DESMOID TUMOR AND MOLECULAR TESTING FROM PATIENT REPORTED DATA IN AN INTERNATIONAL NATURAL HISTORY STUDY

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THE DESMOID TUMOR RESEARCH FOUNDATION

1. BACKGROUND AND AIMS

Desmoid tumors (DTs, also known as aggressive fibromatosis) are non-metastatic, locally invasive sarcoma or mesenchymal soft tissue tumors. Only five to six out of a million people are diagnosed annually with DT. DTs are commonly associated with mutations in the *CTNNB1* gene (sporadic DTs) or the *APC* gene (Familial adenomatous polyposis (FAP)-related DTs). A consensus of DT experts recommend mutational testing to confirm diagnosis and guide treatment options, however, the extent to which testing is being performed is not known. Patient reported data are described here for those participants that received mutational testing of their tumor.

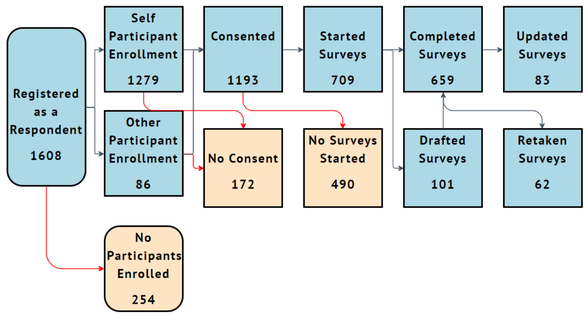
The Desmoid Tumor Research Foundation's (DTRF) mission is to aggressively fund research to accelerate the development of improved therapies, and ultimately find a cure for desmoid tumors. The DTRF launched the patient registry and natural history study (NHS) in 2017 and was one of the inaugural organizations in the I AM RARE project.

This poster describes the on-going molecular and genetic data shared by the participants.

2. METHODS

The DTRF Patient Registry is designed to collect data for 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. Six of the surveys were developed from pre-existing, validated tools and included in a core data dictionary from NORD. These questionnaires are general to all rare diseases. The additional nine surveys were designed to capture information more specific to desmoid tumor patients.

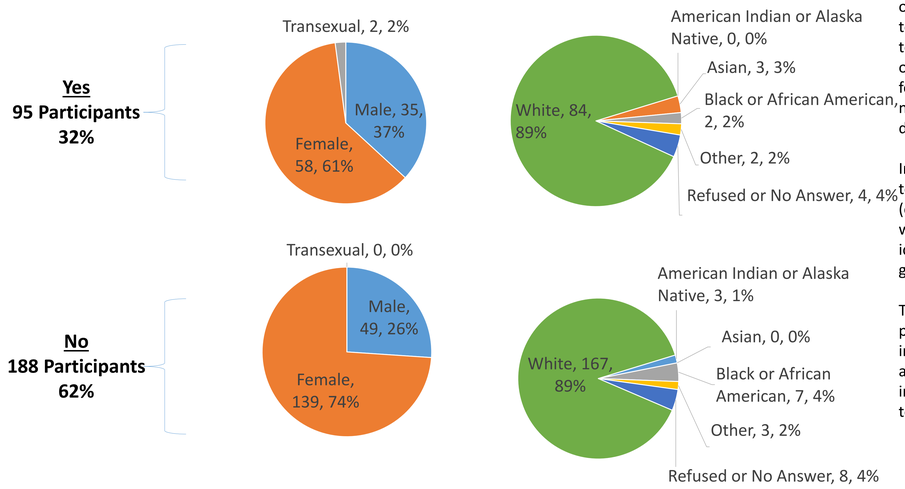
3. STUDY PARTICIPATION



The web-based natural history study launched September 2017 in collaboration with the National Organization of Rare Disorders. It contains 15 surveys covering diagnostics, disease, treatment, care management, and quality of life. This registry and study has ethical approval for global data collection from North Star Review Board IRB (Protocol Number: NB100030).

Data was downloaded for analysis on June 6, 2021. At that time, 302 out of 709 participants who have started to complete surveys had completed surveys pertaining to molecular testing.

4. HAS THE PARTICIPANT HAD ANY GENETIC OR MOLECULAR TESTING? BY DEMOGRAPHICS

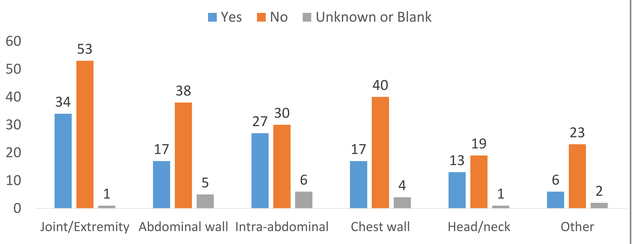


Of the 309 who started the surveys related to genetic or molecular testing, only 32% reported having testing completed; the majority (62%) reported no testing. There were 6% who either did not respond or did not know. There was a higher percentage of females and African American participants who did not receive molecular testing compared to those that did.

Interestingly, the age of those that did not receive testing tended to skew younger than those that did (data not shown). Additionally, the year of diagnosis was evaluated for these participants; no trends were identified to indicate that there was a change in genetic or molecular diagnosis (data not shown).

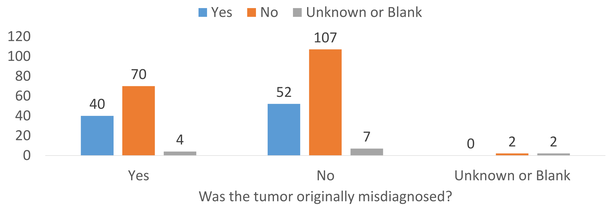
The study demographics highlight that the NHS participants are not diverse, which will be addressed in the coming years with modifications to outreach and engagement. Also, the type of health care institution will be captured (academic vs community) to determine if this is a factor in testing availability.

5. MOLECULAR TESTING AND LOCATION



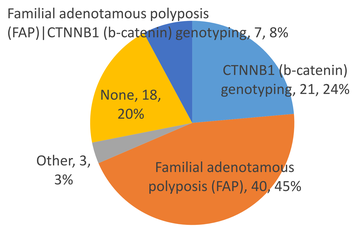
Intra-abdominal tumors were the most likely to have received molecular testing. This is likely because FAP is associated with this anatomic location and *APC* mutations. Head/neck had a similar result, perhaps due to the proximity to critical anatomy.

6. MOLECULAR TESTING AND MISDIAGNOSIS



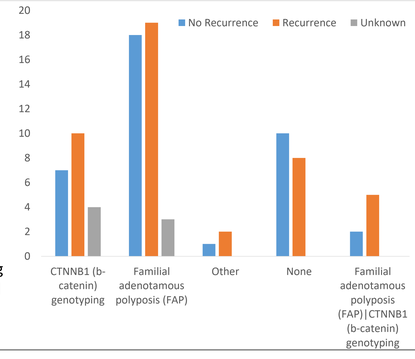
Of the participants who were correctly diagnosed, 49% received molecular testing. Of those who were misdiagnosed, 57% reported molecular testing. Molecular testing is not required for diagnosis, nor is standard of care. The NHS misdiagnosis questions are being revised to understand if these are true misdiagnosis or part of a differential in reaching a final diagnosis.

7. GENETIC MUTATIONS AND RECURRENCE



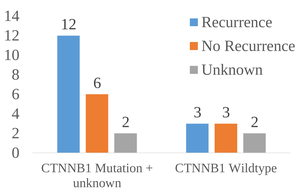
Participants who reported they had molecular testing done were then asked to select the type of mutation reported (left). Some participants chose multiple types of testing ("genotyping"), which may explain why some reported both FAP and *CTNNB1* testing/mutations. These mutations are mutually exclusive. The surveys are being revised to address confusion that can arise between being tested and identifying these mutations.

Any mutation had a higher chance of recurring than not, whereas no mutation reported had a slightly greater chance of not recurring than recurring (right). If the participant reported FAP mutation and a recurrence, they were most likely to have 2 or more recurrences (data not shown).

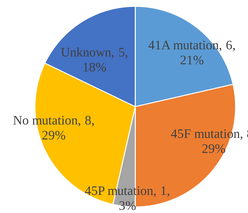


8. *CTNNB1* MUTATIONS

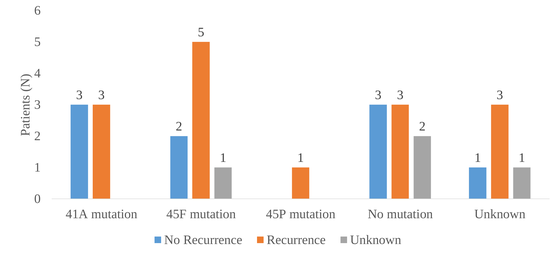
Desmoid tumors are associated with *CTNNB1* mutations in over 75% of cases.[1] As shown (right), those who had a mutation were more likely to have a recurrence, where 12 participants reported having a *CTNNB1* mutation with recurrent disease, while 6 did not. For those with no mutation identified, there was an equal number of participants who had recurrent disease (3 vs 3). Mullen et al.[2] reported slightly worse (non-significant) 5-year recurrence free survival for patients with *CTNNB1* mutation which these results would support.



In addition, the specific mutation in the *CTNNB1* may have prognostic significance. Of the reported mutations in the NHS, most respondents reported either wild type *CTNNB1* (29%) or S45F (29%), as shown to the right.



Several reports indicate that S45F mutation is a risk-factor for recurrence.[3,4,5] Shown below, there are five participants with the S45F CTNNB1 mutation who have reported recurrence.



9. SUMMARY

- Men were more likely to receive molecular testing that women.
- African American participants reported less testing than white participants.
- Intra-abdominal tumors are more likely to be tested than other locations.
- Both *CTNNB1* and FAP related mutations may increase the risk of recurrence, and FAP may increase risk for multiple recurrences.
- The *CTNNB1* S45F mutation may have prognostic value recurrence risk.

As discussed in the earlier sections, there are on-going study modifications to address racial disparities and clarify questions regarding misdiagnosis and molecular testing. Additional information, such as the health care setting (academic or community) and when and which molecular testing was performed, will be collected. These details will provide context to the interpretation (for example if the testing was used to aid in diagnosis or to plan treatments, etc.).

The DTRF NHS researchers are extremely grateful to the participants, caregivers, and the NORD staff for their ongoing engagement in this important study.

References:

1. *Ann Surg.* 258(2): 347-353.
2. *Oncologist.* 18(9): 1043–1049.
3. *Future Oncologist*. 17(4).
4. *Am J Pathol.* 173(5): 1518–1527.
5. *Cancer*. 119(20): 3696-3702.