033907e-03	-0.0006820459	0.0031180528	0.03658316
1099	-1.8888861	3.020583e-03	-0.0006900306	0.0031134458	0.03583307
1108	-1.8506978	3.005362e-03	-0.0006989156	0.0031082228	0.03511521
1134	-1.8134207	2.992350e-03	-0.0007040279	0.0031016706	0.03442459
1137	-1.7770794	2.976533e-03	-0.0007120942	0.0030962108	0.03376607
1156	-1.7392736	2.959096e-03	-0.0007067910	0.0030622243	0.03308429
1306	-1.7005477	2.941145e-03	-0.0007077445	0.0030312641	0.03248329
1409	-1.6624322	2.925030e-03	-0.0007103032	0.0030037389	0.03191886
1424	-1.6251502	2.909397e-03	-0.0007159690	0.0029788842	0.03138149
1454	-1.5877559	2.899412e-03	-0.0007149014	0.0029542550	0.03087988
1512	-1.5477147	2.888934e-03	-0.0006921041	0.0029020541	0.03038163
1547	-1.5064724	2.871731e-03	-0.0006746291	0.0028379543	0.02991832
1598	-1.4662619	2.852918e-03	-0.0006602162	0.0027776383	0.02945555
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1832	-1.3834884	2.791218e-03	-0.0006436455	0.0026476220	0.02864159
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2090	-1.1720667	2.633585e-03	-0.0006371050	0.0023475173	0.02713374
2121	-1.1312694	2.599219e-03	-0.0006451007	0.0022981334	0.02684716
2224	-1.0881836	2.572183e-03	-0.0006423827	0.0022486639	0.02665779
2365	-1.0449331	2.550368e-03	-0.0006371512	0.0022024434	0.02649212
2580	-0.9952765	2.517407e-03	-0.0006362745	0.0021422117	0.02659318
2748	-0.9431376	2.477962e-03	-0.0006359035	0.0020776256	0.02679039
2771	-0.8921450	2.438158e-03	-0.0006371417	0.0020167810	0.02690043
2783	-0.8428619	2.407121e-03	-0.0006335400	0.0019624247	0.02691695
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2946	-0.7428924	2.341445e-03	-0.0006232658	0.0018578781	0.02698201
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3168	-0.5926346	2.253242e-03	-0.0005791098	0.0017090340	0.02699093
3292	-0.5327081	2.200765e-03	-0.0005840151	0.0016526657	0.02753377
3546	-0.4632542	2.158319e-03	-0.0005802001	0.0015951317	0.02871171
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28	-6.1741024	9.059318e-04	0.0013740490	0.0018344366	1.00146245
30	-5.4795942	9.081401e-04	0.0013826791	0.0018347696	0.50146622
164	-5.0675637	8.870549e-04	0.0013787379	0.0018303245	0.33482061

176	-4.7759145	8.759086e-04	0.0013786405	0.0018286484	0.25148413
281	-4.5499643	8.705187e-04	0.0013780837	0.0018273623	0.20147847
354	-4.3643052	8.708740e-04	0.0013864926	0.0018291433	0.16815186
356	-4.2073853	8.702209e-04	0.0013925959	0.0018309233	0.14434624
358	-4.0710902	8.599025e-04	0.0013918381	0.0018318787	0.12649116
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369	-3.7455553	8.526864e-04	0.0013853215	0.0018170687	0.09237782
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376	-3.5745404	8.497199e-04	0.0013804312	0.0018094379	0.07837916
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458	-3.3615445	8.503032e-04	0.0013765141	0.0018016157	0.06394331
638	-3.2973810	8.461964e-04	0.0013761698	0.0017989390	0.06027210
737	-3.2356654	8.388508e-04	0.0013750218	0.0017970267	0.05701718
761	-3.1763597	8.234459e-04	0.0013700273	0.0017917708	0.05410568
765	-3.1202195	8.088531e-04	0.0013647612	0.0017873544	0.05148214
777	-3.0667674	7.924801e-04	0.0013586714	0.0017829320	0.04910637
792	-3.0156527	7.769805e-04	0.0013531176	0.0017781063	0.04694535
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845	-2.9186968	7.381034e-04	0.0013352117	0.0017680344	0.04316739
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457	-2.8851475	2.337003e-03	0.0027349700	0.0029201410	0.06295315
483	-2.8240091	2.334857e-03	0.0027405513	0.0029208951	0.05969495
603	-2.7648231	2.328568e-03	0.0027501788	0.0029189966	0.05678508
609	-2.7087412	2.323254e-03	0.0027592655	0.0029178791	0.05416517
656	-2.6549904	2.313867e-03	0.0027657483	0.0029170856	0.05179542
666	-2.6035346	2.305608e-03	0.0027733365	0.0029173798	0.04964440
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693	-2.5073849	2.295059e-03	0.0027872858	0.0029166621	0.04587392
699	-2.4622457	2.288641e-03	0.0027908466	0.0029169036	0.04421319
706	-2.4188778	2.282533e-03	0.0027939733	0.0029176246	0.04268031
721	-2.3771792	2.277622e-03	0.0027973417	0.0029186173	0.04126109
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956	-2.0536442	2.219730e-03	0.0028285330	0.0029190112	0.03204000
966	-2.0220184	2.212933e-03	0.0028334657	0.0029167091	0.03129129
997	-1.9910139	2.206738e-03	0.0028368296	0.0029137097	0.03058074
1010	-1.9606512	2.199530e-03	0.0028407272	0.0029103327	0.02990633
1017	-1.9308905	2.189136e-03	0.0028428407	0.0029072775	0.02926530
1035	-1.9017425	2.180417e-03	0.0028466357	0.0029049114	0.02865823
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1518	-1.4936084	2.060681e-03	0.0028340302	0.0028154697	0.02175705
1581	-1.4707020	2.053409e-03	0.0028297934	0.0028057651	0.02144414
1593	-1.4481094	2.047549e-03	0.0028249506	0.0027946696	0.02113797
1608	-1.4258859	2.041794e-03	0.0028203518	0.0027842822	0.02084212
1718	-1.4028736	2.037731e-03	0.0028105450	0.0027699801	0.02055601
1774	-1.3798719	2.033328e-03	0.0027994851	0.0027554634	0.02028004
1796	-1.3571234	2.029274e-03	0.0027887731	0.0027418889	0.02001400
1869	-1.3339905	2.025668e-03	0.0027759486	0.0027285542	0.01976280
1905	-1.3112654	2.022820e-03	0.0027640315	0.0027159641	0.01951815
1924	-1.2889201	2.021036e-03	0.0027528186	0.0027036931	0.01927924
1981	-1.2660287	2.022305e-03	0.0027495797	0.0026863544	0.01905176
2005	-1.2434936	2.023378e-03	0.0027460941	0.0026698756	0.01882956
2085	-1.2211504	2.024529e-03	0.0027423551	0.0026542284	0.01861464
2100	-1.1991548	2.026075e-03	0.0027387688	0.0026392192	0.01840444
2108	-1.1774855	2.027711e-03	0.0027351328	0.0026248852	0.01819898
2135	-1.1345476	2.028604e-03	0.0027284056	0.0025978294	0.01780837
2168	-1.1128401	2.024713e-03	0.0027248443	0.0025831822	0.01762449
2193	-1.0907621	2.014099e-03	0.0027204349	0.0025642531	0.01744363
2355	-1.0670733	1.998622e-03	0.0027198626	0.0025394985	0.01728765
2359	-1.0437252	1.983399e-03	0.0027192793	0.0025159577	0.01713321
2462	-1.0197105	1.969078e-03	0.0027207303	0.0024936981	0.01700061
2484	-0.9957275	1.955737e-03	0.0027216708	0.0024706329	0.01687053
2525	-0.9712984	1.942747e-03	0.0027214233	0.0024464999	0.01675163
2563	-0.9469381	1.931104e-03	0.0027213635	0.0024222129	0.01663532
2565	-0.9229457	1.920545e-03	0.0027215577	0.0023989224	0.01651736
2570	-0.8992948	1.910615e-03	0.0027219398	0.0023767390	0.01639867
2577	-0.8759359	1.901537e-03	0.0027238941	0.0023555384	0.01628107
2608	-0.8528942	1.893759e-03	0.0027259614	0.0023348360	0.01616250
2744	-0.8290633	1.887380e-03	0.0027272298	0.0023123293	0.01606033
2750	-0.8055645	1.881911e-03	0.0027289713	0.0022908724	0.01595690
2751	-0.7821149	1.877088e-03	0.0027306383	0.0022702610	0.01585739
2773	-0.7588633	1.870541e-03	0.0027314807	0.0022506915	0.01575845
2881	-0.7355482	1.865670e-03	0.0027316758	0.0022299204	0.01566188
3005	-0.7114046	1.862044e-03	0.0027323621	0.0022098649	0.01558746
3030	-0.6874564	1.860974e-03	0.0027324803	0.0021878678	0.01550778
3098	-0.6630953	1.860567e-03	0.0027309684	0.0021651934	0.01543760
3315	-0.6359438	1.860156e-03	0.0027270989	0.0021404583	0.01543490
3424	-0.6082866	1.860226e-03	0.0027214338	0.0021162494	0.01544458
3463	-0.5798468	1.858586e-03	0.0027165829	0.0020927059	0.01547646
3490	-0.5514434	1.861114e-03	0.0027141916	0.0020702304	0.01550706

3791	-0.5167600	1.877291e-03	0.0026996534	0.0020380764	0.01573666
3899	-0.4788704	1.895690e-03	0.0026920590	0.0019933351	0.01607555
3929	-0.4394599	1.913346e-03	0.0026762403	0.0019483586	0.01645335
3939	-0.4005624	1.931594e-03	0.0026601700	0.0019055760	0.01677758
4028	-0.3597166	1.953433e-03	0.0026507698	0.0018639494	0.01717405
4812	-0.2894217	1.978745e-03	0.0026749638	0.0018111168	0.01975437
5623	-0.1327083	1.919024e-03	0.0027829908	0.0017602023	0.03603402

E. Estimated parameters for survival curves for model in Table 8 after standardizing covariates

This is a different representation of the same model (a different parameterization). The covariates have been standardized first by subtracting the sample mean and dividing by the sample standard deviation.

$\widehat{\boldsymbol{\beta}}$

log(TKV)	Age	eGFR	Age:eGFR	log(TKV):eGFR	log(TKV):Age
0.56837355	0.06885578	0.09828790	-0.24412866	-0.25149514	-0.24403545

Estimated $Var(\widehat{\boldsymbol{\beta}})$

	log(TKV)	Age	eGFR	Age:eGFR	log(TKV):eGFR	log(TKV):Age
log(TKV)	0.0050642962	0.0002500247	0.0026301773	-0.0004510675	0.001451265	0.0001978921
Age	0.0002500247	0.0083450659	0.0066397918	0.0025356895	-0.002349323	-0.0010027221
eGFR	0.0026301773	0.0066397918	0.0117420410	0.0046148526	-0.001886604	-0.0007277362
Age:eGFR	-0.0004510675	0.0025356895	0.0046148526	0.0044427787	-0.002284637	0.0002484310
log(TKV):eGFR	0.0014512648	-0.0023493229	-0.0018866044	-0.0022846375	0.005344154	0.0025998556
log(TKV):Age	0.0001978921	-0.0010027221	-0.0007277362	0.0002484310	0.002599856	0.0052233266

Estimated parameters for survival curves for model in Table 8 (after standardizing covariates).

t (days)	Estimated $\log(\Lambda(t;\mathbf{0}))$	$\hat{\Sigma}_{1,7}$	$\hat{\Sigma}_{2,7}$	$\hat{\Sigma}_{3,7}$	$\hat{\Sigma}_{4,7}$	$\hat{\Sigma}_{5,7}$	$\hat{\Sigma}_{6,7}$	$\hat{\Sigma}_{7,7}$
CT modality								
4	-6.06853096	-1.302725e-03	-0.0012516147	4.283645e-03	8.052349e-04	2.313217e-03	3.143385e-03	1.01085538
5	-5.37419816	-1.303568e-03	-0.0012565315	4.289191e-03	8.068513e-04	2.317104e-03	3.146445e-03	0.51088753
7	-4.96612009	-1.302849e-03	-0.0012619348	4.281138e-03	8.144496e-04	2.322848e-03	3.141874e-03	0.34421739
16	-4.65987403	-1.285311e-03	-0.0012675272	4.240813e-03	8.679973e-04	2.363840e-03	3.106522e-03	0.26103467
18	-4.42441733	-1.280657e-03	-0.0012677485	4.218088e-03	8.977395e-04	2.391430e-03	3.085782e-03	0.21101777
19	-4.23363279	-1.279178e-03	-0.0012659810	4.206609e-03	9.164462e-04	2.408580e-03	3.074549e-03	0.17763674
34	-4.07157056	-1.284352e-03	-0.0012429222	4.204566e-03	9.155231e-04	2.421164e-03	3.059183e-03	0.15379016
35	-3.93151907	-1.289801e-03	-0.0012249769	4.198309e-03	9.148473e-04	2.434022e-03	3.042848e-03	0.13589214
52	-3.80788825	-1.294704e-03	-0.0012107330	4.196364e-03	9.148735e-04	2.444837e-03	3.032129e-03	0.12198129
56	-3.69733888	-1.298776e-03	-0.0012016036	4.193284e-03	9.150471e-04	2.454179e-03	3.023448e-03	0.11085356
100	-3.59502145	-1.296256e-03	-0.0011820798	4.201343e-03	9.312957e-04	2.476813e-03	3.014709e-03	0.10178120
179	-3.49974904	-1.302240e-03	-0.0011609083	4.205950e-03	9.430720e-04	2.503287e-03	3.002721e-03	0.09425899
189	-3.41256167	-1.308539e-03	-0.0011450679	4.206047e-03	9.529118e-04	2.527403e-03	2.990400e-03	0.08788173
305	-3.32620685	-1.298291e-03	-0.0011189241	4.225540e-03	1.000633e-03	2.560430e-03	2.988379e-03	0.08250022
324	-3.24631580	-1.291818e-03	-0.0010927978	4.245428e-03	1.039121e-03	2.587512e-03	2.988157e-03	0.07781631
407	-3.16915053	-1.277496e-03	-0.0010658930	4.270150e-03	1.093765e-03	2.621388e-03	2.990552e-03	0.07375883
436	-3.09564584	-1.260454e-03	-0.0010434393	4.294976e-03	1.146255e-03	2.654895e-03	2.991906e-03	0.07019028
469	-3.02623462	-1.247705e-03	-0.0010267465	4.313407e-03	1.191731e-03	2.684932e-03	2.992700e-03	0.06701117
530	-2.95989049	-1.239820e-03	-0.0010106954	4.326604e-03	1.235332e-03	2.716393e-03	2.990064e-03	0.06417406
553	-2.89648002	-1.235993e-03	-0.0009968811	4.329304e-03	1.276490e-03	2.752120e-03	2.978994e-03	0.06161602
564	-2.83655388	-1.233750e-03	-0.0009862460	4.327632e-03	1.313533e-03	2.786023e-03	2.966499e-03	0.05928320
584	-2.77956994	-1.232894e-03	-0.0009802896	4.326047e-03	1.349237e-03	2.818179e-03	2.955144e-03	0.05716222
625	-2.72305062	-1.228574e-03	-0.0009770091	4.334455e-03	1.350080e-03	2.811976e-03	2.960101e-03	0.05522984
736	-2.66257826	-1.192845e-03	-0.0009592582	4.370614e-03	1.322889e-03	2.729487e-03	2.995069e-03	0.05345510
798	-2.60322803	-1.157473e-03	-0.0009487525	4.402598e-03	1.297761e-03	2.650994e-03	3.029633e-03	0.05184149
814	-2.54669215	-1.125417e-03	-0.0009336001	4.438556e-03	1.276941e-03	2.579955e-03	3.064407e-03	0.05032529
854	-2.49148642	-1.092198e-03	-0.0009179137	4.478471e-03	1.256494e-03	2.515433e-03	3.099201e-03	0.04893890
864	-2.43844812	-1.061583e-03	-0.0008978130	4.515562e-03	1.241795e-03	2.460383e-03	3.128178e-03	0.04762654
870	-2.38765466	-1.033130e-03	-0.0008794821	4.549747e-03	1.229509e-03	2.411108e-03	3.154740e-03	0.04638387
875	-2.33902367	-1.007946e-03	-0.0008619784	4.580208e-03	1.217951e-03	2.367016e-03	3.177954e-03	0.04520408
891	-2.29099486	-9.814893e-04	-0.0008503866	4.610303e-03	1.188941e-03	2.302720e-03	3.208217e-03	0.04409483
897	-2.24389786	-9.549523e-04	-0.0008371069	4.633128e-03	1.173457e-03	2.248995e-03	3.230324e-03	0.04304334
967	-2.19702783	-9.293696e-04	-0.0008274656	4.654466e-03	1.158713e-03	2.194106e-03	3.254158e-03	0.04207677

987	-2.15196498	-9.044067e-04	-0.0008165746	4.678770e-03	1.146197e-03	2.144344e-03	3.278198e-03	0.04115582
1019	-2.10641283	-8.694147e-04	-0.0008038971	4.708124e-03	1.142720e-03	2.093269e-03	3.305493e-03	0.04030810
1030	-2.06214400	-8.378055e-04	-0.0007957491	4.731165e-03	1.140142e-03	2.045842e-03	3.330083e-03	0.03949716
1099	-2.01879834	-8.063968e-04	-0.0007882867	4.753743e-03	1.138113e-03	2.000409e-03	3.354221e-03	0.03872848
1108	-1.97639764	-7.747055e-04	-0.0007817321	4.772349e-03	1.139961e-03	1.957576e-03	3.375669e-03	0.03798682
1134	-1.93497664	-7.410077e-04	-0.0007715124	4.790381e-03	1.152503e-03	1.921770e-03	3.394143e-03	0.03726875
1137	-1.89484284	-7.101933e-04	-0.0007644994	4.804468e-03	1.164404e-03	1.888611e-03	3.410909e-03	0.03657589
1156	-1.85423942	-6.795801e-04	-0.0007526558	4.806345e-03	1.177988e-03	1.864045e-03	3.411936e-03	0.03590902
1306	-1.81307918	-6.536970e-04	-0.0007455224	4.808194e-03	1.191572e-03	1.838132e-03	3.416661e-03	0.03531858
1409	-1.77278101	-6.291314e-04	-0.0007402218	4.811556e-03	1.206167e-03	1.815318e-03	3.422782e-03	0.03475892
1424	-1.73246606	-5.984849e-04	-0.0007423364	4.820484e-03	1.209651e-03	1.785834e-03	3.433649e-03	0.03424973
1454	-1.69255318	-5.736125e-04	-0.0007413095	4.826531e-03	1.207081e-03	1.758763e-03	3.440300e-03	0.03376492
1512	-1.64954355	-5.466680e-04	-0.0007214794	4.809976e-03	1.192849e-03	1.729196e-03	3.417647e-03	0.03330319
1547	-1.60606098	-5.256129e-04	-0.0007072085	4.786706e-03	1.181439e-03	1.701019e-03	3.387686e-03	0.03287862
1598	-1.56410294	-5.072620e-04	-0.0006957378	4.762399e-03	1.171231e-03	1.676242e-03	3.358717e-03	0.03243598
1617	-1.52265053	-4.912041e-04	-0.0006863406	4.731886e-03	1.162719e-03	1.654949e-03	3.326388e-03	0.03199723
1832	-1.47893441	-4.739893e-04	-0.0006805947	4.692227e-03	1.163334e-03	1.638796e-03	3.288778e-03	0.03164987
1866	-1.43542231	-4.566038e-04	-0.0006794955	4.645402e-03	1.168305e-03	1.624729e-03	3.248359e-03	0.03130385
1953	-1.39123295	-4.391873e-04	-0.0006646848	4.619310e-03	1.185797e-03	1.614186e-03	3.218774e-03	0.03102886
2023	-1.34612915	-4.147269e-04	-0.0006734547	4.583780e-03	1.187079e-03	1.597507e-03	3.187721e-03	0.03080682
2072	-1.30178613	-3.910260e-04	-0.0006829915	4.552649e-03	1.189294e-03	1.584160e-03	3.159340e-03	0.03057951
2090	-1.25896157	-3.698704e-04	-0.0006932616	4.524170e-03	1.192201e-03	1.572461e-03	3.133877e-03	0.03031743
2121	-1.21458519	-3.432347e-04	-0.0007089259	4.491461e-03	1.181508e-03	1.537478e-03	3.113225e-03	0.03009909
2224	-1.16801724	-3.254791e-04	-0.0007114239	4.458049e-03	1.152591e-03	1.493143e-03	3.088692e-03	0.02996316
2365	-1.11989027	-2.922151e-04	-0.0007078978	4.439736e-03	1.138215e-03	1.449131e-03	3.071331e-03	0.02990071
2580	-1.06573896	-2.596539e-04	-0.0007197480	4.397752e-03	1.118812e-03	1.414573e-03	3.035812e-03	0.03013096
2748	-1.01044128	-2.319712e-04	-0.0007218772	4.356672e-03	1.108915e-03	1.387160e-03	2.999209e-03	0.03038968
2771	-0.95674128	-2.076207e-04	-0.0007274091	4.312744e-03	1.101260e-03	1.364654e-03	2.962441e-03	0.03052445
2783	-0.90470826	-1.846496e-04	-0.0007254416	4.283048e-03	1.094333e-03	1.342682e-03	2.933911e-03	0.03056429
2911	-0.85323969	-1.696898e-04	-0.0007275659	4.245110e-03	1.083535e-03	1.323685e-03	2.902296e-03	0.03056324
2946	-0.80000002	-1.408822e-04	-0.0007254102	4.209315e-03	1.097918e-03	1.315961e-03	2.868905e-03	0.03063330
3006	-0.74642910	-1.168442e-04	-0.0006991820	4.190444e-03	1.102684e-03	1.305284e-03	2.838403e-03	0.03070279
3066	-0.69154849	-8.431551e-05	-0.0006875824	4.158456e-03	1.102538e-03	1.282053e-03	2.807282e-03	0.03080241
3168	-0.63574768	-4.304766e-05	-0.0006730412	4.110298e-03	1.122155e-03	1.268299e-03	2.761211e-03	0.03088723
3292	-0.56968960	1.413272e-05	-0.0006521471	4.093250e-03	1.161365e-03	1.271235e-03	2.728999e-03	0.03167543
3546	-0.49420196	5.961236e-05	-0.0006365005	4.067474e-03	1.171640e-03	1.276886e-03	2.688011e-03	0.03312530
3721	-0.40477295	7.176347e-05	-0.0006987079	4.002515e-03	1.247065e-03	1.323138e-03	2.646949e-03	0.03582929
MRI modality								
28	-6.50440401	-2.407332e-03	0.0005631056	4.203945e-04	4.251081e-04	9.770945e-04	2.148160e-03	1.00456269

30	-5.81042254	-2.411405e-03	0.0005661861	4.162324e-04	4.234317e-04	9.781435e-04	2.145992e-03	0.50456933
164	-5.40085545	-2.428088e-03	0.0005615338	3.897788e-04	4.237630e-04	9.802105e-04	2.139227e-03	0.33793195
176	-5.11029136	-2.435762e-03	0.0005605581	3.748107e-04	4.258942e-04	9.821600e-04	2.135672e-03	0.25460948
281	-4.88463412	-2.434123e-03	0.0005563799	3.681548e-04	4.252916e-04	9.899345e-04	2.130921e-03	0.20461607
354	-4.69950670	-2.436768e-03	0.0005606501	3.651112e-04	4.243383e-04	9.950148e-04	2.129385e-03	0.17129922
356	-4.54283565	-2.438142e-03	0.0005635454	3.617355e-04	4.238294e-04	9.987008e-04	2.128416e-03	0.14750131
358	-4.40682746	-2.440814e-03	0.0005632889	3.523987e-04	4.222504e-04	9.993016e-04	2.126364e-03	0.12965147
365	-4.28456884	-2.444755e-03	0.0005641135	3.519227e-04	4.085915e-04	9.824108e-04	2.100235e-03	0.11569759
367	-4.17542697	-2.447590e-03	0.0005649989	3.528889e-04	3.977263e-04	9.695012e-04	2.079944e-03	0.10453255
369	-4.07672229	-2.451256e-03	0.0005643224	3.531154e-04	3.896124e-04	9.584906e-04	2.062506e-03	0.09539396
372	-3.98668157	-2.454291e-03	0.0005632232	3.529392e-04	3.827588e-04	9.496588e-04	2.048112e-03	0.08777853
376	-3.90346277	-2.455411e-03	0.0005623839	3.512534e-04	3.759087e-04	9.394021e-04	2.036313e-03	0.08133187
380	-3.82646930	-2.456465e-03	0.0005616287	3.506874e-04	3.700629e-04	9.307796e-04	2.026437e-03	0.07580577
449	-3.75474000	-2.456662e-03	0.0005620262	3.527207e-04	3.656336e-04	9.242115e-04	2.019032e-03	0.07101844
458	-3.68759717	-2.456870e-03	0.0005659268	3.603045e-04	3.605995e-04	9.161058e-04	2.015239e-03	0.06683006
638	-3.62127828	-2.443655e-03	0.0005777422	3.651715e-04	3.766840e-04	9.043319e-04	2.014684e-03	0.06312619
737	-3.55735139	-2.429336e-03	0.0005883023	3.659056e-04	3.896060e-04	8.901612e-04	2.014802e-03	0.05984134
761	-3.49638209	-2.420077e-03	0.0005954479	3.584023e-04	4.013786e-04	8.756327e-04	2.011564e-03	0.05690064
765	-3.43858791	-2.410999e-03	0.0006004029	3.508646e-04	4.099248e-04	8.617416e-04	2.008786e-03	0.05424948
777	-3.38349923	-2.402755e-03	0.0006045806	3.406449e-04	4.174491e-04	8.469775e-04	2.005686e-03	0.05184563
792	-3.33094368	-2.395189e-03	0.0006086245	3.296147e-04	4.264029e-04	8.343552e-04	2.002104e-03	0.04965733
838	-3.28032300	-2.389376e-03	0.0006107026	3.166340e-04	4.336866e-04	8.211028e-04	1.999327e-03	0.04766239
845	-3.23127749	-2.383226e-03	0.0006125100	2.984089e-04	4.415925e-04	8.047776e-04	1.995688e-03	0.04582966
869	-3.18447854	-2.378054e-03	0.0006143502	2.819172e-04	4.487154e-04	7.896906e-04	1.992637e-03	0.04413987
891	-3.13935644	-2.373921e-03	0.0006165807	2.640321e-04	4.559815e-04	7.767260e-04	1.988149e-03	0.04258024
907	-3.09558434	-2.370167e-03	0.0006195066	2.498028e-04	4.614422e-04	7.635275e-04	1.985976e-03	0.04114075
926	-3.05265580	-2.366155e-03	0.0006226374	2.378502e-04	4.671230e-04	7.520819e-04	1.985685e-03	0.03981471
939	-3.01113826	-2.363935e-03	0.0006271132	2.286810e-04	4.722768e-04	7.401415e-04	1.987423e-03	0.03858231
1008	-2.97075667	-2.362961e-03	0.0006285717	2.172946e-04	4.759381e-04	7.283214e-04	1.989213e-03	0.03743506
1013	-2.93180999	-2.362412e-03	0.0006303145	2.056637e-04	4.794960e-04	7.176772e-04	1.990203e-03	0.03635905
1068	-2.89319918	-2.359600e-03	0.0006348294	1.935715e-04	4.889504e-04	7.095916e-04	1.989311e-03	0.03535387
1069	-2.85595589	-2.357223e-03	0.0006388460	1.820443e-04	4.978184e-04	7.021763e-04	1.988523e-03	0.03440623
1072	-2.81982847	-2.355784e-03	0.0006423684	1.701620e-04	5.055474e-04	6.941839e-04	1.988114e-03	0.03351342
1078	-2.78412432	-2.353394e-03	0.0006458846	1.543817e-04	5.129892e-04	6.826419e-04	1.987570e-03	0.03267201
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1085	-2.67924376	-2.342746e-03	0.0006829291	1.521416e-04	5.030967e-04	6.104766e-04	1.958135e-03	0.03032296
1093	-2.64609561	-2.340559e-03	0.0006937701	1.502847e-04	5.010701e-04	5.892077e-04	1.949357e-03	0.02961866
1099	-2.61327624	-2.334909e-03	0.0007045514	1.529285e-04	4.958861e-04	5.690005e-04	1.933194e-03	0.02893552
1113	-2.58105744	-2.329908e-03	0.0007142937	1.547112e-04	4.910265e-04	5.487408e-04	1.917903e-03	0.02828615

1128	-2.54950750	-2.326519e-03	0.0007236632	1.553183e-04	4.859755e-04	5.283166e-04	1.903812e-03	0.02766910
1134	-2.51860455	-2.322946e-03	0.0007321790	1.559903e-04	4.795663e-04	5.075546e-04	1.890922e-03	0.02708028
1137	-2.48846412	-2.318943e-03	0.0007407282	1.570782e-04	4.739042e-04	4.880714e-04	1.878896e-03	0.02651649
1140	-2.45890103	-2.315182e-03	0.0007497538	1.593793e-04	4.683050e-04	4.689090e-04	1.868311e-03	0.02597869
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1160	-2.40155290	-2.308066e-03	0.0007670461	1.638873e-04	4.580927e-04	4.331787e-04	1.849074e-03	0.02497163
1162	-2.37392174	-2.304710e-03	0.0007751787	1.660616e-04	4.534451e-04	4.167884e-04	1.840297e-03	0.02449750
1185	-2.34635993	-2.300813e-03	0.0007836153	1.694646e-04	4.493965e-04	4.009918e-04	1.831895e-03	0.02404651
1267	-2.31848234	-2.295938e-03	0.0007934206	1.701934e-04	4.446859e-04	3.823129e-04	1.823218e-03	0.02361911
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1818	-1.93669205	-2.235068e-03	0.0009052214	9.093649e-05	3.779622e-04	1.744271e-04	1.683091e-03	0.01945249
1874	-1.90921364	-2.221209e-03	0.0009088279	7.983299e-05	3.710053e-04	1.653345e-04	1.666182e-03	0.01924122
1886	-1.88227893	-2.207905e-03	0.0009120342	6.848104e-05	3.642736e-04	1.565549e-04	1.649877e-03	0.01903015
1928	-1.85588021	-2.194980e-03	0.0009151408	5.751476e-05	3.578597e-04	1.482392e-04	1.634318e-03	0.01881972
2102	-1.82971440	-2.183888e-03	0.0009181088	4.619822e-05	3.517301e-04	1.399077e-04	1.619792e-03	0.01861726
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2464	-1.41652005	-2.003040e-03	0.0009354059	-1.839561e-04	2.425854e-04	-1.714981e-06	1.410331e-03	0.01542983
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2498	-1.37712083	-1.988815e-03	0.0009392838	-1.986769e-04	2.309078e-04	-1.535982e-05	1.397820e-03	0.01512920
2528	-1.33802053	-1.974362e-03	0.0009370437	-2.184314e-04	2.177012e-04	-2.747884e-05	1.383977e-03	0.01484626
2529	-1.31879788	-1.966632e-03	0.0009351516	-2.281363e-04	2.107403e-04	-3.253895e-05	1.376746e-03	0.01470813
2541	-1.29984293	-1.959340e-03	0.0009334123	-2.372338e-04	2.040020e-04	-3.759424e-05	1.369980e-03	0.01457209
2543	-1.26239301	-1.943796e-03	0.0009297275	-2.554313e-04	1.898554e-04	-4.795234e-05	1.356924e-03	0.01430861
2567	-1.24402913	-1.936616e-03	0.0009284512	-2.640515e-04	1.830269e-04	-5.306141e-05	1.350907e-03	0.01418039
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2583	-1.20732919	-1.919267e-03	0.0009239799	-2.815461e-04	1.672997e-04	-6.364063e-05	1.337352e-03	0.01393237
2591	-1.18905298	-1.908456e-03	0.0009210801	-2.889869e-04	1.591820e-04	-6.740658e-05	1.329702e-03	0.01381155
2624	-1.17079754	-1.896752e-03	0.0009180390	-2.969938e-04	1.505527e-04	-7.185670e-05	1.322061e-03	0.01369388
2668	-1.15278949	-1.885622e-03	0.0009145246	-3.053776e-04	1.423054e-04	-7.601430e-05	1.314557e-03	0.01357764
2682	-1.13500025	-1.874915e-03	0.0009112784	-3.133997e-04	1.342602e-04	-8.011016e-05	1.307443e-03	0.01346322
2706	-1.11734603	-1.864977e-03	0.0009068082	-3.225215e-04	1.268929e-04	-8.377116e-05	1.300146e-03	0.01335122
2725	-1.09985673	-1.854968e-03	0.0009023798	-3.312618e-04	1.196319e-04	-8.715324e-05	1.293080e-03	0.01324113
2751	-1.08214462	-1.841816e-03	0.0008985323	-3.359227e-04	1.104337e-04	-8.974710e-05	1.282272e-03	0.01312925
2752	-1.06463773	-1.829339e-03	0.0008945177	-3.405150e-04	1.016485e-04	-9.238082e-05	1.271791e-03	0.01301868
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2849	-0.99505055	-1.775172e-03	0.0008789015	-3.564286e-04	6.781465e-05	-1.010394e-04	1.231872e-03	0.01260383
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2928	-0.95998292	-1.745138e-03	0.0008736531	-3.549873e-04	5.290726e-05	-1.033032e-04	1.215515e-03	0.01241728
2934	-0.94253085	-1.730510e-03	0.0008696055	-3.545724e-04	4.554674e-05	-1.040608e-04	1.206956e-03	0.01232636
3052	-0.92343104	-1.710704e-03	0.0008638706	-3.526014e-04	3.542867e-05	-1.014798e-04	1.194988e-03	0.01225767
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3176	-0.88482434	-1.669037e-03	0.0008539647	-3.447068e-04	1.432668e-05	-9.454975e-05	1.172359e-03	0.01213435
3221	-0.86417203	-1.645948e-03	0.0008507268	-3.353548e-04	1.612051e-06	-9.081205e-05	1.162891e-03	0.01209985
3250	-0.84347168	-1.624882e-03	0.0008455624	-3.277207e-04	-9.951550e-06	-8.734821e-05	1.153312e-03	0.01206714
3255	-0.82306326	-1.604997e-03	0.0008406597	-3.205089e-04	-2.121743e-05	-8.411824e-05	1.144200e-03	0.01203069
3293	-0.80186090	-1.585890e-03	0.0008330183	-3.133550e-04	-3.162997e-05	-7.980607e-05	1.133421e-03	0.01200816
3316	-0.77965317	-1.566313e-03	0.0008273277	-3.045969e-04	-3.915050e-05	-7.496848e-05	1.123467e-03	0.01200763
3325	-0.75778372	-1.547932e-03	0.0008206597	-2.974967e-04	-4.607888e-05	-6.990803e-05	1.113621e-03	0.01199998
3524	-0.72839147	-1.522343e-03	0.0008146555	-2.771369e-04	-5.207380e-05	-5.654168e-05	1.102502e-03	0.01220488

3624	-0.69420879	-1.500383e-03	0.0008027526	-2.487049e-04	-5.708632e-05	-4.380780e-05	1.097474e-03	0.01258990
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3711	-0.61989664	-1.473557e-03	0.0007953684	-1.818682e-04	-6.401379e-05	-1.787112e-05	1.098335e-03	0.01357338
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36	-5.87874801	-9.782841e-04	0.0019344223	2.385041e-03	5.133001e-04	7.961887e-04	3.502146e-03	1.00633774
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148	-4.06930585	-9.459511e-04	0.0019952479	2.517346e-03	5.070166e-04	8.071066e-04	3.559998e-03	0.17316408
156	-3.91215634	-9.457617e-04	0.0020031893	2.530652e-03	5.059319e-04	8.052095e-04	3.570716e-03	0.14938324
167	-3.77602142	-9.458638e-04	0.0020098186	2.542261e-03	5.053139e-04	8.040150e-04	3.580326e-03	0.13155132
253	-3.65441898	-9.473700e-04	0.0020287725	2.566860e-03	5.000632e-04	7.936566e-04	3.600763e-03	0.11771312
255	-3.54449314	-9.420876e-04	0.0020498777	2.584892e-03	5.026415e-04	7.822149e-04	3.618839e-03	0.10664455
262	-3.44510319	-9.373670e-04	0.0020660937	2.599708e-03	5.047520e-04	7.737836e-04	3.634237e-03	0.09758903
329	-3.35208539	-9.235433e-04	0.0020869402	2.619665e-03	5.111179e-04	7.706823e-04	3.654292e-03	0.09008689
336	-3.26656704	-9.109277e-04	0.0021107021	2.647033e-03	5.151295e-04	7.652418e-04	3.676254e-03	0.08374087
347	-3.18739513	-8.991936e-04	0.0021319433	2.671560e-03	5.189169e-04	7.610951e-04	3.696167e-03	0.07830283
438	-3.10849684	-8.767181e-04	0.0021932859	2.754635e-03	4.840532e-04	7.020704e-04	3.685125e-03	0.07343589
451	-3.03489828	-8.583976e-04	0.0022446275	2.821263e-03	4.533897e-04	6.502911e-04	3.674384e-03	0.06916807
457	-2.96585832	-8.426097e-04	0.0022907628	2.875894e-03	4.275265e-04	6.059285e-04	3.662826e-03	0.06539571
483	-2.90041091	-8.247377e-04	0.0023329237	2.928176e-03	4.023862e-04	5.664228e-04	3.654652e-03	0.06205039
603	-2.83736028	-8.080683e-04	0.0023731632	2.966891e-03	3.799392e-04	5.327544e-04	3.642481e-03	0.05906813
609	-2.77774530	-7.927056e-04	0.0024094243	3.002021e-03	3.599271e-04	5.029788e-04	3.632356e-03	0.05637988
656	-2.72100431	-7.785222e-04	0.0024419061	3.033370e-03	3.420164e-04	4.776269e-04	3.623163e-03	0.05394804
666	-2.66685790	-7.661025e-04	0.0024724005	3.061034e-03	3.259587e-04	4.549398e-04	3.615112e-03	0.05173820
684	-2.61537329	-7.554140e-04	0.0025001375	3.086356e-03	3.116024e-04	4.342843e-04	3.608439e-03	0.04971682
693	-2.56522584	-7.422742e-04	0.0025321326	3.123765e-03	2.930819e-04	4.089287e-04	3.598926e-03	0.04784672
699	-2.51716913	-7.309959e-04	0.0025589213	3.155934e-03	2.738831e-04	3.834814e-04	3.591502e-03	0.04612582
706	-2.47096191	-7.195425e-04	0.0025832218	3.185883e-03	2.553502e-04	3.599067e-04	3.585294e-03	0.04453821
721	-2.42653839	-7.076862e-04	0.0026063450	3.215642e-03	2.382425e-04	3.389105e-04	3.580391e-03	0.04306932
737	-2.38380752	-6.962865e-04	0.0026283328	3.244569e-03	2.224391e-04	3.197458e-04	3.576659e-03	0.04170584
741	-2.34222125	-6.844074e-04	0.0026504867	3.268704e-03	2.089648e-04	3.004098e-04	3.572259e-03	0.04043568
825	-2.30210765	-6.740224e-04	0.0026694513	3.289944e-03	1.975530e-04	2.832291e-04	3.568037e-03	0.03924847
827	-2.26341817	-6.646679e-04	0.0026870824	3.309571e-03	1.870284e-04	2.673710e-04	3.564381e-03	0.03813718
840	-2.22583828	-6.552723e-04	0.0027087967	3.328735e-03	1.789992e-04	2.537140e-04	3.559749e-03	0.03709622
867	-2.18943513	-6.468293e-04	0.0027283480	3.345329e-03	1.713373e-04	2.408528e-04	3.555421e-03	0.03611812
914	-2.15372633	-6.388986e-04	0.0027464005	3.356614e-03	1.638013e-04	2.290021e-04	3.549367e-03	0.03519891

931	-2.11906419	-6.321269e-04	0.0027642378	3.365739e-03	1.560242e-04	2.183049e-04	3.542483e-03	0.03433140
956	-2.08501098	-6.271614e-04	0.0027831092	3.377906e-03	1.501643e-04	2.047572e-04	3.537513e-03	0.03351059
966	-2.05180221	-6.221267e-04	0.0028017844	3.388915e-03	1.449854e-04	1.919413e-04	3.532769e-03	0.03273484
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1010	-1.98769283	-6.157171e-04	0.0028337814	3.405381e-03	1.378952e-04	1.681751e-04	3.522176e-03	0.03129691
1017	-1.95683741	-6.135410e-04	0.0028478625	3.409798e-03	1.346461e-04	1.576314e-04	3.516111e-03	0.03063048
1035	-1.92670940	-6.128283e-04	0.0028630934	3.414344e-03	1.298013e-04	1.467023e-04	3.510599e-03	0.02999851
1076	-1.89695219	-6.122321e-04	0.0028768320	3.420140e-03	1.252452e-04	1.364577e-04	3.505526e-03	0.02939861
1091	-1.86737978	-6.131645e-04	0.0028965671	3.435576e-03	1.175061e-04	1.173778e-04	3.502770e-03	0.02882126
1099	-1.83819093	-6.139734e-04	0.0029151827	3.448304e-03	1.076717e-04	9.544268e-05	3.500835e-03	0.02827131
1108	-1.80960091	-6.144811e-04	0.0029335311	3.460388e-03	9.836531e-05	7.441172e-05	3.499206e-03	0.02774654
1113	-1.78168791	-6.152966e-04	0.0029504485	3.471007e-03	8.957472e-05	5.452400e-05	3.497647e-03	0.02724385
1134	-1.75428620	-6.172505e-04	0.0029666696	3.481834e-03	8.169733e-05	3.393204e-05	3.496354e-03	0.02675975
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1223	-1.67415701	-6.229428e-04	0.0030094141	3.513863e-03	6.223881e-05	-2.232980e-05	3.492984e-03	0.02542962
1343	-1.64829427	-6.231057e-04	0.0030215281	3.524055e-03	5.604199e-05	-3.799558e-05	3.489840e-03	0.02501780
1469	-1.62177968	-6.154175e-04	0.0030259854	3.529890e-03	3.810643e-05	-4.858589e-05	3.478755e-03	0.02462693
1480	-1.59539659	-6.018174e-04	0.0030258194	3.535610e-03	1.922549e-05	-5.144889e-05	3.460760e-03	0.02424400
1496	-1.56952870	-5.884155e-04	0.0030260085	3.542148e-03	1.052206e-06	-5.400385e-05	3.444014e-03	0.02387519
1501	-1.54363453	-5.766587e-04	0.0030275035	3.552080e-03	-1.809535e-05	-6.212080e-05	3.425573e-03	0.02350937
1509	-1.51812153	-5.667099e-04	0.0030286967	3.562074e-03	-3.586103e-05	-7.167749e-05	3.407779e-03	0.02315264
1518	-1.49320463	-5.576658e-04	0.0030297965	3.571515e-03	-5.256270e-05	-8.091021e-05	3.391040e-03	0.02280640
1581	-1.46866579	-5.500964e-04	0.0030299674	3.579481e-03	-6.805427e-05	-8.936358e-05	3.374785e-03	0.02247206
1593	-1.44431678	-5.456138e-04	0.0030304164	3.587964e-03	-8.234831e-05	-1.021149e-04	3.358984e-03	0.02214257
1608	-1.42041800	-5.415143e-04	0.0030307416	3.595834e-03	-9.607631e-05	-1.142852e-04	3.343911e-03	0.02182364
1718	-1.39549491	-5.353412e-04	0.0030203819	3.600092e-03	-1.087084e-04	-1.207335e-04	3.321948e-03	0.02151646
1774	-1.37011753	-5.267103e-04	0.0030103306	3.605020e-03	-1.247257e-04	-1.333208e-04	3.301888e-03	0.02122617
1796	-1.34507993	-5.183374e-04	0.0030004815	3.610343e-03	-1.401660e-04	-1.451403e-04	3.283010e-03	0.02094587
1869	-1.31957263	-5.076780e-04	0.0029856014	3.615577e-03	-1.565088e-04	-1.532500e-04	3.262478e-03	0.02068358
1905	-1.29441208	-4.954279e-04	0.0029720846	3.623380e-03	-1.724399e-04	-1.601874e-04	3.243312e-03	0.02043024
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2005	-1.21878303	-4.488237e-04	0.0029496145	3.651253e-03	-2.072561e-04	-1.675275e-04	3.174803e-03	0.01972600
2085	-1.19389749	-4.335302e-04	0.0029436916	3.658854e-03	-2.161109e-04	-1.680078e-04	3.151446e-03	0.01950502
2100	-1.16944310	-4.188166e-04	0.0029378145	3.666630e-03	-2.245531e-04	-1.682900e-04	3.129286e-03	0.01928787
2108	-1.14548284	-4.051426e-04	0.0029318725	3.673842e-03	-2.323294e-04	-1.684439e-04	3.108224e-03	0.01907322
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2168	-1.07445220	-3.702186e-04	0.0029155701	3.684608e-03	-2.555017e-04	-1.712190e-04	3.044934e-03	0.01846639

2193	-1.05062707	-3.602718e-04	0.0029092913	3.679462e-03	-2.641625e-04	-1.713688e-04	3.019340e-03	0.01827701
2355	-1.02485661	-3.448438e-04	0.0029054197	3.669856e-03	-2.732688e-04	-1.683797e-04	2.986347e-03	0.01812443
2359	-0.99940528	-3.294346e-04	0.0029013603	3.660385e-03	-2.824929e-04	-1.654312e-04	2.954546e-03	0.01797283
2462	-0.97310080	-3.114509e-04	0.0029016058	3.654202e-03	-2.893319e-04	-1.617526e-04	2.924163e-03	0.01784880
2484	-0.94702689	-2.967818e-04	0.0029015356	3.647255e-03	-2.946075e-04	-1.598809e-04	2.895149e-03	0.01772338
2525	-0.92059803	-2.836131e-04	0.0028990450	3.638332e-03	-2.988706e-04	-1.572512e-04	2.865846e-03	0.01760957
2563	-0.89439456	-2.718910e-04	0.0028973014	3.629609e-03	-3.021026e-04	-1.545451e-04	2.837570e-03	0.01749625
2565	-0.86873103	-2.615241e-04	0.0028957182	3.621383e-03	-3.049061e-04	-1.522649e-04	2.811047e-03	0.01737715
2570	-0.84329919	-2.500546e-04	0.0028941632	3.614560e-03	-3.081628e-04	-1.495690e-04	2.785593e-03	0.01725951
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2608	-0.79336482	-2.271958e-04	0.0028933511	3.603585e-03	-3.158413e-04	-1.427298e-04	2.736310e-03	0.01702348
2744	-0.76773170	-2.187330e-04	0.0028903756	3.597177e-03	-3.184599e-04	-1.407077e-04	2.711095e-03	0.01692179
2750	-0.74238082	-2.097289e-04	0.0028879953	3.592575e-03	-3.211888e-04	-1.383794e-04	2.687261e-03	0.01681999
2751	-0.71699827	-1.999647e-04	0.0028844894	3.588722e-03	-3.242660e-04	-1.351145e-04	2.664102e-03	0.01672415
2773	-0.69195582	-1.911616e-04	0.0028799850	3.582853e-03	-3.271923e-04	-1.315547e-04	2.641169e-03	0.01662474
2881	-0.66683325	-1.842504e-04	0.0028744662	3.577296e-03	-3.288156e-04	-1.290591e-04	2.618608e-03	0.01652840
3005	-0.64051638	-1.709944e-04	0.0028726295	3.578872e-03	-3.245739e-04	-1.230463e-04	2.598056e-03	0.01646662
3030	-0.61404312	-1.584720e-04	0.0028712654	3.584905e-03	-3.203245e-04	-1.201289e-04	2.576521e-03	0.01640424
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3315	-0.55817920	-1.355390e-04	0.0028582566	3.597262e-03	-3.055240e-04	-1.045088e-04	2.532217e-03	0.01636657
3424	-0.52817276	-1.180848e-04	0.0028442434	3.608197e-03	-2.978700e-04	-8.711969e-05	2.506993e-03	0.01640591
3463	-0.49702836	-9.805931e-05	0.0028311904	3.616978e-03	-2.881956e-04	-6.815859e-05	2.479917e-03	0.01647676
3490	-0.46571494	-7.734943e-05	0.0028242610	3.637770e-03	-2.791632e-04	-5.101446e-05	2.458604e-03	0.01655683
3791	-0.42864846	-5.637349e-05	0.0027963072	3.668599e-03	-2.548438e-04	-1.432523e-05	2.436574e-03	0.01685513
3899	-0.39030312	-4.670181e-05	0.0027626572	3.683635e-03	-2.309679e-04	3.121343e-05	2.403269e-03	0.01718467
3929	-0.35101998	-3.495292e-05	0.0027203368	3.701892e-03	-2.029274e-04	8.626883e-05	2.369434e-03	0.01753735
3939	-0.31259669	-2.582367e-05	0.0026780698	3.718331e-03	-1.745186e-04	1.398160e-04	2.338018e-03	0.01782803
4028	-0.27291318	-2.335328e-05	0.0026388351	3.733402e-03	-1.439137e-04	1.965670e-04	2.306210e-03	0.01816165
4812	-0.17596841	2.162791e-04	0.0026948043	3.969163e-03	-1.217145e-04	1.166256e-04	2.339507e-03	0.02385811
5623	0.09500631	1.323852e-03	0.0026623548	4.421470e-03	-3.493462e-04	6.664785e-05	2.157273e-03	0.07118183