


The initiation, design, and establishment of the Desmoid Tumor Research Foundation Patient Registry and Natural History Study

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Abstract

Desmoid tumors are locally invasive sarcoma, affecting 5–6 individuals out of 1,000,000 per year. The desmoid tumors have high rates of recurrence after resection and can lead to significant deterioration of the quality of life of patients. There is a need for a better understanding of the desmoid tumors' patient experience from first symptoms through diagnosis, disease monitoring, and clinical treatment options. With the National Organization of Rare Disorders, the Desmoid Tumor Research Foundation Natural History Study was designed to be collected through the registry. This article describes the protocol for the Desmoid Tumor Research Foundation Natural History Study and some initial findings. The Desmoid Tumor Research Foundation Natural History Study Advisory Committee developed a series of questionnaires and longitudinal surveys, in addition to those from the National Organization of Rare Disorders for all of the rare diseases. These 13 surveys are designed to uncover initial symptoms, diagnosis process, disease monitoring, quality of life, treatments, as well as socioeconomic information. Since launching the Desmoid Tumor Research Foundation Registry and Natural History Study (<https://dtrf.iamrare.org>), more than 300 desmoid tumor patients have consented to the Desmoid Tumor Research Foundation Natural History Study and completed the Participant Profile. The majority of the respondents are between the ages of 21 and 50 years (76%), female (81.2%), White (91.5%), and live in the United States (47.1%). The majority of tumors are in the lower or upper extremity, (22.9%) followed closely by abdominal desmoid tumors (21.5%). Most are willing to donate specimens (89.9%) and participate in trials (97.2%). Ongoing efforts are addressing the demographic differences between the respondents and non-respondents and any selection bias based on access to the registry and study. The Desmoid Tumor Research Foundation Natural History Study is built on the largest desmoid tumors registry and has recruited more desmoid tumors participants since launching in September 2017. It will serve to fill desmoid tumors knowledge gaps and assist other researchers in their recruitment efforts for additional studies.

Keywords

Desmoid tumor, aggressive fibromatosis, β -catenin, familial adenomatous polyposis, rare diseases, natural history study, patient registries, patient-reported outcomes, sarcoma

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Introduction

Desmoid tumors (DTs; also known as aggressive fibromatosis) are benign, locally invasive mesenchymal soft tissue tumors.¹ Currently, there are no standardized treatment plans for DTs and little information is available on tailoring effective therapy to different patient groups based on their

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demographic or clinical characteristics.^{2,3} For example, broad spectrum chemotherapy has shown limited success in patients who have experienced a recurrence of their tumors after surgery and/or radiation.⁴ Up to 50% of DT patients experience recurrence.^{5,6} Young age was found to be a predictor of DT recurrence;^{5,7} therefore, treating children with ineffective, high-risk chemotherapeutic treatments is not advisable.^{8–10} More effective treatment plans are needed for the 5–6 out of a million people who are diagnosed yearly with DT.¹¹ To develop better interventions for DT and improve patient outcomes, there is a need for a better understanding of the DT patient experience from first symptoms through diagnosis, disease monitoring, and clinical treatment options.

Without a clear understanding of rare diseases (RDs), such as DTs, clinical trials and drug discovery are more difficult, if not impossible. The clinical development program for drugs, biologics, medical foods, or medical devices must be built on a foundation of the disease's progression. The U.S. Food and Drug Administration (FDA) noted in a 2017 address to the Regulatory Affairs Professionals Society (RAPS) that the agency was focused on collaborating with researchers on how to develop models for RDs' clinical trials to make recruitment more efficient. According to the FDA, the goal of the Orphan Products Clinical Trials Grants Program (formerly known as Orphan Products Grants) is to encourage clinical development of drugs, biologics, medical devices, or medical foods for use in RDs. There are more than 7000 RDs, which means that 25–30 million people in the United States have been diagnosed with RDs.¹²

Background to the DTRF patient registry

Under a cooperative agreement with the FDA, the National Organization of Rare Diseases (NORD) developed RD patient registries and natural history studies program. NORD developed a web-based platform and prepared survey templates for RD patient organizations. The Desmoid Tumor Research Foundation (DTRF) is a NORD member organization and was chosen to participate. The DTRF Natural History Study (NHS) was designed to be collected through the DTRF Registry that includes surveys for all of the NORD participating groups which describe the natural course of RDs from first symptoms through different clinical stages. The DTRF NHS Committee also developed a series of questionnaires and longitudinal surveys. These surveys are designed to uncover initial symptoms, diagnosis process, disease monitoring, quality of life for individuals with DT, and socioeconomic information.

The DTRF NHS is significant because there are no published data on the natural history of this RD population, including characteristics of patients and the relationship between patient characteristics and treatments received. This critical gap in the scientific literature is adversely impacting this RD patient population. NHSs are the foundation for which basic and clinical researchers base their investigations

and clinical development strategies. This NHS is built on the largest DT registry and has recruited more participants since launching in September 2017.

Materials and methods

Description

The DTRF Patient Registry is a prospective longitudinal web-based observational NHS. Participants with DTs will be followed throughout the course of their lives with either the participant or authorized respondents contributing data at varying intervals throughout the course of the study.

The registry and NHS can be accessed at <http://dtrfiam-rare.org>.

Protection of human participants

This registry and study has ethical approval for global data collection from the Hummingbird IRB (2016-44). To consent to the registry and study, participants read an online consent form explaining the purpose of the DTRF Patient Registry and agree to the use of their personal and medical information, including Personal Health Information (PHI). Participants are also informed that de-identified information is shared with the NORD NHS program. Individuals providing consent are asked to confirm that she/he is the participant or legally authorized representative (LAR) of the participant. Consent from an LAR is required for participants who are minors or who are over the age of 18 years but unable to provide informed consent. Consent is also asked for future contact by the registry staff to clarify data entry should questions arise or by future investigators seeking participants for research studies. Participation in this registry and study and/or consenting to contact in no way obligates to participation in any future studies.

The informed consent is documented by an electronic signature mechanism whereby the individual providing the informed consent checks a box after reading the electronic informed consent document online. There is a list of conditions that demonstrate informed consent, such as confirming they have read the study information, consent form, and any questions they had were answered to their satisfaction. All conditions are required a “yes” check from the respondent before consent is granted.

Registry participants are also asked to provide their permission for the use of registry information for retrospective research studies by registry investigators and staff, as well as by third parties' granted access to registry data. In addition, the participants are asked to provide their permission to allow registry administrators and staff to contact them to ascertain interest in participation in future research studies and/or clinical trials. Interested registry participants contacted for possible participation in future research studies will undergo a separate informed consent process for each such research study.

Table 1. DTRF NHS components.

Item	Calendar date	Survey title	Longitudinal
Protocol approval	5 September 17	Participant Profile	No
		Medical and Diagnostic Data	Yes
		Treatment and Review of Systems	Yes
		Quality of Life Parts I and II	Yes
		Quality of Life Pediatric	Yes
		Medical Data for Desmoid Tumors	Yes
		Diagnostic Data for Desmoid Tumors	No
		Treatment of Desmoid Tumors	Yes
		Desmoid Tumor Monitoring	Yes
		Desmoid Tumors and Pregnancy	Yes
		Desmoid Tumor Symptoms (PRO1 and PRO2)	Yes
Desmoid Tumor and Activities	Yes		
Registry and NHS launch	23 September 17		
Amendment 1	17 April 18	Participant Profile	No
		Other Medical Conditions	Yes

DTRF: Desmoid Tumor Research Foundation; NHS: Natural History Study; PRO: patient-reported outcome.

A participant may revoke his or her consent if they wish to withdraw from the study at any time. If consent is revoked, all participant data will be archived and no longer used for study purposes. However, data shared under the conditions of consent prior to revocation cannot be retrieved and destroyed.

Eligibility criteria

All patients with a confirmed diagnosis of DTs are eligible for inclusion. The registry is open to recruiting patients of all ages who have ever had a diagnosis consistent with DTs. DTs are defined as tumors that are derived from fibroblast cells, which undergo a mutation and begin to grow aggressively. In addition, patients must be willing to provide informed consent and able to comply with web-based study procedures and data collections.

Outreach and recruitment

Information about the existence of the registry is communicated by NORD and the DTRF via mass media (email, website advertisements, flyers, patient foundations, and other mean of mass communication) to interested members of the DT community including patients, physicians, and researchers. In addition, information about the registry disseminated through clinical, professional, research, patient foundations, and support groups including but not limited to the DTRF email distribution list, the DTRF patient meetings, the DTRF social media platforms, including Facebook, Twitter, LinkedIn, and NORD: www.rarediseases.org.

The DTRF Patient Registry data are stored on secure servers located at the NORD. Data entry is performed on the world wide via a web interface.

Data elements and quality

Data are collected at the start of the study (baseline) and 1 year interval, described in Table 1. Some data are only be collected at baseline, while other data will be collected longitudinally (Medical Data for Desmoid Tumors, Diagnostic Data for Desmoid Tumors, Treatment of Desmoid Tumors, Desmoid Tumor Monitoring, Desmoid Tumor Symptoms (PRO module 1), Desmoid Tumor Impact (PRO module 2), Desmoid Tumors and Pregnancy, and Desmoid Tumors and Activities).

The registry participants are not required to provide any documentation to support their DT diagnosis. It has been shown previously that the accuracy of self-reported diagnosis of RDs is 99%.¹³ These preliminary data were pulled from the NHS on 20 December 2018.

Modifications to the study

As the registry and NHS continue to collect information from the participants, the study is evolved. Factors that contribute to this evolution include new scientific knowledge about DTs. The registry participants have provided feedback to the administrator and principal investigator, and a new survey to collect co-morbidities was added in a protocol amendment. This addition was discussed with the NHS committee for their feedback, suggestions, and modifications before IRB approval and publishing.

Updateable surveys

It is probable that the participants undergoing aggressive treatment plans will want to update their quality of life (QOL) and treatment responses more frequently. This study platform permits real-time updates to minimize recall bias. Each update is saved independently.

Data access and sharing

The DTRF Registry and NHS are valuable resources for current and future research, and the DTRF Advisory Board ensures proper evaluation of protocols to use registry data and/or contact registry participants. Investigators wanting to use the registry or contact participants need to apply to the Advisory Board. The application requires information concerning principal investigator, aims and hypotheses of the proposed research, where the research will be performed, and how the research will be funded.

There are three levels of expected engagement for the registry and study data.

Level 1: Study Principal and Co-investigators. The DTRF Study Principal and Co-investigators outlined in the protocol cover page have access to all database elements for analysis and publication; any publication of data will be done so as to protect the confidentiality and the identity of individual registrants. PHI will not be shared with others outside of the registry study staff. Registry investigators do not contact registry participants for new research (work that goes beyond the data collection specified in this protocol) without project-specific IRB approval for the new research project.

Level 2: De-identified and coded data requested. This scenario addresses the need of outside collaborative researchers to scan the registry and view aggregate data on the registered population. The researcher will request as part of the application process the types of research or preparation for research that will be conducted with the data. The registry research team may enter specific search criteria into the DTRF Patient Registry and provide de-identified reports to researchers. Alternatively, upon unanimous Advisory Board approval, researchers may be granted login access to de-identified registry data to perform their own searches. No information that would directly link the data to the registrants will be included in the output data. These data could be used for publication, or as preliminary data for a grant or IRB proposal.

There is no project-specific IRB submission is needed for this level. The DTRF Advisory Board will review the request, and if needed, obtain clarifying information during the approval process. A data transfer agreement will be distributed along with the data specifying the agreed upon

scope of research to be performed on with the registry data and specifying that no attempt may be made to identify the registry participants.

Level 3: An outside investigator would like to contact registry participants to recruit them for other research. The general mechanism by which this contact can be made is that the registry staff would contact the participants on behalf of the outside researcher and give the participant contact information about the researcher, so that the participant can decide whether she/he would like to participate in the new research. Thus, after DTRF Advisory Board approval of the application for registry use, an IRB-approved recruitment flyer will be requested from the researcher offering details about their planned study. This flyer will be reviewed by the DTRF Advisory Board for appropriateness and then sent by mass to all registry participants along with contact information for the researcher.

Requests for recruitment from the registry will only be fulfilled after DTRF Advisory Board approval of the application. A project-specific IRB approval from the researcher's institution must also be provided.

Results

In the first 15 months since the registry was launched, 329 DT patients or LARs of desmoids tumor patients have consented to the DTRF NHS and completed the Participant Profile. Table 2 describes the demographics and nationalities of the registered participants. Of the respondents thus far, 6.3% of them are <20 years old. The majority of the respondents are between the ages of 21 and 50 years (76%). There are more females (81.2%) in the registry than males (18.8%) which is similar to previous studies where female participation is 70%.¹⁴⁻¹⁹ Of the current respondents, the races are 91.5% White, 1.6% Black or African American, 1.6% Asian, 0.3% American Indian or Alaskan native, and 5% other. There have been two published DT studies that included the race and/or ethnicity. Childrens' clinical trial of sulindac and tamoxifen recruited 80% non-Hispanic (NH) or Latino, 14.3% Hispanic/Latino, 4% unknown ethnicity, 72.9% White, 15.7% Black or African American, 2.9% Asian, 1.4% Native Hawaiian or other Pacific Islander, and 7.1% unknown race.²⁰ The distribution of races in a clinical trial of imatinib (Gleevec) was 76% NH White, 18% NH African American, and 1% Other or Unknown.²¹ The majority of the participants are in the United States (47.1%), followed by the United Kingdom (9.7%), Germany (7.1%), and Ireland (6.2%).

The distribution of diagnoses and the primary method of diagnosis are described in Table 3. The majority of respondents reported that they have DT in the lower or upper extremity (22.9%), followed closely by abdominal DTs

Table 2. Demographic information for the DTRF patient registry.

Demographic variables (N=329)	%	Count
Age (years)		
0–2	0.6	2
3–5	0.6	3
6–10	0.9	4
11–17	1.2	4
18–30	1.2	65
31–40	19.8	118
41–50	35.9	75
51–60	22.8	40
61–70	12.2	14
>70	4.3	4
Gender		
Female	81.2	267
Male	18.8	62
Race		
White	91.5	291
Black or African American	1.6	5
Asian	1.6	5
American Indian or Alaskan native	0.3	1
Other or refused	5.0	27
Nationality*		
United States	47.1	219
UK	9.7	45
Germany	7.1	33
Ireland	6.2	29
Italy	2.8	13
Canada	2.2	10
Poland	2.2	10
France	1.9	9
Mexico	1.5	7
Norway	1.5	7
Sweden	1.5	7
Russian Federation	1.1	5
Australia	0.9	4
Denmark	0.9	4
Israel	0.9	4
Austria	0.6	3
China	0.6	3
Hungary	0.6	3
Netherlands	0.6	3
Spain	0.6	3
Argentina	0.4	2
Brazil	0.4	2
Colombia	0.4	2
Cuba	0.4	2
Czech Republic	0.4	2
India	0.4	2
Philippines	0.4	2
Puerto Rico	0.4	2
Romania	0.4	2
Ukraine	0.4	2
Armenia	0.2	1

(Continued)

Table 2. (Continued)

Demographic variables (N=329)	%	Count
Belarus	0.2	1
Belgium	0.2	1
Bhutan	0.2	1
Chile	0.2	1
Croatia	0.2	1
Cyprus	0.2	1
Dominican Rep.	0.2	1
Ecuador	0.2	1
El Salvador	0.2	1
Greece	0.2	1
Guatemala	0.2	1
Haiti	0.2	1
Iran	0.2	1
Japan	0.2	1
Korea (DPR)	0.2	1
Lithuania	0.2	1
Malaysia	0.2	1
New Zealand	0.2	1
Pakistan	0.2	1
Portugal	0.2	1
Samoa	0.2	1
Slovakia	0.2	1
Trinidad & Tobago	0.2	1

DTRF: Desmoid Tumor Research Foundation.

*Participants may select more than one nationality.

(21.5%). Multiple selections were permitted for this question, as it is possible and probable that those who have familial adenomatous polyposis (FAP) will also have abdominal DTs. Most of the responses for the diagnosis method were by biopsy (39%), surgical resection (20.5%), and core-needle biopsy (10.6%).

The study completion rates are outlined in Table 4. Completion of the first survey, Participant Profile, is required to move on to the others. As of mid-December 2018, 376 respondents had completed the profile.

The respondents in the registry and NHS have shared their past experience in biospecimen and clinical trial history and willingness to participate in future studies (Table 5). The vast majority are willing to donate specimens (89.9%) and participate in trials (97.2%). Since launching the study, one pharmaceutical company requested information on the quality-of-life measures collected.

Discussion

The DTRF Registry and NHS are the first of its kind in that they are global and focused solely on the DT patient population. The web-based model permits world-wide access, which is demonstrated by the diverse nationalities of the respondents. It is our intention that this study will be used to fill knowledge gaps in DT research and access to a patient population willing to donate their time and specimens for future studies.

Table 3. Tumor diagnosis/location and primary diagnostic method.

Tumor location ^a : (N=329)	%	Count
Abdominal desmoid tumor	21.5	99
Desmoid tumor in the chest	15.7	72
Desmoid tumor in the lower extremity	12.2	57
Desmoid tumor in the upper extremity	10.7	50
Mesenteric desmoid tumor	10.5	48
Desmoid tumor in other location(s)	7.9	37
Extra-abdominal tumor	7.3	34
Desmoid tumor in the head or neck	6.4	30
FAP	4.5	21
Gardener's syndrome	1.9	9
Neoplasm of uncertain behavior of connective and other soft tissue	0.6	3
Garc	0.2	1
None of the above	0.4	2
Primary diagnosis: (N=151)	%	Count
Biopsy	39.1	59
Surgical resection	20.5	31
Core-needle biopsy	10.6	16
MRI	8.6	13
CT	7.3	11
Incisional Biopsy	5.3	8
Physical exam	2.6	4
Fine-needle Aspirate	2.0	3
Excisional Biopsy	1.3	2
US	0.7	1
Other	2.0	3

FAP: familial adenomatous polyposis; rare diseases; MRI: magnetic resonance imaging; CT: computed tomography; US: ultrasound.

^aDenotes that multiple selections are permitted.

Table 4. The number of study surveys completed by 20 December 2018.

Survey title	Cont
Participant profile ^a	340
Medical and diagnostic data	219
Treatment and review of systems	205
Medical data for desmoid tumors	163
Quality of life (adult, part 1)	163
Diagnostic data for desmoid tumors	151
Treatment of desmoid tumors	149
Quality of life (adult, part 2)	153
Desmoid tumor monitoring	144
Desmoid tumor and activities	144
Desmoid tumor symptoms (pro 1)	139
Desmoid tumor symptoms (pro 2)	130
Desmoid tumor and pregnancy	110
Other medical conditions	60
Quality of life (pediatric)	8

^aThe Participant Profile survey completion count includes 11 updated entries.

Table 5. Past and future biospecimen donation and clinical trial participation willingness.

Contributed biospecimen sample ^a (N=216)	Count	
Tissue		36
Blood		15
Saliva/cheek swab		1
Urine		1
Willingness to contribute biospecimen sample in future (N=216):	%	Count
Yes	89.8	194
No	2.8	6
Do not know	7.4	16
Willingness to participate in future clinical trials (N=216)	%	Count
Yes	97.2	210
No	1.4	3
Do not know	1.4	3

^aDenotes that multiple selections are permitted.

It is probable that there is bias in an Internet-based survey model. The respondents must have access to a computer and the Internet and be willing to consent to participation, leading to obstruction of participation.²² This may lead to differences in the registry participants and non-participants. The advisory committee will continue to monitor the NHS demographics to ensure that any bias is minimized to the best of our ability. Ongoing recruitment efforts are focused on marketing the study to clinicians for their assistance in face-to-face study conversations. While it would be advantageous to be able to translate the registry and NHS into other languages, it is not possible at this time due to limitations of the platform.

Future NHS efforts will focus on continued recruitment, survey completion, and analysis of the responses of all of the survey modules. Of particular importance to the DT community is the quality of life, treatment, and pregnancy surveys. Outreach is ongoing with pharmaceutical companies who are developing treatments for DTs.

Conclusion

In collaboration with the NORD, the DTRF NHS is built on the largest DT registry and has recruited more DT participants since launching in September 2017. It will serve to fill DT knowledge gaps and assist other researchers in their recruitment efforts for additional studies. As of December 2018, more than 300 respondents had completed the first survey in the study, and ongoing activities include addressing access bias, survey completion, and the analysis of all of the surveys.

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Ethical approval

Ethical approval for this study was obtained from Hummingbird IRB (2016-44).

Informed consent

Written informed consent was obtained from the patient(s) for their anonymized information to be published in this article.

Conflict of interest

K.A.M. is an employee of Duke University and has received grants from the Desmoid Tumor Research Foundation.

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