# Is the CADASIL Family Registry Research Ready?

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## BACKGROUND

- In 2015, an online global family registry was created for the rare disease Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL).
- The CADASIL Family Registry is a collaboration between the non-profit patient organization, cureCADASIL, and Invitae (previously PatientCrossroads), using their CONNECT platform.
- Invitae has more than 80 patient registries (also known as Patient Insight Networks) across both rare and common diseases.

## OBJECTIVES

- This study assesses whether the registry data can be used to support cross-sectional or longitudinal research studies, genetic studies, and clinical trial enrollment.

## METHODS

### Registry and Data Sets

- Individuals at least 18 years of age can join the registry and consent to share de-identified information by meeting one of the following inclusion criteria:
  - Diagnosed with CADASIL or at hereditary risk of CADASIL and able to make medical decisions
  - Legal guardian of a child or dependent diagnosed with CADASIL (living or dead) or at hereditary risk of CADASIL for whom the guardian can legally make medical decisions
- Once registered, registry participants can choose to complete any of the 4 surveys:
  - Diagnosis
  - Family History
  - Medical Care
  - General Health
- Each survey varies in length. Surveys can be completed at an individual's leisure and can be updated over time.

### Analyses

- Sample sizes and completion rates for each of the registry's 4 surveys as well as de-identified patient-reported data were analyzed using SAS version 9.4 (Cary, NC).
- Outcomes are summarized using descriptive statistics. Other capabilities of the registry are described.

## RESULTS

### Contact Database

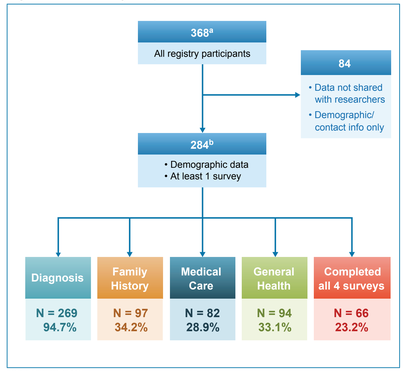
- The registry includes 373 contacts worldwide, with 284 participants consenting to share de-identified survey data with researchers (Figure 1).
- Surveys were completed between June 2015 and June 2018. Among registry participants, the response rate was highest for the Diagnosis survey and substantially lower for the other 3 surveys.

### Cross-Sectional Analyses of Survey Data

- Among registry participants, the response rate was highest for the Diagnosis survey (n = 269/284, 94.7%) and substantially lower for the other 3 surveys (Figure 2).

**Figure 1. Registry Participants by Country of Residence**


**Figure 2. Survey Response Rates**




[a] As of August 13, 2018.
[b] As of June 8, 2018.

- Participants were aged 1 to 80 years at the time of survey completion, with a median age of 50 years (Table 1) (Figure 3).
- The majority of participants live in the United States (US) (77.1%) and are female (58.8%). Nearly half of participants did not provide information on race or ethnicity, nonrequired fields in the registry. Participants most commonly reported being white (33.5%) and non-Hispanic (44.0%) (Table 1).

**Table 1. Demographic Characteristics of Registry Participants**

| | N | % |
|---|---|---|
| Number of registry participants[a] | 284 | |
| Diagnosis status (N, %) | | |
| CADASIL diagnosis | 248 | 87.3 |
| At hereditary risk of CADASIL | 36 | 12.7 |
| Living status (N, %) | | |
| Alive[b] | 279 | 98.2 |
| Dead | 5 | 1.8 |
| Current age (years) | | |
| N (excluding those known to be deceased) | 279 | |
| Mean (SD) | 49.5 (14.8) | |
| Median | 50.0 | |
| Range | 1.0-80.0 | |
| Ethnic origin (N, %) | | |
| Hispanic or Latino | 12 | 4.2 |
| Not Hispanic or Latino | 125 | 44.0 |
| Unknown | 10 | 3.5 |
| Blank | 137 | 50.7 |
| Race (N, %)[c] | | |
| American Indian or Alaskan Native | 2 | 0.7 |
| Asian | 6 | 2.1 |
| Black or African American | 1 | 0.4 |
| Native Hawaiian or Other Native Pacific Islander | 1 | 0.4 |
| White | 95 | 33.5 |
| Unknown | 0 | 0.0 |
| Blank | 183 | 64.4 |

[a] Unique number of registry participants consenting to share de-identified survey data with researchers. Participants could have incomplete or complete surveys.
[b] Number deceased participants was reported only in the General Health survey, which represents a subset of all registry participants. Number and percentage alive were imputed, assuming all registry participants without a General Health survey were alive and not deceased.
[c] Totals may sum to more than 100% because respondents were able to provide multiple answers.

**Table 2. Registry Participants Within the Same Family**

| | N | % |
|---|---|---|
| Number of registry participants[a] | 284 | |
| Participants with > 1 family member in registry | 22 | 7.7 |
| Families with > 1 family member in registry[b] | 5 | N/A |
| Number of registry participants in the same family, among families with > 1 family member in registry | | |
| Mean (SD) | 4.4 (2.6) | |
| Median | 4.0 | |
| Range | 2.0-8.0 | |
| Distribution of number of families with > 1 family member in registry (N, %) | 5 | |
| Families with 2 participants in registry | 2 | 40.0 |
| Families with 3 participants in registry | 0 | 0.0 |
| Families with 4 participants in registry | 1 | 20.0 |
| Families with ≥ 5 participants in registry | 2 | 40.0 |

[a] Unique number of registry participants consenting to share de-identified survey data with researchers.
[b] Among the 5 families with > 1 family member in the registry, all 5 families (100%) had all family members living in the US (i.e., no family members living in countries other than the US).

### Longitudinal Analyses

- Although participants are able to complete surveys more than once to provide updated data, few participants (< 5) completed multiple surveys.

### Feasibility Analyses

#### *Subgroup Analyses Among Individuals at Hereditary Risk of CADASIL*

- Among the 284 participants, 248 (87.3%) reported being diagnosed with CADASIL, and 36 (12.7%) reported being at hereditary risk of CADASIL.

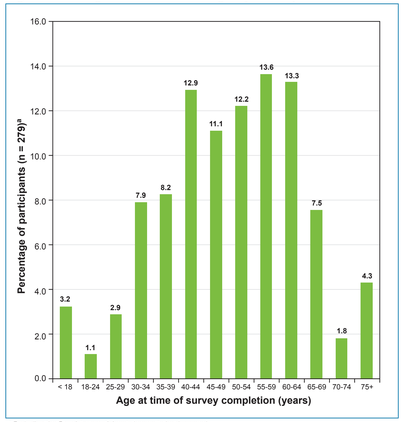
#### *Data for Family Units for Genetic Studies*

- Only 54.5% of participants responding to the General Health survey (36/66, 54.5%) report having a copy of their genetic test.
- Fewer patients (n = 13) have uploaded genetic tests to the registry. These data may include PHI, managed by Invitae only. These are curated only when extensions of the program are developed and in place with patient consent.
- Additional data can be collected for investigators with an IRB-approved human research study requiring further patient consent.
- There were 22 participants with family members in the registry, leading to 5 distinct family units with all family members living in the US (Table 2).

#### *Registry Usability*

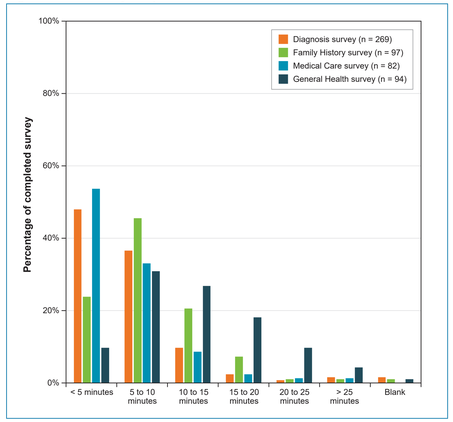
- Because of low survey response rates, usability of the registry was explored.
  - Participants most frequently reported that each survey took fewer than 5 minutes to complete (Diagnosis and Medical Care surveys) or 5 to 10 minutes to complete (Family History and General Health surveys) (Figure 4).
  - Twenty two participants (7.7%) reported using Google translate for languages other than English.

**Figure 3. Age Distribution of Registry Participants**




[a] Excluding the 5 registry paraticipants known to be deceased.
[b] Individuals aged <18 years include data reported by their legal guardian.

**Figure 4. Survey Response Time**




## CONCLUSIONS

- More than 250 individuals have provided patient-reported data in the registry, allowing for identification of participants who meet broad clinical trial enrollment criteria.
  - Queries on specific demographic, diagnostic, or medical criteria can be submitted to the registry partner (Invitae) to identify participants meeting specific criteria for clinical trials or other research studies.
  - Limited patient-reported clinical data specific to CADASIL (e.g., time since symptom onset, co-morbidities) are available that could be used for study enrollment.
  - Clinical or genetics data from patient medical records (i.e., imaging) are not included, limiting the use of the registry data for specific enrollment criteria.
  - Identification of family units for familial genetic studies or participants with uploaded genetic tests is feasible, but participation remains low.
- The CADASIL Family Registry is a unique source of demographic and patient-reported outcomes for individuals with CADASIL or those at hereditary risk who are currently undiagnosed.
- Studies that could be supported now or in the future include:
  - Cross-sectional analyses of the full registry population or US population with a reported CADASIL diagnosis are currently feasible.
  - Analyses of individuals at hereditary risk of CADASIL currently limited due to small sample sizes (< 40 people).
  - Longitudinal analyses are also not possible due to the low number of participants with multiple surveys over time. Low survey response rates and a low number of participants updating surveys may be due to survey length and under-utilization of participant reminders to complete their surveys.

## DATA LIMITATIONS AND FUTURE GROWTH

- Data represent patient-reported outcomes and are not confirmed against patient medical records.
- Data provide useful information on the population of individuals diagnosed with or at risk of the rare disease CADASIL, but efforts could be made to increase survey participation (e.g., participation is low outside the US, response rates are low for specific surveys within the registry and among those at hereditary risk of CADASIL).
- Participants' updates of each survey are critical for the following reasons:
  - To ensure survey data accurately represent their current health status.
  - To allow researchers to conduct future longitudinal studies of changes in CADASIL treatments or health status over time.

## ACKNOWLEDGEMENTS

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## AUTHOR DISCLOSURES

No funding was provided for this study. S Talbird and E La are employees of RTI Health Solutions, which supported their time to conduct this study and related publications. S Talbird has been a board member of the cureCADASIL Association since 2017 and serves as the CADASIL Family Registry Coordinator. E La has no disclosures. N Maurer is the current President of cureCADASIL Association. V Rangel Miller and J Vidal are employees of Invitae, which hosts and manages the registry data.

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