HHS Public Access

Author manuscript

Am J Med Genet C Semin Med Genet. Author manuscript; available in PMC 2020 August 13.

Published in final edited form as:

Am J Med Genet C Semin Med Genet. 2019 March ; 181(1): 135–140. doi:10.1002/ajmg.c.31689.

The Turner syndrome research registry: Creating equipoise between investigators and participants

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Abstract

To address knowledge gaps about Turner syndrome (TS) associated disease mechanisms, the Turner Syndrome Society of the United States created the Turner Syndrome Research Registry (TSRR), a patient-powered registry for girls and women with TS. More than 600 participants, parents or guardians completed a 33-item foundational survey that included questions about demographics, medical conditions, psychological conditions, sexuality, hormonal therapy, patient and provider knowledge about TS, and patient satisfaction. The TSRR platform is engineered to allow individuals living with rare conditions and investigators to work side-by-side. The purpose of this article is to introduce the concept, architecture, and currently available content of the TSRR, in anticipation of inviting proposals to utilize registry resources.

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CONFLICT OF INTEREST

None declared.

Keywords

patient-centered; registry; research; Turner syndrome

1 | INTRODUCTION

The sine qua non of Turner syndrome (TS) is the absence of all, or part, of the second sex chromosome in females (Ford, Jones, Polani, De Almeida, & Briggs, 1959) (Zinn, Page, & Fisher, 1993). In TS, critical triggering events initiated by sex chromosome deficiency are capable of producing numerous phenotypic variations. Clinicians, researchers, and most importantly, girls and women with TS and their families, are concerned and frustrated that little is known about the TS associated mechanisms leading to premature ovarian failure, life-threatening cardiovascular diseases, sensorineural hearing loss, neurocognitive deficits, and early death (Stochholm, Juul, Juel, Naeraa, & Gravholt, 2006). The only X-chromosome gene (*SHOX*) that has been clearly shown to be responsible for a major characteristic of the TS pheno-type, short stature, was discovered more than 20 years ago (Rao et al., 1997). In fact, no sex chromosome genes are known to cause any of the major disorders that are associated with TS (Backeljauw et al., 2015). Identification of genes that contribute to many diseases associated with TS will create new opportunities for treatment and prevention leading to substantial improvement in the health and well-being of the affected women and girls.

Research to identify TS-associated disease mechanisms has been significantly limited by three factors: (a) TS is a rare condition occurring in 1:2000 female live births; (b) Because sex chromosome loss in TS is virtually always a cellular event occurring once the zygote is formed, it is not heritable; and (c) No major research funding body has a substantial commitment to TS research, as the associated diseases affect many different organ systems (Campbell, Shaw, Stankiewicz, & Lupski, 2015; Zhong & Layman, 2012). Accordingly, investigators are limited by the lack of ready access to TS participants who are sparsely distributed throughout the country and the world, do not segregate into families and do not fit into single-disease states. This makes them more difficult to identify and may limit funding opportunities.

To remedy this problem, the Turner Syndrome Society of the United States established the Turner Syndrome Research Registry (TSRR). Like all registries, the TSRR is designed to collect and store data in order to help understand disease mechanisms and natural history. The unique architecture of the TSRR facilitates longitudinal access to research participants, who may grant permission to be recontacted for follow up studies. Another aim of the registry design is to expand the database by requiring researchers to return newly collected data to the registry, thereby continuously increasing the scientific content of the TSRR. Over time, the routine addition of newly acquired data by TSRR-affiliated researchers will create a "virtuous cycle" that will increase the value of the registry to new TSRR investigators.

More than 600 girls and women with TS or their proxies have completed a foundational survey capturing their demographic information, medical conditions, and experiences with medical care. This report is intended to introduce the research community to the unique

aspects of this patient-powered registry and to highlight the potential value of the TSRR to investigators and participants.

2 | MATERIALS AND METHODS

Structure of the Registry:

The TSRR is an observational registry of individuals with TS. Women and girls with TS, or their authorized representatives, may enroll in the registry through an online portal that allows them to customize their profiles and manage access to their information (https://www.turnersyndrome.org/ts-registry-love). Registry participants can adjust multiple privacy options to control access to group-level data, de-identified individual data, or fully identified data, including contact information. All participants completed a foundational survey that includes questions about demographic information, medical history, and willingness to participate in research. A demonstration portal (turnersyndrome.org/registry-demo) illustrates key functions such as registering, choosing privacy levels, and accessing the survey.

Administration of the Registry:

The TSRR utilizes the platform for engaging everyone responsibly (PEER), which was created by Genetic Alliance. A subset of TSRR questions are derived from common data instruments that are identical to other PEER platform registries. The Turner Syndrome Society of the United States (TSSUS) hosts and administers the TSRR. Survey responses are continuously validated using online prompts and electronic monitoring to ensure survey completion, telephone and/or online verification and other quality control measures. Participant registration and data access are regulated by a scientific advisory board (SAB) consisting of clinicians, researchers and advocates, including women with TS. This is discussed in detail below.

Researcher collaboration (Figure 1):

Potential TSRR investigators submit research proposals to the SAB for review. The SAB endorses the most promising data utilization projects and promotes them to TSRR participants. The SAB will consider all basic, clinical or translational research projects that are relevant to Turner syndrome. Approved TSRR investigators must agree that all newly acquired research data (genomic, clinical, and laboratory data) from SAB-approved research projects will be directly incorporated into the TSRR after a mutually agreed-upon embargo period.

Data utilization:

Researchers will obtain access to registry data according to accepted standards for protected health information. We delineated three tiers that reflect increasing engagement of investigators and registry participants in TSRR projects:

- Tier 1: Investigators request access to de-identified data that already exists in the TSRR.

- Tier 2: Investigators request collection of de-identified data that does not currently exist within the TSRR. This may involve collaboration with TSRR staff to create a new survey for distribution to registry participants.
- Tier 3: Investigators request identified data and invite qualified participants to enroll in new research that cannot be accomplished within the scope of the TSRR (such as the collection of images or biological samples).

Registry workflow (Figure 2):

Investigators who wish to participate in the TSRR will submit applications to the SAB for review. After approval, investigators will either: query the database to mine existing de-identified data (Tier 1, a), work with the SAB to submit a new survey to all or a subset of registry participants (Tier 2, b), or contact individual participants to enroll in a new research protocol where PHI will be collected after appropriate informed consent (Tier 3, c). Tier 2 and Tier 3 projects will also require approval by an institutional review board at the investigator's institution. Data from Tier 2 projects will automatically become part of the clinical and biological data repository after a mutually agreed upon embargo period (arrow). At the conclusion of Tier 3 projects, investigators will return data to the repository (arrow). Over time, this will create a "virtuous cycle" in which new data continually improves the quality of the TSRR and simulates new research projects.

Data collection statistical analysis:

Participant responses were extracted from the TSRR on February 27, 2018. The initial 33-item survey included questions about demographics, medical conditions, psychological problems, sexuality, hormonal therapy, genetic and clinical tests, patient and provider knowledge about TS and patient satisfaction (Figure 3). The complete list of survey questions is available in Supporting Information. The survey was also intended to identify participants with specific high-risk conditions such as aortic dissection. Missing data was recoded as "−9." To facilitate data analysis, measurement units and free text responses were standardized. Descriptive statistics were analyzed using STATA (Stata Corp., College Station, TX).

3 | RESULTS

A total of 596 responses were available for analysis. The mean age at the time of the survey was 27 years (Figure 4). Most registry participants (478) identified as Caucasian or European.

In the Danish Cytogenetic Central Registry, 46% of TS patients were diagnosed by age 5 and 90% by age 15 (Gravholt, Juul, Naeraa, & Hansen, 1996). The distribution of age at diagnosis was similar in TSRR data: 88% of respondents were diagnosed by age 15, and the median age of diagnosis was 3 years (Figure 5).

All 596 individuals completed the section of the survey that queried their chronic medical conditions. The most frequently self-reported condition was short stature or growth failure (74%). This question did not distinguish between mature adults and younger individuals

who may not have achieved their adult height. Ovarian failure (44%), hearing loss (39%), chronic ear infections (39%), and visual impairment (37%) were the most prevalent self-reported medical conditions. About 368 (69%) participants reported any use of estrogen replacement therapy. Spontaneous pregnancy is rare in TS, with a greatly increased risk for miscarriage compared to the general population. Ten adult participants (1.7%) reported that they had ever been pregnant. None of the ever-pregnant participants were aware of having aortic complications such as dilation or dissection.

TSRR participants expressed a positive perception of their primary care physician's knowledge about TS: 75% of respondents described their primary care physician as very or somewhat knowledgeable about Turner syndrome. Ten percent of participants did not identify a primary care physician. Similarly, 79% of participants rated themselves as well or moderately well-informed about TS (Figure 6).

TSRR participants also indicated general enthusiasm about participating in future research studies. Almost 90% of participants said that they are likely to take part in additional research related to TS and are willing to provide samples for DNA analysis as part of a research study.

4 | DISCUSSION

The TSRR is a powerful platform that promises to unite all stake-holders in the TS community, including affected individuals, researchers, clinicians, and advocacy organizations in advancing the scientific understanding of TS. The scientific advisory board will mediate these collaborations to ensure that TSRR participants are informed about their choices to participate in high quality, peer-reviewed research that reflects the priorities of the TS community. We define three levels of potential engagement between researchers and participants.

In Tier 1 proposals, investigators will request access to de-identified data that already exists in the registry. Currently, TSRR survey responses are self-reported and have not been independently verified. In addition, some survey questions were frequently left unanswered. Social factors, ambiguity or lack of health knowledge may account for some of the missing data. Nevertheless, some self-reported data have the potential to provide valuable insight into ethnicity, sexual orientation, mental health, access to healthcare, and participant perception of their health and quality of life (Mathes & Pieper, 2018). Self-reported data can also reveal the changing landscape of health care for those with TS. For example, we found that the age of diagnosis has become younger as prenatal genetic testing has become more accessible. We also found that almost half of TSRR participants either did not report or did not know their karyotypes. This may reflect widespread gaps in health awareness, challenges to patient-provider communication, or limited access to care (Amedro et al., 2017). Tier 2 or Tier 3 projects to follow up on these responses could pave the way for interventions to address these disparities. As the TSRR data repository grows, more data will be available for Tier 1 proposals.

In Tier 2 proposals, investigators will request de-identified data that does not currently exist within the TSRR. The SAB will work with individual investigators to craft robust surveys to address their research interests. For example, spontaneous pregnancy has been reported in 5–8% of women with TS, with a markedly increased rate of miscarriage (Bannink, Raat, Mulder, & de Muinck Keizer-Schrama, 2006; Cadoret et al., 2018). Ten TSRR participants (2%) reported that they had been pregnant. Tier 2 surveys can be used to generate new demographic and clinical data about high-risk subgroups, such as ever-pregnant women with TS. Tier 2 projects will enlarge the available dataset by incorporating new and follow-up surveys. In addition, Tier 2 projects will allow researchers to lay the groundwork for future Tier 3 proposals by collecting new information from participants.

In Tier 3 projects, investigators will utilize identified individual-level data and/or communicate directly with participants in order to carry out research proposals that expand the current scope of the TSRR. The purpose of Tier 3 projects will be to moving beyond self-reported information to collect new clinical data, biological samples, or images on specific subgroups of TSRR participants. For example, clinical investigators can recruit participants through the TSRR to perform new diagnostic or procedural studies or to obtain clinical data from electronic health records, which may not be easily accessible to participants. Basic scientists who aim to determine the “molecular phenotype” of TS-related conditions can recruit specific subgroups of registry participants for dense clinical phenotyping in conjunction with genomic, transcriptomic, proteomic, epigenomic, or metabolomic investigations. High-risk subgroups, such as participants who self-identify as survivors of acute aortic dissections or other not well-characterized conditions, may benefit from targeted surveillance or early interventions to reduce morbidity and mortality, which can be tested in future clinical trials (Lin et al., 2016; Silberbach et al., 2018). All data collected as part of Tier 3 projects will eventually be incorporated into the TSRR. As in a virtuous cycle, the increasing volume of data and number of participants that are available to researchers will make the TSRR an attractive platform to test new hypotheses about the etiology and modifying factors of TS-related disorders.

5 | FUTURE PLANS

The current clinical practice international guidelines for the care of girls and women with TS are limited by the lack of evidence-based data (Gravholt et al., 2017). Propelled by hypothesis-driven expansion and continuous quality improvement, the TSRR is well positioned to fill in these knowledge gaps. TSRR data will dynamically and continuously improve as investigators and participants enrich the registry by contributing patient-reported information, clinical records, images, and data. Enrollment will continue to grow through an expanding network of TS comprehensive care centers with support from the Turner Resource Network and the Turner Syndrome Global Alliance. Future versions of the TSRR will include features that streamline recruitment for additional studies by incorporating links to import data from electronic health records, as well as features that facilitate networking and advocacy by allowing participants to view aggregate survey responses, contact other consenting participants, or solicit medical advice from a TSSUS professional. TSSUS will regularly update participants and the TS community with insights and results of TSRR-driven research. Thus, research that emerges from the TSRR will not only increase general

knowledge about TS-related disorders, but will also directly benefit participants and the TS community. Continuous quality improvement will allow registry participants and researchers to contribute more data over time. These features will provide powerful incentives for participants and researchers to remain engaged with the registry in order to improve the clinical care of disorders related to Turner syndrome.

ACKNOWLEDGMENTS

We are very grateful to the Turner Syndrome Society of the United States for continuous support of the TSRR and to all of the registry participants. We would also like to thank Brian Tang, M.S., for assistance with data analysis. This work was partially funded by the Cheves and Isabella Smythe Distinguished Professorship in Medicine at the University of Texas at Houston (SP) and the Ravelle Pittman Research Fund of the Turner Syndrome Society of the United States (MS).

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How to cite this article: Prakash SK, Lugo-Ruiz S, Rivera-Dávila M, et al. The Turner syndrome research registry: Creating equipoise between investigators and participants. Am J Med Genet Part C. 2019;181C:7–12. 10.1002/ajmg.c.31689

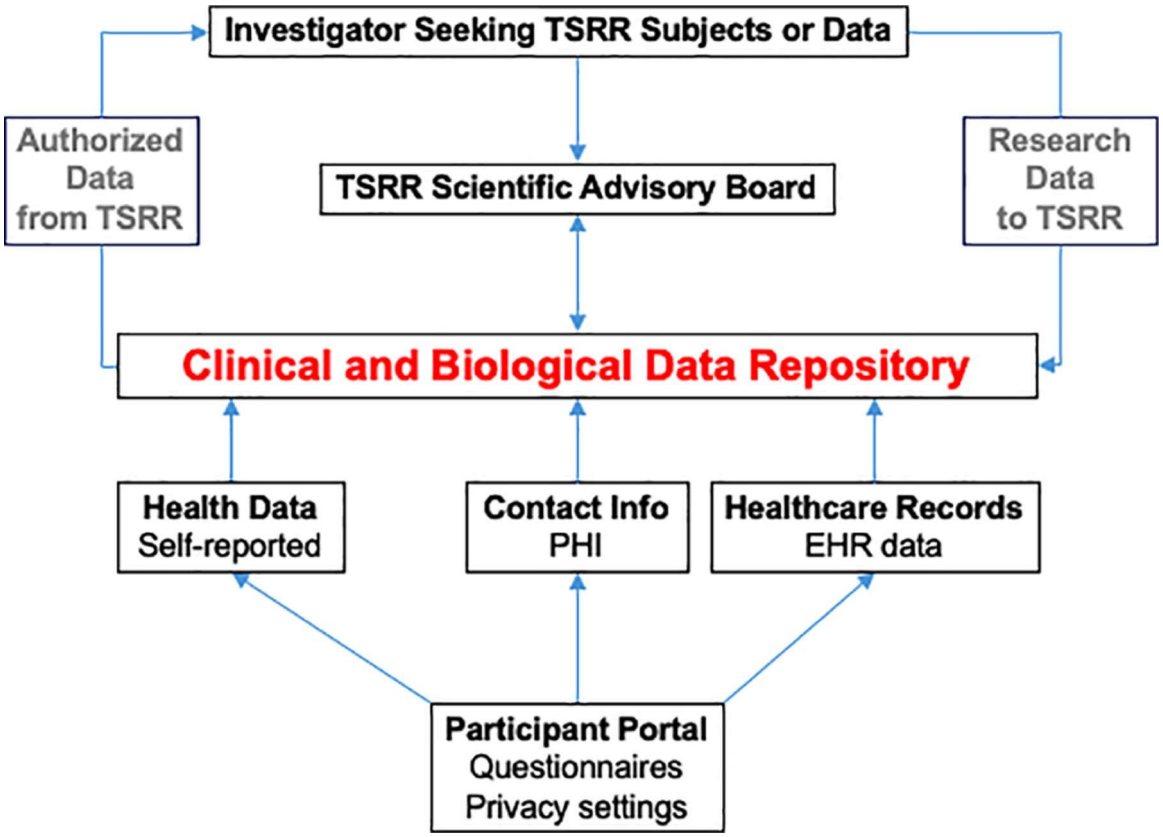

FIGURE 1.

Structure of the Turner syndrome research registry (TSRR). Flow diagram illustrates potential interactions between participants and investigators. The scientific advisory board will vet all scientific proposals and will work with investigators to return new research data to the registry

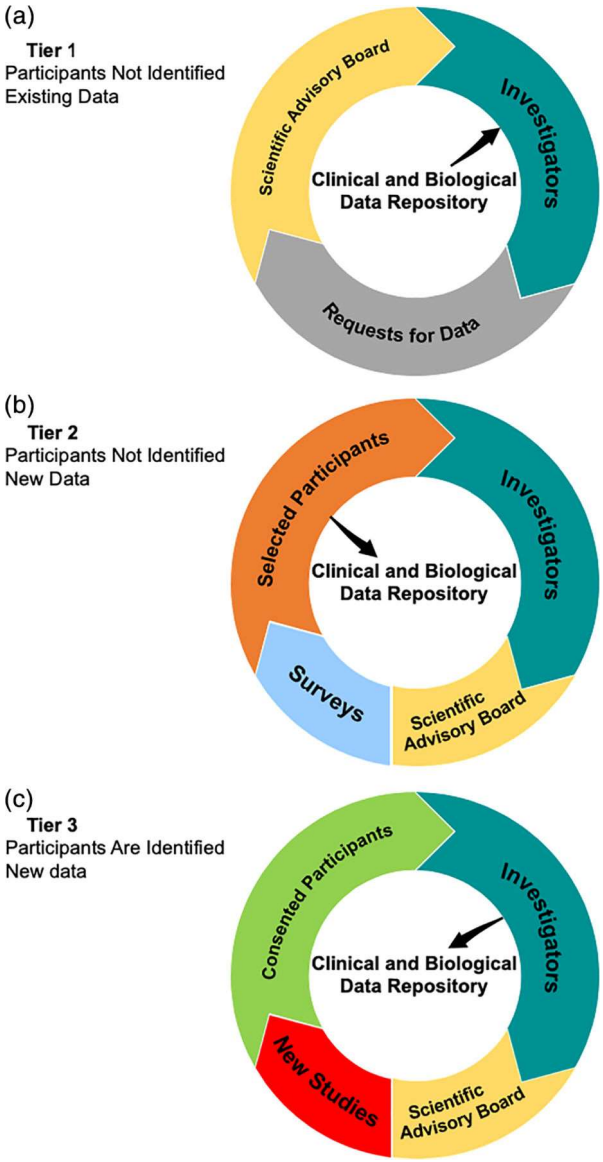

FIGURE 2.

TSRR registry workflows. (a) In Tier 1 projects, investigators retrieve and analyze existing de-identified data from the repository. (b) In Tier 2 projects, investigators work with the scientific advisory board to circulate new or follow-up surveys to groups of participants. New survey data is automatically entered into the repository. (c) In Tier 3 projects, investigators directly contact and enroll individual participants into new research protocols. Investigators will return new clinical data, images and biological samples to the repository. Participants may opt out of Tier 2 or Tier 3 research by selecting appropriate privacy settings

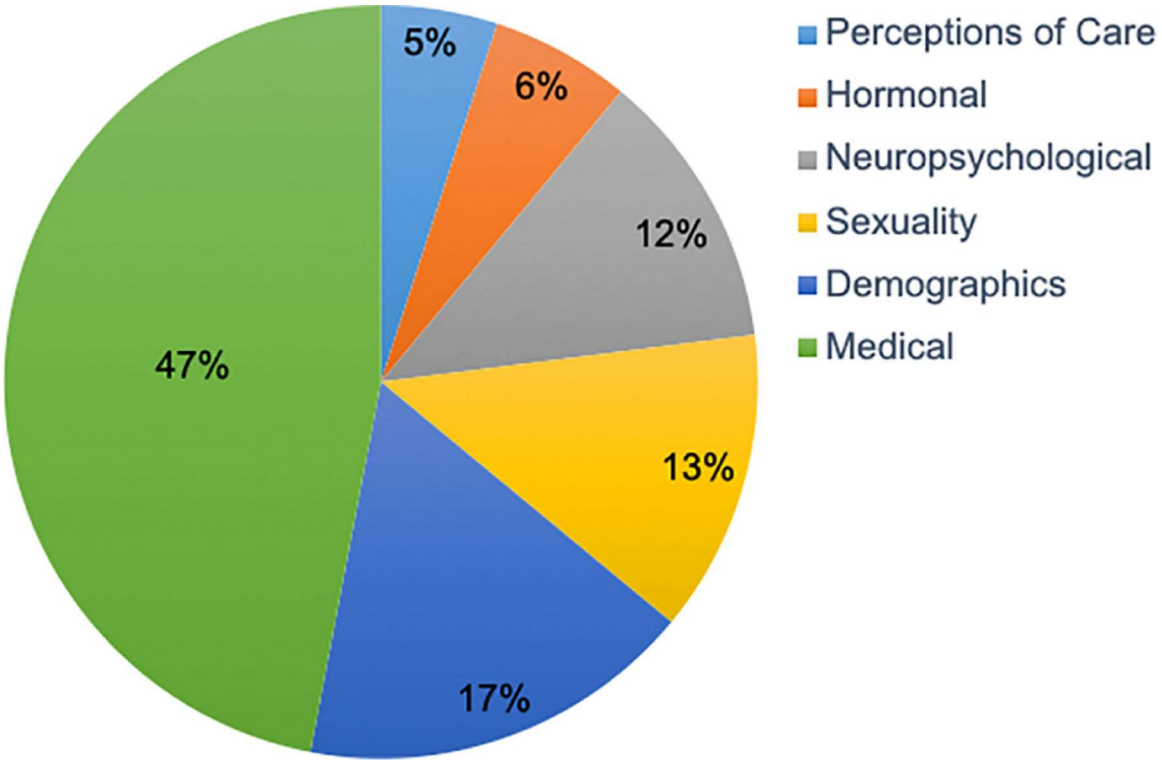

FIGURE 3.
Categories of survey questions. The pie chart shows the percent distribution of different categories. There were 33 total questions

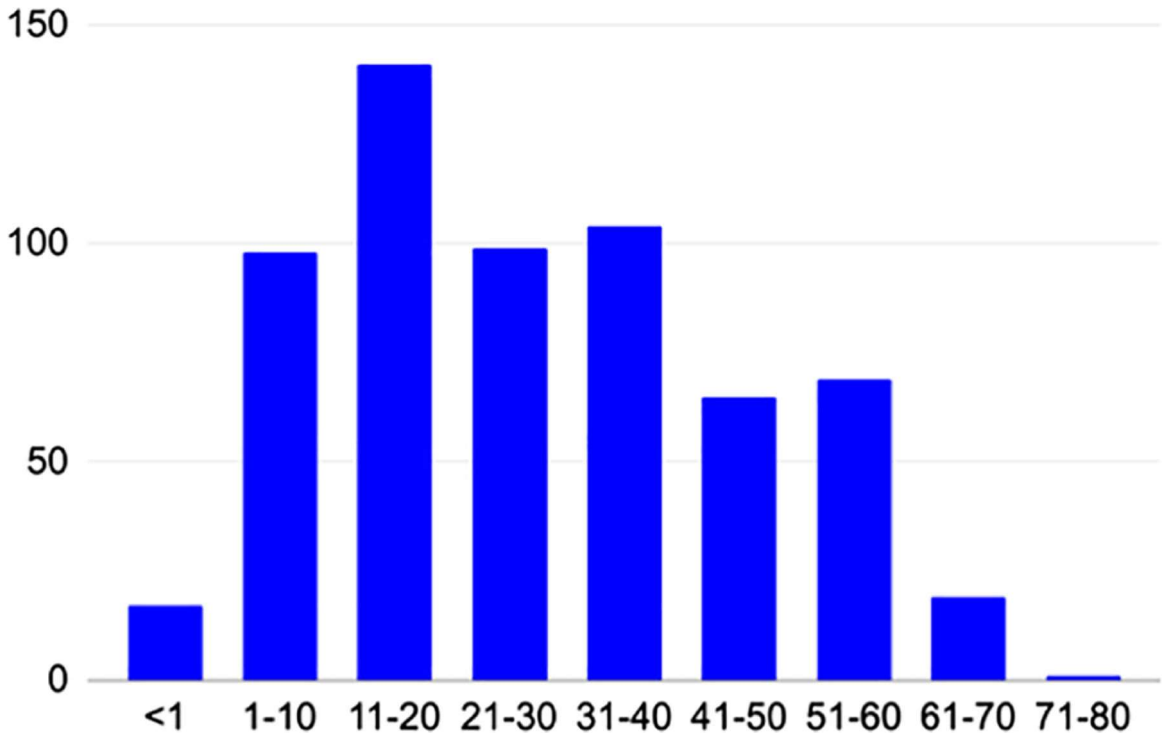

FIGURE 4.
Age distribution of TSRR participants. Numbers of participants are on the Y-axis and ages in years are on the X-axis

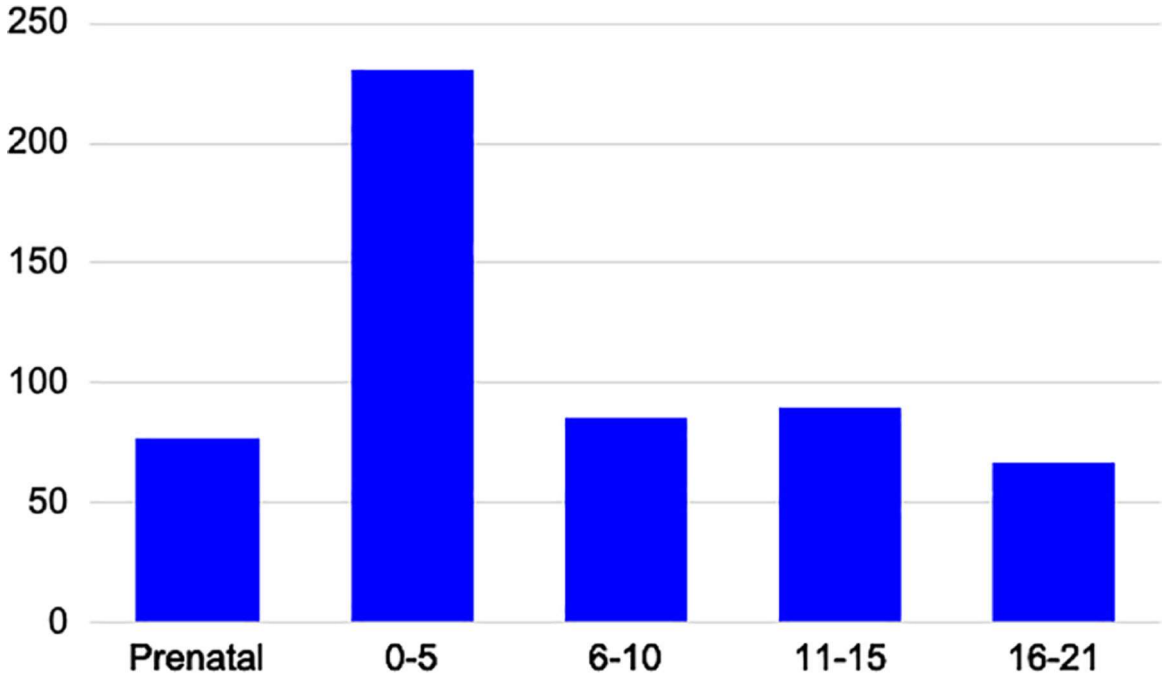

FIGURE 5.
Distribution of ages at the time of diagnosis. Numbers of participants are on the Y-axis and age categories or ranges in years are on the X-axis

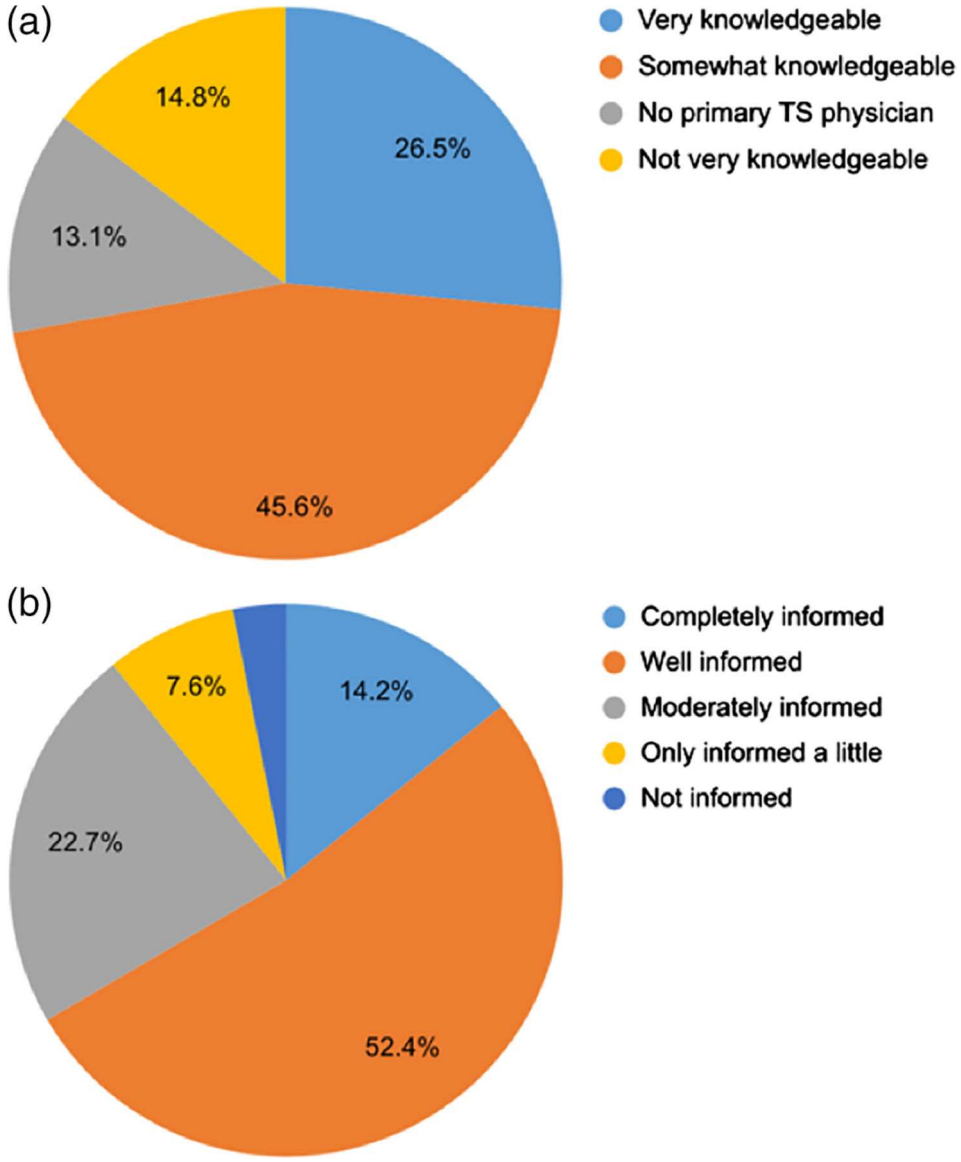

FIGURE 6.

Primary care physician and participant knowledge about TS. (a) TSRR registry participants rated the knowledge of their primary providers about TS. (b) TSRR registry participants rated their own understanding of TS-related medical conditions