# Alport Syndrome Foundation – Alport Patient Registry

**Protocol Title:** Alport Syndrome Foundation Registry

**Protocol ID:** Pulse-ALP-101-000

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# LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

| ABBREVIATION | DEFINITION |
|---|---|
| **ACE** | Angiotensin Converting Enzyme |
| **ADAS** | Autosomal Dominant Alport Syndrome |
| **ADL** | Activities of Daily Living |
| **API** | Application Programming Interface |
| **ARAS** | Autosomal Recessive Alport Syndrome |
| **AS** | Alport Syndrome |
| **ASF** | Alport Syndrome Foundation |
| **CDM** | Common Data Model |
| **EC** | Ethics Committee |
| **ECRF** | Electronic Case Report Form |
| **ESRD** | End Stage Renal Disease |
| **FDA** | Food and Drug Administration |
| **GCP** | Good Clinical Practice |
| **GDPR** | General Data Protection Regulation |
| **GFR** | Glomerular Filtration Rate |
| **GUID** | Globally Unique Identifier |
| **HIPAA** | Health Insurance Portability and Accountability Act |
| **HITRUST** | The Health Information Trust Alliance |
| **IRB** | Institutional Review Board |
| **MDS** | Minimal Data Set |
| **OMOP** | Observational Medical Outcomes Partnership |
| **PARTICIPANT** | Subject enrolled in the registry |
| **PHI** | Protected health information |
| **PHIPA** | Personal Health Information Protection Act |
| **PII** | Person Identifying Information |
| **PRO** | Patient Reported Outcome |
| **PULSE** | Pulse Infoframe |
| **QOL** | Quality of Life |
| **RWD** | Real-World Data |
| **SUBJECT** | An unenrolled potential participant for the registry |
| **XLAS** | X-linked Alport Syndrome |

# SYNOPSIS/SUMMARY

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|---|---|
| **Protocol** | Alport Syndrome Foundation Registry |
| **Protocol ID** | Pulse-ALP-101-000 |
| **Objectives of the Registry** | This open-ended, ambispective registry will collect longitudinal RWD from participants of all ages diagnosed with Alport syndrome (AS) in the US or Canada to enable, characterize, and address current and future needs of the participants and the drug development initiatives, including:<br>▪ Medical history, treatment history, etiology, and natural history.<br>▪ Participant surveys, lifestyle factors and other patient reported outcomes.<br>▪ Prospective collection of clinical and laboratory data from participants. |
| **Rationale** | In order to better address the limitations and deficiencies of other registry approaches, Pulse Infoframe (Pulse) has developed and maintains the *healthie*™ 2.0 platform ("Pulse platform") to orchestrate the curation (collection, ingestion, organization, and maintenance) of retrospective and prospective data for the Alport syndrome registry. The agile Pulse platform, in addition to providing a conventional registry model, enables a decentralized (site independent) federated data model that is direct-to-patient for recruitment, information gathering, advocacy and support. The Pulse platform is well positioned to fulfill the design and approach for rigorous rare disease evaluation, along with a full suite of features for additional RWD dimensions and analytical components. |
| **Registry Design** | The *healthie*™ 2.0 platform ("Pulse platform") will orchestrate the curation of retrospective and prospective data for the Alport syndrome registry. The Pulse platform has a centralized registry data infrastructure with standardized rules, and a decentralized (i.e., site independent) federated data model to automate adherence to regulations for regional governance and the privacy of participant data. This allows the platform to quickly scale to transregional or transnational deployment. |
| **Registry Procedure** | This ambispective non-interventional real-world registry includes subjects of all age. The definition of an Alport syndrome diagnosis for this registry will be a clinical diagnosis by a certified genetic counselor, treating physician or nephrologist, based on familial history, clinical signs, genetic test results, electron microscopy examination of renal biopsy (showing abnormalities |

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|---|---|
| | of the glomerular basal membrane), or immunohistochemical findings on renal and cutaneous biopsy (even if it cannot establish the diagnosis in all the subjects). Molecular genetic testing will confirm the diagnosis but is not required for registry eligibility. Intronic mutations may account for approximately 5% of Alport mutations and likely missed by current standard exomic panel screens. |
| **Data Capture and Management** | All data will be sourced directly from participants and/or their caregivers into the Pulse platform, directly into the electronic case report forms (eCRFs) that are part of the platform. Mandatory fields will be identified to collect a Minimal Data Set (MDS) on each patient to adequately profile the Alport syndrome patient population.<br>The data workflow and schedule of assessments are provided for demographics, medical history, lifestyle factors, participant clinical profile, therapies, and laboratory data will be collected during enrollment. Medical history and laboratory data will be retrospectively collected from the date of clinical diagnosis of AS to the date of enrollment in the registry. When available, additional profiling, routine clinical care, genetic results, audiograms, and labs will be collected. Data will be collected for as long as the participant is enrolled or until registry termination.<br><br>The *healthie*™ platform is managed and deployed in AWS cloud hosting solutions and adheres to country-specific security and privacy regulatory requirements. Data ingestion and management pipelines in *healthie*™ guarantee only high-quality data reside in the platform. Automated processes detect and rectify data anomalies prior to analysis time, and any single source of clinical data is qualified by external data sources. Incoming values are normalized based on industry and medical community standards to provide proper characterization of data, reusability of data sources, and ease of data mobility between platforms. |
| **Eligibility Criteria** | Inclusion Criteria<br>**I 01.** Confirmed diagnosis of AS by a certified genetic counselor, treating physician or nephrologist.<br>**I 02.** Signed informed consent/assent must be provided by the subject and/or caregiver (parent/legal guardian) including compliance with the restrictions listed in the informed consent/assent form and in this protocol.<br><br>Exclusion Criteria<br>**E 01.** [*No exclusion criteria.*] |

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| **Number of Participants and Duration of Participation** | The registry is an open-ended design to collect data about natural history, participant health status and care they receive over time. There is no cap to the enrollment of patients with AS. |
| **Statistical Considerations** | The registry is not hypothesis-driven, and the objectives are to obtain data for specific participant and disease domains. Statistical considerations will be considered independently of this protocol using study-specific protocols for data from this registry. |
| **Participant / Caregiver Data** | ▪ Screening & Consent<br>▪ Participant Identification<br>▪ Demographics<br>▪ Lifestyle Characteristics<br>▪ Disease diagnostics / Participant Clinical Profile<br>▪ Genetic Results<br>▪ Participant Surveys<br>▪ Medical History<br>▪ Treatment History<br>▪ Laboratory Data |

# 1 BACKGROUND / INTRODUCTION

Alport syndrome (AS) is a genetically and phenotypically heterogeneous disorder of the glomerular, cochlear, and ocular basement membranes due to mutations in the collagen IV genes COL4A3, COL4A4, and COL4A5. AS can be transmitted as an X-linked (XLAS), autosomal recessive (ARAS), and/or autosomal dominant (ADAS) disorder (Savige et al., 2022). A fundamental feature of AS is the phenotypic heterogeneity of the network of type IV collagen α3, α4, and α5 chains (the collagen IVα345 network), resulting in a broad range of kidney outcomes and extra-renal manifestations (Kashtan, 2021a). AS patients often present progressive hematuric nephritis, hearing loss, and ocular degradation (Jais et al., 2003). Males with XLAS demonstrate a strong genotype-phenotype correlation, whereas in females prior XLAS studies have not identified a genotype-phenotype correlation for kidney failure, hearing loss or ocular abnormalities (Gibson et al., 2022). In XLAS, there is often a family history of hematuria (with or without proteinuria) or renal failure. In ARAS, families with monoallelic variant carriers are often asymptomatic or show only microscopic hematuria (and mild proteinuria) (Nozu et al., 2019). In one study of ADAS, the median age for developing proteinuria was 17 years old, and the median renal survival time was 70 years (Kamiyoshi et al., 2016). However, reported median renal survival times in men with XLAS; men and women with ARAS; and combined were only 25, 21, and 22 years, respectively (Gross et al., 2020; Jais et al., 2000; Oka et al., 2014).

Alport syndrome is a rare genetic disorder, but it is also underdiagnosed since the mutation can be unknown to the patient. The reported prevalence of Alport syndrome varies from one in 5000 to one in 53,000 individuals (Gibson et al., 2021). The United States Renal Data System (USRDS) showed that approximately 0.2% of adults and 3% of children in the United States with end-stage renal disease (ESRD) carry a diagnosis of Alport syndrome (Kashtan, 2019).

Urinalysis is an extremely effective method of screening for AS. Alport nephropathy begins with isolated hematuria, followed by moderate albuminuria, severe proteinuria, and decline in the Glomerular Filtration Rate (GFR) (Kashtan, 2021a). Some patients will first present with sensorineural hearing loss and ocular abnormalities (Zhang & Ding, 2018).

Clinical diagnosis of AS is based on familial history, clinical signs, electron microscopy examination of a renal biopsy, and the immunohistochemical findings on renal and cutaneous biopsy although it may not establish the diagnosis in all subjects. Genetic analysis should be considered the primary method of definitive analysis (Kashtan, 2022). However, intronic genetic variants can be missed by most next-generation genetic screening panels (Wang et al., 2021). As such cohesive diagnosis based on combined familial history, clinical signs, and renal biopsy can be used for a definitive diagnosis. The clinical sensitivity (true positives) and specificity (true negatives) are dependent on variable factors such as age or family history. For XLAS, clinical specificity is nearly 100% by age 20 in males and is approaching 100% for ARAS by age 20 in both males and females (Hertz et al., 2014) .

There is no cure for AS, and currently the therapy goal for Alport kidney disease is to safely maintain and lengthen the intervals between the milestones of progression to ESRD with angiotensin converting enzyme (ACE) inhibitor treatment (Kashtan, 2021a) or similar (e.g., angiotensin receptor blockers). Gene therapy is now universally recognised as a possible therapeutic application for this rare disease, and using pharmacological repurposed chaperones are also under investigation (Daga et al., 2022).

# 2 RATIONALE

Given that Alport syndrome is a rare disease, the diagnosis and treatment modalities for AS are inadequate, and the mutation is often unknown to the patient, prevalence estimates are difficult to estimate and comprehensive long-term data on patients is limited. Additionally, the most commonly diagnosed Alport X-linked Alport syndrome (XLAS) is associated with higher severity of outcomes in males compared to the less commonly diagnosed ARAS and ADAS types. As a result, estimates of prevalence and other investigations have traditionally relied on data from case-series clinical care of males with significant burdens of illness; whereas females with a milder type are less tested and likely under-diagnosed even though their risk of having Alport is genetically two-fold compared to males (Savige et al., 2016).

To better characterize and study Alport Syndrome, especially the future needs for patients and drug development initiatives, rare disease databases and registries models have been established. However, these models tend to be limited in a variety of ways due to intrinsic difficulties in the design and approach to rare disease evaluation. Existing models are often inadequately designed to answer questions about the disease and its treatment especially in small populations, and the rigid designs prevent the scalability to answer the intended question, or any new interrogations. Deficiencies also include insufficient duration in longitudinal data with most models being cross-sectional; lack of consistent and repeated follow-ups; no integration with disparate real-world data (RWD) sources; and are geographically bound to a specific region or nation. Additionally, for these rare diseases with well-known hereditary links, investigators have encountered registry scenarios where at-risk immediate-family members have never been tested (Kashtan, 2021b).

In order to better address the limitations and deficiencies of other approaches, Pulse Infoframe (Pulse) has developed and maintains the *healthie*™ 2.0 platform ("Pulse platform") to orchestrate the curation (collection, ingestion, organization, and maintenance) of retrospective and prospective data for the Alport syndrome registry. The agile Pulse platform, in addition to providing a conventional registry model, enables a decentralized (site independent) federated data model that is direct-to-patient for recruitment, information gathering, advocacy and support. The Pulse platform is well positioned to fulfill the design and approach for rigorous rare disease evaluation, along with a full suite of features for additional RWD dimensions and analytical components (see Section 4).

# 3 REGISTRY OBJECTIVES

This open-ended, ambispective registry will collect longitudinal RWD from participants of all ages diagnosed with Alport syndrome (AS) in the US or Canada to enable, characterize, and address current and future needs of the participants and the drug development initiatives, including:

- Medical history, treatment history, etiology, and natural history.
- Participant surveys, lifestyle factors and other patient reported outcomes.
- Prospective collection of clinical and laboratory data from participants.

# 4 REGISTRY METHODS

## 4.1 REGISTRY DESIGN

The *healthie*™ 2.0 platform ("Pulse platform") will orchestrate the curation of retrospective and prospective data for the Alport syndrome registry. The Pulse platform has a centralized registry data infrastructure with standardized rules, and a decentralized (i.e., site independent) federated data model to automate adherence to regulations for regional governance and the privacy of participant data. This allows the platform to quickly scale to transregional or transnational deployment.

The Pulse platform is a secure cloud-based Health Insurance Portability and Accountability Act (HIPAA) and General Data Protection Regulation (GDPR) compliant using the US Food and Drug Administration (FDA) endorsed Observational Medical Outcomes Partnership (OMOP). The OMOP common data model (CDM) leverages and delivers centralized standards and consistency enabling rapid synthesis and analysis of data.

At the individual subject level, the decentralized approach enables decentralized consenting/assenting and enrollment with password-protected participant portals. The platform enables direct and continuous participant/caregiver clinical data entry and document upload functionalities for the participant and caregiver (parent or legal guardian) in real-world settings for treatment and outcomes in AS.

Overall, the platform provides consistent, reliable, high-quality data collection, controlled access for users, along with administrative dashboards for population-level insights, and participant and caregiver (i.e., parent or legal guardian) journey dashboards and support capabilities. The platform is extensible to health care providers and advocacy and is a valuable collective resource and referral for future studies.

## 4.2 REGISTRY POPULATION, ENROLLMENT AND WITHDRAWAL PROCESS

This ambispective non-interventional real-world registry includes all subjects regardless of age. The definition of an Alport syndrome diagnosis for this registry will be a clinical diagnosis by a certified genetic counselor, treating physician or nephrologist, based on familial history, clinical signs, genetic test, electron microscopy examination of renal biopsy (showing abnormalities of the glomerular basal membrane), or immunohistochemical findings on renal and cutaneous biopsy (even if it cannot establish the diagnosis in all the subjects). Molecular genetic testing will confirm the diagnosis if possible, but it is not required for registry eligibility.

### 4.2.1 Eligibility Criteria

Inclusion Criteria

**I 01.** Confirmed diagnosis of AS confirmed by a certified genetic counselor, treating physician or nephrologist.

**I 02.** Signed informed consent/assent must be provided by the subject and/or caregiver (parent/legal guardian) including compliance with the restrictions listed in the informed consent/assent form and in this protocol.

Exclusion Criteria

**E 01.** [*No exclusion criteria.*]

### 4.2.2 Enrollment Process

#### 4.2.2.1 Alport Syndrome Foundation (ASF)

ASF will directly contact potential subjects. Communication will be through direct email to its membership of more than 8,000 individuals, e-newsletters, webinars, nephrologists via ASF newsletters, all ASF patient events including ASF's annual Alport Connect meeting, frequent online virtual meetings for patients, and through exhibiting and speaking at nephrology and other related conferences. Social media campaigns may be used in the future to educate the ASF community about this registry. If a subject expresses interest in joining the Alport Syndrome Registry, and if the patient or caregiver has any challenges with signing up, the ASF staff will guide the subject or caregiver (parent or legal guardian) through the enrollment steps. Subjects or caregivers will complete the online eligibility screening and informed e-consent process, or they can contact Alport Syndrome Registry personnel.

#### 4.2.2.2 Enrollment Directed to the General Public

Enrollment directed to the general public are:

- Active electronic enrollment (e-enrollment) through email blasts (e-blasts), and passive e-enrollment through web page strategy mentions (e.g., via Facebook, twitter, etc.).
- Recommendations through peer mentors of ASF.
- National awareness campaigns (directed to the at-risk population).
- Direct media campaigns raising awareness about the registry.
- Other events directed towards the general public.

## 4.3 INFORMED CONSENT PROCESS

All subjects and caregivers will undergo an Institutional Review Board (IRB) approved online consent/assent process prior to any study activity. Subjects/caregivers will be directed during the enrollment process to the AS Registry website registration page. Once the screening registration is completed, access to the platform will be provided through a secure email link for the Pulse *healthie*™ 2.0 platform. Once they are logged in to their Pulse platform portal, the registrant will receive information and be guided through the applicable consent/assent process and complete the appropriate consent/assent online forms via e-Consent using the DocuSign® verification of e-signatures industry standard. General consent and assent guidelines follow (with age customization available to be accordant with local and regional minor/adult regulations and laws as needed):

| Age of Participant | Assent Form Required | Informed Consent |
|---|---|---|
| Infant-6 years old | No | Yes |
| 7-12 years old | Yes | Yes |
| 13-17 years old | Yes | Yes |

| | | |
|---|---|---|
| 18+ years old | Not Applicable | Yes |

## 4.4 Participant Withdrawal

Participants may withdraw from the Alport Syndrome Registry by communicating through the participant portal expressing their intention to withdraw, or by communicating directly with the Alport Syndrome Registry personnel. Participants who withdrawal will receive a confirmation email sent by the registry team. In case of withdrawal, the reason for withdrawal, when available, will be documented. Any data collected prior to withdrawal will be kept and be made available for inclusion in all analyses. Participants who withdraw will be allowed to re-enroll/re-activate at a future date.

## 4.5 Registry Duration and Number of Participants

The registry is open-ended with no cap on the number of participants.

# 5 Data Source and Data Management

## 5.1 Data Source and Data Collection

All data will be sourced directly from participants and/or their caregivers into the Pulse platform, directly into the electronic case report forms (eCRFs) that are part of the platform. Mandatory fields will be identified to collect a Minimal Data Set (MDS) on each patient to adequately profile the Alport syndrome patient population. For example, race and sex at birth are mandatory, but a response to receiving genetic testing is optional. The full set of fields to be collected (mandatory and optional fields) will be found in the registry data dictionary.

The data workflow and schedule of assessments are provided in Table 1. Participant data for demographics, medical history, lifestyle factors, participant clinical profile, therapies, and laboratory data will be collected during enrollment. Medical history and laboratory data will be retrospectively collected from the date of clinical diagnosis of AS to the date of enrollment in the registry. When available, additional profiling, routine clinical care, genetic results, and labs will be collected longitudinally and entered in the participant/caregiver portal and/or by direct document upload. Optional follow-up data, such as participant surveys and patient reported outcomes (PROs) may be collected longitudinally. Data will be collected for as long as the participant is enrolled or until registry termination.

**Table 1: Categories and schedule of assessments for participants and caregivers**

| Data | Screening | Enrollment | Prospective |
|---|---|---|---|
| Screening & Consent | X | | |
| Participant Identification | X | | |

| Data | Screening | Enrollment | Prospective |
|---|---|---|---|
| Demographics | | X | |
| Lifestyle Characteristics | | X | |
| Disease diagnostics / Participant Clinical Profile | X | X | X |
| Genetic Results | | X | X |
| Participant Surveys | | | **X** |
| Medical History | | X | X |
| Treatment History | | X | X |
| PROs[1] | | | **X** |
| Laboratory Data | | X | X |

[1] PROs are optional future additions.

## 5.2 Data Management

The *healthie*™ platform is managed and deployed in AWS cloud hosting solutions and adheres to country-specific security and privacy regulatory requirements. Data ingestion and management pipelines in *healthie*™ guarantee only high-quality data reside in the platforms. Strong confidence can be placed in resultant analyses since automated processes detect and rectify data anomalies prior to analysis time, and any single source of clinical data is qualified by external data sources to enhance the value of any piece of data ingested. Incoming values are normalized based on industry and medical community standards to provide proper characterization of data, reusability of data sources, and ease of data mobility between platforms.

## 5.3 Data Access

All data access requests are processed by Application Programming Interface (API) methods that require authentication and authorization. Authorizations require that the requesting identity has a role that permits the operation to be performed and that the identity has permission to the data requested. Roles include participant, site administrator, clinician, investigator, and system administrator, with other roles authorized as necessary. The *healthie*™ 2.0 platform uses role-based access control in authorizing data access following the principle of least privilege—granting minimum system resources and authorizations that are needed to perform the given function. Further details can be found in Section 10.

## 5.4 Data Quality and Monitoring

Data quality measures include data profiling for analysis and the application of rules and algorithms for refinement. During data entry, *healthie*™ 2.0 performs normalizations, validations, and range checks and applies relational constraints for data consistency. A designated Pulse clinical data specialist will manage the database curation process over the life of the registry.

## 5.5 Missing Data

Since the registry is non-interventional and ambispective, it is understood and expected that some data points will be missing. Missing data will be monitored by the Pulse team to ensure that there is not one data point that is routinely not being captured. Several processes will be put into place to ensure the accuracy and reliability of data. Pulse analysts review data collection, the rate of missing data, and any concerns about compliance with data entry. Data entry forms (e.g., data element constraints, such as independent range and/or format limitations or 'relative' referential integrity limitations) and automated error checking will be employed.

Within *healthie*™ 2.0, data standards tools allow for quality assessment at the point of data entry. Task completion indicators will flag unanswered questions as a reminder, and the participant will not be able to advance to the next screen until answers are provided for required questions (e.g., items within validated instruments).

In addition, periodic checks of completed data will ensure data quality and identify potential issues, including end-to-end monitoring and assessment via data provenance and lineage. Manual checks will be conducted to evaluate data completeness and the ratio of "unsure/unknown" and blank answers. When issues arise, they will be routed for evaluation and triage. Remediation of issues may include the following:

- If participant questionnaires are incomplete, reminder emails will be sent to encourage completion of the information for the minimal dataset (MDS).
- If data are identified as being low quality, they can be marked to be excluded from analytics (the submission is never deleted, but the data is not used in downstream analytics or visualizations).

## 5.6 Registry Sample Size and Statistical Power

The registry, by definition, is not hypothesis-driven. It is an open-ended design to collect data about natural history, participant health status and care they receive over time. There is no cap to the enrollment of patients with AS.

# 6 Strengths and Limitations of Registry Methods

## 6.1 Strengths

The main strength of this registry is the ability to recruit participants with a confirmed AS diagnosis and treated data provided by participant or caregiver in real-world routine clinical practice that will enable more comprehensive data collection for the natural course of the disease and treatment modalities of interest both in clinical and in real life setting.

## 6.2 Limitations

The general limitation in a non-interventional observational registry is that the causal relationship of treatments and clinical outcomes cannot be rigorously ascertained.

# 7 PROTECTION OF PARTICIPANT CONFIDENTIALITY

All personal data collected and/or processed in relation to this study will be handled in compliance with all applicable Privacy & Data Protection laws and regulations, including the GDPR (General Data Protection Regulation). When archiving or processing personal data pertaining to the participants or caregivers, Pulse takes all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

Several precautions will be taken to assure the confidentiality of participants. Immediately after enrollment, each participant will be assigned a Globally Unique Identifier (GUID) and the registry specific identifier, which will be used to identify the participant's database records. This unique identifier will not contain any participant identifiers. The database will employ multiple security features to limit access to any Protected health information (PHI) to authorized registry team members only. Data will be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. The computerized database will tag all PHI data and not permit the viewing of such data except by authorized parties. Strict control over data viewing based on role-based permissions will be enforced. All registry Personnel, whose responsibilities require access to personal data will agree to keep the identity of registry participants confidential. Data containing direct identifiers or person identifying information (PII) will be restricted from access and not be available for export at any time. Qualified Researchers, who apply for access to the database, will have a limited dataset access after receiving proper approval with direct participant identifiers removed and transmitted securely using downloadable Excel compatible file formats.

# 8 ADVERSE EVENTS

As it is a non-interventional observational registry and consists of primarily *secondary* data (originally collected by someone other than the patient for other purposes), no risk of adverse events resulting from physical harm is expected from participation in this registry.

# 9 PROVIDING RESULT TO PARTICIPANTS

Through the Pulse platform portal, the participant/caregiver can track previously entered data. As more data becomes available, population-level summaries of the data will populate the portal so the participant/caregiver can visualize and compare their data characteristics with the broader population. When data from the registry are used in a research publication, the title and abstract from the publication may be shared through the portal.

# 10 USE OF INFORMATION AND PUBLICATIONS

The information that will be accrued during the conduct of this registry will be strictly confidential. This information may be disclosed only as deemed necessary. All informational distributions outside of the

reporting and dashboards in this registry protocol will be done under the auspice of a *Study Protocol* with Alport Syndrome Foundation and Pulse. The Registry data may also be used to support data for clinical trials. To access data in the Registry, interested researchers will need to have their research plan approved by the Principal Investigator(s). Once a plan is approved, the researchers would only be provided with the specific de-identified data required for their project in a secure environment.

List of Supplements

- Informed Consent form (ages 18 years and older)
- Assent forms
  - Ages 13 – 17 years
  - Ages 7 – 12 years
- Data Variables/Dictionary
- Recruitment Materials (to be submitted for review one a continual and as-needed basis)

# 11 REFERENCES


Daga, S., Ding, J., Deltas, C., Savige, J., Lipska-Ziętkiewicz, B. S., Hoefele, J., Flinter, F., Gale, D. P., Aksenova, M., Kai, H., Perin, L., Barua, M., Torra, R., Miner, J. H., Massella, L., Ljubanović, D. G., Lennon, R., Weinstock, A. B., Knebelmann, B., … Renieri, A. (2022). The 2019 and 2021 International Workshops on Alport Syndrome. In *European Journal of Human Genetics 2022 30:5* (Vol. 30, Issue 5). Nature Publishing Group. https://doi.org/10.1038/s41431-022-01075-0

Gibson, J., Fieldhouse, R., Chan, M. M. Y., Sadeghi-Alavijeh, O., Burnett, L., Izzi, V., Persikov, A. V., Gale, D. P., Storey, H., & Savige, J. (2021). Prevalence estimates of predicted pathogenic col4a3-col4a5 variants in a population sequencing database and their implications for alport syndrome. *Journal of the American Society of Nephrology*, *32*(9), 2273–2290. https://doi.org/10.1681/ASN.2020071065/-/DCSUPPLEMENTAL

Gibson, J. T., de Gooyer, M., Huang, M., & Savige, J. (2022). A Systematic Review of Pathogenic COL4A5 Variants and Proteinuria in Women and Girls With X-linked Alport Syndrome. *Kidney International Reports*, *7*(11), 2454–2461. https://doi.org/10.1016/J.EKIR.2022.08.021

Gross, O., Tönshoff, B., Weber, L. T., Pape, L., Latta, K., Fehrenbach, H., Lange-Sperandio, B., Zappel, H., Hoyer, P., Staude, H., König, S., John, U., Gellermann, J., Hoppe, B., Galiano, M., Hoecker, B., Ehren, R., Lerch, C., Kashtan, C. E., … Wilkening, F. (2020). A multicenter, randomized, placebo-controlled, double-blind phase 3 trial with open-arm comparison indicates safety and efficacy of nephroprotective therapy with ramipril in children with Alport's syndrome. *Kidney International*, *97*(6), 1275–1286. https://doi.org/10.1016/J.KINT.2019.12.015

Hertz, J. M., Thomassen, M., Storey, H., & Flinter, F. (2014). Clinical utility gene card for: Alport syndrome – update 2014. *European Journal of Human Genetics 2015 23:9*, *23*(9), 1269–1269. https://doi.org/10.1038/ejhg.2014.254

Jais, J. P., Knebelmann, B., Giatras, I., de Marchi, M., Rizzoni, G., Renieri, A., Weber, M., Gross, O., Netzer, K. O., Flinter, F., Pirson, Y., Dahan, K., Wieslander, J., Persson, U., Tryggvason, K., Martin, P., Hertz, J. M., Schröder, C., Sanak, M., … Gubler, M. C. (2003). X-linked Alport syndrome: Natural history and genotype-phenotype correlations in girls and women belonging to 195 families: A "European Community Alport Syndrome Concerted Action" study. *Journal of the American Society of Nephrology*, *14*(10), 2603–2610. https://doi.org/10.1097/01.ASN.0000090034.71205.74

Jais, J. P., Knebelmann, B., Giatras, I., de Marchi, M., Rizzoni, G., Renieri, A., Weber, M., Gross, O., Netzer, K.-O., Flinter, F., Pirson, Y., Verellen, C., Wieslander, J., Persson, U., Tryggvason, K., Martin, P., Hertz, J. M., Schröder, C., Sanak, M., … Gubler, M. C. (2000). X-linked Alport Syndrome. *Journal of the American Society of Nephrology*, *11*(4), 649–657. https://doi.org/10.1681/ASN.V114649

Kamiyoshi, N., Nozu, K., Fu, X. J., Morisada, N., Nozu, Y., Ye, M. J., Imafuku, A., Miura, K., Yamamura, T., Minamikawa, S., Shono, A., Ninchoji, T., Morioka, I., Nakanishi, K., Yoshikawa, N., Kaito, H., & Iijima, K. (2016). Genetic, clinical, and pathologic backgrounds of patients with autosomal dominant alport syndrome. *Clinical Journal of the American Society of Nephrology*, *11*(8), 1441–1449. https://doi.org/10.2215/CJN.01000116/-/DCSUPPLEMENTAL

Kashtan, C. E. (2019). Alport Syndrome. *NCBI Bookshelf*, 1–18. https://www.ncbi.nlm.nih.gov/books/NBK1207/

Kashtan, C. E. (2021a). Alport Syndrome: Achieving Early Diagnosis and Treatment. In *American Journal of Kidney Diseases* (Vol. 77, Issue 2, pp. 272–279). W.B. Saunders. https://doi.org/10.1053/j.ajkd.2020.03.026

Kashtan, C. E. (2021b). Evolving role of patient registries in Alport syndrome. *Https://Doi.Org/10.2217/Frd-2021-0001*, *1*(2). https://doi.org/10.2217/FRD-2021-0001

Kashtan, C. E. (2022). What the Adult Nephrologist Should Know About Alport Syndrome. *Advances in Chronic Kidney Disease*, *29*(3), 225–230. https://doi.org/10.1053/J.ACKD.2021.08.003

Nozu, K., Nakanishi, K., Abe, Y., Udagawa, T., Okada, S., Okamoto, T., Kaito, H., Kanemoto, K., Kobayashi, A., Tanaka, E., Tanaka, K., Hama, T., Fujimaru, R., Miwa, S., Yamamura, T., Yamamura, N., Horinouchi, T., Minamikawa, S., Nagata, M., & Iijima, K. (2019). A review of clinical characteristics and genetic backgrounds in Alport syndrome. *Clinical and Experimental Nephrology*, *23*(2), 158–168. https://doi.org/10.1007/S10157-018-1629-4

Oka, M., Nozu, K., Kaito, H., Fu, X. J. un, Nakanishi, K., Hashimura, Y., Morisada, N., Yan, K., Matsuo, M., Yoshikawa, N., Vorechovsky, I., & Iijima, K. (2014). Natural history of genetically proven autosomal recessive Alport syndrome. *Pediatric Nephrology (Berlin, Germany)*, *29*(9), 1535–1544. https://doi.org/10.1007/s00467-014-2797-4

Savige, J., Colville, D., Rheault, M., Gear, S., Lennon, R., Lagas, S., Finlay, M., & Flinter, F. (2016). Alport syndrome in women and girls. *Clinical Journal of the American Society of Nephrology*, *11*(9), 1713–1720. https://doi.org/10.2215/CJN.00580116

Savige, J., Renieri, A., Ars, E., Daga, S., Pinto, A. M., Rothe, H., Gale, D. P., Aksenova, M., Cerkauskaite, A., Bielska, O., Lipska-Zietkiewicz, B., & Gibson, J. T. (2022). Digenic Alport Syndrome. *Clinical Journal of the American Society of Nephrology : CJASN*, *17*(11), 1697–1706. https://doi.org/10.2215/CJN.03120322

Wang, X., Zhang, Y., Ding, J., & Wang, F. (2021). mRNA analysis identifies deep intronic variants causing Alport syndrome and overcomes the problem of negative results of exome sequencing. *Scientific Reports*, *11*(1), 18097. https://doi.org/10.1038/S41598-021-97414-0

Zhang, Y., & Ding, J. (2018). Renal, auricular, and ocular outcomes of Alport syndrome and their current management. *Pediatric Nephrology (Berlin, Germany)*, *33*(8), 1309–1316. https://doi.org/10.1007/S00467-017-3784-3