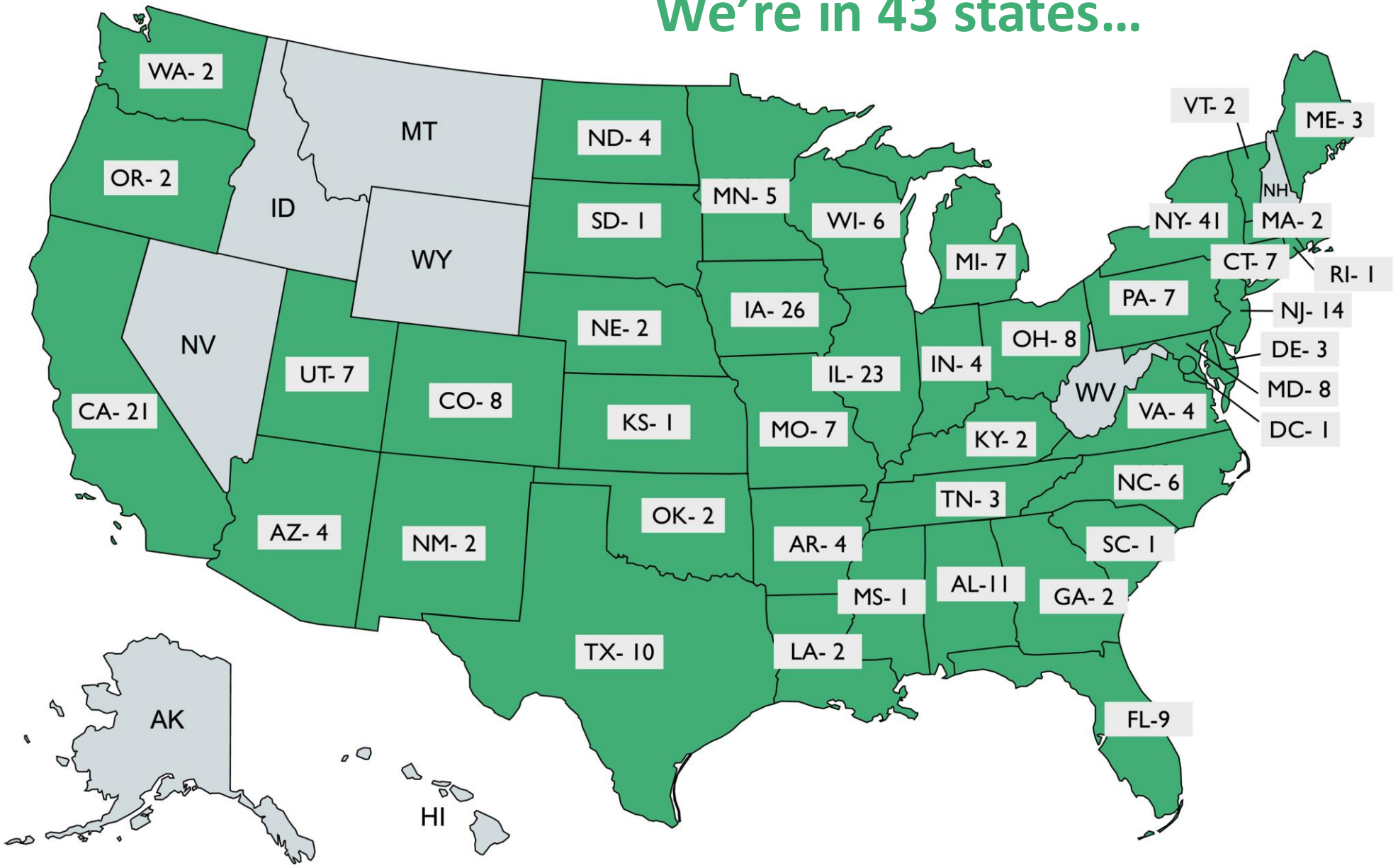
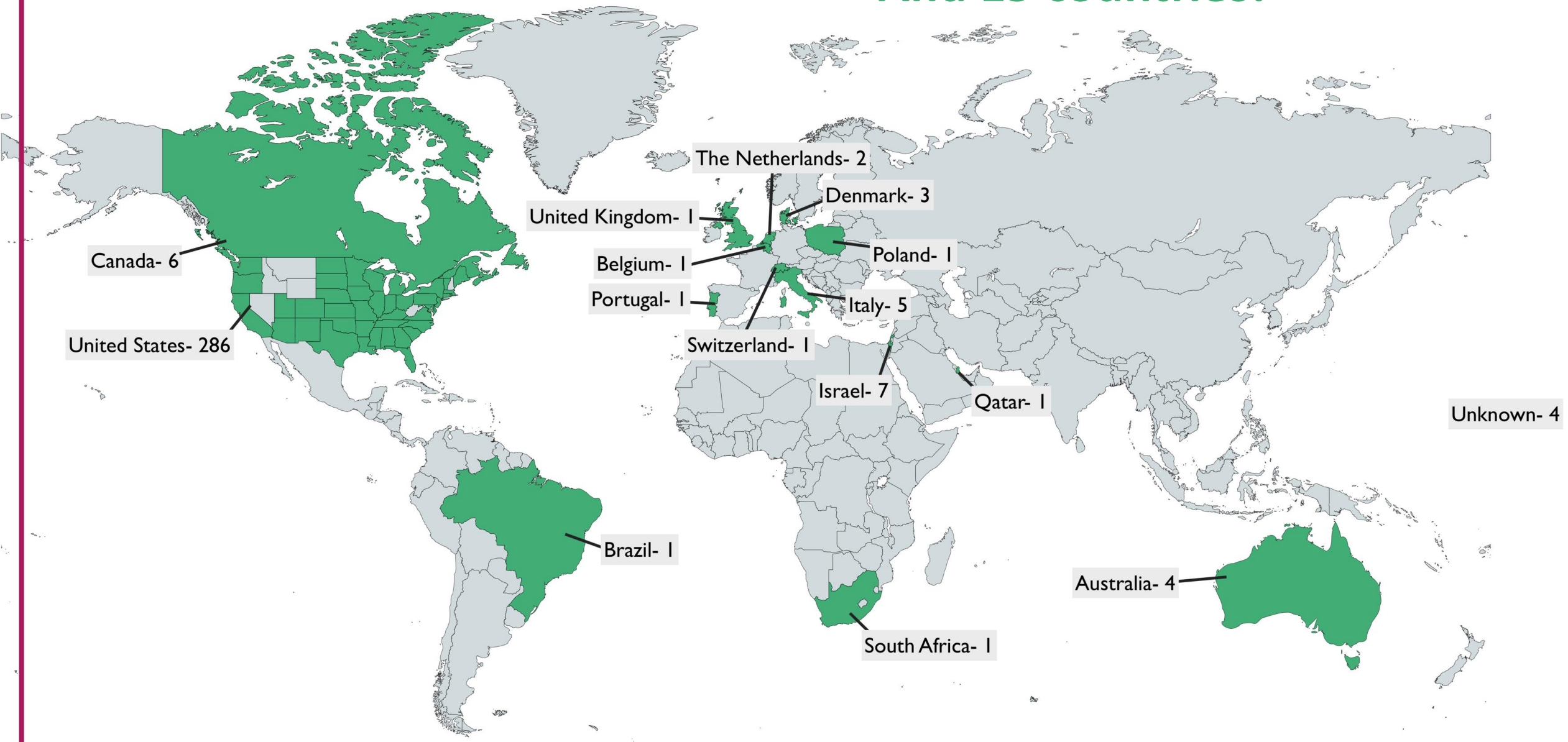

Welcome to Iowa!

Natural History Studies gather information on how a disease affects a person over a lifetime.

We're in 43 states…



And 15 countries!



Education

This pamphlet was made possible through the generous donations of rare disease family members.

Clinical Biomarker Trend in C3 Glomerulopathy

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Background

There is a paucity of data defining the natural history of the clinical and complement biomarker characteristics of C3 Glomerulopathy (C3G) patients. Whether there are disease related trends or relationships between the markers of disease is unknown. In a series of C3G patients, we sought to describe the trend of the three most commonly available markers of disease over a one year time period: complement C3, urine protein-to-creatinine ratio (UPCR), and eGFR. We hypothesized that lower C3 levels, as a reflection of ongoing complement activity would be associated with progressive renal disease – represented by changes in UPCR and /or eGFR.

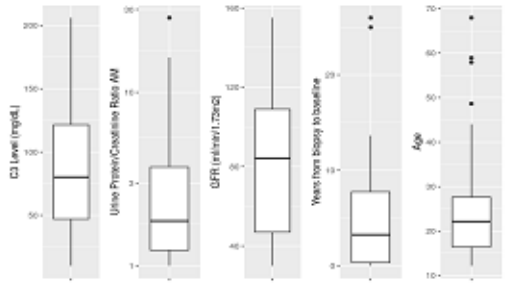
Methods

All patients met the consensus, renal biopsy definition of C3G[1]. Thirty-two subjects with an age > 12 years and GFR > 30ml/min were included. Data were analyzed in 1-year spans of data. Analyzed data included all spans for which paired C3, UPCR and GFR data were available - demarcating the beginning and end of a given span. A total of 61, one year spans were identified. Mean and median statistics across all spans were reported as percent change per year and standard regression analyses were used to define the relationship between variables

Results

Fig 1. Baseline Clinical Characteristics

Age at Diagnostic Biopsy, mean (SD)	20.08 (9.58)
Biopsy Gap*, mean (SD)	4.90 (5.57)
Sex = Male %	53%
Race = White, %	82%
C3GN	25
DDD	6

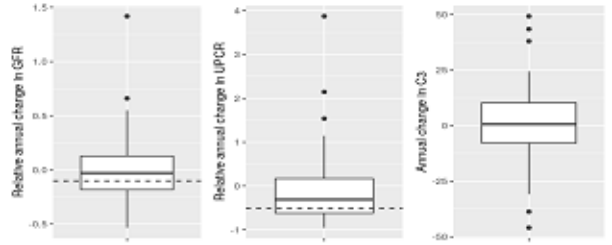


Baseline C3, mg/dl (SD)	84 (51)
Baseline UPCR, mg/mg (SD)	3.3 (4.1)
Baseline eGFR, ml/min/m^2	83 (36)

The majority of patients were white, and below the age of 30 at the time of the diagnostic biopsy. M~F. C3 Glomerulonephritis was the most common diagnosis.

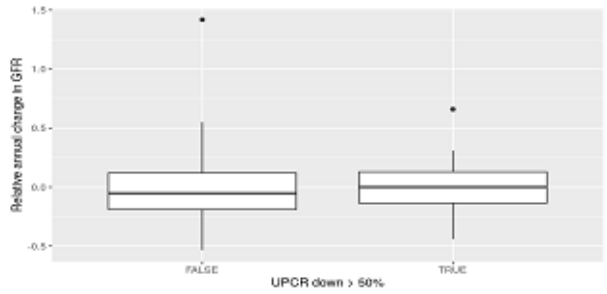
Results

Fig 2. Annual change in clinical parameters



	Mean	Median
GFR slope	-1.7%	-2.9%
UPCR slope	-12.5%	-31.0
C3 slope	1.5mg/dl	0.8mg/dl

Fig 3. Annual change in GFR stratified by UPCR reduction



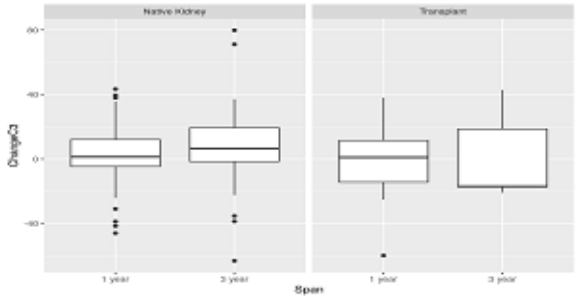
	Mean	Median
GFR slope (UPCR down > 50%), % change/yr	0.2	0.0
GFR slope (otherwise), % change/yr	-2.8	-5.2

P = 0.45

Change in C3:

1. In the 37 spans where a patient had a low C3 at baseline, only 1 (2.7%) achieved a stable GFR and a UPCR reduction of > 50%.
2. The tendency of C3 to change over a one-year period:
   a. In 53.2% of 1-year spans C3 remained within 10 of its baseline level.
   b. In 88.9% of spans C3 remained within 25 of its baseline C3 level.

Fig 4. Variability of C3 over time



	eGFR decrease > 10% No	eGFR decrease > 10% Yes	Percent
Baseline C3 > 90			
UPCR decrease < 50% - No	10	6	37.5%
UPCR decrease < 50% - Yes	6	2	25.0%
Baseline C3 < 90			
UPCR decrease < 50% - No	11	11	50%
UPCR decrease < 50% - Yes	10	5	33.3%

Other than a modest tendency for patients on ACE inhibitors to experience a decline in proteinuria (p = 0.14), no association existed between concomitant medication use and clinical outcomes. (Data not shown)

Conclusions

- An annual change in urine protein (mean decline of 12.5%) was noted under current cares.
- Minimal change in eGFR was noted in a 1 year span.
- C3 appeared to be remarkably stable over a 1-year time span.
- When using a C3 cut off of 90mg/dl (normal), there appear to be no association with baseline C3 level and change in UPCR or GFR over a 1 year time span.
- The two major weaknesses of the current study are the small number of patients and an accounting of the effect of time since biopsy.

Future Directions

- The cohort has now been expanded to 85 patients. Future studies include evaluating the longitudinal history of these same clinical biomarkers from the time of diagnostic kidney biopsy until the time of last follow up (without separation into yearly spans of disease).
- Reassessment will re-stratify based on quartile categories of baseline C3 level.
- Future studies will expand the number of clinical and research biomarkers of disease to be characterized.

References

1. *Kidney Int.* 2013 Dec;84(6):1079-89
2. *Nat Rev Nephrol.* 15(3), 129-143 (2019)
3. *Kidney Int.* 89, 278-288 (2016)
4. *Kidney Int.* 82, 1084–1092 (2012).
5. *Clin. J. Am. Soc. Nephrol.* 7, 265-274 (2012).

Research is funded in part by the NIH (CMN and RJHS) and an unrestricted grant from Novartis.

- **C3 tends to stay within ± 25 mg/dL of baseline value**
- Minimal change in eGFR over 1 year span
- **No association of baseline C3 level and change in UPCR/GFR**
- **Individuals with low C3 at baseline rarely achieve stable GFR or UPC reduction**
- Modest association between ACE inhibitor use (Lisinopril/Enalapril) and decline in proteinuria

Pregnancy Outcomes in C3 Glomerulopathy

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The University of Iowa

Background

C3 Glomerulopathy (C3G) is a glomerular disease characterized by underlying dysregulation of the alternative complement pathway. Most patients approach ESKD within ten years of diagnosis. Recurrence in renal transplants is high. Little is known of the role of pregnancy in the natural history of C3G or whether a coincident diagnosis affects comorbidities or maternal-fetal outcomes.

Methods

Female subjects in the University of Iowa's C3G Natural History Study who met consensus biopsy criteria (n=76) and had at least one pregnancy (n=17) were included in the cohort. Clinical and lab data, including genetic and/or acquired drivers of disease studies were assessed. Standard peri-pregnancy outcomes were considered.

Results

Figure 1- Peri-Pregnancy Outcomes in C3G Mothers

	n=	Sample %	Healthy %	p value	Glomerular Disease %	p value
# of Pregnancies					44	
# of Live Births					34	
Average Age at Conception					26	
Average # of Children/Mother					2	
# of Preeclamptic Pregnancies	11	32.40%	4%	<.0001	approx. 9% (IgA nephropathy), 16-58% (unspecified GN)	<.0001 for IgA, .29 for unsp. GN (avg of 37%)
# of Premature Infants	7	20.60%	9.80%	0.0171	14.2% (IgA)	0.1425 (IgA)
# of Low Birth Weight Infants	5	14.70%	8%	0.075	13.1% (IgA)	0.3911 (IgA)
# of Eclamptic Pregnancies	0	0%	0.30%	0.625	N/A	N/A
# of C-Sections	6	17.60%	17%	0.46	49.1% (IgA)	0.0001 (IgA)
# of Miscarriages	8	18.20%	15%	0.2761	0-30% (IgA nephropathy), 5-27% (unspecified GN),	.35 for IgA (avg of 15%), .28 for unsp. GN (avg of 16%)
Biopsy Performed	Before pregnancy n= 4		Between pregnancies n= 2		After pregnancy n= 11	
C3G Symptoms	Before pregnancy n= 4		Between pregnancies n= 2	During pregnancy n= 6	After pregnancy n= 5	

A one-proportion z-test was utilized to calculate p values from the cohort data and literature values for healthy populations and for other glomerular diseases, with a significance level set at .05. Low birth weight cutoff was 5.5 lbs, while premature birth cutoff was 37 weeks.

Results

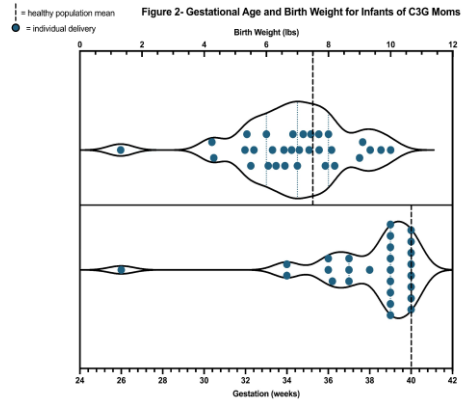

Figure 2- Gestational Age and Birth Weight for Infants of C3G Moms

Average gestational age was 37w 5d, with a range from 26w 2d-40w 3d. Average birth weight was 6.9 lbs, ranging from 1.3-10 lbs.

44 pregnancies and 34 deliveries were identified. Non-live birth pregnancy outcomes included eight miscarriages, one ectopic pregnancy and one elective abortion. The presumed driver of disease was known for eight patients; gene variants of unknown significance (n=3), nephritic factors (n=4), and a monoclonal protein (n=1). Six patients presented first C3G symptoms during pregnancy. Preeclampsia developed in 11. Six infants were premature. Five were born with low birthweight. One infant suffered a stroke. One infant presented with AKI. [Maternal nephritic factor was identified in neonatal sera.]

Conclusions

We provide a summary of maternal-fetal outcomes in C3G mothers. Our data support an increased risk of preeclampsia and prematurity in C3G mothers as compared to healthy mothers. There was no excess risk of miscarriage, cesarean section, ectopic pregnancy, or low birth weight. This data indicates a relatively higher risk of preeclampsia and lower risk of cesarean section compared to women with IgA Nephropathy. A similar risk of miscarriage, prematurity, and low birth weight as other glomerular diseases was evident. Our data supports a reasonable maternal-fetal risk profile for C3G patients.

Limitations and Future Directions

The limitations of our study include small sample size and limited availability of comprehensive retrospective data. Future research will include investigating trends in lab values over the course of the pregnancy and an exploration of the role of complement biomarkers in C3G related pregnancies.

References

1. *Am. J. Nephrol.*, 44(3), 187–193, (2016)
2. *Clin. J. Am. Soc. Nephrol.*, 12(11), 1862-1872, (2017)

Research is funded in part by the NIH (CMN and RJHS) and an unrestricted grant from Novartis.

- Most pregnancies are uneventful and have good outcomes for both mom and baby
- Higher risk of developing preeclampsia (1/3 of C3G pregnancies)
- Higher risk of delivering before 37 weeks gestation (1/5 of C3G pregnancies)
- No excess risk of miscarriage, low birth weight, ectopic pregnancy, or needing a c-section compared to a typical pregnancy

Predicting Post-Transplant Disease Recurrence in C3 Glomerulopathy

Lauren Fergus [1], Monica Hall [1 2], Gabriella Pitcher [1], Nicole Meyer [1], Angela Nelson [1], Nicolo Borsa [1], Amanda Taylor [1], Stephanie Houston [2], Jason Misurac [2], Yuzhou Zhang [1], Richard J. H. Smith [1 2], Carla Nester [1 2]
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Background

- C3 Glomerulopathy (C3G), defined by dominant C3 deposition on kidney biopsy, is a rare kidney disease characterized by persistent dysregulation of the alternative complement pathway.
- >50% of patients progress to ESKD within 10 years
- Post-transplant recurrence of disease manifests in nearly 67% of patients.
- We sought to examine demographic features, drivers of disease, and pre-transplant complement biomarkers in our cohort to identify parameters which may predict disease recurrence.

Methods

- Forty transplanted C3G patients from the University of Iowa's C3G Natural History Study were included in the cohort.
- Demographic data included sex, age at transplantation, race, transplant institution, time from diagnostic biopsy to transplant, and disease category (DDD vs C3GN).
- Clinical genes tested included *CFH, CFI, MCP, CFB, C3, CFHR5, DGKE, ADAMTS13, PLG,* and *THBD.*
- Biomarkers reviewed included C3, C3c, Bb, C5, C3Nef, C5Nef and sC5b-9. A C3c/C3 ratio was also calculated.
- The Mann-Whitney U test and chi-square analysis (95% CI) were applied. Receiver Operator Characteristic (ROC) curves were utilized to characterize each assay's diagnostic potential.
- Pre-transplant risk of recurrence (PTxRR) scores were calculated for each patient based on the extent of complement dysregulation as predicted by C3, C3c, C5, C3Nef, C5Nef, sC5b-9, and the genetic profile. Each parameter was chosen for their statistically significant difference between the study groups (recurrence vs. no recurrence). Abnormal values were assigned one point on a scale of zero to six.

Figure 1: Cohort Selection Flow Chart

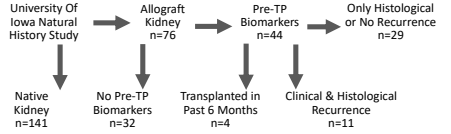

Figure 1- Blue boxes represent various exclusions from the cohort. The cutoff for date of transplant to be included in the cohort was 1/30/2022.

Results

- 11/40 (27.5%) patients in the cohort had documented recurrence.
- There were no significant differences in any of the demographic characteristics examined between groups.
- Compared to the non-recurrence group, recurrence patients had elevated C3Nef, C5Nef, C3c, C3c/C3 ratio, and sC5b-9, while C3 was depressed.
- Bb and C5 showed slight elevation and depression, respectively, in the recurrence group, but did not meet the threshold of statistical significance.
- Genetics were not a significant individual factor at the 95% confidence level but did increase the sensitivity of the PTxRR score when factored into the calculation.
- PTxRR scores were significantly higher for recurrence patients, with a median recurrence score of 4.5 points compared to the median non-recurrence score of 1 point.
- Utilizing a PTxRR score cutoff of ≥ 3 points identified 100% of individuals whose disease recurred after their tranpslant.

References

1. *Nat. Re. Nephrol.*, **15**, 129-143, (2019)
2. *J Am Soc Nephrol.*, **5**, 1110-7, (2014)

Research is funded in part by the NIH (CMN and RJHS), an unrestricted grant from Novartis and generous family related philanthropy.

Results

Figure 2: Complement Biomarker Estimation Plots and Median Differences

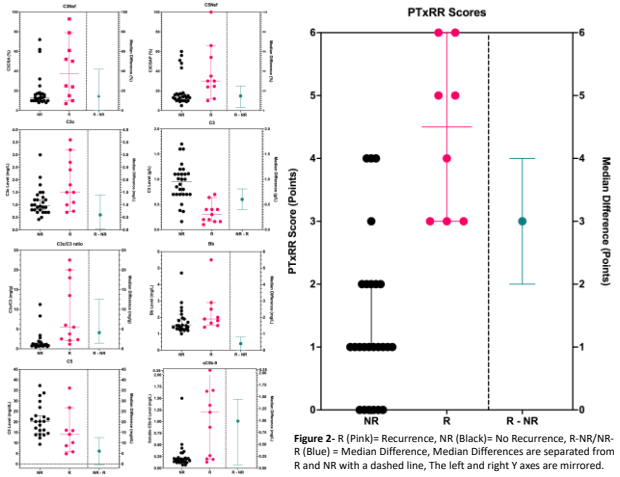

Figure 2- R (Pink)= Recurrence, NR (Black)= No Recurrence, R-NR/NR-R (Blue) = Median Difference, Median Differences are separated from R and NR with a dashed line, The left and right Y axes are mirrored.

Table 1: Recurrence and Non-Recurrence Demographic, Genetic, and Complement Biomarker Profiles

	Recurrence n	Non-Recurrence n	Yate's X^2 & z Statistic (df)
Male/Female	8 / 3	13 / 16	2.49, 1.22 (1)
White/Other Race	6 / 5	21 / 8	0.63, 0.70 (1)
C3GN/DDD	9 / 2	18 / 11	0.66, 0.81 (1)
Iowa/Other Institutions	2 / 9	9 / 20	0.17, 0.42 (1)
+/- Genetics	6 / 3	8 / 21	2.99, 1.73 (1)

	Recurrence n / Non-Recurrence n	Non-Recurrence Median [Range]	Recurrence Median [Range]	Difference Between Medians (95% CI)	Mann Whitney U Value & Z-Score	ROC AUC (95% CI)	Relative Risk (95% CI)
Age at Transplant (years)	11 / 29	25.5 [17.4-54.9]	22.0 [18.2-28.0]	3.5 (-4.3-8.7)	139, -0.61	0.56 (0.37-0.76)	X
Time from Diagnostic Bx to TP (years)	11 / 29	7.6 [2.0-12.1]	6.1 [4.1-9.3]	1.5 (-3.5-3.9)	146, -0.39	0.54 (0.33-0.75)	X
Time from Biomarkers to TP (years)	11 / 29	0.4 [1.3- 0.3]	1.8 [5.6- 0]	1.4 (2.9- 0)	102, 1.73	0.68 (0.46-0.90)	X
C3Nef (%) *	10 / 28	13.0 [10.0-17.0]	37.5 [10.0-79.0]	24.5 (0-42.0)	79, **-2.00**	0.72 (0.50-0.93)	5.1 (1.7-15.7)
C5Nef (%) *	10 / 28	13.5 [10.0-17.0]	30.0 [12.0-66.0]	16.5 (3.0-25.0)	68, **-2.37**	0.76 (0.57-0.94)	8.7 (2.5-32.6)
C3 (g/L) *	11 / 28	0.95 [0.70-1.10]	0.30 [0.16-0.64]	0.65 (0.40-0.81)	24, **4.04**	0.92 (0.84-1.00)	13.8 (2.0 - ∞)
C3c (mg/L) *	11 / 26	0.97 [0.80-1.20]	1.50 [0.75-3.20]	0.53 (0.05-1.40)	76.5, **-2.19**	0.73 (0.54-0.92)	3.0 (1.2-7.1)
C3c/C3 Ratio (mg/g) *	11 / 26	1.0 [.8-1.4]	5.5 [2.1-20.0]	4.5 (1.4-12.6)	27, **-3.84**	0.91 (0.81-1.00)	14.7 (2.9-84.5)
Bb (mg/L)	9 / 24	1.5 [1.3-1.9]	1.9 [1.5-2.9]	0.4 (0-0.8)	58.5, -1.97	0.73 (0.55-0.90)	1.9 (0.6-5.0)
C5 (mg/dL)	9 / 22	20.3 [14.6-23.0]	14.1 [5.8-26.8]	6.2 (-0.3-12.6)	57, 1.81	0.71 (0.48-0.94)	1.3 (0.5-3.9)
sC5b-9 (mg/L) *	11 / 28	0.20 [0.14-0.21]	1.20 [0.19-2.81]	1.00 (0.07-1.45)	57.5, **-3.00**	0.81 (0.65-0.98)	3.5 (1.3-9.6)
PTxRR Score (0-6 points) *	8 / 25	1.0 [1.0-2.0]	4.5 [3.0-6.0]	3.5 (2.0-4.0)	12, **-3.68**	0.94 (0.86-1.00)	28.0 [1] (1.8 - ∞)

Table 1- Statistically significant parameters are identified with an asterisk, a bolded title, and a bolded z score. Ranges are indicated with brackets and confidence intervals are indicated by parentheses. * = p < 0.05, [1] (with a cutoff of 3 points determined by ROC).

Conclusions

- Absolute risk of recurrence was lower than previously reported estimates but may represent better patient outcomes for patients closely monitored with complement biomarkers.
- Demographic characteristics **had no statistical value** for predicting recurrence of C3G.
- Carrying a genetic variant was not a good indicator of recurrence on its own but did enhance the diagnostic potential of the PTxRR score.
- Pre-transplant excess complement activity was associated **with increased post-transplant recurrence risk**, both cumulatively (PTxRR score) and individually (C3, C3c, C3Nef, C5Nef, sC5b-9, and C3c/C3 ratio).
- Our data suggests that the PTxRR score may be useful for identifying patients at higher risk of post-transplant C3G recurrence.
- Possible limitations include the timing of biomarker draws and the limited cohort size. Future directions include exploring the role of Factor H and other complement biomarkers in C3G recurrence, in addition to improving the PTxRR score's statistical power.

- Looked at a group of 40 C3G patients who received a kidney transplant - 11 had disease recurrence.
- Demographic characteristics (sex, ethnicity, age, DDD vs. C3GN) do not increase risk of recurrence.
- Everyone who recurred had a C3 <90, but so did ½ of the non-recurrence group. Having a low C3 does not necessarily mean you will recur.
- Developed scoring system for forecasting outcome, showing that excess complement activity across multiple biomarker assays was the best predictor of recurrence.
- Looking at all the biomarkers and genetic variants, 5 biomarkers that were significantly different between recurrence and non-recurrence groups.
- On evaluating each patient post kidney transplant, 1 point was awarded for each abnormal biomarker or genetic variant.
- A total score of 3 or greater indicated high-risk for C3G recurrence (100% of the recurrence group had 3+ points).

C3G Surveillance Post-Transplant Protocol

1. Consider pre-transplant complement biomarkers (and genetics). We tend to get these q 6 month (or with reappearance of clinical disease) if abnormal pre-transplant. Pre-transplant biomarkers may help predict risk for recurrence. [To be clear, after recurrence, they are less likely to be useful – though are checked q6 months in our natural history study.]
2. In an adult – would rule out a paraprotein prior to transplant. [Treatment of the clone has been met with improved renal survival in native kidneys – so we presume the same would be the case in transplant kidneys.]
3. Transplant as usual
4. There are no C3G related data to support choosing one induction regimen over another.
5. Once the stent is out (if used) – begin monitoring for urine blood and protein
6. The appearance of urine blood may be the first sign of return of inflammation (though to be clear is NOT an indication for biopsy).
7. Appearance of urine protein is more likely to represent *significant* recurrence. [Of course, an elevated creatinine may also – however given the other things that cause that post-transplant – the urine protein is more specific.]
8. If a biopsy is performed – note that C3 deposition may be present in up to 90% of C3G patients – however IF positivity alone is not a sign of "actionable" recurrence. Ie there must also be a clinical parameter to trigger treatment OR, at the least – some degree of significant proliferation on biopsy.
9. Once recurrence has been confirmed – assess the eligibility for clinical trial.
10. If no trial is available – consider terminal complement blockade or upstream blockade via managed access.

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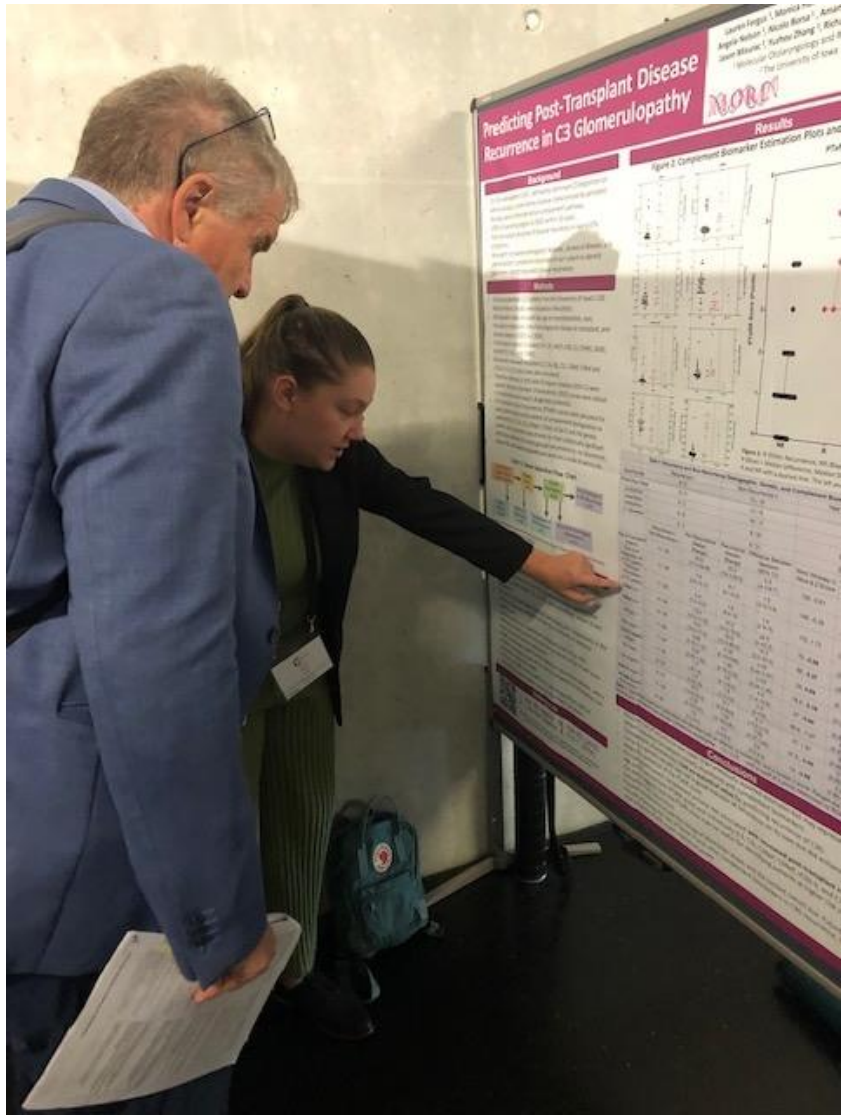
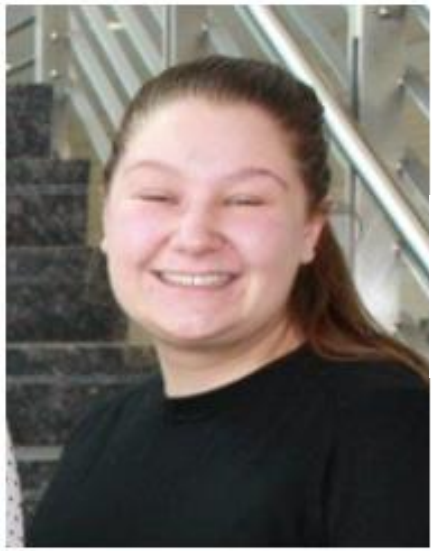

Predicting Post-Transplant Disease Recurrence in C3 Glomerulopathy
Background
Results


VERSA


TEAMWORK

C3G Natural History Study Student Team



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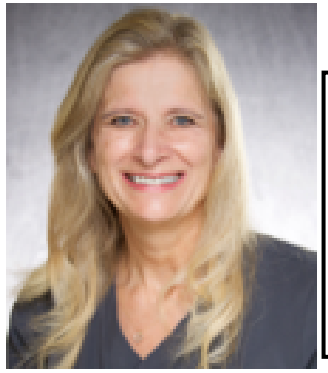

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The MORL Bunch


Thanks for listening!
Any questions?


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