Scalable Modeling of Multivariate Longitudinal Data

for Prediction of Chronic Kidney Disease Progression

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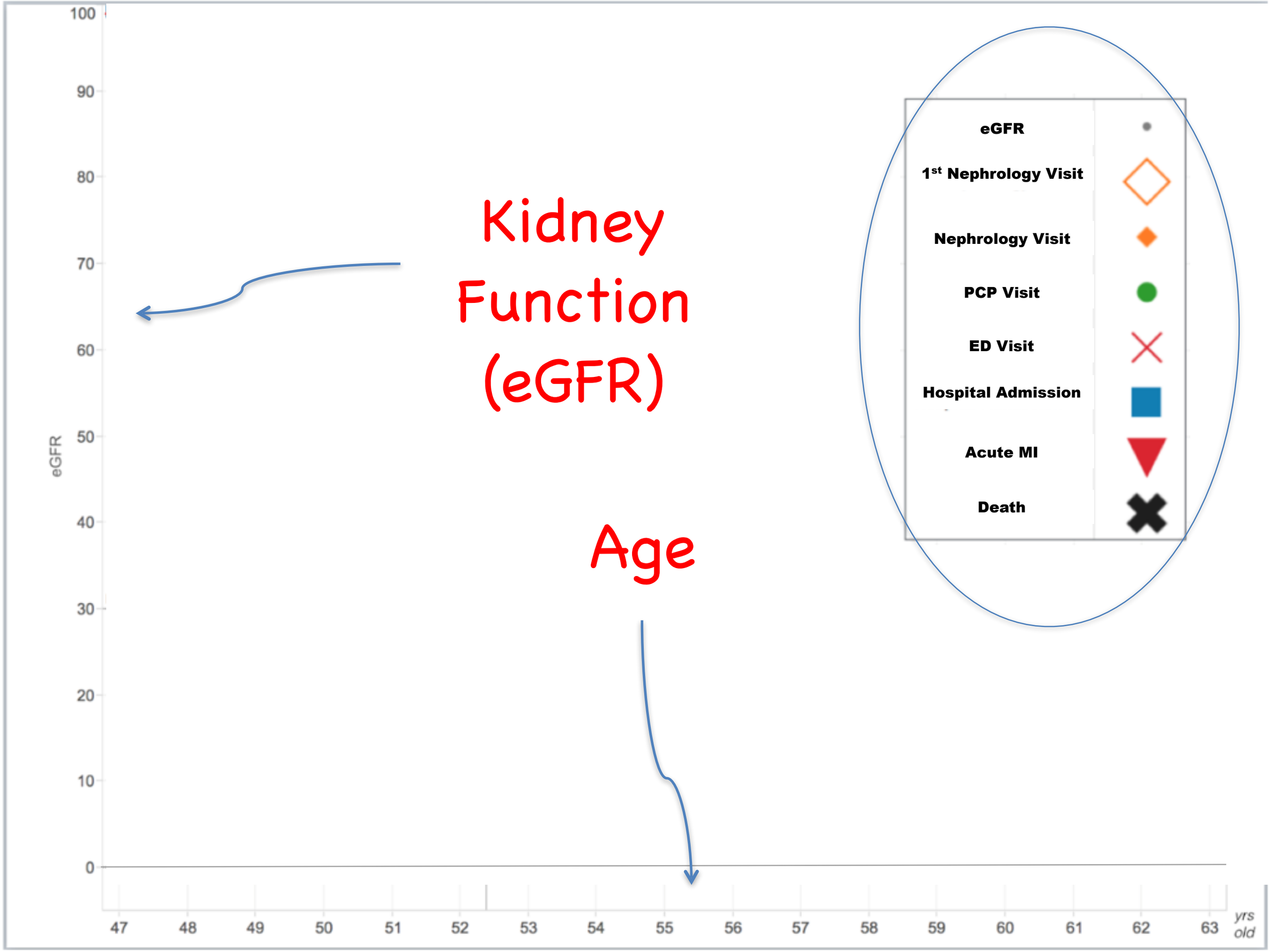
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eGFR
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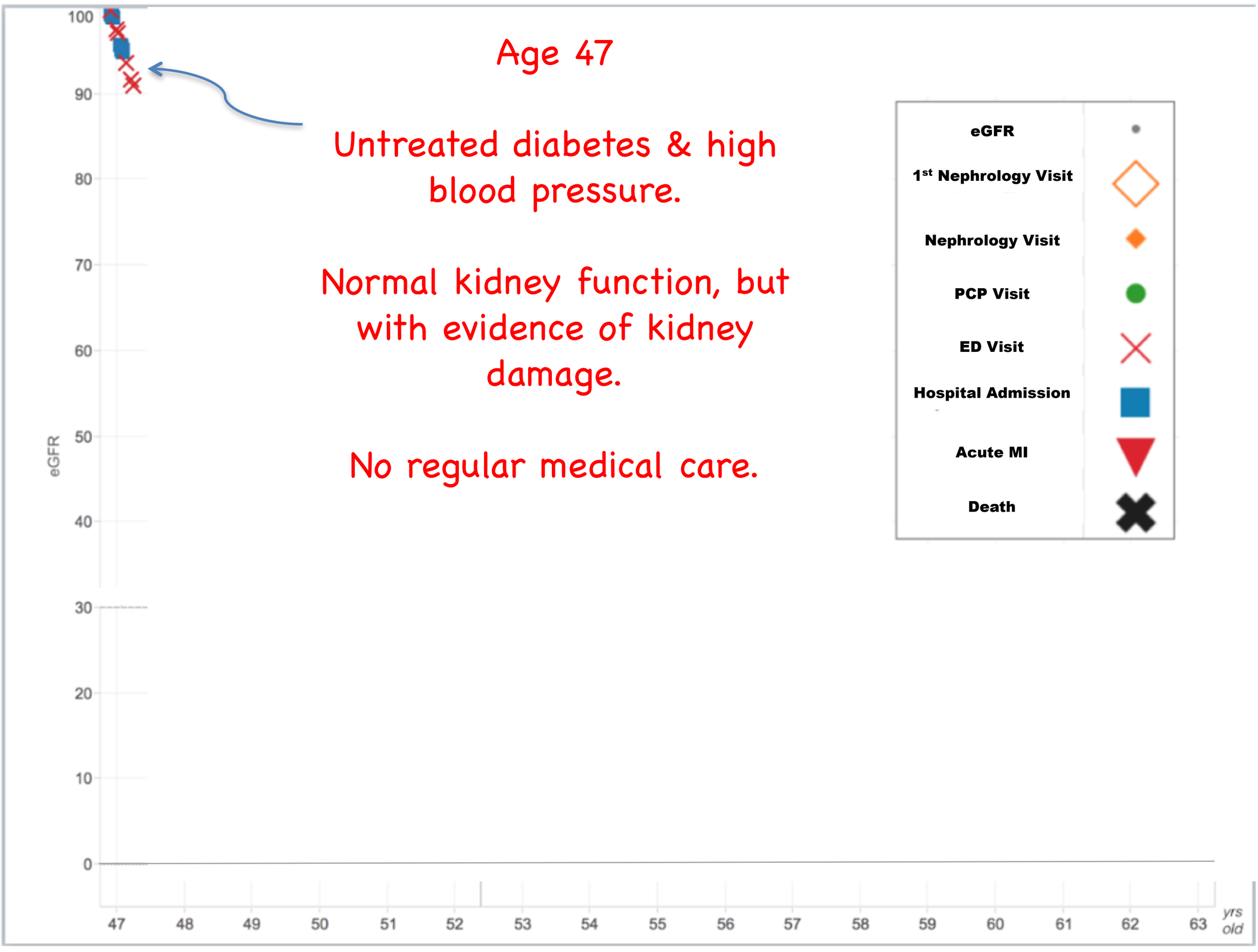
yrs old
Kidney Function (eGFR)
Age
eGFR
1st Nephrology Visit
Nephrology Visit
PCP Visit
ED Visit
Hospital Admission
Acute MI
Death

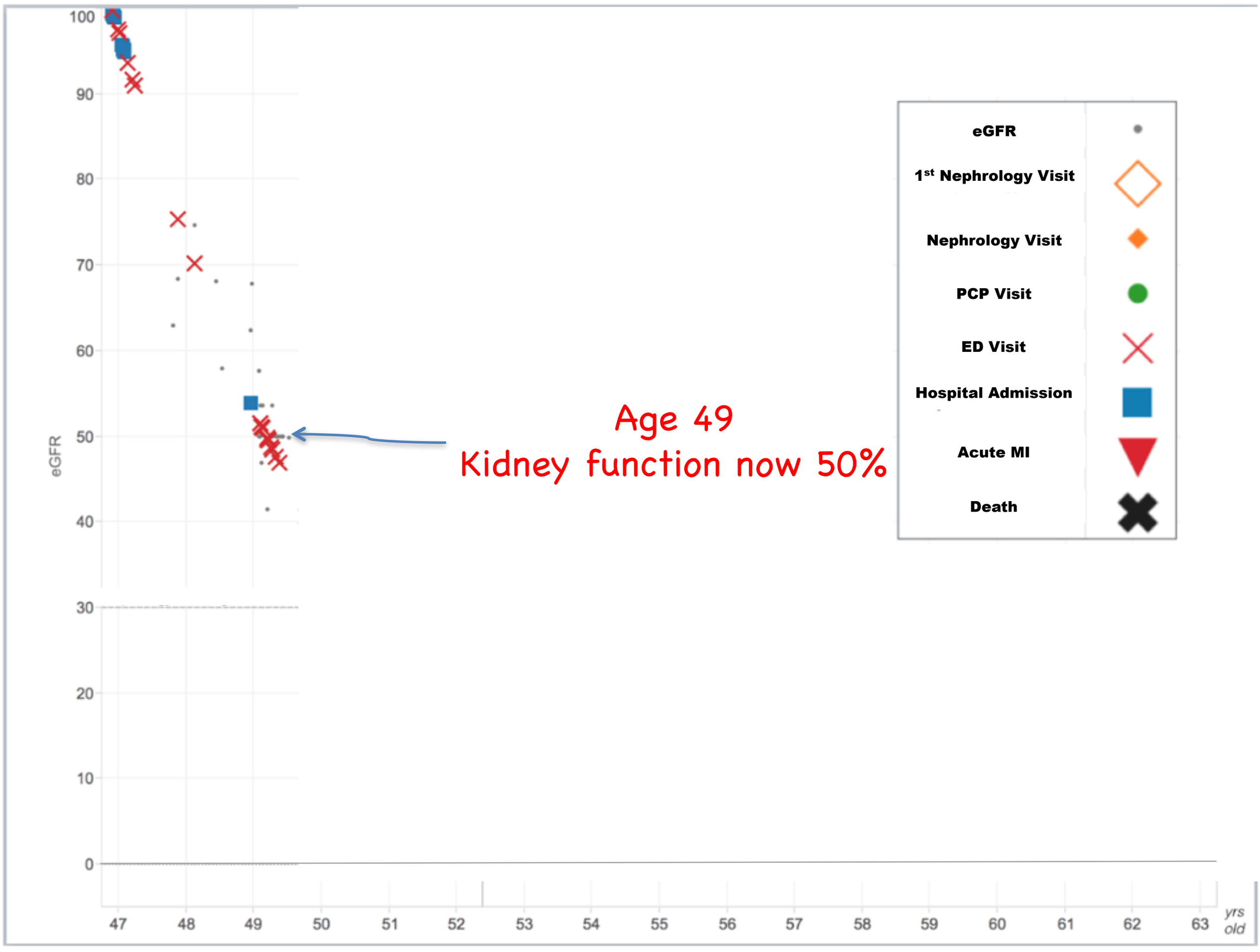
Age 47

Untreated diabetes & high blood pressure.

Normal kidney function, but with evidence of kidney damage.

No regular medical care.

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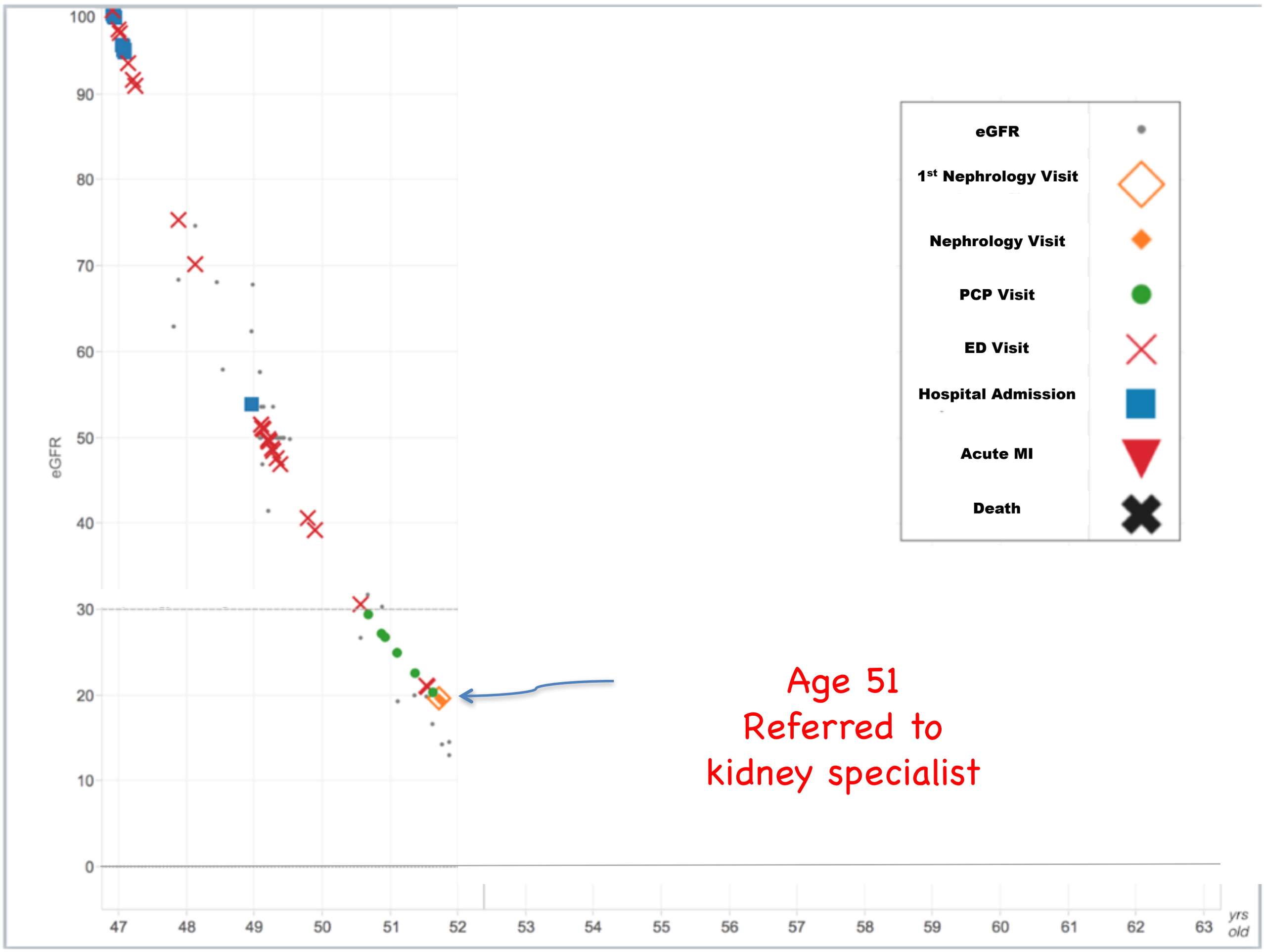
yrs old
Age 49
Kidney function now 50%
eGFR
1st Nephrology Visit
Nephrology Visit
PCP Visit
ED Visit
Hospital Admission
Acute MI
Death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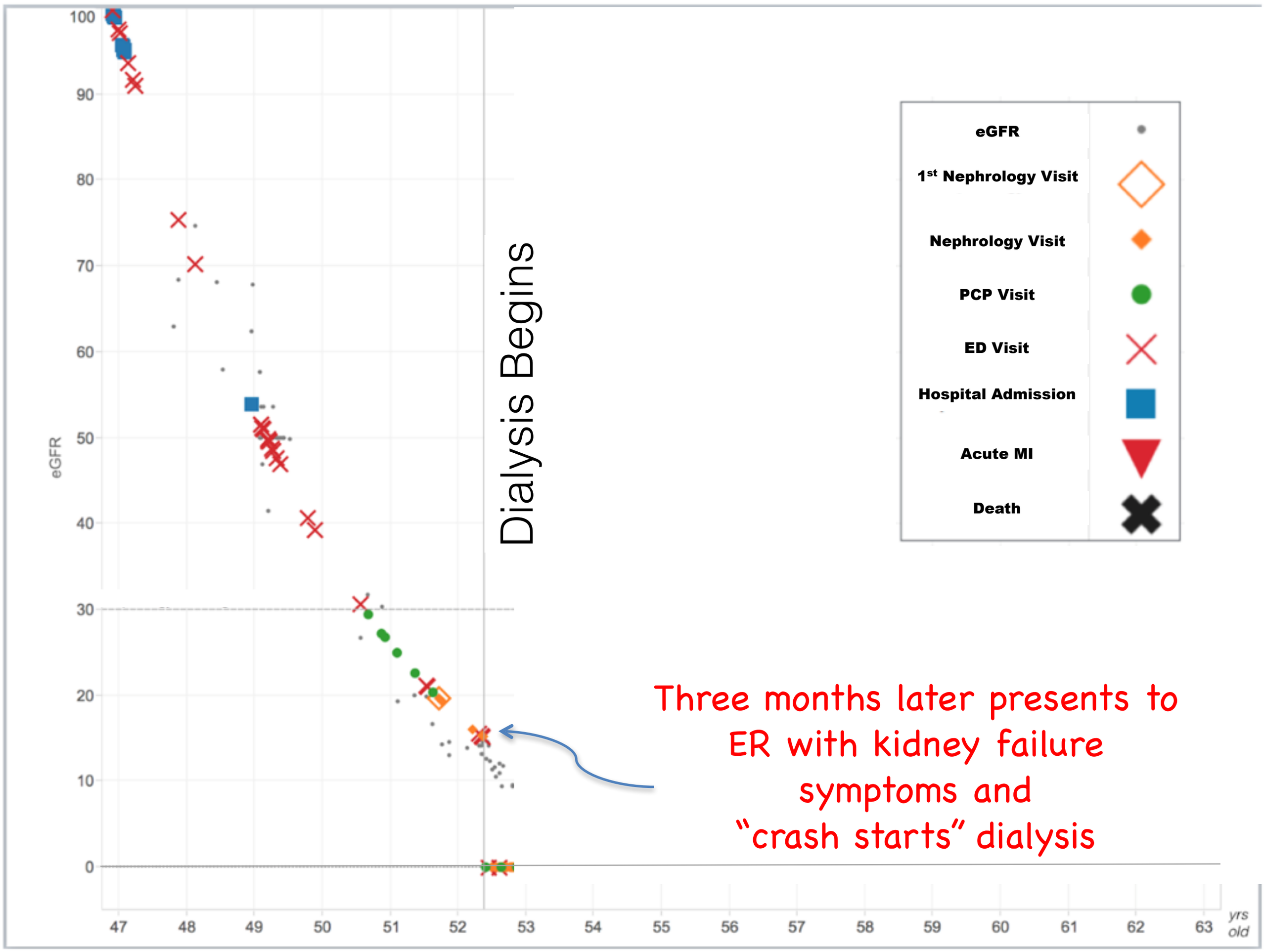
62
63
yrs old
eGFR
1st Nephrology Visit
Nephrology Visit
PCP Visit
ED Visit
Hospital Admission
Acute MI
Death
Age 51
Referred to
kidney specialist


eGFR
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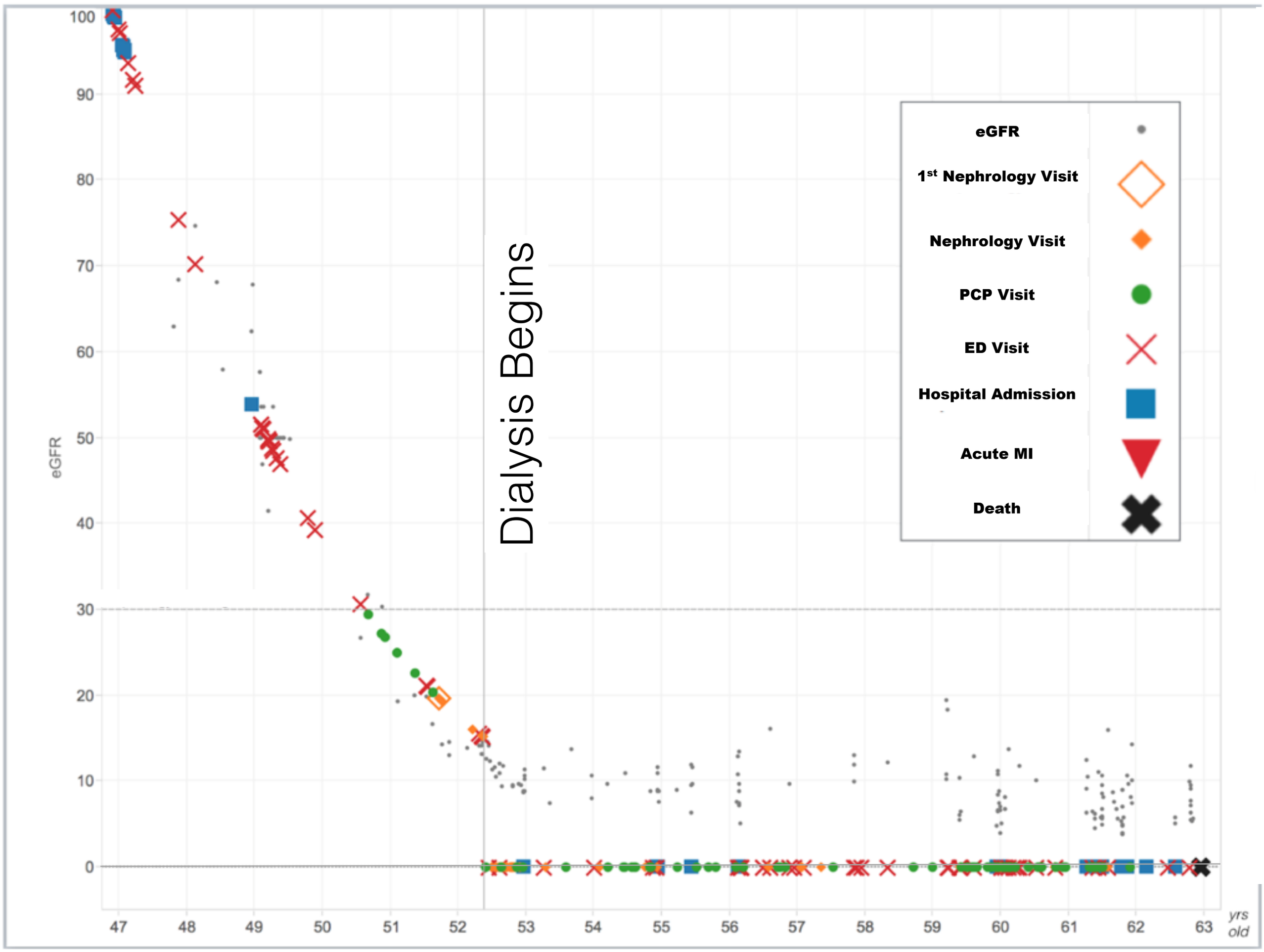
yrs old
Dialysis Begins
eGFR
1st Nephrology Visit
Nephrology Visit
PCP Visit
ED Visit
Hospital Admission
Acute MI
Death
Three months later presents to ER with kidney failure symptoms and "crash starts" dialysis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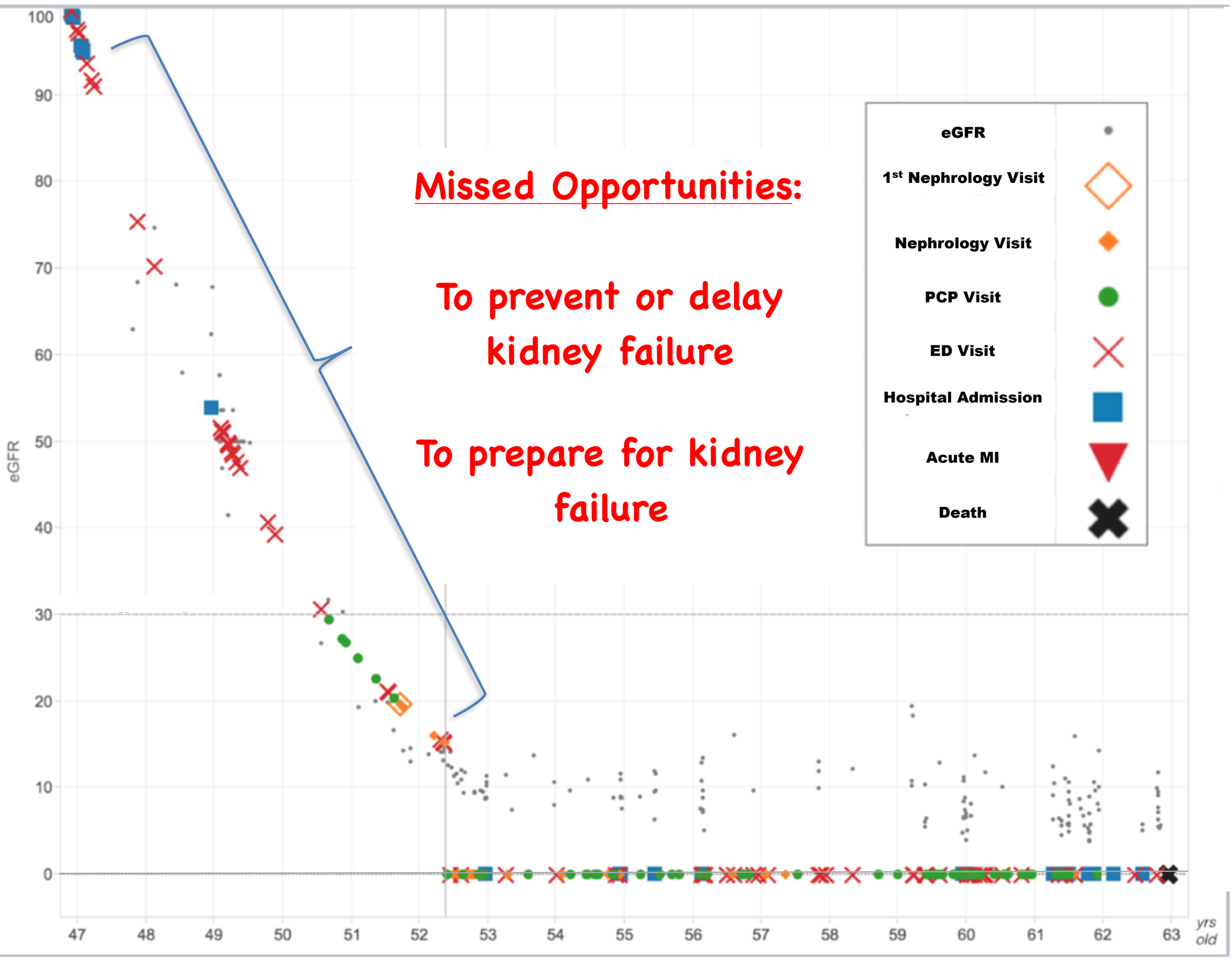
yrs old
Dialysis Begins
eGFR
1st Nephrology Visit
Nephrology Visit
PCP Visit
ED Visit
Hospital Admission
Acute MI
Death

Missed Opportunities:

To prevent or delay kidney failure

To prepare for kidney failure



42%

starting dialysis have no prior nephrology care

2013 USRDS ANNUAL DATA REPORT *volume one*

Atlas of Chronic Kidney Disease in The United States

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DIVISION OF KIDNEY, UROLOGIC, & HEMATOLOGIC DISEASES

<10% with moderate CKD

<50% with severe CKD

even aware of illness!

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Renal Function Trajectory Is More Important than Chronic Kidney Disease Stage for Managing Patients with Chronic Kidney Disease

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- Can we use other clinical data (labs and/or vitals) to improve prediction of disease progression?
- Goal: flexible model for multivariate longitudinal data

Model for a single trajectory

Conditional likelihood factorizes across P labs: $p(\vec{y_i}|z_i, b_i, c_i; x_i) = \prod_{p=1}^{P} p(\vec{y_{ip}}|z_i, b_i, c_i; x_i)$

$$y_{ip}(t) \sim N(\mu_{ip}(t), \sigma_p^2)$$

$$\mu_{ip}(t) \sim \mathcal{GP}(\Lambda^{(p)} x_i + \Phi_z(t)^\top \beta_{z_{ip}}^{(p)} + \Phi_l(t)^\top b_{ip}, K_p)$$

Population effect

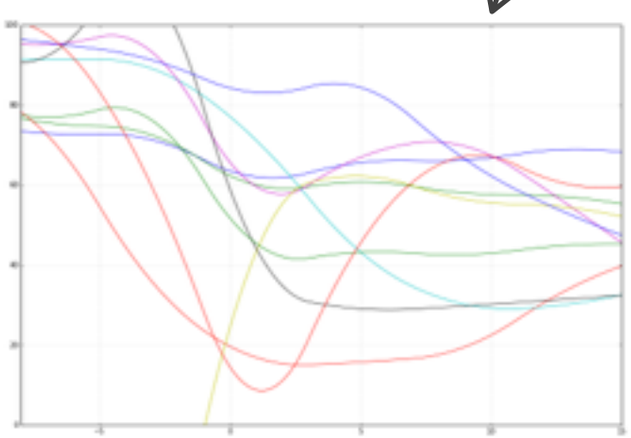
Latent subpopulation curve

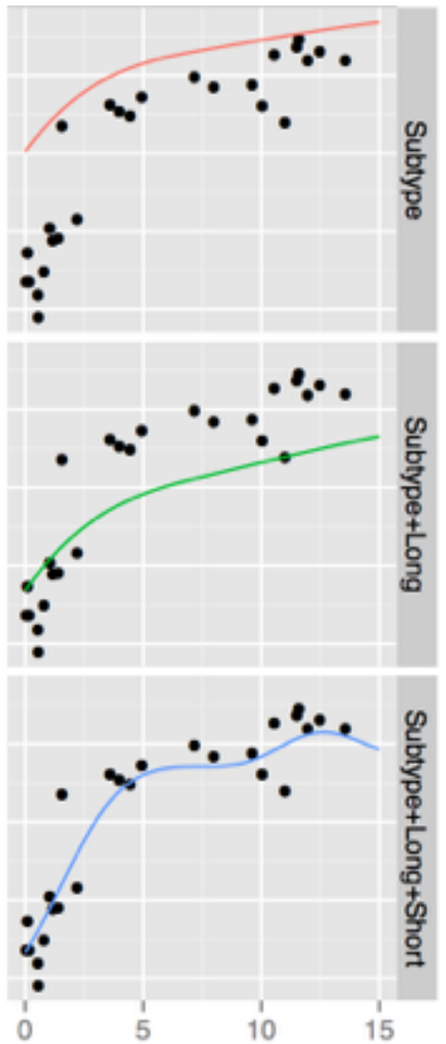
Individual long-term deviations

Individual transient deviations (GP)

$K_p(t, t') = a_p^2 \exp\{-l_p^{-1}|t - t'|\}$

Curves per subtype





Inducing Dependence

Dependence between mean functions
for the P labs in 2 ways:

$$\mu_{ip}(t) \sim \mathcal{GP}(\Lambda^{(p)} x_i + \Phi_z(t)^\top \beta^{(p)}_{z_{ip}} + \Phi_l(t)^\top b_{ip}, K_p)$$

Long-term deviations are correlated
via multivariate normal:

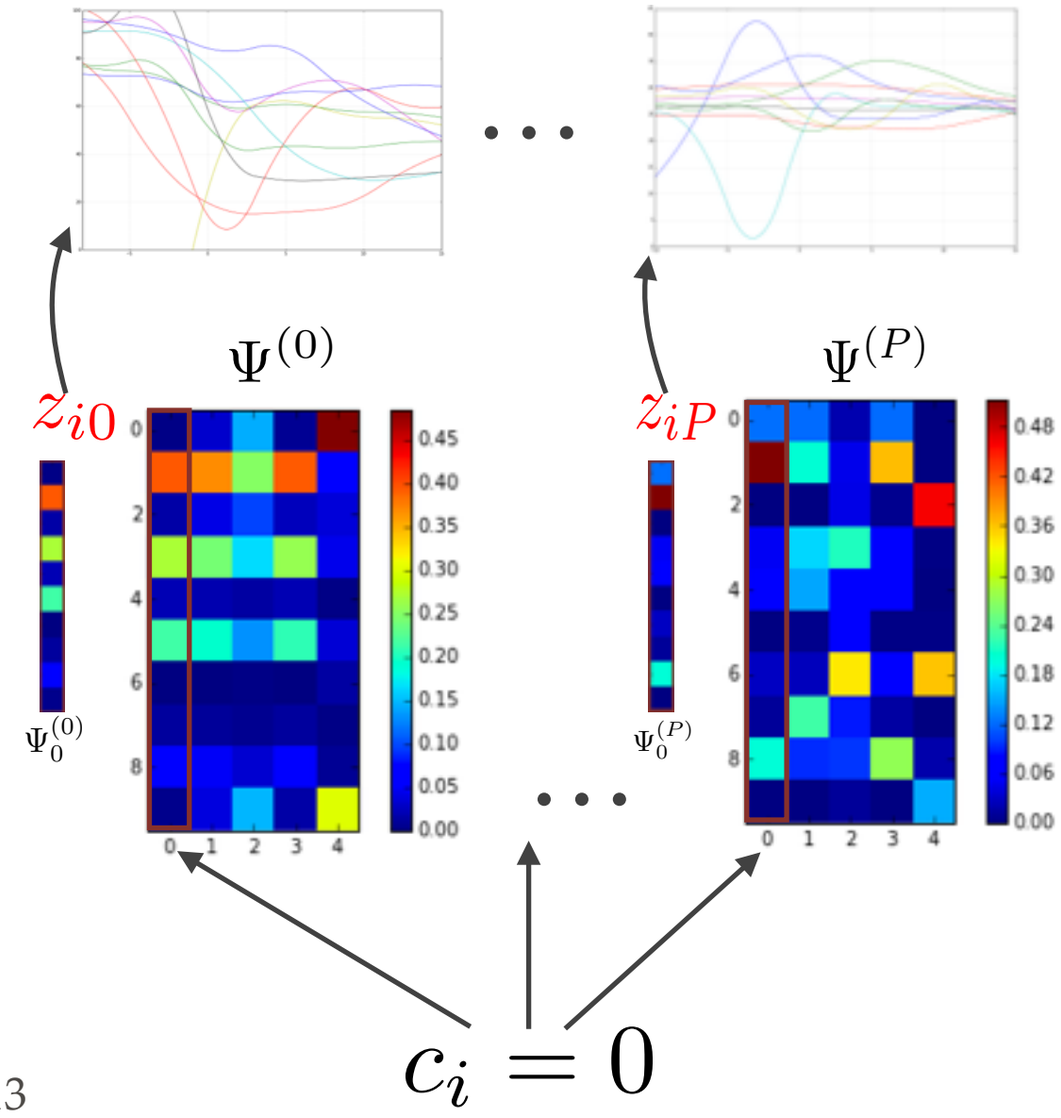
$$\vec{b_i} = (b_{i1}, \ldots, b_{iP})^\top \sim N(0, \Sigma_b)$$

Subtypes/clusters per lab are correlated
via mixture of multinomials:

$$z_{ip}|c_i = g \sim \text{Multinomial}(\Psi^{(p)}_g)$$

$$c_i \sim \text{Multinomial}(\pi_i)$$

$$\pi_{ig} = \frac{e^{w_g^\top x_i}}{\sum_{g'=1}^{G} e^{w_{g'}^\top x_i}}$$



Experimental Setup

- 6 variables of interest: eGFR, 5 other labs relevant to CKD
- Cohort of 44,000 patients at Duke with at least moderate stage CKD (Stage 3+) and 5+ measurements for eGFR
- For each test patient: use data before *t* to predict future labs
- Evaluation for each lab:
  - average MAE across test patients, in future time windows
- Baseline: [Schulam & Saria, 2015] trained independently

Quantitative Results

Table 1: Mean Absolute Errors across all labs from 10 fold cross validation. Bold indicates p-value from one-sided, paired t-test comparing methods was $< .05$. *,**,*** indicate $p < .01, < .001, < .0001$, respectively.

Predictions with data up to...		$t = 1$				$t = 2$			$t = 4$	
Lab	Model	(1, 2]	(2, 4]	(4, 8]	(8, 19]	(2, 4]	(4, 8]	(8, 19]	(4, 8]	(8, 19]
eGFR	Schulam	**8.86***	**10.43***	**12.05**	**13.69**	**8.84*****	**11.08****	**13.23***	**9.39*****	**12.29***
	Proposed	9.12	10.67	12.28	14.21	9.26	11.73	13.99	10.12	13.07
Serum Alb.	Schulam	0.59	0.79	1.09	1.53	0.60	0.88	1.28	0.63	0.96
	Proposed	**0.34*****	**0.39*****	**0.47*****	**0.63*****	**0.35*****	**0.45*****	**0.63*****	**0.40*****	**0.58*****
Serum Bicarb.	Schulam	1.92	2.06	2.13	2.31	1.93	2.06	2.21	1.89	**2.14**
	Proposed	1.87	1.97	2.04	2.31	1.89	1.99	2.31	1.87	2.24
Serum Calc.	Schulam	0.74	1.02	1.62	2.89	0.72	1.26	2.27	0.85	1.53
	Proposed	**0.37*****	**0.44*****	**0.58*****	**0.80*****	**0.39*****	**0.54*****	**0.80*****	**0.46*****	**0.73*****
Serum Phos.	Schulam	1.02	1.35	1.46	1.44	1.17	1.36	1.34	1.13	1.15
	Proposed	**0.57*****	**0.68*****	**0.88*****	**1.23**	**0.65*****	**0.88*****	1.25	**0.82*****	1.23
Urine ACR	Schulam	1.17	1.30	1.44	1.64	1.14	1.30	1.53	1.11	1.41
	Proposed	**0.92*****	**1.02*****	**1.17*****	**1.44**	**0.96*****	**1.13***	1.45	**1.02**	1.42

Conclusion

- Novel model for multivariate longitudinal clinical data
- Current clinical practice: “clinical gestalt”, no evidence-based method to inform decision-making process
- Future work:
  - More flexible dependence between labs
  - Jointly predict with events of interest (hospital admissions / high utilization, cardiac events, etc)
  - More clinically actionable metrics to evaluate models

Thank you!

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  - C. Blake Cameron, M.D.
  - Katherine Heller, Ph.D.

Presenting tomorrow at clinical talks!

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