**Slide 1: Introduction**

**Good morning, everyone. Thank you for coming.**

Today, I am humbled to present my thesis, **"Evaluating Disparities in End-Stage Renal Disease Risk Prediction Using the All of Us Cohort.”**

**Slide 2: Public Health Crisis**

This study addresses inequities in kidney disease prediction, an issue that resonates deeply with me as someone from The Gambia, where kidney disease is a growing public health crisis.

Chronic kidney disease affects 19.8% of the population in West Africa, with an estimated prevalence of 13% in The Gambia and a staggering 49.4% mortality rate among hemodialysis patients.

CKD affects over 850 million people globally, more than 10% of the population, surpassing diabetes and cardiovascular disease in prevalence. Over 90% of cases go undiagnosed until advanced stages like End-Stage Renal Disease (ESRD), where irreversible kidney failure occurs, requiring dialysis or a transplant to survive. The image on the bottom right, illustrates the natural progression of CKD through its five stages, beginning with normal kidney function (Stage 1) and culminating in complete kidney failure (Stage 5). This progression visually highlights the critical opportunity for early detection and treatment to halt disease progression and improve outcomes.

This immense gap in disease outcome inspired my research: how can we ensure that risk prediction models—tools meant to save lives—work equitably for vulnerable populations? Today, I'll discuss the disparities we identified, our methods, and how we can refine these tools to better support vulnerable communities.

**Slide 3: Prevalence**

Between 2001 and 2021 in the United States, ESRD cases have grown. Annual incidents now exceed 130,000 cases per year, while prevalence surpassed 800,000 total cases in 2021, reflecting rising demands for dialysis and Kidney transplants.

Racial disparities are stark. Black individuals face an incidence rate at about 1,000 cases per million persons per year—four times higher than White individuals. Prevalence among Black patients consistently exceeds 6,000 cases per million persons, more than three times that of White individuals. Native American and Hispanic patients also face elevated prevalence at about 4,000 cases per million persons.

These statistics underscore persistent racial disparities in incidence, prevalence, and outcomes.

**Slide 4: eFGR Equations and Case Study**

Moreso, One of the key factors contributing to disparities in kidney disease prediction is the role of race in calculating kidney function.

For decades, equations like MDRD and CKD-EPI 2009 ,factored race explicitly into their formulas. As shown in number 1, the MDRD equation weighs in a multiplier 1.21 for Black individuals and 1 for non-black individuals in kidney function assessment. Similarly, the CKD-EPI equation from 2009 used a race weight of 1.159 for Black and 1 for non-black.

At the bottom of the slide, we have a **case study** comparing two patients: Patient A, White, and Patient B, Black. Both are 55-year-old females with identical serum creatinine levels—1.5 Milligrams per Deciliter. Based on the 2009 CKD-EPI equation, the calculated eGFR for Patient A is 42.3, while for Patient B, it is 61.2. The clinical implications are significant. Patient A, with a lower eGFR, is flagged for referral to a nephrologist, while Patient B is classified as having normal kidney function and does not receive intervention. The only difference? Race.

In 2021, a new version of the CKD-EPI equation was introduced, eliminating race as a variable. This equation not only removes race but also modifies the alpha (α) parameters while maintaining a consistent kappa (κ) factor, influencing the formula's sensitivity and resulting outcomes. This marked a pivotal step forward, but it raises important questions: How do we ensure that predictive models are equitable? How do we ensure the accuracy and fairness of predictions across all groups?

**Slide 5: Model Misclassification**

On the left, we have a density plot from a study by Tsai et al. (2021). This study demonstrated that including the race multiplier shifts estimated Glomerular Filtration Rate (eGFR) values higher for Black individuals, insinuating "better" kidney function. However, this might not accurately reflect actual kidney health, raising critical concerns about the fairness and accuracy of this adjustment.

The bar chart on the right from our study demonstrates how different eGFR models classify CKD stages across racial groups using the same dataset. The Race-neutral model (CKD-EPI-2021) identifies more Black individuals as having CKD or being in early stages compared to race-inclusive models. Conversely, for Asians and Whites, the race-neutral model classifies more individuals as "Normal," reducing CKD detection rates for this subpopulation.

This comparisons underscores how race adjustments in eGFR calculations affect classification outcomes, with implications for diagnosis, care access, and health equity.

**Slide 6: Overview**

On this matter, I will go through our study objectives. In Chapter 1 of our study, we aim to assess the predictive performance of both race-inclusive and race-neutral eGFR equations for estimating ESRD risk across population groups.

In Chapter 2, our goal is to enhance ESRD risk prediction by developing models that integrate comorbidities and other predictors.

Finally, in Chapter 3, we work towards refining risk stratification. This includes integrating genetic markers, like APOL1 variants, and polygenic risk scores, alongside socioeconomic factors, to enhance prediction accuracy.

For this work, we leveraged data from the All of Us Research Program, which is a national, longitudinal dataset that aims to represent the diversity of the U.S. population. This program is one of the most comprehensive efforts to capture data from people of all racial and ethnic backgrounds, as well as varying socioeconomic status, geographic regions, and health conditions. The dataset includes biospecimens, genetic information, and survey data, making it highly suitable for studying health disparities and the factors contributing to outcomes like ESRD. Its representative nature allows us to ensure that our findings are broadly applicable across the US population, which is critical when evaluating disparities.

**Slide 7: Study Cohort**

We designed a cohort study.

On the left, we have the **inclusion and exclusion criteria** that helped define our study cohort. The process began with over 413,000 participants aged 18 and older. From there, we applied several filters. First, we excluded about 36,000 participants with congenital abnormalities—conditions that could skew kidney function measurements. Next, we removed an additional 84,000 participants of unspecified or other races, narrowing our focus to Black, White, and Asian participants to ensure we had sufficient data for meaningful subgroup analyses.

Further exclusions included participants missing creatinine lab values, and those with ESRD diagnosed prior to the index date. These exclusions were vital to ensure the integrity of our analysis.

Displayed on the right is the final study cohort, comprising over 127,000 participants aged 18 years and older. Sex at birth was recorded as either male or female for all included individuals.

This comprised of, over 93,000 White participants, including 794 cases and more than 92,000 controls. Around 30,000 Black participants, with 803 cases and about 29,000 controls.

Just over 4,000 Asian participants, with 58 cases and over 4,000 controls.

In the second layer of the population breakdown, we focused on participants with available albumin lab values, a key variable for assessing kidney damage. Here, the sample sizes decrease further, but this sub-cohort provides critical insights into kidney function disparities.

From this point forward, I’ll outline the statistical methods and models we used, commencing with chapter 1 .

**Slide 8: Chapter 1: Methodology**

The core model used in this study is the 4-variable Kidney Failure Risk Equation (KFRE), which is widely utilized in clinical practice to predict ESRD risk. The KFRE incorporates eGFR, albumin to creatinine ratio, age, and sex to estimate the likelihood of ESRD progression.

Going forward, eGFR values were calculated using three different equations: MDRD, CKD-EPI 2009, and CKD-EPI 2021.

Herein, we assessed the assumptions underlying the 4-variable KFRE to ensure the model's validity. By addressing these assumptions, we ensured that the KFRE model was appropriately specified for accurate risk prediction.

To that end, we applied the KFRE to calculate risk scores. In the risk prediction phase, we used the KFRE beta coefficient sums to estimate both 2-year and 5-year risks for each participant. These scores were further categorized into CKD risk levels based on Kidney Disease Improving Global Outcomes (KDIGO) guidelines, which stratify patients by eGFR and Albumin to Creatnine Ratio thresholds to inform risk levels.

Therein, the model evaluation phase assessed performance within defined risk groups. This included analyzing predictive performance for CKD medium to very high risk groups, diabetic and hypertensive patients, subpopulations at heightened risk for ESRD.

To quantify the accuracy of the models, we evaluated several performance metrics including C-statistics to assess overall predictive discrimination.

Subsequently, we employed computationally intensive nonparametric bootstrapping with replacement to calculate confidence intervals for the C statistics, ensuring reliable error estimation.

In the coming steps, I will present the results.

**Slide 9: Results**

**On the left we have the KFRE model equations for 2 year risk and 5 year risk, and moving to the right,** let’s examine the predictive accuracy of the three eGFR equations when used in the KFRE in combined populations.

Looking at the **C statistic** for the 2-year prediction, the MDRD model demonstrated the highest predictive accuracy in hypertensive individuals, with a C statistic of 0.94 (95% CI: 0.89–0.98). In contrast, its accuracy was lower in medium-risk CKD populations, populations defined by KDIGO guidelines as individuals with an eGFR between 30 and 59 or mild albuminuria —where the C statistic was 0.71 (95% CI: 0.64–0.79). Similar patterns were observed with the CKD-EPI-2009 and CKD-EPI-2021 models.

In like manner, The 5-year prediction, showed insufficient evidence of a difference in C statistics among models within risk groups when used in combined populations.

To follow, I will present results of the subgroup analysis.

**Slide 10: Comparison of C Statistics**

The analysis is divided into two sections: 2-year predictions on the left and 5-year predictions on the right. For both time frames, we assessed predictive performance differences across key risk groups—diabetic, hypertensive, and CKD risk levels from medium to very high. The objective was to determine whether the race-free model showed improvement over the race-inclusive models by evaluating if the confidence intervals for the differences in C-statistics excluded zero.

In the All Populations Group, for both 2-year and 5-year predictions, confidence intervals for the difference in C-statistics generally **included** zero across all risk groups.

Shifting focus to the Black population, a different story emerges. For both 2-year and 5-year predictions, the race free model demonstrated improvement over the race models, in the CKD High Risk and Very High Risk groups. In these categories, the entire confidence intervals for the difference in C-statistics were above zero, indicating improved predictive accuracy.

For the Asian population, confidence intervals included zero across all risk groups for both 2-year and 5-year predictions.

In the White population, there was insufficient evidence of a difference among models across risk groups for 2-year predictions. However, for 5-year predictions, the CKD-EPI 2009 model outperformed in the CKD very high-risk group (**point left**), with the confidence interval for the difference in C-statistics **excluding zero**. Conversely, in the medium-risk group (**point right**), the CKD-EPI 2021 model demonstrated better predictive accuracy compared to the MDRD race-based model.

These findings underscore the variability in model performance across different racial and risk subgroups. While CKD-EPI 2021 marks progress by removing race as a variable, its predictive superiority isn’t universal, in our data.

In some cases, particularly for the Black population’s CKD high risk groups (**point right**), it performs better relatively, but in others, such as the White population’s CKD Very High Risk group (**point left**), it underperformed relatively. These disparities highlight the critical need for tailored approaches in model evaluation and clinical decision-making, motivating chapter 2 of our analysis.

**Slide 11: Chapter 2 Methodology\*\*\***

In Chapter 2, we retrieved 254 predictors from the ONCE framework and converted them from PheCodes into standardized SNOMED codes. These codes were then used to extract EHR data from the All of Us research benchmark, ensuring consistency in the dataset.The predictors represented chronic and acute risk factors collected over a 1-year period before the index date. The selection process, spanning four months, involved meticulous manual validation to ensure high-quality dataset tailored for the analysis.

Herein, we split the data into training and testing sets using a 70-30 split, motivated from the literature. Seventy percent of the data was used to train the model, and the remaining 30 percent was allocated for independent testing to evaluate model predictive performance.

For handling missing data we applied a complete case analysis.

To address potential multicollinearity, we applied a correlation threshold of 0.7. For highly correlated variables, only the variable with the higher case count was retained, while the other was excluded. This reduced redundancy and improved model stability.

We also examined the data for perfect separation—ensuring predictors did not perfectly delineate cases and controls, as this could lead to overfitting. Cases and controls with fewer than 10 observations were excluded. This step was particularly important for achieving generalizability across populations.

Data was right censored at 2 years for 2 year risk prediction and 5 years for 5 year risk prediction. This allowed the model to focus on specific time horizons for ESRD progression, providing insights into short- and long-term risk.

In our analysis, we tested key assumptions for the Cox Proportional Hazards model, including the proportional hazards assumption. Assumptions for the Boruta algorithm, were also assessed. These steps ensured the validity and reliability of our results.

**Slide 12: Feature Selection \*\*\***

As outlined in the methodology, the 254 potential predictors used in chapter 2 are derived from the ONCE framework. ONCE is a powerful tool for developing clinical prediction models.

On the right, you can see how ONCE allows you to specify your target condition, in this case, ESRD. It leverages insights from published scientific literature to propose a broad set of features, such as comorbidities, laboratory parameters, and therapeutic interventions, which are then ranked by their relevance and importance scores.

To refine these features, we carefully defined each one to ensure clinical relevance. We conducted rigorous screening to remove redundancy, prioritize statistical performance, and address missing data. This process ensures that only the most relevant, evidence-backed, and reliable features are included in our models.

Next we look at variable selection.

**Slide 13: Variable Selection**Moreso, we utilized the Boruta Algorithm, an advanced machine learning method that uses a random forest classifier to systematically identify and prioritize relevant predictors. By refining the model-building process, this approach ensures the creation of highly accurate and effective models, ultimately driving improvements in health outcomes.

We shall now analyze the Variable Importance plots:

In the Race-Specified Model, which includes racial identity as one of the variables, the most significant predictors are eGFR, age, and systolic blood pressure. Both racial identity and ethnicity were selected as key features in the model.

In the Race-Free Model, where race was excluded as a variable, the feature set remained largely consistent.

For both models, the variables identified by the Boruta algorithm were incorporated into the Cox proportional hazards model.

Proceeding further, we shall examine the results of the Cox models.

**Slide 14: Cox Model**

Below we have the model equations for both the race free and race specified models.

Starting with the development set metrics at the top, we see that both the race-free model and the race-specific model achieve identical predictive performance, with a C-statistic of 0.89, 95% confidence interval 0.87 to 0.91. This indicates that both approaches have strong discrimination capabilities.

Notwithstanding, there are slight differences in the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC), which measure model fit. The race-specific model has lower values, suggesting it captures nuances that improve model fit, due to the inclusion of race and ethnicity as variables.

The models were validated with 30% of the data across population groups, looking at the C-index on the validation set, there is insufficient evidence of a difference among the models in discriminatory performance due to overlapping confidence intervals.

Calibration was assessed using the Nam and D’Agostino chi-squared statistic, with both models achieving values around 8,222.

The line graphs provide a visual comparison of predicted versus observed risk quintiles. Observed is in grey and predicted is in blue, the race-specific model shows relatively better calibration, moreso, in the highest-risk quintile, where accurate prediction is most critical for clinical intervention.

These findings underscore that there is insufficient evidence of a difference between the two models, motivating chapter 3 of our analysis.

**Slide 15: *Integrating Genetic and Socioeconomic Determinants for Enhanced Prediction of Kidney Damage \*\****

In **Chapter 3**, we set forth, to improve risk prediction for ESRD by integrating both genetic and socioeconomic factors. The objective, to refine our risk stratification models and address health disparities in ESRD outcome. To ensure consistency, we utilized the same methodology as outlined earlier in Chapter 2.

I’ll walk you through the key components.

**Genetic Factors:**

First, we included **APOL1 G1 and G2 variant carrier status**. APOL1 is a gene that produces a protein involved in lipid transport and immunity. Two specific variants, G1 and G2, are strongly associated with a higher risk of CKD, moreso, in individuals of African ancestry. These variants originally evolved as protection against African sleeping sickness, however, amplify the likelihood of kidney disease.

To follow, we incorporated **Polygenic Risk Scores** (PGS), which are composite genetic measures derived from diverse ancestry groups, including African, American, European, and East Asian populations. We used 15 different PGS measures to capture broader genetic contributions to ESRD.

**Socioeconomic Factors:**

On the socioeconomic front, we utilised **health insurance coverage** as a key variable. This was derived from survey responses where participants were asked: *“Are you covered by health insurance or any other healthcare plan?”*

We also evaluated **healthcare access and utilization**. Participants were asked if they had a usual place to seek care when they were sick. Responses were categorized into three groups: "Urgent care," "Emergency room," and "Doctor’s office."

By combining these genetic and socioeconomic factors, we were able to build a more comprehensive model. This approach not only improves prediction accuracy but also provides insights into how social and biological factors coexist to influence ESRD outcome. Ultimately, it helps address health disparities in kidney disease progression.

**Slide 16: *Survival analysis***

Starting with the survival curves based on race. The results show that Black participants experience significant lower survival probabilities compared to White and Asian participants. While this highlights the persistent disparities in kidney disease outcomes, it also underscores the limitations of using race as a variable—it reflects systemic inequities rather than intrinsic biological differences, as race is a social construct, not a biological factor.

Let’s address the role of genetics. Survival analysis was conducted to evaluate the effect of APOL1 G1 and G2 variant carrier status on outcome, using a Kaplan-Meier estimator to compare survival probabilities over time between carriers and non-carriers. The resulting survival curves demonstrate a significant difference in survival probabilities. Specifically, APOL1 gene carriers consistently exhibit lower survival probabilities compared to non-carriers, with the difference becoming more pronounced over time.

We conducted a comparative analysis of four models: the race-based model, the socioeconomic model, the genetic model, and the integrated model, which combines genetic and socioeconomic factors, to evaluate predictive performance.

**Slide 17: 2 Year Prediction**

Henceforth, I shall present the findings of the 2-Year Prediction, comparing the performance of the four distinct models.

The Race model served as the baseline, achieving a C-statistic of 0.88 95% Confidence Interval: 0.86–0.90. The Socioeconomic model showed marginally higher point estimate, with a C-statistic 0.89 95% Confidence Interval: 0.87–0.91. Both the Genetic and Integrated models matched the Race model’s performance.

For model fit, the **Race model** demonstrated the best fit among the four models, having the lowest AIC at 3,229 and BIC at 3,266.5.

In the stratified analysis, , in the validation set with 30% of the data, there was insufficient evidence of a difference in discriminatory performance among the 4 models, within population subgroups due to overlapping confidence intervals.

Calibration was assessed using the Nam and D’Agostino chi-squared statistic, the Genetic and Integrated models demonstrated the best calibration with chi square statistics 6,604.5.

The calibration plots revealed, the Genetic and Integrated models showed strong alignment with observed rates in the lower to moderate quintiles but misestimated the risk in Quintiles 4 and 5.

We shall now evaluate the outcomes of the 5-year prediction analysis.

**Slide 18: 5 year Prediction**

In the 5 year instance, the Socioeconomic model showed relatively higher point estimate, with a C-statistic of 0.86 95% Confidence Interval: 0.84–0.88.

By Model fit, the Integrated model demonstrated the best fit among the four models, achieving the lowest AIC at 5,025 and BIC at 5,074.7.

In the stratified analysis, in the validation set, there was insufficient evidence of a difference among the models due to overlapping confidence intervals

In calibration assessment, the Genetic and Integrated models exhibited superior calibration with chi square statistics 6,504.7. Calibration plots indicate these models aligned closely with observed outcomes, particularly, in the highest risk qualtiles 4 and 5, surpassing the Race model in capturing high-risk groups accurately.

Based on model fit and calibration fit, the 5-year prediction findings indicate that the integrated model, which combine socioeconomic and genetic factors, offer a compelling alternative to the use of race in predictive modelling for ESRD.

In conclusion, I shall address the limitations of the study and put forward suggestions for future avenues of research.

**Slide 19: Conclusion and Limitation:**

* Firstly, this study demonstrates that in eGFR calculations, the race free model, outperform traditional models that rely solely on race, in high risk black populations.
* The integrated model outperform the race-based model for long term prediction of ESRD.
* The genetic and integrated models demonstrate superior calibration and discrimination, especially in high-risk groups long term. This conclusion is supported in our data by the Nam and D’Agostino χ² statistics and calibration plots, which indicate that these models align more closely with observed outcomes and are better at identifying individuals at higher risk.
* Finally, the results emphasize the importance of social determinants of health. Incorporating socioeconomic factors enhances the ability to address renal health disparities, especially for vulnerable populations.

Limitations:

* There are, however, a few limitations to note. First, the sample size for Asian participants in the dataset was limited, which may have affected the model's performance for this subgroup.
* Additionally, our study included only two socioeconomic determinants of health, which may not fully capture the broader impact of socioeconomic factors on health outcomes.
* Finally, while the findings are promising, broader validation in diverse clinical settings is needed to ensure the generalizability of these models.

**Slide 20: Future Work**

As I wrap up this discussion, I want to highlight how the prediction models built for this thesis can be extended in future work.

**First, Advanced Fairness-Aware Machine Learning Methods:**  
Going forward, we aim to implement fairness-aware methods to address biases. These methods are designed to identify and mitigate disparities in model predictions, ensuring equitable outcomes.

**Next, Advanced Multi-Task Learning Methods:**  
The models developed focus on specific outcomes, but healthcare challenges are rarely that isolated. Future work will involve incorporating multi-task learning approaches, allowing the models to predict multiple, related outcomes simultaneously. For example, instead of singularly predicting the risk of ESRD, the model could simultaneously evaluate other chronic conditions that are often comorbid, making it more comprehensive and actionable.

**Generalizing Results to Low-Income Populations:**  
At present, the models have been trained on data derived from the All of Us cohort which, whilst diverse, may not entirely capture the realities of low-resource settings such as The Gambia. The subsequent step involves adapting and validating these models for application within such contexts. By customising prediction thresholds and performance metrics to address the distinctive challenges faced by low-resource healthcare systems, these models have the potential to become invaluable tools for fostering meaningful impact within these communities.

**Slide 21: Acknowledgements \*\*\*\*\***

Finally, this journey has been as much about the knowledge I’ve gained as it has been about the incredible people I’ve had the privilege to learn from along the way.

I would like to take a moment to express my deepest gratitude to leaders in public health, biostatistics and epidemiology who have supported and guided me throughout this journey.

First and foremost, to my advisor, Dr. Duan, thank you for your mentorship, your unwavering support, and for challenging me to grow as a researcher and thinker. Your guidance has been invaluable, and this work would not have been possible without you.

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Chronic kidney disease is a silent but devastating reality, affecting millions globally. Now is the time to act—raise awareness, promote early detection, and advocate for equitable care. Together, we can combat this hidden epidemic and save lives.

Thank you!!! \*\*\*\*\*