

THE POWER OF PATIENTS

*Informing Our Understanding
of Rare Diseases*



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Foreword

There are approximately 7,000 rare diseases affecting an estimated 30 million people in the United States. In the vast majority of these cases, an FDA-approved treatment for a rare disease indication will be altogether lacking, and physicians, who may encounter one or two such patients in the course of their careers, will typically have to rely on trial-and-error approaches, along with their own intuition, to provide care. We often hear that the paucity of medical products on the market for rare diseases reflects economic pressures that drive developers to invest their resources into more prevalent diseases, where the financial payoff for new drug development is potentially greater and more immediate. But the tremendous medical need that remains unmet today within the collective rare disease community, in fact reflects a fundamental truth about rare diseases that goes beyond economics. By their very definition, rare diseases may be difficult to localize and subject to concerted methods of investigation, creating huge barriers to understanding for stakeholders who might otherwise define and pursue opportunities for developing new therapeutics. This problem has been central to the collaborative efforts between the FDA and NORD for many years. The very gratifying progress that we've seen in surmounting hurdles to the understanding of rare diseases is evidenced in the NORD natural history registries discussed in the following chapters.

The “natural history” contained in the registries NORD has compiled within the organization's IAMRARE™ program, represents the enactment of strategies to harness the very type of knowledge so essential for the design and execution of clinical trials of potential new therapies, but which has been lacking in the rare disease space. This natural history information is built on the unique insights of those patients living with rare disease. At the FDA, we have found in our patient-focused drug development meetings—for example, with people living with chronic disease—that patients really are the experts in their particular disease. They may not know all the medical jargon and all the laboratory terms familiar to medically trained professionals, but their expertise, built on their experience of living day-in and day-out through the course of their disease, is the cornerstone of the natural history contained in the NORD registries presented in this volume. This information encompasses how these diseases progress over time, what symptoms may occur and how these might be measured, how many patients may be expected to develop the disease, and how patients may have responded, both positively and negatively, to various treatments.

Knowledge of the natural history of rare diseases informs the design of efficient clinical trials in many ways, helping reduce the length and cost of drug development and contributing toward greater predictability of clinical development programs. But in addition to the natural history information they contain, natural history registries also subserve the enormous benefit of enabling people with rare diseases to find each other and to come together to access their collective experience. Additionally, drug developers who are planning clinical trials often consult with patients with the disease to be targeted, who may best know what is feasible to do in a clinical trial, what might not work for certain patients, and may even be able to suggest patients for a trial or participate themselves. If patients aren't consulted in a good part of the trial design process, we frequently end up with clinical trials that are weakened, with multiple patient enrollee drop-outs, because people find they can't participate in a trial that has not been suitably designed.

A great deal of useful information, very valuable to the work the FDA does in the rare disease space, can come from patient registries and from having patients robustly participate and share information about their disease, among themselves and with their caregivers and clinicians. Patient input drives the collection of natural history information and is the basis for the considerable success of the NORD registries program, complementing the FDA's work in bringing new therapeutics into clinical use. On behalf of the FDA, I encourage people who are touched by rare disease to participate in the development of these registries and in the initiation of those yet to come.



Janet Woodcock, MD
Director
Center for Drug Evaluation and Research
US Food and Drug Administration

Alone we are RARE. Together we are STRONG.®



At NORD we believe that research has the power to inform and transform people's lives. This book was developed to amplify the experiences of individuals and families living with rare conditions, and to demonstrate the power of natural history data to shape the rare disease landscape. By sharing individual stories, celebrating community-driven collaborations, and exhibiting data from NORD's registries, this book aims to illustrate the promise and potential of longitudinal natural history studies.

NORD's highest priority is to create meaningful change and accelerate progress for the rare disease community. In NORD's registry community, our rare disease research partnerships reflect authentic engagement and sustained collaboration. NORD works alongside and together with rare communities to advance research, drive new scientific findings, and create real impact for rare diseases.

Who we are

NORD

The National Organization for Rare Disorders (NORD®) is the leading independent advocacy organization representing all patients and families affected by rare diseases. NORD is committed to the identification, treatment and cure of the more than 7,000 rare diseases, of which approximately 90% are still without an FDA-approved treatment or therapy.

The organization began as a small group of patient advocates that formed a coalition to unify and mobilize support to pass the Orphan Drug Act of 1983. For more than 35 years, NORD has been leading the fight to improve the lives of patients with rare disease by supporting patients and organizations, providing education, driving public policy, advancing medical research and providing patient and family services for those who need them most. NORD is made strong together with more than 280 disease-specific member organizations and their communities. NORD also collaborates with many other organizations on specific causes of importance to the rare disease patient community.

Patient-powered natural history studies are transforming how patients and caregivers inform and shape medical research and translational science for rare diseases. After a multi-year planning process, NORD developed and launched our IAMRARE registry program in 2014. This was done with guidance from patients, caregivers, researchers, and clinicians, as well as key opinion leaders from regulatory agencies, including the FDA and the NIH, to address persistent knowledge gaps and promote equitable and sustained progress on rare disease research. NORD's registry program unites the rare disease community on a common data collection platform that supports research-grade, longitudinal, patient-experience natural history data.

By bringing interdisciplinary teams together, NORD has created a successful model of developing patient-driven research outlets that complement clinical data sources. NORD takes a multidisciplinary approach to supporting research efforts through the development of consortia, partnering with different stakeholders to accelerate the generation of data, translating findings to inform meaningful outcomes, and providing pathways for the dissemination of information within the rare disease and broader health communities.



Who we are

TRIO HEALTH

Trio Health is pleased to offer our team and capabilities to assist NORD and its member organizations in the pursuit of their mission to identify, treat, and cure patients with rare disorders.

The mission of Trio Health, founded in 2013, is to collect and analyze real-world evidence that may be used to improve the quality of health care available to all patients. We achieve our mission by understanding not only the patient, but also the “trio” of other stakeholders—physician, pharmacy, and insurance company (payer)—and by evaluating how each clinical decision and the workflow have an impact on the overall care of the patient.

Our approach to real-world evidence is predicated on 3 factors: high-integrity data, the right statistical approach to analyze the data, and study conclusions without bias.

To build a high-integrity disease database requires that Trio combine disparate data from each patient stakeholder to form a 360-degree view of the patient. Cross referencing each data source to validate and track the patient journey is unique to Trio Health. Since each patient has his or her own clinical story, our collaboration with each of the patient stakeholders provides unparalleled insight.

To ensure that Trio publishes without bias, Trio retains an independent Scientific Steering Committee (SSC) for each disease that collaborates with our analytics team to author all studies. Sponsorship of each study by a pharmaceutical company, payer, or health plan is classified as investigator-sponsored research (ISR) to prevent any bias from the sponsor of the study. We thank and greatly appreciate all of our partners who respect and support our methodology.

High-integrity real-world evidence will play an important role in establishing the equilibrium between the competing forces among all of the patient stakeholders. Physicians, pharmacies, pharmacy benefit managers, payers, and pharmaceutical companies all share a common goal to provide the right treatment to the right patient. Trio’s position is that real-world evidence provides the path to achieve this goal.

If the patient wins, all stakeholders will achieve clinical excellence.

TABLE OF CONTENTS



| | |
|-----------------------------------------------------------------|-----|
| Foreword by Janet Woodcock, MD, Director, CDER, USFDA | 2 |
| Who We Are – NORD | 4 |
| Who We Are – Trio Health | 7 |
| OMS – Opsoclonus-Myoclonus Syndrome | 11 |
| PKU – Phenylketonuria | 29 |
| Pemphigus and Pemphigoid | 43 |
| SYNGAP1-related NSID | 57 |
| Desmoid Tumor | 73 |
| ITP – Immune Thrombocytopenia | 91 |
| Posters | 109 |
| Acknowledgments | 130 |

DESMOID TUMOR



THE DESMOID TUMOR
RESEARCH FOUNDATION

REGISTRY POWERED BY NORD

Meet Desmoid Tumor Warrior DEANN



Deann

In 1996 my oncologist had no idea what he was dealing with because he had no information about desmoids. He recommended amputation, but I wanted to save my leg. I underwent 6 surgeries to remove the mass and to repair the damage it had caused. This left me with 40% blood circulation and nerve damage, and I am permanently paralyzed from the knee down. Ten years after my original diagnosis we found 2 more tumors in my leg. I was told again to have an amputation, and again I decided on an alternate route. Tamoxifen along with sulindac stabilized my tumors, and as I continue to get older and my own hormones decrease, my tumors are slowly shrinking. I am still permanently disfigured and paralyzed, but after 22 years, my tumors are finally under control.

I was a 25-year-old loan officer and mother of 3 small kids when I was diagnosed. I have been unable to work a conventional job since then. Now I'm an admin of a patient support group page called the Desmoidian. I know there wasn't much research being done at the time, but I am so thankful it is being done now. There are more treatment options given to patients today, and I imagine that with continuing research the treatment options will be better and more catered to this disease. I have watched the science change patient outcomes and it is amazing to see.

What is DESMOID TUMOR?

Summary

Desmoid tumor commonly develops in the fibrous (connective) tissues of the body that connect, support, and surround other body parts and organs. The myofibroblast is the cell responsible for the desmoid tumor. Desmoid tumors may invade surrounding tissues and be difficult to control, and they may develop at any body site. Superficial desmoids tend to be less aggressive than deep desmoids (abdominal, extra abdominal, mesenteric). The desmoid tumors, which look like dense scar tissue, adhere to surrounding structures and organs, and are often difficult to remove. Although surgery has been the traditional therapy for desmoid tumors, approximately 20% to 30% will recur after surgery.

Introduction

Desmoid tumor is also called aggressive fibromatosis, as it has similarities with a malignant (cancerous) tumor called fibrosarcoma. It is, however, considered benign because it does not metastasize (spread) to other parts of the body.

Signs and Symptoms

While each child or adult may experience symptoms differently, the following are the most common symptoms of desmoid tumors. The symptoms vary greatly depending on size and location:

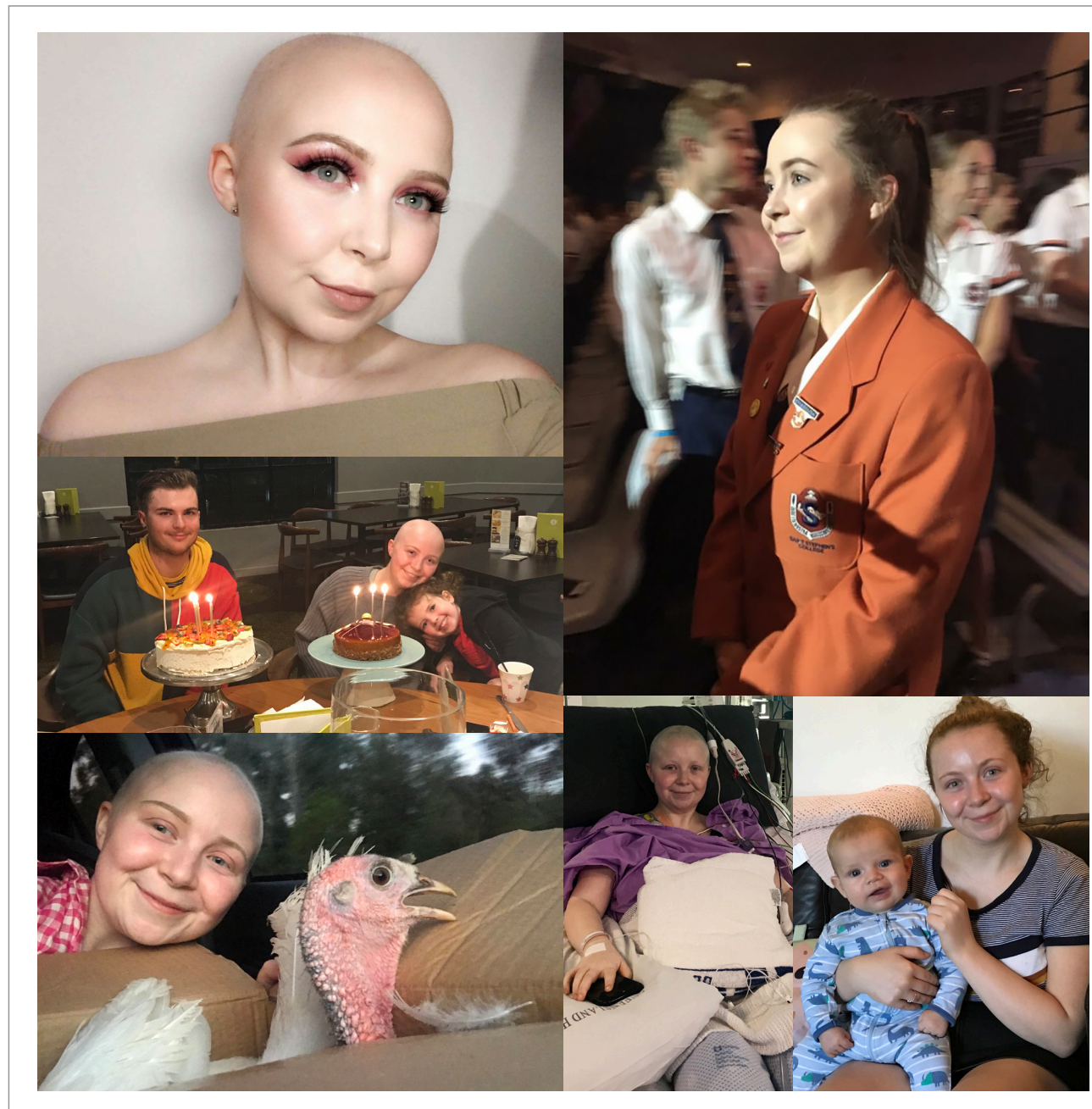
- A painless swelling or lump
- Pain or soreness caused by compressed nerves or muscles
- Pain and obstruction of the bowels
- Limping or other difficulty with using the legs, feet, arms, and/or hands or other affected parts of the body

Causes

The cause of desmoid tumor remains unknown. Desmoid tumors may present sporadically or as a manifestation of hereditary familial adenomatous polyposis (FAP). FAP is a familial cancer predisposition syndrome which, if left untreated, results in colorectal cancer. Up to 32% of patients with FAP will develop desmoid tumors in their lifetime. These desmoid tumors are the result of mutations, or changes, in the adenomatous polyposis coli APC gene.

continued on page 77

Meet Desmoid Tumor Warrior CHARLOTTE



Charlotte (written by her mom, Rebecca)

My daughter Charlotte and I migrated from the UK to Australia when Charlotte was 7 years old. Here we created a lovely life—going to work and school, living on acreage with our dogs Max and Daisy, our cheeky chickens, and Mavis the Turkey. In 2014, I married my best friend John and we became a busy, blended family with 6 children between us, ranging from 1 year old to 20. I am a lawyer and my husband is in law enforcement.

In 2016, Charlotte graduated high school, attended her prom, and was looking forward to a bright future involving animal welfare, her passion. Around this time, she began to complain of mild intermittent pain in her pelvic area. Eventually—some months later after much misdiagnosis—we received the news that our beautiful Charlotte had a desmoid tumor.

Just like that, everything changed. I worked late at night searching for answers and treatments to try or doctors to speak with. We traveled the country talking with different doctors and trying treatments, many only available privately at significant cost. Charlotte became sicker as time went on, and the tumor grew and grew, eventually growing to more than 18 cm x 11 cm x 11 cm. High-intensity focused ultrasound (HIFU) failed, as did tamoxifen, Zolodex®, pazopininib, sorafenib, and chemotherapy. Finally, massive surgery was the only option left and now Charlotte has a lifetime of living with mesh, lost stomach muscle, and she cannot

have children. Her first post-op check-up is coming up and it weighs heavily on our family. Fortunately, Charlotte has just returned to working with animals and is studying again.

Our journey has been one of discovery. We found some of the most talented and caring health professionals, a Facebook group filled with people just like us, and love—love of family, love of friends, and love of community.

As a mother, my biggest struggle was the burden of feeling alone in being Charlotte's advocate. Oftentimes doctors would not know anything about her illness. I recall once going to a local hospital (not the one usually attended) late one night with Charlotte in terrible pain. We were seeking pain management and we found ourselves in an ultrasound room with Charlotte being prepped for an ovary scan. It turned out that her extra-abdominal desmoid tumor had been incorrectly noted on admission as a dermoid cyst. I felt a huge, often overwhelming, sense of responsibility to ensure that I was thoroughly educated so that I could make sure Charlotte received the best treatment available.

It is essential that more dedicated research into desmoid tumors and their treatment is undertaken. It would also help if medical professionals, as well as the broader community, received information and education about desmoid tumors. With respect to medical professionals, a global, best practice treatment/management strategy would assist in reducing the significant variation of treatment standards and confusion around the management of desmoid tumors.

What is DESMOID TUMOR?

continued from page 75

In most patients, desmoid tumor occurs sporadically, meaning that it is not caused by predisposing genetic disease. People who develop desmoid tumors sporadically have no other APC gene-associated health problems. Repeated irritation or trauma to a certain body area, including surgical trauma, may increase the risk of developing desmoid tumor, and estrogen may also play a role in its development.

Affected Populations

Desmoid tumors constitute .03% of all tumors. The estimated incidence in the general population is 5 to 6 per million people per year. Desmoid tumors are observed to be more common in persons aged 10 to 40 years, but they may occur in other age groups, too. Desmoid tumors, which may commonly first occur in women after childbirth, have a female:male gender ratio of 2:1. The gender incidence is the same in children.

Related Disorders

Gardner's syndrome is a genetic disorder characterized by multiple colonic polyps and tumors outside the colon. The extra-colonic tumors may include osteomas of the skull, thyroid cancer, epidermoid cysts, fibromas, and sebaceous cysts, and the multiple colon polyps predispose an individual to the development of colon cancer. Gardner's syndrome, caused by a mutation in the APC gene located on chromosome 5q21, is recognized as a phenotypic variant of FAP. Typically, as one parent has Gardner's syndrome, each of his or her male or female children are at 50% risk of inheriting the APC gene and manifesting Gardner's syndrome themselves.

Dermatofibrosarcoma is a cutaneous malignancy that arises from the dermis and invades deeper subcutaneous tissue such as fat tissue, fascia, muscle, and also bone. Its cause is unknown. Chromosomal aberrations may contribute to the pathogenesis of dermatofibrosarcoma, especially a chromosomal translocation t(17;22) that fuses the collagen gene (COL1A1) with the platelet-derived growth factor gene. No evidence of hereditary or familial predisposition exists, and in 10% to 20% of affected patients, trauma at the site may be incriminated. Surgical, old burn, and sites of vaccination scarring have all been reported as sites of dermatofibrosarcoma. Dermatofibrosarcoma is a slow-growing tumor. Because of slow progression and initial growth as a small asymptomatic papule, the diagnosis is often delayed. The tumor may gradually enlarge into a lumpy nodule or evolve into an atrophic and/or sclerotic plaque.

Fibrosarcomas are malignant tumors derived from fibrous connective tissue; they are characterized by immature proliferating fibroblasts or undifferentiated anaplastic spindle cells. Fibrosarcoma originates in the connective fibrous tissue at the ends of arm and leg bones, then spreads to other surrounding tissues such as fat, muscles tendons, nerves, joint tissue, or blood vessels.

There are two forms of fibrosarcoma. Infantile, or congenital, fibrosarcoma is the most common soft tissue sarcoma found in

continued on page 79

Meet Desmoid Tumor Warrior ANNA



Anna

In 2017 I had a golf ball-sized lump right above my navel that started to hurt. I ended up in the ER because we thought it might be a hernia. Tests ruled that out, and I was sent to a general surgeon who told me I had the choice of a biopsy or removal of the mass. I went with removal of the mass because at that time it was thought to be a buildup of scar tissue from numerous surgeries. Pathology came back and I was told it was a desmoid tumor, after which I was referred to a sarcoma specialist at the University of Colorado. An MRI and consult with UHealth showed my tumor had grown back to the size of a baseball in just 5 weeks. Surgery was not recommended, and after discussing all the options, I went with chemo of vinblastine and methotrexate for a year. I experienced many side effects from the chemo that made us push things to biweekly after my fourth treatment. The first scan showed significant shrinking and the second scan showed even greater shrinking: the tumor was down to the size of a raisin! Because of the side effects, Dr. V thought the tumor was small enough to begin a watch-and-wait regimen after treatment #14. I had another scan 6 months later and my tumor was GONE!

I am 54 years old, and my husband and I live out in the country in southern Colorado. My husband works at the local sawmill and I work part time at home as a virtual assistant and the remainder of the time as a happy homemaker.

It was the outpouring of love and support of family and friends that got me through this ordeal. My mantra was "A positive attitude leads to positive outcomes. NEVER GIVE UP!" A dear friend has a circle of lifelong friends called the "sock sisters" who show their support by wearing crazy socks on your chemo day. It was an amazing spirit lifter. As other friends saw this happening, I started receiving socks in the mail to wear on chemo day. I don't think I will ever have to purchase a pair of socks again!

My greatest challenge is the unknown. Am I making the right treatment choice, is this treatment working, will it wreak havoc on my quality of life and my relationships, how long will I have to go through this, what are the long-term effects of my treatment choice, and will this tumor come back? Having more information about desmoid tumors available to everyone would be a great help. I did not know what a desmoid tumor was before getting my diagnosis and I was amazed at how many professionals had no experience with them either.

What is DESMOID TUMOR?

continued from page 77

children less than one year of age. It presents as a rapidly growing mass at birth or shortly after. This fibrosarcoma is usually slow growing, and tends to be more benign than fibrosarcoma in older children, which behaves more like the type found in adults. Adult-form fibrosarcoma may occur in older children and in adolescents, especially those between the ages of 10 to 15.

Diagnosis

The conclusive diagnosis of desmoid tumor requires a biopsy. On microscopic examination, which confirms the diagnosis, the spindle cells of desmoid tumors appear to be myofibroblasts. The spindle cells are thought to be an abnormal proliferation of myofibroblasts, which normally disappear gradually during the later stages of wound healing. Additionally, immunohistochemical stains can establish the nuclear accumulation of beta-catenin, a protein caused by the genetic mutations usually found in desmoid tumors. Nuclear reactivity shows relatively high specificity, detected in up to 90% of desmoids, regardless of site. Finally, antibodies are often examined in desmoid tumors, including smooth muscle actin, desmin, and KIT, to aid in distinguishing them from other tumors.

Standard Therapies

TREATMENT

Depending on the extent of tumor growth and the overall condition of the patient, the following treatment options are utilized. Surgery alone is often the only treatment needed, however, the recurrence rate of desmoid tumor is often as high as 30%, and more than one surgery may be needed. The tumor tends to become more aggressive when it recurs after resection. For patients who are not appropriate candidates for surgery or who have recurrences not responding to repeated surgeries, the following options may be considered:

Watch-and-wait policy: Because desmoid tumors do not metastasize and are easily followed closely for growth, a watch-and-wait policy is often adopted on presentation. Further, as treatment options (surgery, radiation, and/or chemotherapy) may cause significant morbidity and even mortality, patients with asymptomatic or minimally symptomatic disease with stable appearance on screening, may appropriately be treated with a period of watchful waiting.

Anti-inflammatory drugs: These may cause the tumor to slowly shrink. Non-steroidal anti-inflammatory drugs (NSAIDs) and drugs such as imatinib (generic Gleevec®) are used to treat desmoid tumors.

Hormone therapy: Some hormones seem to promote the growth of desmoid tumors, so anti-hormonal medications such as anti-estrogens and prostaglandin inhibitors may also be used therapeutically.

Chemotherapy: If surgeons cannot remove the desmoid tumor because of size or location, chemotherapy may be used to reduce tumor size. Agents include doxorubicin (Adriamycin®, Rubex®), dacarabazine (DTIC-Dome®), and carboplatin (Paraplatin®).

continued on page 81

Meet *Desmoid Tumor Warrior* TIFFANY



Tiffany

My name is Tiffany. I am 35, married with two beautiful children, and I work full time as a medical biller for a local pediatric office. I was 26 and pregnant with our second child when something felt “off.” I asked my midwife about an odd feeling in my left hip. It didn’t hurt, but it didn’t feel right. She said it was sciatica, which plagues most pregnant woman at some point, and that made complete sense. About 6 months after our son was born, however, that odd sensation was still there. It didn’t hurt, but it was annoying. At one point, our 2- year-old daughter climbed up on the couch where I was laying. She accidentally hit my hip with her knee, and it felt like someone had hit me with a baseball bat. I spoke with my PCP, an X-ray, MRI, and lab work all showed normal results. It was now painful, and I started to panic. My left hip seemed to grow larger than the right, but everyone said it felt normal.

I cannot count every doctor I went to for the next 5 years. They all ended the same: No one knew what was wrong and no one could help me. I switched to a new PCP, who brought up imaging again, so I had another X-ray. It was normal, so I declined another MRI. I couldn’t sleep because of the pain and I was having trouble walking. I cried every day. Over-the-counter medications didn’t provide relief anymore, so I started to drink at night for pain relief and sleep. My PCP suggested I see a pain management provider for trigger point injections. I thought it was pointless, but a path not yet tried, so I went. After a few appointments, the

ultrasound picked up some fluid, so I had an MRI. I had a tumor the size of an orange that had been growing and pressing on my sciatic nerve, causing my pain. I was sent to a specialist in Pittsburgh, who explained that estrogen hormone levels during pregnancy are linked to desmoid tumors.

He said he could remove it if I wanted, but because the reoccurrence rate is so high, they do not like to remove them unless necessary. The pain was debilitating, so I had it removed. The tumor grew back within a year, bigger than the first one, but I was lucky because my tumor developed outside of my organs, so removal and treatment were not that risky. Because I had a reoccurrence, however, I needed radiation. It’s been a little over a year since my second surgery, and the tumor is stable. A lot of muscle mass has been removed from my hip area, so I walk with a limp and I am regularly uncomfortable, though not usually in pain.

The radiation treatment, which hopefully halted my tumor growth permanently, has also unintentionally induced other medical issues that will be permanent and require medication. The biggest burden might be that I do not trust doctors or radiologists like before. After the MRI that confirmed a tumor, a CT scan was done and read as normal. I am not sure that there is any one solution, but I am most disappointed that the orthopedists who treated me were so lacking knowledge. Looking back, not one exam went the way I thought it should. I also feel at fault because I didn’t question them. I should not have left an appointment without understanding why something was or wasn’t done. Maybe I didn’t want to be rude or sound like an idiot, but perhaps if I had been more aggressive in that way, I could’ve been diagnosed earlier.

What is DESMOID TUMOR?

continued from page 79

Novel molecular-targeted therapies: Kinases are regulators of cell growth, differentiation, and motility. Because these processes are deregulated in tumors cells, a new class of drugs called receptor kinase inhibitors has been developed. Gleevec and sorafenib (Nexavar®) are two kinase inhibitors useful in treating desmoid tumors.

Radiation therapy: As a treatment for recurrent disease or as primary therapy to avoid mutilating surgical resection, radiation is high-energy rays from a specialized machine to damage or kill cancer cells and to shrink tumors.

Monitoring: After surgery, magnetic resonance imaging (MRI) is used to monitor recurrence in the arms and legs. Computed tomography (CT) scans are used to monitor intra-abdominal and chest desmoids.

Investigational Therapies

Angiogenesis inhibitors: Newer substances that may be able to prevent the growth of tumors by blocking formation of new blood vessels that feed the tumors are being currently investigated.

Chemotherapy agents: Researchers are also testing several chemotherapy drugs, or combinations of drugs, that could prove to be most effective in treating desmoid tumors to avoid radical management via surgery.

Mutations in the gene for beta-catenin have been found to commonly occur in desmoid tumor. Mutation analysis may soon be used to predict the risk of recurrence and to aid in the design of individual therapies.

Information on current clinical trials is posted on the Internet at www.clinicaltrials.gov. All studies receiving US government funding, and some supported by private industry, are posted on this government web site.

For information about clinical trials being conducted at the NIH Clinical Center in Bethesda, MD, contact the National Institutes of Health (NIH) Patient Recruitment Office:

Toll-free: (800) 411-1222

TTY: (866) 411-1010

Email: prpl@cc.nih.gov

Current clinical trials are also posted on the NORD website:

www.rarediseases.org

For information about clinical trials sponsored by private sources, contact:

www.centerwatch.com

For information about clinical trials conducted in Europe, contact:

www.clinicaltrialsregister.eu

Meet Desmoid Tumor Warrior **MATT**



Matt

I am a 36-year-old father, loving husband, avid bowler, and workaholic, or at least I was until my journey with a desmoid tumor began. In my early 20s I was diagnosed with familial adenomatous polyposis syndrome, which I figured I would because most of my mother's family has inherited it and my mother even passed away from this disease at the age of 49. At that time I had my colon partially resected, but continued to live my life as normally as possible. On January 25th, 2017, however, my life changed forever. I had gone to the ER thinking I had a bowel obstruction, but after tests came back, I learned that I had a giant desmoid tumor the size of a watermelon wrapped around my colon and attached to major arteries. I was transported to a different hospital much larger than my local hospital, and I waited for a team of surgeons to create a plan to treat this tumor. While waiting, part of my tumor ruptured and I became severely septic. I had to be put on a ventilator and go through 4 different life-saving surgeries within a week. At one point the trauma surgeons even came to my wife and mother-in-law to inform them that I would probably not make it through the night because of my condition and the fact that they could not safely remove the tumor. My total hospital stay was more than 30 days and I ended up in a nursing home for 5 days before finally returning home with home care to help treat the fistula holes I was left with in my abdomen. While I was happy to be home I discovered that no one in my area knew how to treat desmoid tumors, and I even once drove 5 hours to the Mayo Clinic in

Rochester, Minnesota to seek help. Another time I drove 2 hours to Northwestern Hospital in Chicago, Illinois. Finally, with the help of the DTRF, I was sent to Ohio State University in Columbus, Ohio, to Dr. Pollock and Dr. Chen. They put me on Nexavar® and Celebrex®, and my tumor has shrunk 40%.

Through this whole journey the biggest challenge with my desmoid tumor is the lack of knowledge people have concerning this disease. People honestly have no clue the pain I experience on a day-to-day basis, and trying to receive disability or any other form of help from people when they think this disease will not affect my daily activities is almost unheard of. In fact, if it weren't for the team at Ohio State University I may not be alive today. I also have PTSD and a form of depression from all the trauma I have faced. I sometimes feel that since I can no longer provide for my family that I am not of any use. My biggest burden is not being able to enjoy the activities I used to, or help provide for my family like I once did. The solution to all of my challenges and burdens is to make people more aware of what desmoid tumors are and what they can do to someone's life. If we make people aware that desmoid tumors are just as bad as cancer or even worse at times, then maybe I can get the help I need to live my daily life.

Who we are: THE DESMOID TUMOR RESEARCH FOUNDATION

Description

The mission of the Desmoid Tumor Research Foundation (DTRF) is to aggressively fund research to accelerate the development of improved therapies, and to ultimately find a cure for desmoid tumors. The DTRF also collaborates with dedicated researchers and clinicians worldwide to improve the lives of patients through education, awareness, and support.

Research funding: Founded in 2005, the DTRF is the only foundation in the United States solely dedicated to funding desmoid tumor research and to finding a cure for this rare disease. The funding of cutting-edge collaborative research at the world's top sarcoma cancer research centers is the DTRF's priority. Researchers are making significant advancements as new clinical trials and treatments emerge. Discoveries made through desmoid tumor research may also potentially be applied to many other more common diseases such as colon, breast, and ovarian cancers. The DTRF's Scientific and Medical Advisory Boards comprise the world's top desmoid tumor experts.

Patient support: The DTRF holds an annual fall Patient Meeting and regional patient meetings that bring patients, physicians, and researchers together for education, support, and collaboration. These meetings provide a supportive environment for patient interaction and informative lectures by clinicians and researchers. Most of all, we support patients by being a supportive partner in fighting this disease and inspiring hope through funding research for a cure.

Research workshops and international collaboration: The annual DTRF International Desmoid Tumor Research Workshop brings together a diverse group of scientists from around the world, including experts in desmoid tumor research, human genetics, drug development, and related fields. The Workshop facilitates an enthusiastic and collegial atmosphere as researchers across disciplines and institutions collaborate around the shared goal of improving treatments for patients with desmoid tumor, establishing research priorities, and moving the field forward toward a cure. The DTRF also helped fund the first International Consensus Paper of experts from around the world on the medical treatment of desmoid tumors.

Patient registry: The DTRF partners with NORD and the FDA to maintain the first-ever patient registry in the United States specifically for patients with desmoid tumor. This registry collects and aggregates data from patients and makes the de-identified data available to researchers to advance the medical science of desmoid tumors.

Virtual tumor board: The DTRF maintains the international DTRF Virtual Tumor Board where experts on desmoid tumors, including clinicians, radiologists, pathologists, and others from around the world, meet quarterly via videoconference. This resource offers a new source of support and collaboration for physicians to present their difficult cases of desmoid tumor.

Website: The DTRF's website, www.dtrf.org, is a clearinghouse of information on desmoid tumors and published desmoid tumor research. Its target reach comprises physicians, researchers, and patients around the globe. The organization provides patients with critical information and also directs them to additional resources for support.

For more information or to donate to help support desmoid tumor research, please visit www.dtrf.org.

ADDRESS

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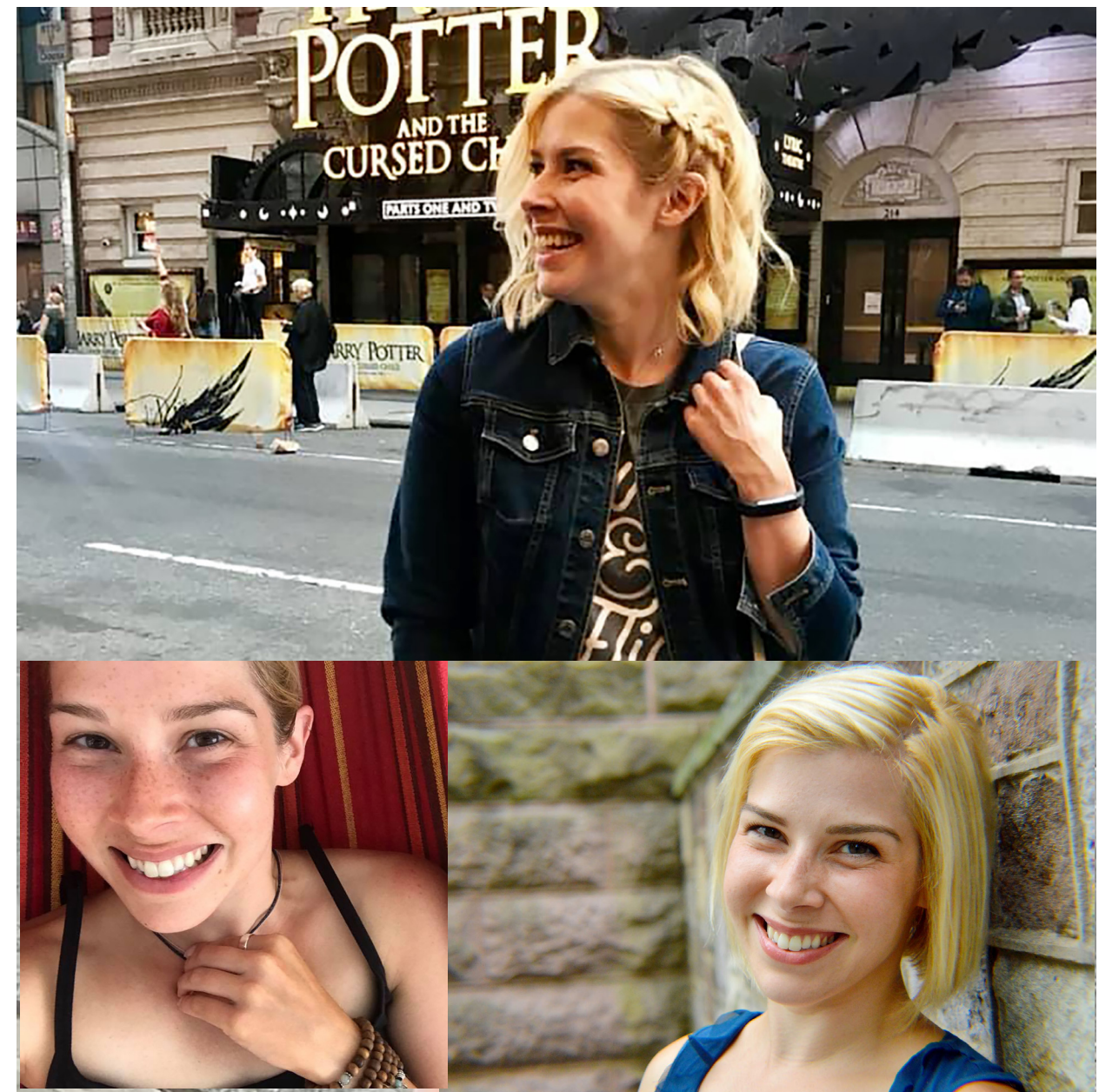
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www.dtrf.org

Meet Desmoid Tumor Warrior **CHRISTINA**



Christina

My name is Christina, and I have a desmoid tumor. I'm a teacher at an all-girls school in New Jersey, where I teach drama and theology. In addition to teaching, I direct and choreograph many of the school's productions and I also perform in local community theatre productions.

My diagnosis process began in January 2017 when I noticed a decreased range of motion in my right shoulder, which became sore and slightly painful. As a yoga teacher and practitioner, I challenged my range of motion and strength daily by playing with arm balances and handstands. My chest began to look swollen, and after seeking imaging, I was told I had a lipoma. I was seen by a general surgeon and underwent surgery on September 29, 2017 to remove the suspected lipoma. When I came out of surgery, I was heartbroken to learn that the doctor described the surgery as "confusing." During the procedure, no lipoma was located. By December, I was tired, angry, and in pain. After seeking help at the University of Pennsylvania, I was finally diagnosed in February 2018 with a desmoid tumor in my right chest wall, attached to my clavicle. As of now, it's as large as a softball at its widest point. My biggest struggle is living a double life as both a patient with a rare disease and a normal woman in my twenties. While I have continued to work full time, my quality of life

has suffered immensely due to physical pain, treatment side effects, and the emotional toll this diagnosis has taken. I never know what the next few months will bring, and I live scan-to-scan hoping to find a treatment to eventually shrink my tumor.

We need to change the perception of this diagnosis within the medical community in particular and in the world at large. While some doctors do not consider desmoid tumors cancer, very few understand that they can be anything but benign. Desmoid tumors are erratic, unpredictable, and extremely recurrent in nature. Doctors need to take patients at their word when they say their lives are harder and irrevocably more challenging because of this diagnosis. For me, documenting my journey on a blog has allowed me to explain to friends and family members the daily challenges I face. I'm a woman with a desmoid tumor, but I am so much more: I'm a teacher, a daughter, an artist, and now, a rare disease activist. While I would never ask for this responsibility, I'm committed to capturing the good, the bad, and the ugly, not only to change the perception of my "normal" life, but so I can give hope to new patients who are overwhelmed and lost, desperate to find out if there can be life post-diagnosis. We may be rare, but together we can find hope.

Desmoid Tumor IN THE REAL WORLD

Clinical Story

Desmoid tumors develop in connective tissues of the body. While these tumors do not have the capacity to spread distantly (metastasize) through the body, they are able to invade surrounding tissues. When that occurs, it results in destruction of vital structures, compromised organ function, debilitating pain, and other serious and sometimes fatal complications. The diagnosis rate of 5 to 6 per 1 million people annually may be an underestimate of the actual affected population due to difficulty in correctly diagnosing the disease. To improve awareness of desmoid tumors and to better inform treatment development, the DTRF, in partnership with NORD, launched the DTRF Desmoid Tumor Patient Registry and Natural History Study (NHS). Here, we describe patient demographics, tumor location, and quality of life in the NHS patient population. The registry launched September 2017 and contains 15 surveys covering diagnostics, disease, treatment, care management, and quality of life. As of January 2019, 357 patients have completed 2,371 surveys.

The NHS participants are mostly white (88%, 313/357) and female (78%, 277/357). Ongoing recruitment efforts are poised to address the sampling bias apparent to date with increased outreach to sarcoma centers around the world. Patients reside in 27 countries; 80% (285/357) are US-based. Median age at diagnosis is 33 years (mean of 32.6 years). The time from onset of symptoms to diagnosis was more than 1 year for 53% (189/357). Moreover, the time to diagnosis was more than 10 years for 8% (29/357) of respondents.

Quality of life was reported as excellent for 27% (14/51) of patients without current tumors, while only 13% (16/124) of those with current tumors reported excellent quality of life, which is statistically significant ($z=2.320$, $P=.0203$). Desmoid tumor location was reported for 119 respondents at time of data collection. The most prevalent tumor locations were joint/extremities (23%, 27/119), intra-abdominal (24%, 28/119), and chest wall (24%, 29/119). Multiple tumor locations were indicated for 22% (26/119) of patients. Quality of life varied based upon tumor location; it was reported as very good or excellent from 28% (2/7) of patients currently with tumors located in the head and neck to 60% (12/20) of patients with tumors located in the abdominal wall, though the difference was not statistically significant, possibly due to small sample size ($z=-1.432$, $P=.153$). Though the sample size for specific locations of tumors is small, data collection through the registry is ongoing.

continued on page 87

Meet Desmoid Tumor Warrior SHONEY



Shoney

My name is Shontel, but everyone calls me Shoney. I live in the LA area and I work at Kaiser Permanente as a sonographer. I'm a single mom with a 4-year-old daughter and a two-and-a-half-year old son.

2018 started off great! My divorce was finalized and I had a great support system around me. I had lost 40 pounds for my upcoming 40th birthday and I had just qualified for a position with benefits at work. Coincidentally, in Oct 2017 I decided to get the Mirena IUD. But in 2018, I started to notice that I was having adverse effects. So I made appointments to have my physical/lab work and first mammogram; everything was normal. In July I opted to have the Mirena removed.

On July 19, 2018 I felt a lump on my upper right chest. At work the next day I showed a radiologist and she ordered a diagnostic mammogram with ultrasound. The following week I had an ultrasound-guided biopsy. At this point I became obsessed with trying to figure out what this mass was. By the time I received the results from the biopsy I already knew it was a desmoid tumor.

I was then told to make an appointment at the Breast Clinic and underwent an MRI. I was scheduled with a nurse practitioner who knew nothing about desmoids. She examined me and scheduled me for a lumpectomy on September 7. By this point I had dubbed the mass "Baby Groot," from Guardians of the Galaxy. I met with

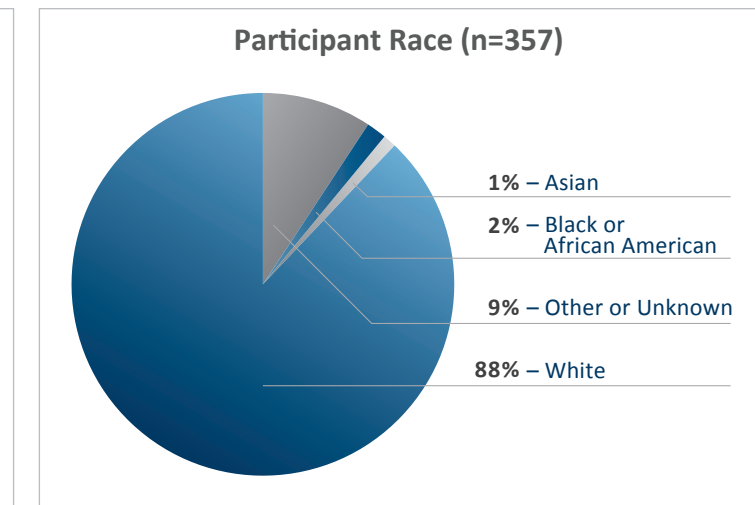
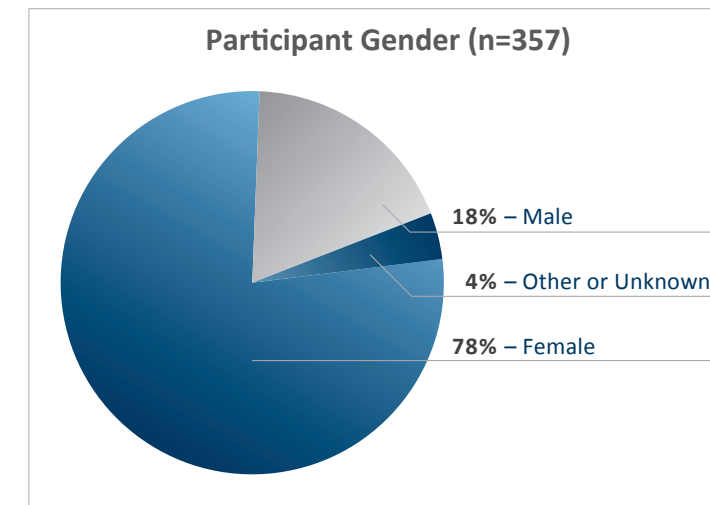
the surgeon and oncologist a few days before surgery, and they assured me surgery and possibly radiation were the best options.

My biggest struggle was trying to get clear and concise answers with how to proceed. I kept hearing a lot of "I don't know." I had to push for an appointment with an oncologist and geneticist, and most of my coworkers and friends kept telling me to have the surgery because, "It's not a real cancer, so you'll be okay."

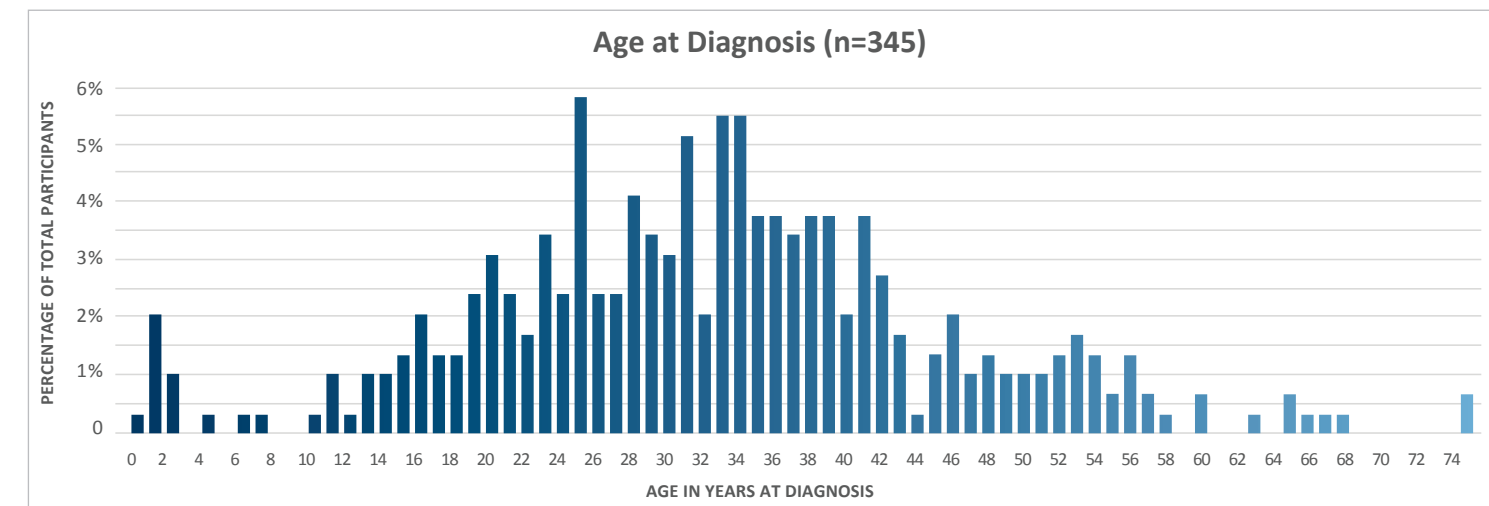
The morning of my surgery, I put on my shirt that I had made with Baby Groot. I was extremely anxious, but ready. The surgeon had to remove a small bit of muscle to achieve negative margins within 2 mm. Even with small margins and the probability of recurrence, the radiation oncologist didn't believe I needed radiation. I ended up going back to work after 2 weeks and probably could have used another week due to how physically demanding my job is.

More research will definitely help, so that's why I donated my tissue. More importantly, since I had had so many problems with the IUD, more research with birth control and its affects needs to be included. It was a very big coincidence that I found the lump after getting the IUD and not after having my children. I asked to have the mass tested for estrogen receptors and it came back negative; maybe it's a coincidence, but no one seems to be sure. Also, a clearer standard of care needs to be in place, such as those provided by the National Comprehensive Cancer Network (NCCN) Guidelines®. They provide clear, easy-to-understand tables to guide both providers and patients.

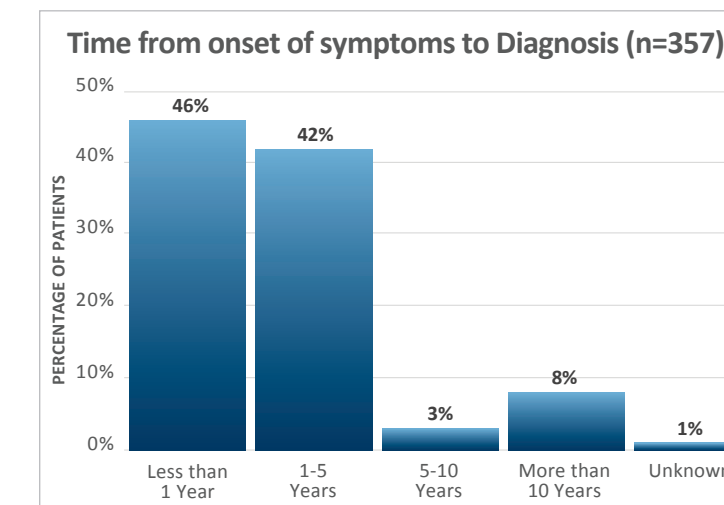
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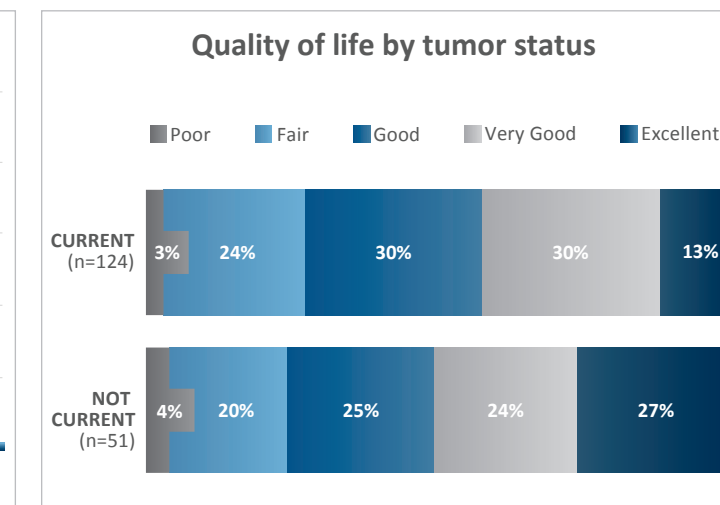
Patients in the registry are mostly female (78%, 277/357) and white (88%, 313/357), though this may differ from the demographics of the total population of patients with desmoid tumors.



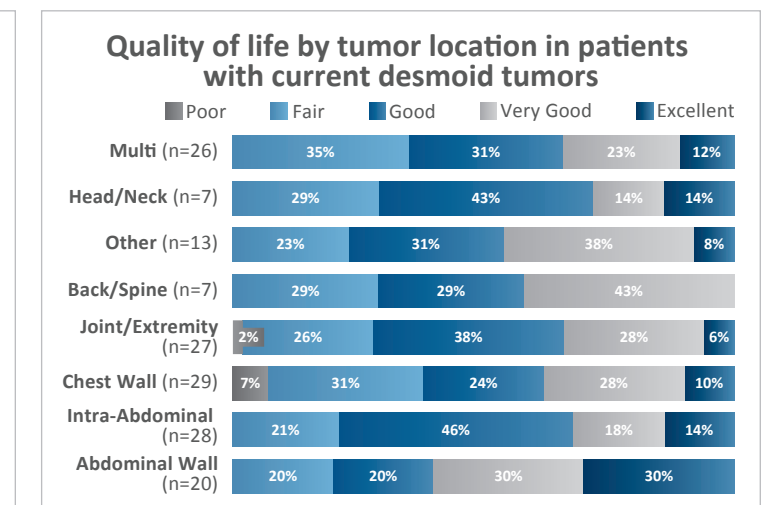
Participants in the registry were diagnosed at ages ranging from less than 1 year to 74 years, with a median age of 33.



Most patients in the registry were diagnosed in less than one year after the onset of symptoms, however, for 8% of participants, diagnosis was made more than 10 years after the onset of symptoms.



The number of participants who rated their quality of life as excellent varied significantly depending on whether or not the participant had a tumor at the time (z=2.320, P=.020, significant at P<.05).



Patient quality of life may vary by tumor location for patients with desmoid tumors.

Meet Desmoid Tumor Warrior DR RAPHAEL POLLOCK



Dr Pollock

How many patients with desmoid tumors do you see in a year?
Approximately 25 newly diagnosed patients per year.

How many are FAP cases vs sporadic?
95% are sporadic.

Is there a mechanism for consulting with patients who can't travel to see you in person?
Yes, I'm always happy to do a teleconference!

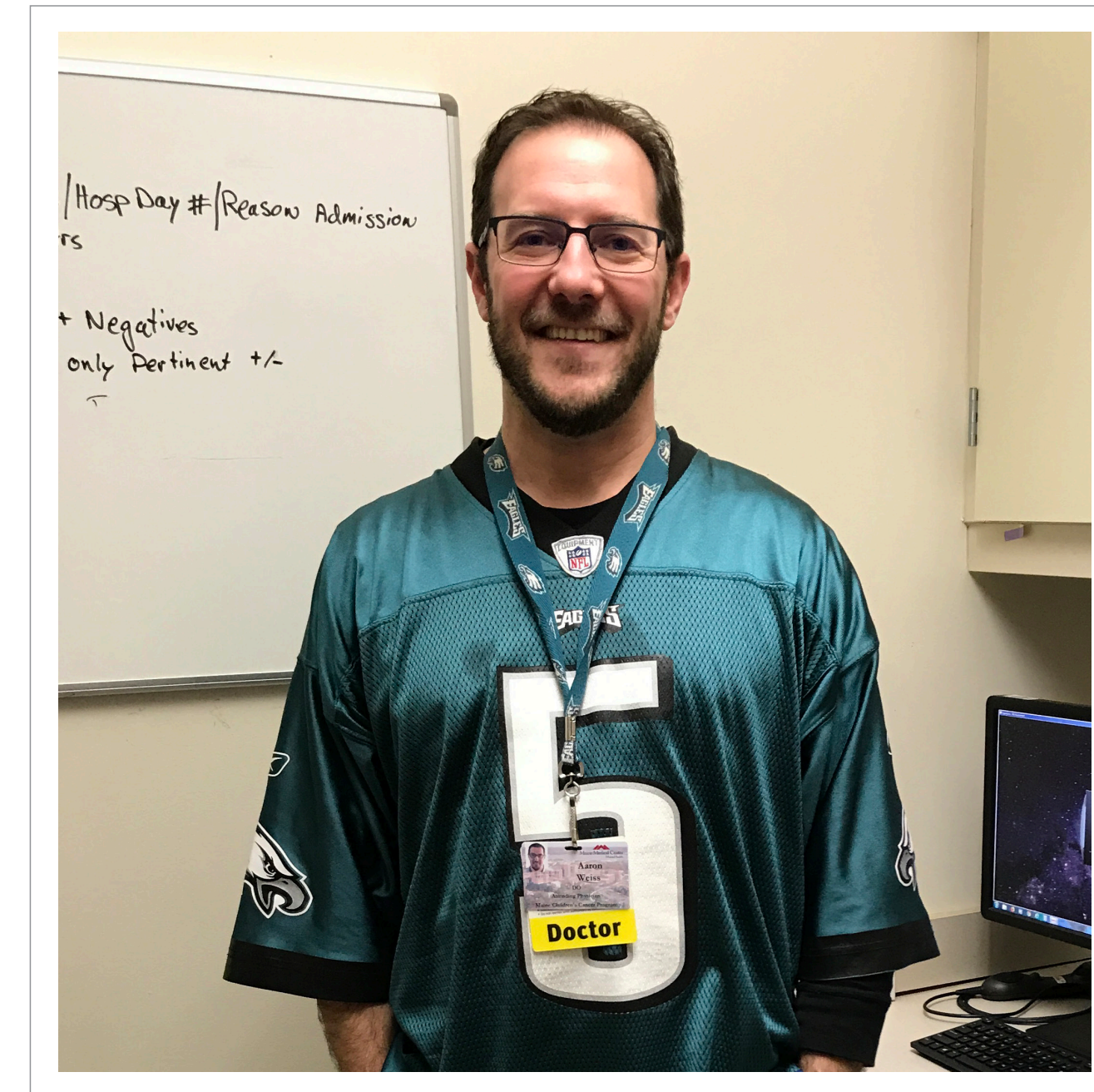
Who am I?
I am a soft tissue tumor surgical oncologist as well as translational researcher in these diseases. I have been caring for this cluster of patients for more than 35 years. I was at the University of Texas MD Anderson Cancer Center for 31 years, the last 17 of which I served as Head of the Division of Surgery. I was recruited to The Ohio State University Wexner Medical Center in 2013 to serve as Director of the Division of Surgical Oncology. This was followed by appointment to serve as Surgeon-in-Chief for The Ohio State University Wexner Medical Center in 2015 and then appointment as the Director of The Ohio State University Comprehensive Cancer Center in 2017, my current position.

How did I get to where I am?
My interest in desmoid tumors extends back 35 years to when I was in training as a Fellow in Surgical Oncology at the University of Texas MD Anderson Cancer Center. The challenge of working with this group of patients by helping to integrate surgery, radiation, and the various systemic therapies has been a remarkable opportunity to be of service to a very courageous group of patients.

What is my biggest challenge?
We need to arrive at a better understanding of the molecular drivers of this disease if we are to develop improved therapies. This is difficult because the relative rarity of desmoid means there are few institutions able to sustain the much-needed molecularly oriented research effort necessary to make that type of progress in this disease.

What would help?
Improved funding for rare diseases such as desmoid is desperately needed. The rarity of the disease, however, means it is difficult to attract funding prioritization.

Meet Desmoid Tumor Warrior DR AARON WEISS



Dr Weiss

I am a pediatric hematologist-oncologist at Maine Children's Cancer Program within the Barbara Bush Children's Hospital at Maine Medical Center in Portland, Maine. Since our program is relatively small, I only see a few primary patients with desmoid tumor per year, but I have previously worked at larger institutions with a greater number of cases. The majority of these patients have sporadic desmoid tumor. I receive a number of requests each year from providers, patients, and families for management advice. Due to the complexities of the cases and challenges in travel, I was part of an effort to initiate a virtual desmoid tumor board sponsored by the DTRF. Meetings occur quarterly and include specialists in the fields of pediatric and medical oncology, pathology, radiology, surgery, and radiation oncology. The program started in December 2017 and has been highly successful. We also have robust international participation.

I grew up in the Philadelphia area and attended medical school and residency there. Although I always dreamed of becoming a general pediatrician, some special exposures during my residency training changed my life forever as I decided to pursue a career in childhood cancer. My pediatric hematology-oncology fellowship training took place at St. Jude Children's Research Hospital in Memphis, Tennessee. After starting my career in New Jersey, I moved to Portland, Maine in 2012. My interest in desmoid tumor started shortly after fellowship when a mentor asked me to co-develop a clinical trial for children and young adults with

desmoid tumor funded by the DTRF. After attending my first DTRF meeting I was hooked; it was inevitable based on the passion of the founding members and support staff.

The more time I spent with patients, families, clinicians, and researchers involved with desmoid tumor, the more I realized the great unmet needs and potential for positive change. So much so that in a relatively short period of time I have served as the director of the Medical Advisory Board for the DTRF, joined an international collaborative effort to standardize the management of desmoid tumors, run clinical trials for novel therapies in desmoid tumor, and now chair an international virtual tumor board for providers of patients with desmoid tumor. As a pediatric oncologist, there is a great need to better understand desmoid tumor biology in children in order to develop more effective and targeted therapies that provide good quality of life and minimize long-term toxicities in this highly vulnerable population. Clinical trials are one way to overcome these needs. This requires funding, pharmaceutical support, provocative research questions, and patient participation. Grassroots organizations committed to rare tumors are one way to facilitate this process. I look forward to continuing this journey and gaining strength and inspiration along the way from the numerous patients and families affected by desmoid tumor every day.

POSTERS

QUALITY OF LIFE (QOL) AND TUMOR LOCATION IN PATIENTS WITH DESMOID TUMORS; DATA FROM THE DESMOID TUMOR RESEARCH FOUNDATION (DTRF) NATURAL HISTORY STUDY

Kelly Mercier^a, Lynne Hernandez^a, Vanessa Boulanger^b, Allison Seebald^b, Suzanne Rossov^b, Kelsey Milligan^c
^aDesmoid Tumor Research Foundation, Suffern, NY, USA; ^bNational Organization for Rare Disorders (NORD); ^cTrio Health Analytics



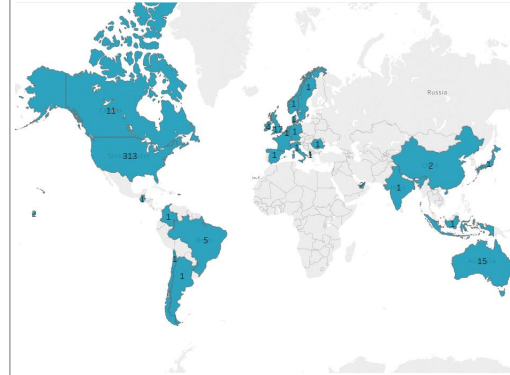
1. BACKGROUND AND AIMS

Desmoid tumors occur in connective tissues of the body. These noncancerous tumors may invade surrounding tissues resulting in compromised organ function and complications. As few as 5-6 per 1 million people are diagnosed with desmoid tumors annually, which may be an underestimate of the actual affected population due to difficulty in correctly diagnosing the disease. To improve awareness of desmoid tumors and better inform treatment development, DTRF in partnership with the National Organization for Rare Disorders launched the DTRF natural history study. Here, we describe patient demographics, tumor location, and QOL in registry patients.

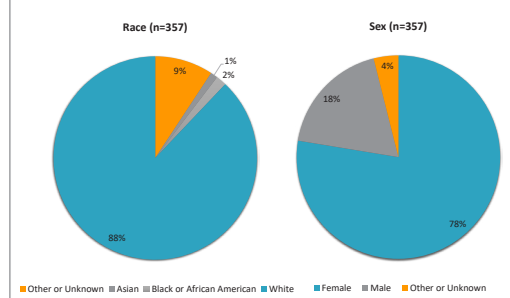
2. METHODS

The registry initiated February 2017 and contains 15 surveys covering diagnostics, disease, treatment, care management, and quality of life. As of January 2019, 357 patients have completed 2,371 surveys.

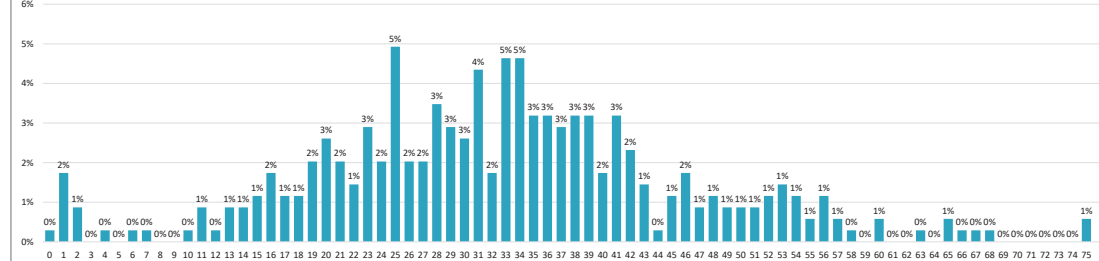
3. COUNTRY OF RESIDENCE



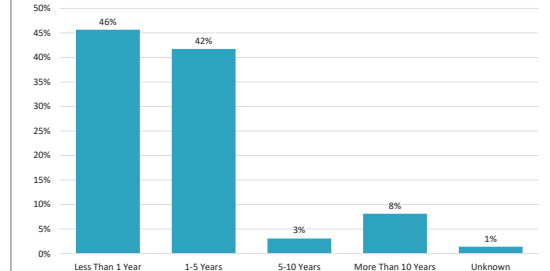
4. RACE AND SEX



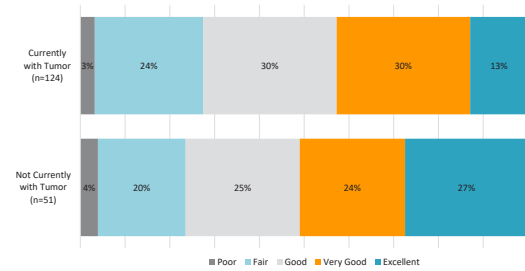
5. AGE (YEARS) AT DIAGNOSIS (N=345)



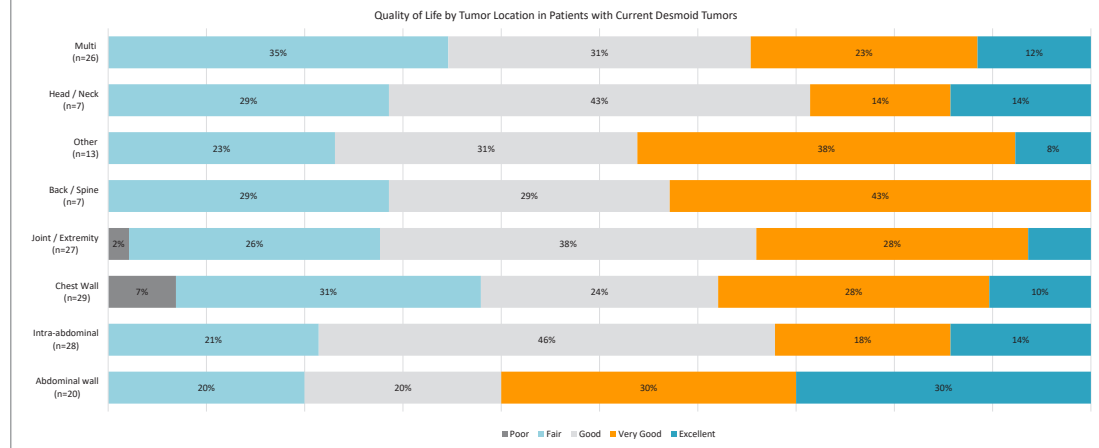
6. TIME FROM ONSET OF SYMPTOMS TO DIAGNOSIS (N=357)



7. QUALITY OF LIFE BY TUMOR STATUS



8. QUALITY OF LIFE BY LOCATION OF TUMOR



9. SUMMARY

Desmoid tumors occur in connective tissues of the body. These noncancerous tumors may invade surrounding tissues resulting in compromised organ function and complications. As few as 5-6 per 1 million people are diagnosed with desmoid tumors annually, which may be an underestimate of the actual affected population due to difficulty in correctly diagnosing the disease. To improve awareness of desmoid tumors and better inform treatment development, DTRF in partnership with the National Organization for Rare Disorders launched the DTRF natural history study. Here, we describe patient demographics, tumor location, and QOL in registry patients.

Location

- Registry participants are located in 28 countries
- Participants are mostly US-based (80%, 313/390)

Race and Sex

- Registry participants are mostly white (88%, 313/357)
- Registry participants are mostly female (78%, 277/357)

Age at Diagnosis

- The median age of diagnosis is 33 years
- The mean age of diagnosis is 32.5 years

Time from Onset of Symptoms to Diagnosis

- 46% of participants were diagnosed within one year after onset of symptoms
- Most participants (88%) were diagnosed within 5 years of onset of symptoms

Quality of Life by Tumor Status

- The number of participants who rated their quality of life as excellent varied significantly depending on whether or not the participant currently had a tumor at the time ($\chi^2=2.320$, $p=0.020$, significant at $p < .05$).

Quality of Life by Location of Tumor

- Desmoid tumor location was reported for 119 respondents with tumors at time of data collection.
- Most prevalent tumor locations were joint /extremities (39%, 47/119), intra-abdominal (24%, 28/119), and chest wall (24%, 29/119). Multiple tumor locations were indicated for 22% (26/119) of patients.
- Participant quality of life may vary by tumor location for patients with current desmoid tumors.
- Participant quality of life may also vary depending on whether the participant has tumors in multiple locations compared to those with tumors in one location.

10. CONCLUSION

Patients with desmoid tumors have varied QOL and tumor locations. Data collection through the registry is ongoing and essential to raising awareness of this disease and improving care for these patients.

MISDIAGNOSIS OF DESMOID TUMORS; INSIGHT FROM THE DESMOID TUMOR RESEARCH FOUNDATION (DTRF) NATURAL HISTORY STUDY

Kelly Mercier^a, Lynne Hernandez^a, Vanessa Boulanger^b, Allison Seebald^b, Suzanne Rossov^b, Kelsey Milligan^c
^aDesmoid Tumor Research Foundation, Suffern, NY, USA; ^bNational Organization for Rare Disorders (NORD); ^cTrio Health Analytics

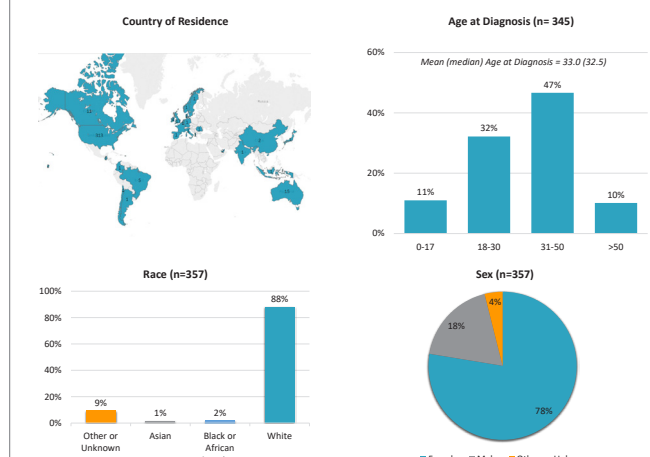


1. BACKGROUND AND AIMS

As few as 5-6 per 1 million people are diagnosed with desmoid tumors annually, which may be an underestimate of the actual affected population due to difficulty in correctly diagnosing the disease. These locally invasive, noncancerous tumors can yield a wide range of symptoms including no symptoms at all. Conclusive diagnosis requires biopsy and a pathologist experienced in or knowledgeable of rare cancers. To improve awareness of desmoid tumors, DTRF in partnership with the National Organization for Rare Disorders launched the DTRF natural history study. Here, we describe patient-reported data on their experience with misdiagnosis.

2. METHODS

The registry initiated February 2017 and contains 15 surveys covering diagnostics, disease, treatment, care management, and quality of life. As of January 2019, 357 patients have completed 2,371 surveys.



Data regarding the diagnosis of their desmoid tumor was provided by 171 registrants. Comparisons of properly diagnosed vs initially misdiagnosed groups were made by chi-square or Fisher's Exact test (categorical) or Student T test (continuous) in SPSS 25.

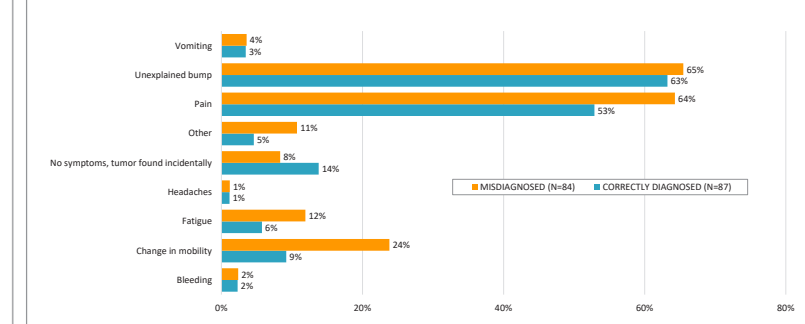
3. DEMOGRAPHICS

49% (84/171) of respondents indicated initial misdiagnosis of their desmoid tumor. Differences between the groups were not broadly identified by gender, age, location of residence, race, payer coverage, or known relative with same diagnosis.

| DISTRIBUTION WITHIN GROUPS UNLESS NOTED | CORRECTLY DIAGNOSED n=87 | MISDIAGNOSED n=84 | TOTAL N=171 | p |
|-----------------------------------------|--------------------------|-------------------|-------------|-------|
| GENDER | | | | |
| FEMALE | 79% | 80% | 80% | 0.942 |
| MALE | 21% | 20% | 20% | |
| AGE - MEAN (SD) | | | | |
| AT SYMPTOM ONSET | 31.4 (16.0) | 29.5 (14.3) | 30.5 (15.1) | 0.411 |
| AT DIAGNOSIS | 33.6 (14.9) | 31.7 (13.6) | 32.6 (14.2) | 0.391 |
| RESIDES | | | | |
| OUTSIDE US | 18% | 10% | 14% | 0.095 |
| US | 82% | 90% | 86% | |
| RACE | | | | |
| BLACK | 2% | 2% | 2% | 0.25 |
| WHITE | 90% | 95% | 92% | |
| OTHER | 5% | 1% | 3% | |
| UNKNOWN | 3% | 1% | 2% | |
| PAYER | | | | |
| MEDICAID | 3.4% | 7.1% | 5.3% | 0.542 |
| MEDICARE | 11.5% | 14.3% | 12.9% | |
| PRIVATE | 65.5% | 65.5% | 65.5% | |
| OTHER | 8.0% | 8.3% | 8.2% | |
| UNKNOWN | 11.5% | 4.8% | 8.2% | |
| RELATIVE WITH DIAGNOSIS | 10.3% | 10.7% | 10.5% | 0.790 |

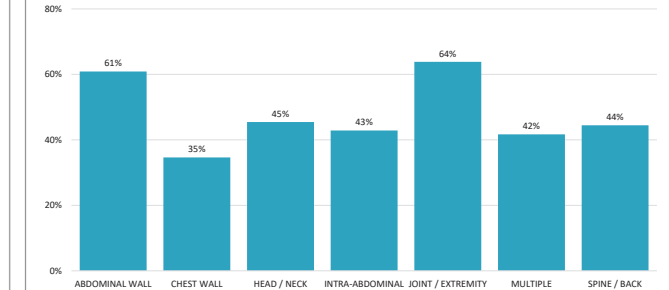
4. SYMPTOMS LEADING PATIENT TO SEEK CARE

Symptoms were not significantly different between groups. However, a significantly larger fraction of misdiagnosed patients had multiple symptoms compared to the correctly diagnosed group (57% v 43%, $p < 0.05$).



5. MISDIAGNOSIS BY INITIAL TUMOR LOCATION

Misdiagnosis rates varied by initial tumor location and are highest for abdominal wall and joint / extremity. Assessments of proportions using z-test with Bonferroni correction identified only joint / extremity as more prevalent (e.g. reaching significant of $p < 0.05$) in misdiagnosed patients.



6. SUMMARY

In this study of patient registry data, nearly half (49% (84/171) of respondents indicated initial misdiagnosis. Patient demographics at a top level were not significantly different, though further studies will continue to evaluate the role of age, location, and payer on diagnosis.

Patients in this study originally sought care for wide range of symptoms, with unexplained bump and pain being the most common issues. While individual symptoms were not associated with misdiagnosis, having multiple symptoms was more associated with initial misdiagnosis.

Tumor location varied as expected based upon the nature of the disease. While both abdominal wall and joint / extremity locations were more often diagnosed than other locations, only joint / extremity reached statistical significance.

The challenge of correct initial diagnosis remains. Data collection through the DTRF patient registry continues with increasing awareness of desmoid tumors.

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Notes

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