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RESOLVE: Recurrence Posttransplant Observational Study in Focal Segmental Glomerulosclerosis and Minimal Change Disease

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Abstract
Introduction: The morbidity of recurrent focal segmental glomerulosclerosis (FSGS) and minimal change disease (MCD) after transplant is well recognized. Additional collaborative research is necessary to advance understanding of recurrence epidemiology, mechanisms, interventions, and outcomes, particularly in children. ***Methods:*** RESOLVE is a multicenter, observational cohort study examining the posttransplant course of patients with FSGS and MCD across the lifespan. Multiple enrollment options will facilitate both retrospective and prospective collection of biospecimens, self-report items, and electronic health record data across pediatric and adult participants. The study offers a unique mobile health option for participants to enroll and engage with the study remotely. Logistic regression using a log link function will evaluate recurrence risk within 3 months of transplant based on clinical characteristics and assess the impact of social determinants of health on time to graft failure, following adjustment. Cox proportional hazards models with primary outcome of graft failure with competing risk of death will evaluate the impact of recurrence therapy and access to preventative versus reactive recurrence therapy. Independent logistic regression will evaluate the impact of recurrence therapy and endophenotypes on proteinuric outcomes. ***Conclusion:*** Multiple enrollment approaches and tailored site participation are needed while studying recurrent FSGS (rFSGS) due to its rarity and phenotypic variability. RESOLVE provides a framework for international collaboration to unravel the course of rFSGS through a biospecimen and data repository. It also explores the potential for mobile health tools to enhance recruitment

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of participants and to promote cooperation among researchers to advance understanding of recurrence mechanisms and treatments.

Introduction

The morbidity burden of recurrent focal segmental glomerulosclerosis (FSGS) and minimal change disease (MCD) after kidney transplant is well recognized and includes reduced quality of life, early graft loss, and augmented mortality. Previous studies have identified several risk factors for recurrence, including older age at native kidney disease onset, initial kidney biopsy consistent with MCD and subsequent one with FSGS, and onset with response to immunosuppression therapy that evolved to late steroid resistance in children [1–3]. Research and clinical implementation of genetic testing in patients with FSGS affecting the native kidneys have improved FSGS recurrence risk prediction in children and adults in recent years. Specifically, individuals with pathogenic, Mendelian causes of FSGS are at very low risk for FSGS recurrence [3, 4]. The genetic predisposition to rFSGS for children without Mendelian causes of primary disease is unknown.

Recent advances in the understanding of the mechanisms of FSGS in the native kidney have reinvigorated the scientific community to develop a collaborative community to advance research into the epidemiology, mechanisms, interventions, and outcomes [5]. However, efforts to understand its epidemiology, disease mechanisms, and optimal treatment have been limited by small sample sizes in single-center studies and potential misclassification in registry studies.

In response to the current state-of-the-art, the recurrence posttransplant observational study in FSGS and minimal change disease (RESOLVE) has been developed following a large, international collaborative meeting focused on advancing understanding of recurrent FSGS (rFSGS) and MCD. RESOLVE is designed to: (1) develop a shared resource for collaborative biomedical research that requires state-of-the-art phenotyping and bio-banked specimens to better define the incidence and prevalence of FSGS/MCD recurrence, (2) describe the posttransplant course of patients with FSGS and MCD across the lifespan, and (3) support future translational research to explore relevant disease mechanisms and identify candidate treatment targets. The purpose of the present work was to provide a description of the RESOLVE study methods and design. The study was reviewed and approved by the Institutional Review Board at the University of Michigan (HUM00221714).

Methods

Hypothesis and Specific Aims

Specific aims for this project are available in Table 1. RESOLVE will test the hypothesis that organizing rFSGS/MCD phenotypes into clusters or endophenotypes, based on features including age of onset of primary disease in the native kidney/timing of progression to kidney failure, treatment response patterns, and timing of disease recurrence in the kidney allograft will facilitate the prediction of health outcomes and identification of therapeutic targets. This lifespan perspective acknowledges that multiple pathways can contribute to recurrence, and their relative importance may vary with age, genetic ancestry, and social determinants of health, including education and insurance status.

Study Population

RESOLVE features a multicenter, observational cohort design with four cohorts to allow for multiple enrollment options:

- *Cohort A*: participants are consented prior to a first or subsequent transplant. Collected data include patient-reported information, electronic health record (EHR) extraction, and biospecimens.
- *Cohort B*: participants are consented posttransplant including individuals who have returned to dialysis following a prior transplant. Collected data include patient-reported information, EHR extraction, and biospecimens.
- *Cohort C*: only secondary use of EHR data as accepted by the Institutional Review Board. Individuals who received a transplant from the year 2000 and onward are eligible for this cohort.
- *Cohort D*: participants from cohorts A, B, or C are invited to enroll in an optional mobile health platform. Additionally, participants who meet eligibility criteria and are outside the study may self-identify and remotely enroll through the mobile health platform. Collected data include patient-reported information via surveys housed on the mobile health platform, as well as EHR extraction via direct EHR linking to the mobile platform.

Complete eligibility criteria are listed in Table 2. For cohorts with biospecimen collection requirements (i.e., A and B), target enrollment across sites is estimated to be

Table 1. Specific aims

1. Define the endophenotypes (subgroups) of recurrent FSGS and MCD
2. Assess risk of recurrence by demographic, clinical, genetic, and pathology characteristics
3. Define the association between posttransplant proteinuria, time to graft failure, and endophenotypes and recurrence therapy
4. Assess the association of social determinants of health and recurrence therapy
5. Assess the association of social determinants of health and outcomes
6. Define tissue and non-tissue based prognostic biomarkers of clinical outcomes
7. Compare posttransplant quality of life between recurrence and non-recurrence

Table 2. Participant eligibility criteria

Inclusion
I All Participants: diagnosis of FSGS or MCD in the native kidney (i.e., prior to transplant) by biopsy. Cases with a known or suspected genetic cause also are welcome
II Cohort A: must provide informed consent/assent and complete enrollment visit prior to transplant
III Cohort B: must provide informed consent/assent and complete enrollment visit after transplant
IV Cohort C: scheduled to receive and/or have a kidney transplant from year 2000 onward
Exclusion
I Kidney biopsy with diagnosis other than FSGS or MCD
FSGS or MCD secondary to a known disorder (i.e., lupus nephritis, IgA nephropathy, malignancy)

300 participants. Study sites will include both adult and pediatric nephrology practices to allow for more comprehensive sample recruitment.

Participant Visits and Biospecimen Collection

Visit schedule and biospecimen collection varies by participant's cohort and recurrence status. Participants in cohorts A and B will be identified by the study investigators and screened for eligibility, prior to enrollment. Once eligibility is confirmed, a member of the research team will approach the patient or parent/guardian for consent/assent and enrollment. The enrollment visit will include collection of demographic information, detailed kidney and medical history, medication use, physical examination, and biospecimens. Follow-up visits will capture updates to general and kidney health, post-transplant procedures and medications, disease recurrence, physical exam information, and biospecimen collection. The average prospective biospecimen collection is expected to last up to 2 years, over a series of 3–6 follow-up visits. A schedule of events for cohorts A and B is shown in Table 3. In the event that participants are unable to return to the study site for follow-up, a remote video visit will be scheduled and, on a case-by-case basis, collection of biospecimens can be organized via local blood draws/urine collection and shipment with express courier. It is possible that participants in cohort B may receive a subsequent transplant while enrolled in the study. These participants remain eligible to participate and will undergo a cohort transfer to cohort A. Thus, they will retain the same study identifier but will follow the cohort A schedule from 0 h through the end of the study.

Biospecimen collection may be limited for some participants due to decreased/absent urine production or blood collection volume restrictions. Once procured, biospecimens will be processed per protocol and frozen at −80°C for short-term storage at the study site. Following a quarterly cadence, available specimens will be shipped to the University of Michigan Central Biorepository (CBR) for long-term storage and future analyses. A detailed description for collection of biospecimens is available in Table 4.

Participants in cohorts C and D will not have in-person visits, given the nature of their data collection. After biospecimen collection is complete for cohorts A and B, long-term clinical outcomes for these individuals

Table 3. Cohorts A and B visit and biospecimen collection schedule

	Enrollment visit	0 h	Transplant +1 week	At any biopsy	Transplant +1 month[a] (nonrecurring)	Transplant +6 months[a] (nonrecurring)	At any recurrence, pretherapy	Rituximab and/or pheresis +1 month	Rituximab and/or pheresis +6 months
Cohort A pretransplant (enrolled pretransplant)									
Window	−30 days of transplant		±1 weeks		−15 days to +2 months	−2 months to +3 months	Prior to therapy	±2 weeks	±2 months
Consent	x								
Data collection	Retro- and prospective data collection from EHR								
Blood	x	x	x	x	x	x	x	x	x
Urine	x[b]		x	x	x	x	x	x	x
Apheresis effluent								At weeks 2, 4, 6 of pheresis sessions	
Excess kidney biopsy tissue		x		x					
Historic biopsy paraffin block	x			x					
Kidney slide digital images	x			x					

	Enrollment visit[c]	At any transplant[d]	At any biopsy	Enrollment +1 month[a] (nonrecurring)	Enrollment +6 months[a] (nonrecurring)	At any recurrence, pretherapy	Rituximab and/or pheresis +1 month	Rituximab and/or pheresis +6 months
Cohort B posttransplant (enrolled posttransplant)								
Window				−15 days to +2 months	−2 months to +3 months	Prior to therapy	±2 weeks	±2 months
Consent	x							
Data collection	Retro- and prospective data collection from EHR							
Blood	x	x	x	x	x	x	x	x
Urine	x[b]		x	x	x	x	x	x
Apheresis effluent							At weeks 2, 4, 6 of pheresis sessions	
Excess kidney biopsy tissue		x	x					
Historic biopsy paraffin block	x		x					
Kidney slides digital images	x		x					

[a]If recurrence occurs, skip these visits. If no recurrence, collect specimens at 1-month and 6-month posttransplant. [b]If available. [c]If on dialysis, only enrollment samples will be collected until transplant occurs. [d]If subject receives subsequent transplant post-study enrollment, move to a modified schedule and follow cohort A schedule going forward.

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Table 4. Collected biospecimens

Blood
Blood collection volume is based on participant body weight (i.e., ≥ 52 lbs or < 52 lbs). If concerned about draw volume (e.g., several concurrent clinical blood draw, hematocrit < 28%), research collection may be reduced at the investigator's discretion. Available blood specimen types include serum, plasma, RNA, DNA, and PBMCs
Urine
First morning or spot urine samples may be collected. Given varying degrees of urine production in the study population, as little as 10 mLs may be used for processing. A maximum of 70 mLs will be utilized, with excess discarded per protocol. Available urine specimen types include whole urine, urine supernatant, and urine pellet.
Kidney tissue
New and historic kidney tissue will be collected. For participants that undergo a renal biopsy, any excess kidney tissue that is not required for clinical evaluation will be designated to the research study. Tissue will be placed in RNAlater for long-term storage. If available, historic kidney tissue in paraffin block or digital slides may be de-identified and provided to the study. Historic tissues/slides will be used to create a digital pathology core at a future date
Apheresis effluent
For participants that undergo apheresis treatment, apheresis effluent will be collected. Effluent from both plasmapheresis and lipopheresis is permitted. Effluent will be collected by an apheresis unit nurse and provided to the study staff for further aliquoting prior to long-term storage

will be available through linkage with data from cohort C and/or D, increasing the potential granularity of the generated endophenotypes.

Data Collection and Mobile Health

For cohorts A and B participants, clinical data will be collected using a variety of methods including participant self-report, programmed EHR data extraction, and manual chart review. Data collection will occur at the time of scheduled follow-up visits (see Table 3), as well as at 12- and 24-month post-enrollment/visit using standardized clinical report forms. Programmed and/or manual chart extraction for cohort C will occur on an annual basis following enrollment. The research team will work to alleviate potential barriers to participation, such as commitment to in-person study visits, travel time to study site, proximity to an enrolling site and/or medical center.

In response to these challenges, the RESOLVE study offers an optional mobile health platform as an enrollment and data collection pathway. Participants in cohorts A, B, or C may elect to enroll in the mobile health platform in parallel to the onsite study or as a study continuation tool once visit completion has been reached. Additionally, participants not currently enrolled in RESOLVE can self-identify and enroll independently through the study application, supported by MyDataHelps (Care Evolution; Ann Arbor, MI). Individuals who self-identify will complete a prescreening assessment to confirm eligibility prior to enrollment. Individuals will then complete an e-consent that is available through the platform.

Once enrolled, participants will receive push reminders through the app, via email and/or text, to complete self-reported surveys related to their demographics, general and kidney health history, family history, transplant status and history, native kidney/posttransplant medication and procedure history, social determinants of health. Survey completion will be solicited at different time points: at the time of enrollment, 2- and 4-week post-enrollment, monthly ×2, quarterly ×3, and then annually. In addition, participants will be prompted to connect to their local EHR system(s), to allow for direct data sharing. Data are extracted via the shared app connection and will be available to the study team for export. Finally, the mobile platform will provide disease metrics tracking that can be displayed back to the participant via their mobile dashboard. Participants can provide real-time data entry regarding measures of interest such as blood pressure, swelling status, and urine protein. This information is available to the study team at the time of data export and is displayed to participants as an in-app health trend.

Planned Statistical Analyses

Planned statistical analyses will evaluate the risk of recurrence within 3 months of transplant based on clinical characteristics of individuals in all cohorts after adjusting for demographic, genetic, and pathology

characteristics, using logistic regression with a log link function. Enrollees will be classified into endophenotype determined through nonhierarchical clustering techniques. Two separate Cox proportional hazards models with the primary outcome of graft failure with a competing risk of death will evaluate the impact of recurrence therapy and the endophenotypes, respectively, on time to graft failure, adjusting for clinical, demographic, genetic, and pathology characteristics. A similar pair of independent logistic regression will evaluate the impact of recurrence therapy and endophenotypes on proteinuric outcomes, such as complete remission (UP:C <0.3), partial remission (UP:C 0.3–1.5), and relapse (UP:C >3), adjusted for clinical, demographic, genetic, and pathology characteristics.

The impact of the social determinants of health on time to graft failure and access to preventative versus reactive recurrence therapy will be investigated with a Cox proportional hazards model and a logistic regression model with log link, respectively, both adjusted for clinical, demographic, genetic, and pathology characteristics. Insurance type will serve as one proxy measure of the social determinants of health.

Deep biobanking provides the advantage of linking molecular phenotypes to detailed clinical information for cohorts A and B. Promising molecular biomarkers and related pathways will be identified using a hypothesis generating series of regressions. The relevant level of significance from each regression will be used to flag potentially important biomarkers, after careful consideration for the false discovery rate of such serial regressions. The selected biomarkers will be grouped according to biological relevance and their impact on clinical outcomes can be further investigated via ridge regression.

Discussion

RESOLVE is a multicenter, observational cohort study to examine the posttransplant course of patients with FSGS and MCD across the lifespan. The study is designed to collect both retrospective and prospective clinical data as well as biospecimens and patient-reported information. With multiple enrollment options, the study will enable investigators to define the incidence and prevalence of FSGS recurrence, to describe the posttransplant course of patients with FSGS and MCD across the lifespan, and to refine current endophenotypes for outcome prediction. The study also develops a biorepository to support future translational research studies to explore relevant disease mechanisms.

Two features of RESOLVE will support more widespread study enrollment, namely, engagement via continuous visit windows for participants in cohorts A and B and the opportunity to enroll in the optional mobile health platform. The continuous visit model allows participants' increased flexibility to plan their study visits around already scheduled clinical care, thus reducing participant burden and travel to the study center. This approach also allows for aligned clinical and research blood draws, reducing the number of venipunctures received by a participant, and ensures consistent biospecimen collection scheduling.

The use of a mobile health application offers a unique opportunity for participants to continue interaction with the study after all visits have been completed. Researchers will continue to receive follow-up data via participant self-report surveys and EHR linkage for participants who choose to enroll in the mobile platform. To date, over 6,000 EHR systems across the USA are linkable within the application allowing for more widespread data capture not limited to that of a physical enrolling site. Remote enrollment via the mobile health platform also will provide an opportunity to participate in research for participants who otherwise may not have access to this kind of activity. Participants who reside in rural areas, do not have access to transportation, or are located away from physical study sites can enroll independently, allowing researchers to capture a more representative sample of individuals and addresses some equity concerns in access to research opportunities. Once enrolled, mobile health participants can track self-report and EHR variables of interest, including blood pressure, swelling, and eGFR, on a personalized dashboard. To the research team's knowledge, this is the first mobile health tool of its kind being used in the kidney health space.

Barriers to research participation may also exist at the site level, prompting the design of a tailored site participation approach. For interested investigators with competing protocols or inability to participate in biospecimen sharing, a RESOLVE data sharing only protocol has been established. Sites are invited to participate in cohort C collection by completing automated EHR extraction and manual chart review of eligible participants. At any point, investigators are welcome to modify engagement to the full RESOLVE protocol, pending appropriate staffing and patient volume. By allowing for a more tailored approach to site participation, the study team will be able to broaden collaboration across centers

that may not have the resources to participate in the full study protocol.

However, despite these strengths, the present study is not without limitations. A targeted recruitment and digital advertising strategy is needed to promote widespread remote enrollment. Additionally, limited specimen processing and short-term storage conditions are necessary for sites to collect biospecimens, which can create barriers to participation for sites with staffing and/or resource constraints. While sites can participate in a data sharing only capacity, biobanking of specimens remains a primary objective of the study. Further, differences in adult and pediatric transplant clinic structure may affect participant follow-up along with transitions of care. Transparent conversations regarding these concerns are necessary to make sustainable modifications to biospecimen collection strategies and site participation as needed.

The present paper provides a description of the RESOLVE study design and methods. Unique design features include multiple enrollment options, tailored site participation, and incorporation of a novel mobile health tool that will allow investigators to achieve the study's objectives. Future research is needed to explore the implications of mobile health use within the study's population. Further, persistent promotion of collaborative research efforts is necessary to continue scientific advancement and understanding of rFSGS epidemiology, mechanisms, and treatments.

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Statement of Ethics

This study protocol was reviewed and approved by the Institutional Review Board at University of Michigan (HUM00221714). Written informed consent will be obtained from participants (or their parent/legal guardian/next of kin) to participate in cohorts A, B, and D of the study.

Conflict of Interest Statement

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Author Contributions

E.S.: conceptualization, methodology, project administration, and reviewing and editing. A.R.: project management and original draft. H.D.: conceptualization, methodology, and project administration. N.P.: methodology. E.M.: reviewing and editing. E.H.: participation and reviewing and editing. S.M. and P.V.: conceptualization and investigation. S.S.C. and M.K.: conceptualization. A.N.: methodology and reviewing and editing. H.T.: supervision. Z.M.: resources and reviewing and editing.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

References

1 Uffing A, Pérez-Sáez MJ, La Manna G, Comai G, Fischman C, Farouk S, et al. A large, international study on post-transplant glomerular diseases: the TANGO project. BMC Nephrol. 2018;19(1):229. https://doi.org/10.1186/s12882-018-1025-z

2 Saleem MA, Kobayashi Y. Cell biology and genetics of minimal change disease. F1000Res. 2016;5:F1000 Faculty Rev-412. https://doi.org/10.12688/f1000research.7300.1

3 Pelletier J, Kumar K, Engen RM, Bensimhon A, Varner JD, Rheault MN, et al. Recurrence of nephrotic syndrome following kidney transplantation is associated with initial native kidney biopsy findings. Pediatr Nephrol. 2018;33(10):1773–80. https://doi.org/10.1007/s00467-018-3994-3

4 Trautmann A, Bodria M, Ozaltin F, Gheisari A, Melk A, Azocar M, et al. Spectrum of steroid-resistant and congenital nephrotic syndrome in children: the PodoNet registry cohort. Clin J Am Soc Nephrol. 2015;10(4):592–600. https://doi.org/10.2215/CJN.06260614

5 Gipson DS, Wang CS, Salmon E, Gbadegesin R, Naik A, Sanna-Cherchi S, et al. FSGS recurrence collaboration: report of a symposium. Glomerular Dis. 2024;4(1):1–10. https://doi.org/10.1159/000535138