

USING PSYCHOSOCIAL THERAPY TO IMPROVE THE QUALITY OF LIFE OF  
PATIENTS WITH NEUROFIBROMATOSIS TYPE 1: A REVIEW

Presented by Farzam Farahani

in partial fulfillment of the requirements for completion of the  
Health Science Scholars honors program in the College of Natural Sciences at  
The University of Texas at Austin

Spring 2018

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**Using Psychosocial Therapy to Improve the Quality of Life of Patients with Neurofibromatosis Type 1: A Review**

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### Acknowledgements

I would like to first thank Dr. John Slopis at the University of Texas MD Anderson Cancer Center in Houston, Texas for allowing me to shadow him and his colleagues in the Neurology and Neurosurgery departments. Dr. Slopis' patient population primarily consists of patients with Neurofibromatosis Type 1, Neurofibromatosis Type 2, and Schwannomatosis. While shadowing him, I had the opportunity to learn a great deal about Neurofibromatosis and the complications his patients presented. I got to interact a lot with patients with the disease and consequently, understand just how much of a physical and emotional toll the disease has on an individual. It is for this reason that I decided to center my capstone thesis around Neurofibromatosis Type 1—so that I can make some sort of positive impact on these individuals.

Next, I would like to thank Dr. Sandy Magaña at the Steve Hicks School of Social Work at The University of Texas at Austin for guiding me through the thesis writing process and teaching me how to approach a systematic literature review. Dr. Magaña has spent a significant amount of time reviewing my methodology to ensure that I was on the right track for this project. I truly could not have written this thesis without her help.

And lastly, I would like to thank Dr. Rebecca Wilcox at the Honors Center in the College of Natural Sciences at The University of Texas at Austin. Especially this last year, she has been incredibly helpful in the development of my thesis topic. Her thesis writing seminar classes truly painted a clear picture on how to start, execute, and complete my research project. Like Dr. Magaña, she has also allocated a significant amount of her time reviewing my methodology to ensure my thesis was on the right track. She has never failed to give me helpful advice and encouragement during this whole process.

Abstract

Neurofibromatosis Type 1 is an autosomal disorder of the central and peripheral nervous system and affects 1 in 3000 individuals. Patients with the disease have a significantly lower quality of life than the general population. Many manifestations of the disease contribute to this discrepancy, including anxiety, depression, learning disabilities, and cutaneous and plexiform neurofibromas. In addition, due to the number of complications that are present, patients need to visit their neuro-oncologists regularly in order to ensure that they are in good health. This only adds on to the quality of life discrepancy by making patients feel as if the disease is truly taking control of their lives. There is no current cure for Neurofibromatosis Type 1, so symptom relief is a priority for the time being. Through a literature review, this thesis assesses the state of current psychosocial therapy programs and research related to improving the quality of life of patients with Neurofibromatosis Type 1. Incorporation of therapies such as the Relaxation Response Therapy, the Acceptance and Commitment Therapy, and the Creative Arts therapy have shown to have a significant, positive impact on the quality of life of patients with Neurofibromatosis Type 1 and patients with similarly manifesting diseases. These findings open the door towards developing new therapeutic programs that contain aspects of each of the three previously listed therapies in order to most effectively improve the quality of life of Neurofibromatosis Type 1 patients. Although twenty-four relevant sources were identified, there is still much research and development that must be done to continue to evaluate and improve complementary medicine treatments to better improve the quality of life of Neurofibromatosis Type-1 patients.

## Introduction

Neurofibromatosis Type 1 (NF1) is a common autosomal dominant genetic disease found in humans with a prevalence of 1 in 3,000 individuals (US National Library of Medicine, 2018). The disease is caused by mutations in the NF1 tumor suppressor gene and is characterized by the presence of multiple neurofibromas (tumors of the nerve sheath, which consists of the tissues covering nerves), café au lait spots (skin spots), and freckling. Neurofibromas are benign nerve sheath tumors that are expressed intra- or extra-neurally. Intra-neural neurofibromas, especially ones that impinge on neighboring organs, significantly increase morbidity and mortality by compromising organ functions, whereas extra-neural neurofibromas cause cosmetic disfigurement. Other common complications of patients with NF1 include malignant transformation of peripheral nerve sheath tumors, brain tumors, pain, epilepsy, growth problems, depression, anxiety, and perceptual and information processing learning disabilities (US National Library of Medicine, 2018). There is currently no cure for the disease, but there are treatment plans to deal with some of the complications (US National Library of Medicine, 2018). This highlights a gap in the model of care, however, because there currently are no treatment plans that addresses the lower quality of life of NF1 patients compared to the general population.

Quality of life (QoL) is a concept that incorporates all factors that affect an individual's life. Studies have shown that patients with NF1 have a significantly lower quality of life compared to individuals without the disease (Ferner *et al.*, 2017). It is important to assess the QoL of patients with NF1 in order to improve quality of clinical care of these patients. The techniques used to measure the QoL of patients are questionnaire based. NF1 and other rare genetic conditions have factors beyond the physical manifestations of the disease that contribute to the poor QoL. Psychological well-being, coping, and illness perceptions—all of which are exacerbated by the co-morbidity of

depression and anxiety—are a few QoL factors that are significantly reduced in NF1 patients and serve as potential directions of treatment (Ferner *et al.*, 2017).

Recently, one systematic literature review focusing on patients with rare diseases recommends QoL improvement by developing psychosocial interventions to be used in conjunction with advancing primary medicine (Cohen *et al.*, 2010). Cohen *et al.* (2010) found that of the factors involved in the concept of QoL, the psychosocial ones are the more readily modifiable ones. One potential psychosocial treatment direction is mind-body therapy. Mind-body therapy is a therapeutic method designed to enhance the mind's impact on the body in a positive manner (Park *et al.*, 2013). Since depression, anxiety, and other manifestations of the disease lead to increased stress and vice-versa, utilization of this psychosocial intervention can ultimately improve depression, anxiety, and factors that lower NF1 patient's QoL. Another treatment direction is cognitive-behavioral therapy. Cognitive-behavioral therapy aims to correct misconceptions attributed towards a certain subject (Hollan *et al.*, 1994). Since people respond differently to certain situations based on underlying beliefs, the therapy aims to identify and correct areas in an individual's thought process that may be overgeneralized, or too pessimistic. Since pain is a common manifestation of NF1, utilization of this psychosocial intervention can ultimately improve and pain-related QoL deficits a patient may have.

The two objectives of this thesis are as follows: First, a review of the literature will determine the most significant factors that are associated with the diminished QoL of NF1 patients. The medium to determine the QoL of a patient is questionnaire-based, and many different variations of QoL questionnaires have been developed and used. The difference in questionnaires also leads to a difference in factors that are being measured. However, there is some overlap between variables, and the data from these questionnaire tools can be extrapolated and regrouped to fit a more universal variable. Effectively, the first portion of



this literature review aims to unify and standardize the factors associated with the diminished QoL of NF1 patients.

The second aim of this thesis is to assess publications that aim to improve the quality of life of NF1 patients as well as individuals who have similarly manifesting disorders. The latter is an important aspect to this thesis because there are treatment methods that certainly work for other diseases to improve the quality of life of patients with other diseases, but have not yet been considered for the NF1 population. The second part of this literature review will essentially attempt to find treatment plans that effectively improve the observed QoL discrepancies found in the NF1 population compared to the general population.

## **Background**

### **Overview of Neurofibromatosis**

Neurofibromatosis is generally characterized as a disorder that leads to the growth of tumors in the nervous system. Neurofibromatosis is divided into three unique diseases: Neurofibromatosis Type 1 (NF1), Neurofibromatosis Type 2 (NF2), and Schwannomatosis.

### **Types of Neurofibromatosis**

**Neurofibromatosis Type 1 (NF1)** is the most common (1 in 3,000 individuals) Neurofibromatosis disorder and involves cosmetic and bone structure disfigurement (US National Library of Medicine, 2018). The disease is caused by mutations in the NF1 gene. NF1 patients develop nerve sheath tumors along the nerves of the skin, brain, and other body regions. Optic gliomas (cancer of the optic nerve) are a possible complication. Benign growths, called Lisch Nodules appear commonly on the iris as well. Cosmetically, NF1 patients can have a large variety of cutaneous neurofibromas and café au lait (large freckles on the skin) spots on their face and body. The disease usually presents itself during early childhood and many development issues such as learning disabilities, ADHD, scoliosis, and

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abnormal bone formation and growth arise as a child with NF1 ages. A patient is formally diagnosed with Neurofibromatosis Type 1 if he or she presents with two or more of the standard features of the disease (National Institutes of Health (NIH) Consensus Development Conference, 1987):

- I. Six or more café au lait spots (dark skin spots) of  $\geq 5$  mm in diameter before puberty or  $\geq 1.5$  mm in diameter after puberty
- II. Axillary or inguinal skinfold freckling
- III. Two or more cutaneous neurofibromas or one plexiform neurofibroma
- IV. Two or more Lisch nodules
- V. An optic pathway glioma
- VI. A first-degree relative (mother, father, or siblings) with Neurofibromatosis Type 1

**Neurofibromatosis Type 2 (NF2)** is also characterized by nerve sheath tumors along the nerves throughout the body, but the hallmark of the disease is the development of vestibular schwannomas or acoustic neuromas along the acoustic nerve, which carries information from the inner ear hair cells to the auditory cortex (US National Library of Medicine, 2018). The disease is caused by mutations in the NF2 gene. The signs and symptoms of NF2 include loss of hearing, tinnitus, and balance issues and do not present themselves until adolescence/early adulthood. Although rare, some NF2 patients might also develop cataracts during childhood. NF2 occurs in roughly 1 in 33,000 individuals.

The last form of Neurofibromatosis, called **Schwannomatosis**, is the development of tumors of the Schwann cells of the nervous system (US National Library of Medicine, 2018). Schwann cells are the specialized cell bodies that insulate nerves to allow successful electrical signal transduction. The disease stems from the mutation of two genes, SMARCB1 and LZTR1. The signs and symptoms of Schwannomatosis vary depending on where the tumor is located. They can include pain, numbness, weakness, tingling, and

headaches. The most common symptom is severe chronic pain affecting some region of the body. The signs and symptoms do not reveal themselves until early adulthood. The incidence of Schwannomatosis has not fully been determined; some populations observe a frequency of 1 in 40,000 individuals, while some other populations observe a frequency as high as 1 in 1.7 million individuals (US National Library of Medicine, 2018).

Although certainly each disease constitutes a lowered quality of life for the patient, this thesis aims to specifically address the quality of life deficits of patients with Neurofibromatosis Type 1. This is because some aspects of each disease are similar, but NF1 patients tend to have more complications beyond just tumor development that lead to a lowered quality of life such as physical and mental disabilities/disorders. These complications will be explained in further detail in the following sections and then related to quality of life in the “Concept of Quality of Life in Relation to Neurofibromatosis Type 1” section of this thesis. Furthermore, the prevalence of NF1 is significantly higher than the prevalence of NF2 or Schwannomatosis. Centering this thesis explicitly on NF1 will effectively benefit a large majority of Neurofibromatosis patients.

### **Genetic Basis of Neurofibromatosis Type 1**

Neurofibromatosis can best be explained as being a tumor disposition syndrome, meaning that individuals with the disease are more likely to develop neurological tumors compared to the general population. The genetic basis of the disease stems from the mutation of the NF1 gene. These mutations can include missense, nonsense, insertion, and deletion mutations (US National Library of Medicine, 2018). Research is still uncovering why the NF1 gene mutation causes the variance in the phenotype of neurofibromatosis patients, but what is known is that the mutation of the NF1 gene leads to the loss of expression of the protein neurofibromin (Kim *et al.*, 2017). The loss of neurofibromin leads to the activation of the RAS transcription pathway. RAS signaling and its numerous

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downstream effectors are known to be involved in the cell cycle and dysregulation of the pathway can lead to malignant peripheral nerve sheath tumor formation. Several drugs have been developed to closer regulate the RAS pathway in order to suppress the proliferation of tumor cells, however no drug has succeeded in showing clinical activity in human patients (Kim *et al.*, 2017). Consequently, there is no cure for the Neurofibromatosis Type 1 disease at this time (Zale *et al.*, 2018). This emphasizes the importance of developing treatment plans that deal with the various complications that NF1 patients deal with for the time being.

### **Cancer in Neurofibromatosis Type 1**

Because Neurofibromatosis Type 1 originates from a lack of neurofibromin expression, leading to dysfunctional cell cycle monitoring, it is understandable how the disease makes patients predisposed to malignant tumor development (Kim *et al.*, 2017). The cumulative risk of cancer in all areas for NF1 males and females ages 0-50 is 32.0% and 45.2%, respectively (Uusitalo *et al.*, 2016). This is significantly higher than those of the general population, where cancer risks only reach up to 2.8% for males and 5.0% for females (Uusitalo *et al.*, 2016). The cancers that NF1 patients are specifically predisposed to are malignant peripheral nerve sheath tumors, gliomas, and leukemia (Korf *et al.*, 2000).

Malignant peripheral nerve sheath tumors (MPNST) are cancers that develop along the nerves from the spinal cord to the body. 81% of MPNSTs arise from preexisting neurofibromas and may occur anywhere around the body (Korf *et al.*, 2000). The risk of developing a MPNST is significantly increased with NF1. In a clinical study, nearly 52% of all MPNSTs were from patients that had NF1 (Ducatman *et al.*, 1986). Typically, surgical resection is used to remove the MPNSTs since radiation and chemotherapy do not improve the prognosis of cancer patients (Ducatman *et al.*, 1986). Unfortunately, the outcome of MPNST is also significantly lower in NF1 patients compared to the general population. The 5-year survival rate of NF1 patients with MPNST is 16%, which is considerably lower when

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compared to the 53% in the general population. Additionally, 39% of NF1 MPNST cases metastasize to other regions (Ducatman *et al.*, 1986). The difficulty in detecting MPNSTs stems from the fact that a majority of them are derived from preexisting neurofibroma bodies, and typical MRI scans cannot distinguish between the malignant and non-malignant bodies within the neurofibroma.

NF1 individuals are at high risk for developing optic gliomas (cancer of the optic nerve) during infancy and early childhood. Approximately 15-20% of NF1 patients will develop an optic glioma during the first 6 years of their life. 6-7% of optic gliomas in NF1 individuals will progress towards malignancy (Gutmann *et al.*, 2017). Subsequently, if an optic glioma forms, it must be carefully monitored every three months to ensure that tumor progression does not persist. The deterioration of vision is a possible consequence of a growing optic glioma. Careful monitoring of vision is only necessary early on in life, since as the individual ages, tumor growth will typically halt altogether. Chemotherapy (carboplatin and vincristine) is the primary form of treatment for optic gliomas (Gutmann *et al.*, 2017).

As an NF1 patient reaches adolescence, the risk for brainstem gliomas increases. 5% of patients will develop a brainstem glioma (Gutmann *et al.*, 2017). The major complication with brainstem gliomas is an obstruction of the ventricles in the brain, leading to hydrocephalus (a buildup of cerebrospinal fluid in the brain). Like optic gliomas, brainstem gliomas tend to remain static as a patient continues to age.

### **Neurological Co-Occurring Disorders**

In addition to the predisposition of neurological tumors, NF1 also holds a psychological burden on patients. NF1 patients are more likely to develop numerous neurological co-occurring disorders, such as depression, anxiety, attention-deficit/hyperactivity disorder (ADHD), social perception problems, various types of

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learning disabilities, and pain compared to the general population. How the disease manifests the co-morbidity of these diseases is not well understood. It is speculated, however, that the decrease in volume of the white-matter microstructures in the brain might in part explain the neurocognitive defects found in NF1 patients (Karlsgodt *et al.*, 2012). The white matter in the brain is characterized as neuronal bundles that send information from one region of the brain (gray-matter) to other regions (other gray-matter). The loss of white-matter volume in the brain might compromise the extent of communication between brain regions, ultimately resulting in neurocognitive limitations (Karlsgodt *et al.*, 2012).

Depression and anxiety in particular seem to commonly present amongst NF1 patients. One study found 37% of males and 46% of females with the Neurofibromatosis disease (NF1, NF2, and Schwannomatosis) to have scored at or above a 16 on the Center for Epidemiologic Studies Depression (CESD) Scale, which suggest clinical depression (Wang *et al.* 2012). A larger study, done by Cohen *et al.* 2015, found that 55% of all NF1 patients (61% of women and 43% of men) scored at or above the threshold score of 16 on the CESD scale. Additionally, Johnson *et al.*, (1999) found that 16% of children of NF1 have suicidal thoughts, which is significantly higher than the 3% observed in the general population.

Attention-deficit/hyperactivity disorder (ADHD) is a neurocognitive disorder that results in inattentive behavior, hyperactivity, and impulsivity. ADHD is prevalent in about 30-50% of children with NF1. The disorder manifests itself strongly in the classroom setting—NF1 Children with ADHD have much more difficulty following complex instructions by their teacher, and have trouble learning how to read and do mathematical calculations (Cohen *et al.*, 2015). The complications associated with ADHD persist past childhood and adolescence and carry over into adulthood. Furthermore, one study found that NF1 patients with ADHD had lower life satisfaction, more excitability, aggressiveness, and more emotional instability than NF1 patients that did not have ADHD. The study also found

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that NF1 patients with ADHD appeared to be more emotionally unstable compared to ADHD patients without NF1. (Mautner *et al.*, 2015). Emotional stability is an important factor to consider for coping with chronic diseases. Since NF1 is a chronic, neurological disorder, NF1 patients with ADHD are at a high risk for psychological morbidity.

In addition to ADHD, NF1 patients have additional learning disabilities that are more prevalent than in the general population. 81% of children with NF1 have cognitive impairment in at least one area of cognitive functioning. 51% of children with the disease had a poor performance in reading, spelling, and mathematic tasks, and 20% of the children were diagnosed with a specific learning disability, a two and a half times higher rate than found in the general population (Hyman *et al.*, 2005). A specific learning disability is a deficit in one of the following eight domains: oral expression, listening comprehension, basic reading, reading comprehension, reading fluency, written expression, mathematical calculation, and mathematical problem solving (Colorado Department of Education, 2018). Lastly, it was found that both fine motor skills and motor speed was reduced in NF1 children. Hyman *et al.*, (2006), constructed a neuropsychological profile for NF1 children that consist of visuospatial and visuoperceptual deficits, executive functioning deficits, and attention deficits. Treatment of the learning disabilities found in NF1 patients is crucial to begin at an early age in order to ensure that the children do not have continual learning discrepancies later on during adolescence and adulthood (Hyman *et al.*, 2006). The underlying cause of these deficiencies (including ADHD) have not yet been explained, but it is hypothesized that it is related to lower dopamine levels as a result of a lack of neurofibromin expression. The biallelic loss of the NF1 gene in mice models has shown to cause defects in hippocampal learning and brain attention system functioning (Diggs-Andrews *et al.*, 2013). Furthermore, in studies using knock-out mice models, dopamine uptake inhibitors have shown to ameliorate the hippocampal learning and attention system

defects. But these drugs have shown to be ineffective in improving learning during clinical trials (Gutmann *et al.*, 2017), highlighting a gap in NF1 treatment.

NF1 patients also exhibit social deficits. This leads to poor social participation, peer relationships, and self-esteem. Roughly 40% of NF1 children show autism spectrum disorder-like symptoms and 13% are diagnosed with autism (Garg *et al.*, 2013). These high statistics may partially explain NF1 patient's social behavior, as one symptom of autism is the difficulty to decipher the emotional state of others. Additionally, NF1 children are reported by their parents and teachers to have more limited social skills compared to their peers (Johnson *et al.*, 1999). These social deficits continue to present themselves into adulthood. Namely, it is the lack of prosocial behavior (using eye contact, showing interest in what others are saying, etc.) that leads to the social problems faced by NF1 patients and not an increase in antisocial behavior (rudeness, insensitiveness, arguing, etc.). These deficits were found to be more prevalent in males compared to females (Pride *et al.*, 2013). The social behavior exhibited by NF1 patients is believed to be due in part to the impairments in executive and attention functioning.

A great deal of pain also arises from plexiform neurofibromas as they can press against vital organs and sensitize the nociceptor activity of those organs. Surgical intervention may be an option to correct the cosmetic disfigurement or alleviate pain, but is not always feasible. Surgical resection of neurofibromas might be impossible to execute if the neurofibromas are too large, too many, too inaccessible, or too close to vital body structures. There are two drugs, Sirolimus and Selumetinib, currently undergoing clinical trials that aim to alleviate the pain induced by plexiform neurofibromas. Sirolimus has shown effectiveness in reducing pain levels but did not succeed in decreasing the size of the plexiform neurofibromas (Hua *et al.*, 2014). The drug was, however, only administered in cases of extreme pain and was used only if surgical intervention was not an option. In



patients who were administered Selumetinib, there was an observed decrease in tumor size, pain, disfigurement, and functional impairment of subjects after treatment (Dombi *et al.*, 2016). But again, these drugs are only under clinical trials at the moment and are not accessible for every NF1 patient. Indeed, a number of neurofibromatosis patients are prescribed painkillers to deal with their pain, which can potentially pose larger health risks associated with opioids and opioid addiction (Paice *et al.*, 2018).

### **Cosmetic Disfigurement**

Although some tumors that NF1 individuals have may be benign, this does not mean that they do not lower their quality of life. Many benign neurofibromas can reveal themselves cutaneously, leading to displeasing cosmetic disfigurements (Wolkenstein *et al.*, 2001). Cutaneous neurofibromas may be presented in certain regions or all over the body and the frequency of cutaneous neurofibromas presenting themselves are highly variable from patient-to-patient. The cause of high variability in the number of neurofibromas is still unknown. The social stigma caused by the cutaneous neurofibromas can lead to patients being labeled as “freaks” or social outcasts. This may have an effect on a NF1 patient’s social and emotional functioning and can be a potential reason why many neurofibromatosis patients have depression.

Some neurofibromatosis patients may also experience precocious puberty during childhood, followed by stagnated growth during adolescence and shortened height during adulthood. Although not necessarily a cosmetic disfigurement, the stunted height associated with the disease may contribute to the body-image issues seen by many NF1 patients (Cohen *et al.*, 2015). This pattern of linear accelerated growth may occur in patients who develop optic chiasm pathway gliomas due to an increase in growth hormone production. Adult height can be preserved, however, with careful monitoring of pediatric growth charts

and administration of a luteinizing hormone-releasing hormone (a growth promoting hormone) agonist (Gutmann *et al.*, 2017).

Of the many bone deformities that NF1 patients are at risk for, such as osteopenia (lower bone density) or osteoporosis (weakening of bones), tibial dysplasia (bowing of the leg bone) is the most significant. The bowing of the tibia can cause a noticeable cosmetic deformity and a weakened bone that is prone to fractures (Gutmann *et al.*, 2017).

Consequently, patients with tibial dysplasia will typically need to have an Ilizarov external fixation brace in order to realign the bone and allow for proper healing. The brace itself is strikingly more noticeable than the bowing of their legs and can be a continual reminder to the patient of their condition. Additionally, this places patients in a situation where playing physical sports is very dangerous for them. The condition stems from defective bone mineral production. Currently, a drug named BMP2 has proven to correct these defects in bone remodeling in NF1 knock-out mice strains, however clinical trials are still to be approved.

### **The Concept of Quality of Life in Relation to Neurofibromatosis Type 1**

According to the World Health Organization (WHO), quality of life is defined as:

“An individual's perception of their position in life in the context of culture and value systems in which they live in relation to their goals, expectations, standards, and concerns affected in a complex way by the person's physical health, psychological state, level of independence, social relationships and their relationships to salient features to their environment.”

QoL can essentially be interpreted as how “happy” a patient is with their life. It is difficult to make an objective assessment of an individual's QoL, which is instead

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determined by physicians through questionnaires that incorporate physical, psychological, and social variables. Some of the questionnaires include The Pediatric Quality of Life Inventory (PedsQL), Short Form 36 health survey (SF-36), TNO AZL Children's Quality Of Life (TACQOL), and the Impact of NF1 on Quality of Life (INF1-QOL).

When considering all of the complications, both mental and physical, that NF1 patients have to deal with, it is understandable that they might have a lower QoL compared to the general population (Page *et al.*, 2006). Cancer, in particular the malignant peripheral nerve sheath tumors, certainly negatively effect an individual's outlook on life due to the psychological burden associated with the possibility of not surviving. The risk of severe visual deficits and blindness by optic gliomas can also be understood as a potential area that can lower a patient's QoL. The neurological co-occurring disorders may have a significant effect on a NF1 patient's QoL as well. Depression and anxiety certainly may alter an individual's outlook on life, making it hard to find life enjoyable because of his or her mood. ADHD and other learning disabilities may also affect one's perception of life. Learning disabilities can take an emotional toll on an individual, making them feel as if they are not smart enough or inadequate in a particular subject. When comparing themselves to their normal peers who do not have as much trouble learning, it makes sense that this aspect of the disease could lower the individual's QoL. Lastly, the cosmetic disfigurement caused by the cutaneous neurofibromas, stunted growth, and bowed legs may be potential catalysts for bullying and social exclusion. These hinder many physical, psychological, and social aspects of a NF1 patient's life and may account for a diminished QoL. To add on to all of the psychological stress that this disease creates, patients are also reminded that there is no cure for the disease, meaning that whatever complications they have are more than likely here to stay. Thus, while there is still no cure for NF1, the one aspect of patient's lives that can be adjusted is their quality of life. It is critical for the healthcare sector to establish

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treatment options for the NF1 population in order to raise their QoL while researchers continue to learn more about this rare disease.

### **Methods**

#### **Sources**

An initial search was performed using the Medline (EBSCO) database, a database consisting of peer-reviewed biomedical literature, using the following terms: Neurofibromatosis, quality of life, well being, skin diseases, oncology, complementary medicine, psychosocial therapy, cognitive-behavioral therapy and mind-body therapy. The first two terms were primarily used to identify any literature that assesses the quality of life of NF1 patients while the rest of the terms were directed towards identifying treatment methods that help improve the QoL of patients. Another search was conducted using the Google Scholar database using the same terms. Google Scholar has a feature that automatically includes synonyms of each given terms in the search so additional sources were identified beyond the scope of the specific terms listed above. Lastly, additional relevant sources were found by reviewing the reference lists of found publications. The first thirty relevant matches were reviewed in each search due to the trend of a loss of topic relevance after the first thirty matches on average.

### **Selection and Assessment Criteria**

Publications were included in the literature review if they met the criteria listed below:

- I. The study population focused on, or at least included, patients with NF1 for QoL assessment.
- II. A standardized QoL measure is used to assess the QoL of the studied population.
- III. The study focused on the utilization of a complementary medicine treatment method in an attempt to improve the QoL of patients.
- IV. The treatment method employed on the disorder population being studied has similarly manifesting characteristics as NF1.
- V. The treatment method employed on the disordered population attempts to measure a quality of life change throughout the course of treatment.
- VI. The study was a peer-reviewed publication.
- VII. The study is available in English.
- VIII. The study was published after January 1<sup>st</sup>, 2000.

The topic criterion was included in the database search and was screened for manually as well. Criteria V did not require a standardized QoL measure due to the lack of publications addressing changes in QoL domains through QoL-assessing questionnaires. Instead, more specific questionnaire measures, such as the Center for Epidemiological Studies Depression Scale (CES-D scale), which measures the level of depression an individual has, were used instead to measure improvements in QoL domains.

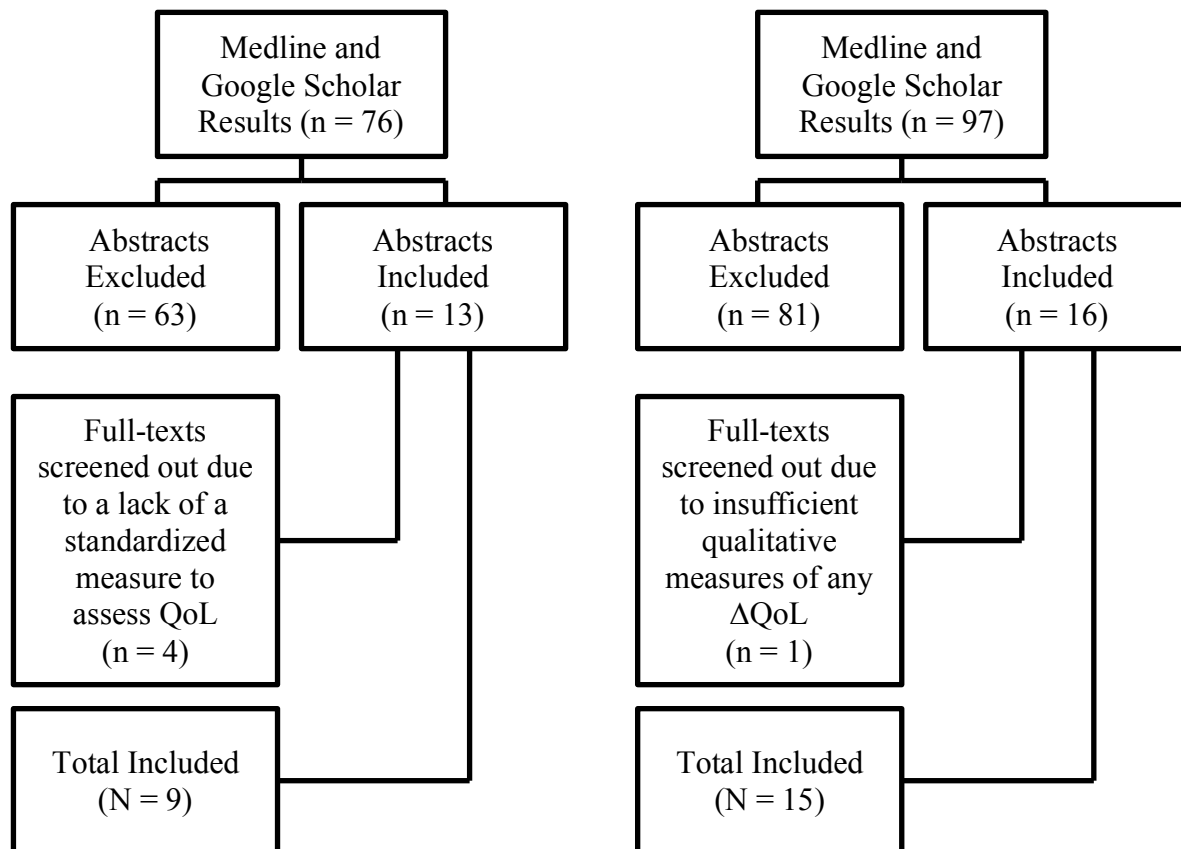
## **Results**

### **Selections**

The search of the Medline (EBSCO) and Google Scholar databases to assess the diminished QoL of NF1 patients yielded seventy-six results. Of these seventy-six results, sixty-three did not meet the inclusion criteria. Seventeen of these did not address individuals with Neurofibromatosis type-1, thirty-two did not address quality of life, eleven were case studies, and three were not in English. This left thirteen remaining abstracts that met the inclusion criteria for the assessment of QoL in NF1 patients. The full-texts were then assessed for further eligibility. Four studies did not have a standardized measure to assess quality of life and were thus excluded from the review, leaving nine studies remaining in the review.

The search of the Medline (EBSCO) and Google Scholar databases to assess publications that aim to improve the quality of life of NF1 patients as well as individuals that have similarly manifesting disorders yielded ninety-seven results. Eighty-one did not meet the inclusion criteria. Of these, fifty-four pertained to diseases that were not similar to NF1, twelve did not employ complementary medicine techniques, ten did not focus on measuring improvement in QoL during the treatment program, three were case study reports, and two were not in English. This left sixteen remaining abstracts that met the inclusion criteria for the assessment of treatment methods that can improve the QoL of NF1 patients and patients with similarly manifesting characteristics. The full-texts were assessed to ensure there was a sufficient qualitative method to measure QoL improvement, such as the CES-D scale to assess changes in depression or the Pain Interference Index to assess changes in pain thresholds. One study did not have a qualitative method to measure QoL improvement and was thus removed from the literature review, resulting in fifteen relevant publications. Figure 1 illustrates the literature review processes.

Figure 1  
*Literature Review Selection Process for: a.) QoL assessment of NF1 patients and b.) Treatment methods to improve QoL*



### Quality of Life Assessment in Patients with Neurofibromatosis Type 1

In total, nine relevant sources were identified in this section of the literature review. Four peer-reviewed publications studied children and adolescents with NF1 (n = 4), while six publications addressed adults with NF1 (n = 5). In eight of the studies (n = 8), the NF1 patient population was being compared to the QoL scores of the general populations, all of which displayed a diminished quality of life in nearly every domain of the questionnaire. Ferner et al. (2017) aimed to produce an NF1-specific QoL questionnaire, which was compared to a previously developed QoL questionnaire to test internal reliability. Cohen et al. (2015) measured the internal variance between specific domains of the QoL index and how it contributes to the overall variance in QoL scores for NF1 patients. The validated

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instruments used to measure QoL in these publications were either general measures or disease-specific measures. Some general measures used the Short-Form 36 Questionnaire (SF-36), the PedsQL, TNO-AZL Questionnaire for Children Health-Related QoL, and the Child Health Questionnaire. The Skindex and the Impact of NF1 on Quality Of Life Questionnaire (INF1-QOL) are NF1-specific questionnaire tools. The former is used primarily in NF1 patients who have facial or external deformities as a primary marker of their disease. The general measures are used as good indicators on the general functioning of a patient while the more specific questionnaire measures help pinpoint more of the disease-specific symptoms in relation to overall QoL. In total, one thousand three hundred and twenty-one (n = 1,321) patients with NF1 were surveyed. The takeaway from this part of the literature review was that patients with NF1 had significantly lower QoL scores in nearly every domain of the QoL Questionnaire that was used. Table 1 displays the literature review results.

Table 1

### *QoL Literature Review Results*

<u>Study &amp; Location</u>	<u>Participants</u>	<u>Questionnaire Type</u>	<u>General Conclusion</u>
Cipolletta et al., 2017 Northern Italy	Children and Adolescents (n = 60)	PedsQL	Subjects have a significantly lower QoL score in all areas of the PedsQL Questionnaire. The most profound differences were in social life, physical health, and school activities.
Cohen et al., 2015 United States	Adults (n = 498)	QoL Index	Depression accounts for approximately 32% of the total variance in QoL scores for NF1 patients.
Ferner et al., 2017 United States	Adults (n = 50)	INF1-QOL	Highest impacts on QoL of NF1 patients are depression and anxiety (32%) and the negative effects of NF1 on the role and outlook on life (42%).



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Graf et al., 2006 Netherlands	Children and Adolescents (n = 46)	TNO-AZL QoL	Subjects have a significantly lowered QoL score in most domains of the questionnaire. Namely, motor, cognitive, emotional, and social functioning. Subjects also had higher scores in internalizing and externalizing factors.
Krab et al., 2008 Netherlands	Children and Adolescents (n = 58)	Child Health Questionnaire (CHQ)	NF1 children experienced the largest deviances from normal population QoL in general health perception, physical functioning, role functioning, mental health, and self-esteem.
Merker et al., 2014 United States and Germany	Adults (n = 142, 107 from the USA, and 35 from Germany)	SF-36	Internal tumor volume does not contribute to a diminished QoL but instead is caused by psychosocial factors. The most profound differences in QoL scores in comparison to the general US population were physical role, emotional role, mental health, and physical functioning.
Oostenbrink et al., 2007 Netherlands	Young Children (n = 34)	ITQoL	NF1 children experienced the most significant deviations from the general Dutch population in the general health perceptions (large effect), growth and development (moderate effect), and physical functioning (moderate effect) domains.
Page et al., 2006 United States	Adults (n = 176)	SF-36 and Skindex	SF-36: Patients had a significantly lower QoL score for all domains of the questionnaire. The most profound differences were in physical functioning, emotional role, general health, and mental health domains. Skindex: As NF1 visibility increases, so does the skin diseases' effects on each aspect of their QoL(emotion, symptoms, and functioning).
Wolkenstein et al.,2001 France	Adults (n = 128)	SF-36 and Skindex	SF-36: Patients had a significantly lower QoL score for all domains of the questionnaire. The most profound differences were in mental health, emotional role, social functioning, and general health perceptions.

Skindex: Participants with more visible NF1 reported more effects of skin disease on each aspect of their QoL (emotion, symptoms, and functioning).

### **Quality of Life Findings**

Overall, the literature review of the ten publications addressing the QoL of NF1 patients finds patients with NF1 to have a significantly lower QoL compared to the general population in nearly every domain of each questionnaire tool. The majority of studies used the SF-36 to assess the QoL discrepancies between the general population and patients with NF1. Because of how general each domain of the SF-36 questionnaire is, the questionnaire will serve as a sufficient template in determining the most significant determinants of a diminished quality of life. The results from other survey tools will be categorized into one of the eight specific domains of the SF-36 questionnaire to determine the most significant aspects of QoL that are diminished in the NF1 population. Thus, before continuing, each domain of the SF-36 questionnaire must be addressed.

The SF-36 questionnaire is divided into eight scaled scores (vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, and mental health). Vitality measures the level of energy/fatigue a patient experiences. Physical functioning measures the extent at which patients are able to perform physical activities such as walking, running, lifting heavy objects, and bathing/dressing themselves. Bodily pain indicates to what extent the patient's experience of pain hinders their performance of everyday activities. General health perception measures how healthy the patient believes they are relative to other people they know. Physical role functioning refers to the extent to which performance of roles in the patient's daily life is affected by their physical state of health. Emotional role functioning assesses the extent to which the emotional condition of the patient limits their daily functioning. Social role functioning refers to the social interactions with family members,

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friends, neighbors, and other social relations. Lastly, Mental Health measures the extent to which an individual is feeling both positive and negative emotions. Due to the similarities between physical functioning and physical role functioning (the primary difference being the patient's perception vs. the patient's performance on the success of every day physical activities due to their condition), these two will be grouped together when categorizing data from other questionnaire tools that are not a part of the SF-36 questionnaire. Furthermore, due to the similarities between the emotional role functioning and mental health domains (the extent to which emotions effect daily life and the extent at which one is feeling happy or sad), these two will be grouped together as well.

Three studies (Merker et al., 2014, Page et al., 2006, and Wolkenstein et al., 2001) used the SF-36 questionnaire to measure the QoL of NF1 patients. The findings amongst these three publications reveal that the most significant domains of the SF-36 questionnaire that impact the QoL of NF1 patients are general health perceptions, mental health, social functioning, emotional functioning (grouped with mental health), and physical functioning. In addition, Page et al. (2006) and Wolkenstein et al. (2001), also found through the Skindex questionnaire that these domains are more significantly impacted when the visibility of neurofibromas are more prevalent.

Amongst the studies for children with NF1, Cipolletta et al. (2017) found that children with NF1 scored significantly lower in all areas of the PedsQL Questionnaire, with the most profound differences being in social life (social functioning), physical health (physical functioning), and school activities. Graf et al. (2006) utilized the TNO-AZL QoL questionnaire and found that NF1 patients scored significantly lower in all domains of the questionnaire with the most profound differences being in the motor functioning (physical functioning), cognitive functioning, emotional functioning (mental health), and social functioning domains of the questionnaire. Additionally, patients also had higher scores in

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internalizing and externalizing behaviors. Higher rates of internalizing behavioral problems equate to a patient experiencing more social withdrawal (social functioning) and more depressive and anxiety symptoms (mental health). Higher rates of externalizing behavior equates to more aggression and dissocial behavior (social functioning). Through utilization of the Child Health Questionnaire, Krab et al. (2008) found that the largest deviances NF1 patients experienced from the normal population in QoL were general health perception, physical functioning, mental health, and self-esteem (can be grouped with mental health). Lastly, Oostenbrink et al. (2007), found through the Infant/Toddler Quality of Life Questionnaire, that NF1 children experience the most significant deviations from the general Dutch population in general health perceptions, growth and development (can be grouped with physical functioning), and physical functioning.

Among the remaining publications with adult subjects, Cohen et al. (2015) found that depression accounts for approximately 32% of the total variance in the QoL scores for NF1 patients using the QoL Index questionnaire (mental health). Furthermore, Ferner et al. (2017) confirm that the highest impacts on QoL in NF1 patients are depression and anxiety (mental health) as well as the negative effects of NF1 on the role and outlook on life (general health perceptions) of these patients.

The QoL literature review findings reveal that the most significant factors that contribute to the diminished quality of life in NF1 patients are physical functioning, mental health, social functioning, and general health perceptions. Table 2 reveals the frequency of each category that is deemed to cause a profound difference between the general population and the NF1 population. Note is that in nearly every publication, there was a significant difference in all domains of QoL (including vitality and bodily pain in the SF-36 questionnaire studies), but table 2 is primarily concerned with the most significant discrepancies in each domain. Having determined the most significant factors associated

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with the diminished quality of life of NF1 patients, potential treatment methods can be reviewed and analyzed in order to determine their effectiveness in improving these domains of quality of life.

Table 2

*Number of Publications in which there is a significant discrepancy between general and NF1 population in each generalized domain of QoL.*

Vitality	Physical Functioning	Mental Health	Social Functioning	Bodily Pain	General Health Perceptions
0	8	8	7	0	7

### **Treatment Plan Assessment in Improving the Quality of Life of Patients with Neurofibromatosis Type 1**

In total, fifteen publications were reviewed that address treatment plans that improve domains of QoL (N = 15). Amongst the fifteen publications, there are two general types of therapies: Mind-Body therapies (n = 9), and Cognitive Behavior therapies (n = 6). The diseases of patients undergoing these therapies include Neurofibromatosis Type 1 (n = 4), Neurofibromatosis Type 2 and Schwannomatosis (n = 1), Cancer (n = 3), Irritable Bowel Syndrome (n = 1), Fibromyalgia (n = 2), Bipolar Disorder (n = 1), Depression (n = 1), and general chronic illness and mental health issues (n = 2). The questionnaire measures varied from study-to-study due to the variations in the disease studied as well as treatment goals, but each can be related to a QoL domain from the SF-36. These questionnaires were performed pre-test and post-test to measure any changes. In total, two thousand seven hundred and eighteen patients (n = 2,718) underwent a treatment program for their complication. Table 3 displays the literature review results.

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Table 3

*Treatment Plans Literature Review Results*

<u>Study &amp; Location</u>	<u>Participants &amp; Disease</u>	<u>Treatment Type</u>	<u>Questionnaires Used</u>	<u>General Conclusion</u>
Decker et al., 1992 United States	Adults with Cancer (n = 82)	Relaxation Therapy (Mind-Body Therapy)	Profile of Mood States	There is a significant reduction in tension, depression, anger, and fatigue in cancer patients undergoing radiation therapy.
Kuo & Bhasin et al., 2015 United States	Adults with Irritable Bowel Syndrome (IBS) (n = 48)	Mind-Body Therapy	Trait Anxiety Scores, IBS QoL, IBS Symptom Severity Index, IBD Questionnaire	Anxiety, quality of life, and symptom severity scores improved significantly post intervention and at short-term follow-up appointments.
Luciano et al., 2013 Spain	Patients with Fibromyalgia (n = 156)	Group Acceptance & Commitment Therapy (Cognitive Behavior Therapy)	Fibromyalgia Impact questionnaire, Pain Catastrophizing Scale, Hospital Anxiety and Depression Scale, Pain visual analogue scale, EuroQoL	Subjects showed improvement on coping with the disease, and reduced pain levels.
Madden et al., 2010 United States	Children with Brain Tumors (n = 16)	Creative Arts Therapy (Mind-Body Therapy)	Faces Scale and Emotional Responses Checklist	Subjects showed an improvement in pain tolerance and were more excited, happier, and less nervous.
Martin et al., 2016 United States	Children with NF1 (n = 17)	Acceptance And Commitment Therapy (Cognitive Behavior	Modified Brief Pain Inventory, Pain Interference Index, Acceptance of Pediatric Disease	Patients reported significant declines in pain interference at 3 months post-treatment. Pain intensity declined from baseline and

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		Therapy)	Questionnaire	parents reported greater acceptance of their child's pain.
Miller et al., 2015 United States	Adults with Depression (n = 24)	Mind-Body Therapy	Center for Epidemiological Studies Depression Scale, Health-Promoting Lifestyle Profile II, QoL-5	Significant post-treatment improvements were shown for depression, spiritual growth, mental health, and quality of life.
Noroozi et al., 2017 Iran	Patients with Type 2 Diabetes comorbid with Depression (n = 30)	Group Cognitive Behavior Therapy	Beck Depression Inventory, World Health Organization QoL	Intervention group experienced a decline in depressive symptoms as well as an improved quality of life compared to the control group.
Pankowski et al., 2017 United States	Patients with Bipolar Disorder (n = 26)	Group Acceptance & Commitment Therapy (Cognitive Behavior Therapy)	The Beck Anxiety Inventory, The Beck Depression Inventory, QoL Inventory, Acceptance and Action Questionnaire	Patients reported significant improvements in anxiety, depression, quality of life, and psychological flexibility.
Puetz et al., 2013 United States	Patients with Cancer (n = 1576)	Creative Arts Therapy (Mind-Body Therapy)	Trait anxiety scores, Center for Epidemiological Studies Depression Scale, Pain interference index	Treatment significantly reduced anxiety, depression, pain, and increased quality of life.
Samuelson & Foret et al., 2010 United States	Mental health outpatients (n = 331)	Mind-Body Therapy	Medical Symptom Checklist, Health Promoting Lifestyle Profile	Significant post-treatment improvements symptom frequency, health responsibility,

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			II, and Symptom Checklist- 90R	spiritual growth, nutrition physical activity, relationships, stress management, depression and anxiety.
Vranceanu et al., 2014 United States	Adults with NF1, NF2, and Schwannomatosis (n = 20)	Relaxation Response Resiliency Program (Mind-Body Therapy)	Satisfaction with life scale, Resiliency scale, Perceived stress scale, Epworth sleepiness scale, and Patient-Health Questionnaires for Depression, Somatic Symptoms, and Anxiety	Significant post-treatment improvement in resiliency, satisfaction with life, stress, depression, anxiety, somatization, sleepiness, mindfulness, and post traumatic growth (effect sizes ranging from moderate to high).
Vranceanu et al., 2014 United States	Adults with chronic physical, mental and co-morbid health issues. (n = 226)	Mind-Body Therapy	Medical Symptoms Checklist, Health Promoting Lifestyle Profile, Symptom Checklist 90R	Patients showed significant improvement on 9/23 medical symptoms, all health promoting lifestyle behaviors, and all mental health symptoms.
Vranceanu et al., 2016 United States	Adults with NF1 (n = 63)	Relaxation Response Resiliency Program for patients with NF1 via Videoconferencing (Mind-Body Therapy)	World Health Organization QoL abbreviated instrument, 9-item Patient Health Questionnaire for Depression, Generalized Anxiety Scale, Brief Pain Inventory	Patients participating in the 3RP-NF program showed greater improvements compared to the control mind-body therapy program in psychological, environmental, and social QoL as well as anxiety. Both treatment programs showed improvement in depression and pain



				intensity. These improvements sustained themselves during the 3-month follow-up period.
Wicksell et al., 2012 Sweden	Adults with Fibromyalgia (n = 40)	Acceptance & Commitment Therapy (Cognitive Behavior Therapy)	Fibromyalgia Impact questionnaire, Pain Catastrophizing Scale, Hospital Anxiety and Depression Scale, Pain visual analogue scale, EuroQoL	Patients in the ACT group showed significant differences in pain-related functioning, mental health-related QoL, depression, and anxiety.
Zale et al., 2017 United States	Adults with NF1 (n = 63)	Relaxation Response Resiliency Program for patients with NF1 (Mind-Body Therapy)	Measure of Current Status-A, The Medical Outcomes Study Social Support Survey, The Gratitude Questionnaire, Life Orientation Test Optimism Scale	Patients who received the 3RP-NF program vs. the control mind-body therapy program reported more substantial improvements in perceived coping abilities, perceived social support, and mindfulness. These improvements sustained themselves during the 6-month follow-up period.

### Mind-Body Therapies

Nine publications utilized a mind-body therapeutic approach towards improving the QoL or symptoms of the patients' disease. Mind-body therapies focus on the cooperation between the mind and the body in the experience of a stress response in order to effectively suppress the stressor. Two specific types of mind-body therapies were identified: The Relaxation Response and Resiliency Program and the Creative Arts Therapy.

**The Relaxation Response** is characterized by a decrease in the arousal of the sympathetic nervous system (Park et al., 2013). Stress involuntarily activates the sympathetic nervous system, which leads to an increase in cortisol, norepinephrine, and epinephrine levels, ultimately leading to an increase in metabolism, blood pressure, and heart rate. The relaxation response, on the other hand, combats these responses, and has the opposite effect. The importance of the relaxation response boils down to how human stress affects the allostatic load of the brain. Allostasis refers to the capacity of the brain to maintain a stable physiological state in the face of environmental changes, such as stress. When an individual is experiencing a stressful situation, the brain expends a great deal of energy to combat the stressful situation and allow the brain to return back to the baseline state. The consequence is metabolic wear and tear, however, making the brain less effective in combatting a second stressful response until a sufficient amount of time passes to allow the brain to return to the baseline state. This is where chronic stress or severe exposure to a higher metabolic state comes into play; with continual stressors cueing the brain to maintain homeostasis, there is an inability to return back to baseline due to a lack of time for the brain to recover from the stressful cue. This eventually leads to an increase in allostatic load, which has been shown to increase the vulnerability to illness (Park et al., 2013). Eliciting the relaxation response however has been shown to reduce the allostatic load of a stressful situation by buffering the heightened metabolic state of the stress response (decrease in sympathetic arousal). The relaxation response can be elicited in numerous ways, including meditation, yoga, and muscle relaxation (Park et al., 2013) and is the basis of the mind-body therapy techniques employed by the publications identified in this literature review.

**The Relaxation Response and Resiliency Program** is a mind-body approach that elicits the relaxation response. There are five non-NF1 publications that utilize the Relaxation Response in order to improve the QoL of their patients. Decker et al. (1992)

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showed that relaxation therapy resulted in a significant reduction in depression, anger, and fatigue in cancer patients undergoing radiation therapy. In the scope of the SF-36 domains for QoL, this equates to an improvement in mental health (depression and anger), as well as vitality (fatigue). Kuo & Bhasin et al. (2015) showed that relaxation therapy in adults with Irritable Bowel Syndrome experienced a decrease in anxiety (mental health), and symptom severity (bodily pain) as well as an increase in QoL of these patients. Miller et al. (2015) used relaxation therapy on patients with depression and found significant post-treatment improvements for QoL, mental health, and depression. Vranceanu et al. (2014) showed that mind-body therapies improve the health-promoting lifestyle behaviors (general health perceptions) and mental health symptoms (mental health) of adults with chronic physical, mental, and comorbid health issues. Lastly, Samuelson & Foret et al. (2010) showed improvements in symptom frequency (mental health), health responsibility, physical activity (physical functioning), nutrition, interpersonal relations (social functioning), stress management (mental health), and depression and anxiety (mental health) in mental health outpatients.

In addition to the five Relaxation Response Therapies listed above, there were three publications that specifically addressed the NF1 population. Vranceanu et al. (2014) showed an improvement with resiliency, satisfaction with life, depression and anxiety, and stress (mental health) after the intervention for patients with NF1. Additionally, Vranceanu et al. (2016) implemented the Relaxation Response Therapy for NF patients via videoconferencing, and not only observed a higher turnout rate of participants compared to the non-videoconferencing group in Vranceanu et al. (2014) but also an improvement in psychological, environmental, and social QoL as well as anxiety (social functioning and mental health). Lastly, Zale et al. (2017) found that patients who received the 3RP-NF program compared to the control mind-body therapy program reported more substantial

improvements in perceived coping abilities (mental health), perceived social support (social functioning), and mindfulness.

**The Creative Arts Therapy** is another mind-body therapeutic approach that utilizes the arts, such as music, art, drama, dance, and poetry in order to elicit similar relaxation responses as the Relaxation Response and Resiliency Program. Two publications utilized the creative arts therapy in order to improve the quality of life and symptoms of the patient population. Madden et al. (2010) showed an improvement in pain tolerance (bodily pain) in children with brain tumors after the Creative Arts Therapy intervention. Additionally, the patients were more excited, happier, and less nervous (mental health) compared to before intervention. Puetz et al. (2013) also showed a significant reduction in depression and anxiety (mental health) and pain (bodily pain), as well as an increase in quality of life in patients with cancer.

### **Cognitive-Behavioral Therapies**

The basis of cognitive-behavioral therapy is to correct the faulty assumptions or misconceptions an individual has toward a certain subject. It is based on the fact that people respond to situations based on how these situations are processed in relation to relevant underlying beliefs a patient might have (Hollon et al., 1994). Cognitive behavioral therapy aims to identify areas in an individual's thought process that may be deemed as overgeneralizing, magnifying negatives, or minimizing the positives, leading to emotional distress and self-fulfilling prophecies. Once these errors in thinking are identified, the patients are then taught to think in a more all-encompassing manner in order to be able to look through their misconceptions and have a more positive outlook on a certain situation. In the case of Noroozi et al. (2017) researchers utilized a cognitive-behavioral therapy in order to improve the self-care methods of patients with type II Diabetes. The intervention

group experienced a decline in depressive symptoms (mental health) as well as an increase in quality of life compared to the control group in this study. Although there was no specific type of cognitive-behavior therapy employed in Noroozi et al. (2017) four publications (n = 4), used the Acceptance and Commitment Therapy in order to improve the QoL of patients and minimize disease-related pain.

The **Acceptance and Commitment Therapy** is a specific domain of Cognitive Behavioral therapy that aims to improve the quality of life and minimize pain in adults and children with chronic pain (Wicksell et al., 2009). The misconception in the thought process of patients undergoing this sort of intervention is based on the fact that individuals with chronic pain tend to spend extensive energy in an attempt to avoid or control their pain (Martin et al., 2016). Thus, the goal of the acceptance and commitment therapy is not to rid the patient of pain, but instead is to change the person's relationship with pain such that they do not consider it to be the defining feature of their life. This shift in perspective aims to allow patients to let go of the struggle against pain and instead focus on things that matter more to them.

Three publications (n = 3) utilized the Acceptance and Commitment Therapy in patients without NF1. Luciano et al. (2013) showed that patients with fibromyalgia demonstrated an improvement in coping with the disease as well as reduced pain levels (bodily pain) in a group therapy setting. Wicksell et al. (2012) also aimed to improve the pain and QoL in patients with fibromyalgia in a non-group therapy-based setting. Patients in the acceptance and commitment therapy group showed significant differences in pain-related functioning (bodily pain), mental health related QoL, and depression and anxiety (mental health) compared to the control group undergoing no therapy. Pankowski et al. (2017) found that patients with bipolar disorder reported significant improvements in anxiety and depression (mental health), quality of life, and psychological flexibility post-treatment. Lastly, there

was one NF1-specific publication by Martin et al. (2016) that utilized the acceptance and commitment therapy on children. In the study, patients reported significant declines in pain interference and intensity (bodily pain).

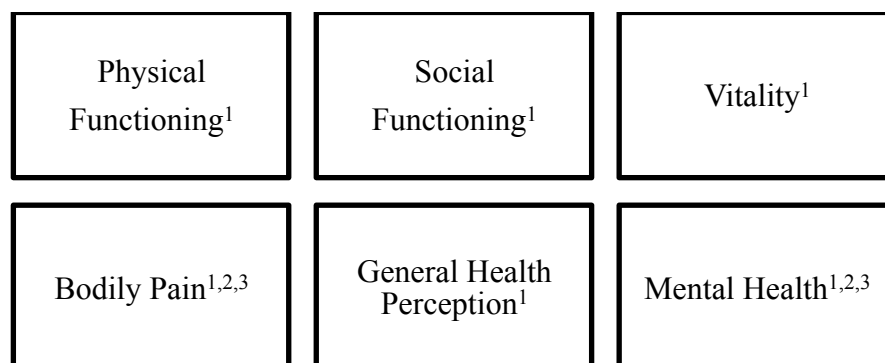
## **Discussion**

### **Overview**

The three complementary medicine approaches discussed in the previous section (The Relaxation Response and Resiliency Program, Creative Arts Therapy, and Acceptance and Commitment Therapy) not only address the domains of QoL in which NF1 patients experienced the most profound differences in comparison to the general population, but also addresses the less profound QoL domains that are still significantly lower in comparison to the general population. Of the six modified domains of the SF-36 questionnaire (Physical Functioning, Social Functioning, Vitality, Bodily Pain, General Health Perception, and Mental Health), the combination of all three therapy programs addresses each domain at least once. This is illustrated by Figure 2. The Relaxation Response and Resiliency Program succeeds in addressing an improvement in every domain in Figure 2. The acceptance and commitment therapy and creative arts therapy may not touch as many areas as the relaxation response and resiliency therapy, but do show potential in facilitating the improvement of both bodily pain and mental health. Considering that 32% of the variance in QoL in the NF1 population comes from depression and anxiety (Cohen et al., 2015 and Ferner et al., 2017), mental health is a very important domain that should be focused on when implementing complementary medicine techniques to improve the quality of life of NF1 patients.

Figure 2

*Domains of the modified SF-36 questionnaire that is addressed by the therapeutic methods found in the literature review.*



<sup>1</sup>Indicates areas improved by the Relaxation Response and Resiliency Therapy

<sup>2</sup>Indicates areas improved by the Acceptance and Commitment Therapy

<sup>3</sup>Indicates areas improved by the Creative Arts Therapy

In addition to finding three promising therapeutic techniques that may improve the QoL of NF1 patients, two additional mediums of care have been identified: videoconferencing and group therapy. Videoconferencing is a good alternative to weekly in-person appointments, especially for an individual who lives far away from their care provider. Vranceanu *et al.* (2016) actually showed a higher patient enrollment when given the opportunity to conduct the therapy via Skype video calls in comparison to in-person therapy sessions. Group therapy is another alternative treatment option, which may increase the efficiency of patient care. This method of treatment may only be particularly useful in large cities due to the rarity of the disease. Nevertheless, with multiple group therapy sessions, more patients can be cared for at once, allowing for a greater volume of care towards the NF1 population. Additionally, patients might feel more inclined to participate in the therapy session when they see other individuals with the same complication as them, making them not feel alone in the experience.

### **Addressing Limitations and Counterarguments**

One area of this study that evokes skepticism is the measurement of QoL improvement in treatment plans. As stated above, the measure of QoL improvement was not explicitly conducted through QoL-based questionnaires. This is due to the stark lack of existing research that specifically addresses improvements in QoL. The primary reason for this due to the fact that QoL questionnaires are not necessarily the most effective ways to measure an improvement in a certain variable. For instance, it is much more reasonable to measure pre- and post-test results for depression using the Center for Epidemiologic Studies Depression (CESD) Scale instead of the SF-36 mental health domain. The same goes for many other variables measured, such as anxiety and pain. We therefore cannot explicitly state that a certain treatment method improved a domain of the SF-36 questionnaire. We can instead use inductive reasoning to hypothesize that since there was an improvement in the depression scores (for instance) after a certain treatment intervention, and since the mental health domain of the SF-36 is in part related to depression, that the mental health domain of the SF-36 will also show improvement after the treatment intervention.

Another limitation is that the variation in patient population and protocol for a specific treatment method such as the Relaxation Response and Resiliency Program leads to the combined results observed in Figure 2, meaning that no publication managed to improve so many domains of the SF-36 questionnaire individually. Although there is some validity to this argument, it can still be used to our advantage: By recognizing the subtle differences from publication to publication, a modified treatment plan can be devised such that components of each study can be included in order to produce the same aggregate results that were observed in Figure 2. This is an important idea to keep in mind, especially when evaluating the effectiveness of the NF1-specific therapies identified in the literature review. Since the NF1-specific studies did not necessarily have the same exact results as other



publications, we can use the other publications to assess aspects of the NF1-specific studies that might have been ineffective or less effective, such that a better-developed treatment plan is produced.

Finally, some readers might be skeptical of complementary psychosocial therapies altogether. One might argue the fact that many of the complications that lower the quality of life of patients can be treated using medicine such as antidepressants or anti-anxiety medication. Prescribing medications for every complication can be viewed partially as counter-intuitive. Having a large number of medications a patient must take might remind the patient even more of their current condition, and cause a downward spiral of negative emotions towards themselves and the disease. In addition, antidepressants or pain and anxiety medications do not actually heal the patient, they just keep the symptoms from presenting themselves. Once the patient stops taking his or her medications, the symptoms will usually reveal themselves again. In the case of complementary medicine however, there is no pill involved. Any change in symptom expression solely results from the mind and body healing themselves. Furthermore, the lack of symptoms is sustained for months post-treatment, confirming that the patient is indeed, healthier. It might make sense, however, to administer traditional medical approaches in conjunction with complementary medicine in order to have a more profound effect, assuming that there are no issues with drug interaction.

### **Future Directions in Neurofibromatosis Quality of Life Care**

In light of results of this literature review, psychosocial complementary medicine approaches for improving the Quality of Life of NF1 patients appears to be promising. Martin, Vranceanu and Zale are pioneers in implementing complementary medicine approaches towards the NF1 population. While their proposed therapy methods do show promise for the field, much more research is needed in order to develop an effective therapeutic plan that addresses multiple domains of QoL.

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Based on the findings of this thesis, one future direction of this field of research is the implementation of a therapeutic program that incorporates the Relaxation Response and Resiliency Program, the Creative Arts Therapy, and the Acceptance and Commitment Therapy. The therapy program should provide options for participation one-on-one, via videoconferencing, or in a group setting, since each has its benefits and allows for patients to enroll in a treatment program more tailored towards their own needs.

Another area that shows potential for future research is the INF1-QoL survey. The questionnaire is the first of its kind to address the QoL discrepancies of NF1 patients specifically. This questionnaire should be used more frequently by neuro-oncologists when assessing the particular domains in which NF1 patients have a diminished QoL. This questionnaire can also be incorporated into the potential therapeutic program proposed in the previous paragraph in order to have a more accurate measure on the change of QoL in NF1 patients post-treatment.

### **Conclusion**

The quality of life of patients with Neurofibromatosis Type 1 is significantly lower than that of the general population. When assessing the complications and comorbidities associated with the disease, it is clear why these disparities are prevalent. Due to the lack of promising advancements towards finding a cure for patients with this disease, it is important to minimize the complications of the patients. This opens the door for complementary medicine approaches that aim to suppress the complications experienced by patients as well as to improve their quality of life.

Through this literature review, the quality of life domains in which NF1 patients are most distant from the general population were identified. A second literature review was conducted in order to determine the most effective therapeutic methods to improve the QoL of the NF1 population. The Relaxation Response and Resiliency Program, Creative Arts

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Therapy, and Acceptance and Commitment Therapy treatment plans are mind-body and cognitive-behavioral therapeutic methods that have been identified and shown to individually improve in the domains of quality of life. The work from this thesis can be used by institutions committed to serving the NF1 population, such as The University of Texas MD Anderson Cancer Center or the Department of Neurology and Cancer Center at Massachusetts General Hospital, or institutions committed to developing psychosocial therapies, such as the Benson-Henry Institute for Mind Body Medicine, to create more effective therapies for individuals with Neurofibromatosis Type 1. The three therapies listed above cover the basis for effective quality of life improvement in all domains, and incorporation of all three therapies into a psychosocial therapeutic program may shed light on more effective strategies to improve the quality of life of patients with Neurofibromatosis Type 1.

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