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## **Predictors of Progression to Kidney Failure in Patients with Focal Segmental Glomerulosclerosis**

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- KD, CJ, LK: Providence Health Washington
- MB, KMT, LP, KW: Travere Therapeutics Inc
- **DA:** Genesis Research LLC
- KN, SN: University of California, Los Angeles, David Geffen School of Medicine

- FSGS is a glomerular disease phenotype that often progresses to kidney failure
- However, to risk stratify patients treated in usual clinical practice, predictors of progression are not well-delineated
- The study aim was to use real-world data to identify patients with FSGS and determine predictors of substantial eGFR decline, which is associated with a high risk of reaching kidney failure

## **Study Time Periods**

- Entry: Date of FSGS identification between 2016-2020
- Baseline period: Date of FSGS identification through the next 180 days
- Follow-up period: After baseline period until study outcome or censorship for last eGFR measure calculated by CKD-EPI 2021

## **Inclusion Criteria**

- Data source is the CURE-CKD Registry based on electronic health records from Providence and UCLA Health<sup>1,2</sup>
- Adults, ≥18 years
- FSGS identified by ICD-10 diagnosis codes

## **Exclusion Criteria**

- Kidney failure before or during baseline period:
  - Baseline eGFR <15 mL/min/1.73 m<sup>2</sup>
  - Diagnosis code for kidney failure (ICD-10)
  - Procedure (ICD-9/10) or diagnosis (ICD-10) codes for dialysis
  - Procedure code for kidney transplant (ICD-9/10)
- No eGFR measurements during baseline or follow-up

1. Tuttle KR, et al. JAMA Netw Open. 2019;2(12):e1918169; 2.Norris KC, et al. BMC Nephrol. 2019;20(1):416.

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### Outcomes

- Primary: Composite of ≥40% eGFR decline or kidney failure
- Secondary:
  - ≥40% eGFR decline: Indicator of high risk for kidney failure
  - Kidney failure:
    - eGFR <15 mL/min/1.73 m<sup>2</sup>
    - Diagnosis code for kidney failure (ICD-10)
    - Procedure (ICD-9/10) or diagnosis code (ICD-10) for dialysis
    - Procedure code for kidney transplant (ICD-9/10)

## **Statistical Analyses**

- Kaplan-Meier survival estimates of time to first event for primary composite outcome and secondary outcomes
- Cox Proportional Hazard modeling to identify baseline predictors of primary composite outcome (N=325)
- Sensitivity: Macroalbuminuria (UACR >300 mg/g)/overt proteinuria (UPCR >0.5 g/g) status was added to the model for the subset of patients with available baseline measures (N=195)

## Table 1. Characteristics of Patients with FSGS, 2016-2020 (N=325)

Demographics					
Sex, n (%)					
Men	175 (53.8)				
Women	150 (46.2)				
Race and ethnicity, n (%)					
American Indian or Alaska Native	5 (1.5)				
Asian	49 (15.1)				
Black	33 (10.2)				
Hispanic or Latino(a)	12 (3.7)				
Native Hawaiian or Pacific Islander	4 (1.2)				
White	168 (51.7)				
Other <sup>a</sup>	46 (14.2)				
Missing	8 (2.5)				
Age, y, mean, SD	51, 17				
Primary health insurance, n (%)					
Medicare	81 (24.9)				
Medicaid	26 (8.0)				
Commercial	177 (54.5)				
Uninsured	5 (1.5)				
ai Milasingtients that did not identify with main census categories.	36 (11.1)				

ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; FSGS, focal segmental glomerulosclerosis; HbA1c, hemoglobin A1c; UACR, urine albumin-creatinine ratio; UPCR, urine protein creatinine ratio.

Baseline Medications, n (%)					
ACE inhibitor/ARB	216 (66.5)				
Calcineurin inhibitor	52 (16.0)				
Glucocorticoid	115 (35.4)				
Baseline Clinical Characteristics					
Hypertension, n (%)	276 (84.9)				
Diabetes, n (%)	112 (34.5)				
eGFR, mL/min/1.73 m <sup>2</sup>					
n (%)	325 (100.0)				
mean, SD	58.4, 29.1				
CKD Stage 1-2: ≥60, n (%)	139 (42.8)				
CKD Stage 3a: 45-59, n (%)	57 (17.5)				
CKD Stage 3b: 30-44, n (%	61 (18.8)				
CKD Stage 4: 15-29, n (%)	68 (20.9)				
HbA1c, %					
n (diabetes) (%)	68 (60.7)				
mean, SD	7.0, 1.2				
UACR, mg/g					
n (%)	109 (33.5)				
median (IQR)	939 (156-2134)				
UPCR, g/g					
n (%)	106 (32.6)				

#### 6

# Figure 1. Kaplan-Meier Survival Analysis for (a) Composite ≥40% eGFR Decline or Kidney Failure (b) ≥40% eGFR Decline (c) Kidney Failure



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## **Outcomes Frequency**

- Primary composite outcome  $\geq$ 40% eGFR decline or kidney failure
  - 88/325 (27.1%) reached a first event at a median of 1.2 years
- ≥40% eGFR Decline
  - 75/325 (23.1%) total events
- Kidney Failure
  - 61/325 (18.8%) total events
- In the presence of unmeasured competing risks (eg, death) predictors are limited to the cause-specific hazard function



# Figure 2. Predictors of Primary Composite Outcome of ≥40% eGFR Decline or Kidney Failure in Patients with FSGS (N=325)

Predictors			Hazard Ratio (HR), 95% CI	P value
Lov	ver risk of kidney outcome	Higher risk of kidney out	come	
eGFR (per 10 mL/min/1.73 m²)	⊷		0.67 [0.59, 0.75]	<0.001
Age (per 10 years)	H•	ô.	0.84 [0.72, 0.98]	0.03
Outpatient Visits (average per quarter)		<b>1</b> 69	1.04 [1.01, 1.06]	0.003
Calcineurin Inhibitor (yes/no)		• • •	1.87 [1.00, 3.50]	0.049
Diabetes (yes/no)		• •	1.10 [0.65, 1.88]	0.72
Hypertension (yes/no)	<b></b>	• •	1.34 [0.67, 2.68]	0.40
Glucocorticoid (yes/no)	, <u> </u>	• 1	1.14 [0.67, 1.94]	0.63
ACE inhibitor/ARB (yes/no)			0.86 [0.53, 1.41]	0.56
Race (non-White vs. White)	-	•	1.40 [0.89, 2.21]	0.15
Sex (female vs male)	<b>—</b>	<u></u>	0.96 [0.62, 1.51]	0.87
Insurance (noncommercial vs commercial)	·	i	1.20 [0.75, 1.93]	0.45
Providence vs UCLA Health	•	• •	1.12 [0.68, 1.86]	0.65
Hospitalization (yes/no)			0.88 [0.46, 1.69]	0.70
Concordance: 0.77	1.25 1 HR (9	.0 2.0 3.0 4 95% CI)	0	

ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate, FSGS, focal segmental glomerulosclerosis.



Risks of progression to kidney failure are high in real world patients with FSGS treated in usual clinical practice.

Earlier detection, with particular attention to younger patients, is needed to detect FSGS when therapeutic strategies may be most beneficial.

## Predictors of Progression to Kidney Failure in Patients with Focal Segmental Glomerulosclerosis

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#### **Background and Study Aim**

Focal segmental glomerulosclerosis (FSGS) is a glomerular disease Table 1. Characteristics of Patients with FSGS, 2016phenotype that often progresses to kidney failure. However, to risk stratify patients treated in usual clinical practice, predictors of progression are not well-delineated.

The study aim was to use real-world data to identify patients with FSGS and determine predictors of substantial estimated glomerular filtration rate (eGFR) decline, which is associated with a high risk of reaching kidney failure, or kidney failure.

#### Methods

- **Study Time Periods**
- Entry: Date of FSGS identification between 2016-2020
- Baseline period: Date of FSGS identification through the next 180 davs
- Follow-up period: After baseline period until study outcome or censorship for last eGFR measure calculated by CKD-EPI 2021 Inclusion Criteria
- Data source is the CURE-CKD Registry based on electronic health records from Providence and UCLA Health<sup>1,2</sup>
- $\circ$  Adults. ≥18 vears
- FSGS identified by ICD-10 diagnosis codes

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- Kidney failure before or during baseline period:
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- Procedure code for kidney transplant (ICD-9/10)
- No eGFR measurements during baseline or follow-up

#### Outcomes

- $\circ$  Primary: Composite of ≥40% eGFR decline or kidney failure
- Secondarv:
- $\geq$  240% eGFR decline: Indicator of high risk for kidney failure > Kidnev failure:
  - eGFR <15 mL/min/1.73 m<sup>2</sup>
  - Diagnosis code for kidney failure (ICD-10)
  - Procedure (ICD-9/10) or diagnosis code (ICD-10) for dialvsis
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#### Statistical Analyses

- Kaplan-Meier survival estimates of time to first event for primary composite outcome and secondary outcomes
- Cox Proportional Hazard modeling to identify baseline predictors of primary composite outcome (N=325)
- Sensitivity: Macroalbuminuria (UACR > 300 mg/g)/overt proteinuria (UPCR > 0.5 q/q) status was added to the model for the subset of patients with available baseline measures (N=195)

2020 (N=325)		≥40% eGFF	₹ decline or k	<i (<="" th=""></i>
Demographics		decline (c)	kidney failu	re
Sex, n (%)		a Com	posite > 40% /	of
Men	175 (53.8)	100	poone a vera v	ੰ
Women	150 (46.2)	8	-	
Race and ethnicity, n (%)		₹ 75		-
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Other <sup>a</sup>	46 (14.2)	0	2010	÷,
Missing	8 (2.5)		11111111111111	1
Age, y, mean, SD	51, 17	Numbe	r at risk	
Primary health insurance, n (%)		- 325	172	
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Commercial	177 (54.5)	_ 100   -		
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Baseline Clinical Characte	ristics	-0 <sup>-0</sup>		
Hypertension, n (%)	276 (84.9)	Ó	1	
Diabetes, n (%)	112 (34.5)			Y
eGFR, mL/min/1.73 m <sup>2</sup>		Numbe	r at risk	
n (%)	325 (100.0)	- 325	185	
mean SD	58 4 29 1		100	
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UPCR. g/g		ó	1	-
ainclude's patients that did not identify with mair	census categories	~		Y
median (IOR)	1.8 (1.0-3.5)	Numbe	a at risk	
			170	
		320	11.9	



#### posite ≥ 40% eGFR Decline or Kidney Failure

Years After Baseline

2

2

101

Years After Baseline

Years After Baseline

3

40

**Outcomes Frequency** ○ Primary composite outcome ≥40% eGFR decline or kidney failure > 88/325 (27.1%) reached a first event at a median of 1.2 years

- CURE CKD -

Providence

- ≥40% eGFR Decline
  - > 75/325 (23.1%) total events
- Kidney Failure
  - > 61/325 (18.8%) total events
- In the presence of unmeasured competing risks (e.g., death) predictors are limited to the cause-specific hazard function

#### Figure 2. Predictors of Primary Composite Outcome of $\geq$ 40% eGFR Decline or Kidney Failure in Patients with FSGS (N=325)

Predictors	Hazard Ratio (HR), 95% CI	P value
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Diabetes (yesho)	1.10(0.65, 1.80)	0.72
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Insurance (hotcommercial vs commercial)	1.20 (0.7%, 1.80)	0.45
Providence vs UCLA Health	1.12 (0.68, 1.94)	0.65
Noxpitelation (yesha)		0.70
Concordiance: 8.77 6.25 HR (HP)s Cl	20 20 42	

#### Sensitivity Analysis

- Macroalbuminuria/overt proteinuria (HR: 4.06, 95% CI: 1.34-12.34, p=0.01) was an independent predictor for the composite outcome
- Overall model stability persisted for other predictors

#### Summarv

- $\circ$  Real world patients with FSGS have high rates of ≥40% eGFR decline or kidney failure within a relatively short timeframe
- Younger patients and those with lower kidney function were at greater risk
- More frequent outpatient visits and calcineurin inhibitor use may reflect bias by indication in higher risk patients

#### Conclusions

Risks of progression to kidney failure are high in real world patients with FSGS treated in usual clinical practice.

Earlier detection, with particular attention to younger patients, is needed to detect FSGS when therapeutic strategies may be most beneficial.

> References 1. Tuttle KR, et al. JAMA Netw Open. 2019;2(12):e1918169 2. Norris KC. et al. BMC Nephrol. 2019:20(1):416