2016

Neurofibromatosis type 1: natural history and impact on quality of life

https://hdl.handle.net/2144/19425

Boston University
NEUROFIBROMATOSIS TYPE 1: NATURAL HISTORY AND IMPACT ON QUALITY OF LIFE

by

ZAIDAL ASEEL OBAGI

B.A., Boston University, 2015

Submitted in partial fulfillment of the requirements for the degree of Master of Science

2016
Approved by

First Reader

Ayman Grada, M.D., MSc.
Dermatology Fellow

Second Reader

James McKnight, Ph.D.
Associate Professor of Physiology and Biophysics
DEDICATION

I would like to dedicate this work to my sister Sandra, who blessed earth with her kindness and guidance, who always lifted the mood of those around her with her positive energy, and who is a role model for never letting anything get in the way of achieving happiness and dreams.

I would also like to dedicate this work to my father Zein, from whom I derived my passion for science and for helping others. He has demonstrated to me and so many others that anything is accomplishable with dedication.
NEUROFIBROMATOSIS TYPE 1: NATURAL HISTORY AND IMPACT ON QUALITY OF LIFE

ZAIDAL ASEEL OBAGI

ABSTRACT

Neurofibromatosis Type 1 (NF1, von Recklinghausen’s disease) is among the more common autosomal dominant genetic disorders, with a worldwide incidence of approximately 1 in 3000 live births. NF1 can occur as either an inherited defect or as a spontaneous “de novo” mutation. NFI is caused by mutation of the neurofibromin gene that leads to a lack of neurofibromin in the cytoplasm of the cell. Neurofibromin, among other cytoplasmic roles, is a key regulator of certain cellular growth pathways. There is currently no cure for NF1. The disorder has an almost 100% penetrance, but is widely variable in its manifestation. NF1 is a progressive multisystem disorder, and the clinical manifestations tend to worsen with advancing age. NF1 typically manifests as multiple benign skin tumors (neurofibromas), café-au-lait spots, axillary freckles, optical nerve gliomas, iris hamartomas (Lisch nodules), learning disabilities, speech impairment, and orthopedic and cardiovascular problems. More severe manifestations can cause vision loss, headaches, seizures, chronic pain, and orthopedic problems limiting physical activity. Patients with NF1 are four times more likely to develop malignancies than the general population.

Several studies have shown that NF1 impairs the patient’s quality of life through association with more severe complications, impacts on the patient’s appearance, and through learning disabilities and depression. In both mild and severe cases, there seemed
to be an equal emotional impact on the patient. The psychosocial impact manifests in various ways, including loss of confidence and self-esteem. This can stem from insecurity due to an underlying learning disability or insecurity due to NF1-related cosmetic damage. The academic and emotional damage that follow the learning disability or the lack of confidence, if not treated with appropriate therapy, can go on to impact the patient’s relationships and career. The patient may suffer from social exclusion, financial hardship and inability to obtain health insurance. Patients may be unwilling to have children out of fear of passing on the mutation.

This thesis seeks to present in detail the impacts on quality of life that neurofibromatosis causes, and discuss current management and treatment strategies that exist and what can be done further to improve these people’s lives. Early individualized treatment is necessary to achieve better outcomes. Support groups can help educate NF1 patients and their family members and may help alleviate stress. Widespread public education about the condition would help remove the public stigma of Nf1, and allow for patients to feel normal and valued in society. Early individualized treatment is necessary to achieve better outcomes.
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>TITLE</td>
<td>i</td>
</tr>
<tr>
<td>COPYRIGHT PAGE</td>
<td>ii</td>
</tr>
<tr>
<td>READER APPROVAL PAGE</td>
<td>iii</td>
</tr>
<tr>
<td>DEDICATION</td>
<td>iv</td>
</tr>
<tr>
<td>ABSTRACT</td>
<td>v</td>
</tr>
<tr>
<td>TABLE OF CONTENTS</td>
<td>vii</td>
</tr>
<tr>
<td>LIST OF TABLES</td>
<td>ix</td>
</tr>
<tr>
<td>LIST OF FIGURES</td>
<td>x</td>
</tr>
<tr>
<td>LIST OF ABBREVIATIONS</td>
<td>xi</td>
</tr>
<tr>
<td>INTRODUCTION AND HISTORY</td>
<td>1</td>
</tr>
<tr>
<td>MANIFESTATION AND PROGRESSION</td>
<td>6</td>
</tr>
<tr>
<td>Neurofibroma</td>
<td>8</td>
</tr>
<tr>
<td>Café-au-lait spots and freckling</td>
<td>10</td>
</tr>
<tr>
<td>Optical complications</td>
<td>11</td>
</tr>
<tr>
<td>Learning disabilities</td>
<td>12</td>
</tr>
<tr>
<td>Orthopedic manifestations</td>
<td>14</td>
</tr>
<tr>
<td>Vascular manifestations</td>
<td>16</td>
</tr>
<tr>
<td>Malignancy</td>
<td>17</td>
</tr>
<tr>
<td>Section</td>
<td>Page</td>
</tr>
<tr>
<td>------------------------------------------------------------------------</td>
<td>------</td>
</tr>
<tr>
<td>Other manifestations</td>
<td>18</td>
</tr>
<tr>
<td>PATHOGENESIS OF NF1 AND THE IMPORTANCE OF NEUROFIBROMIN</td>
<td>20</td>
</tr>
<tr>
<td>QUALITY OF LIFE</td>
<td>31</td>
</tr>
<tr>
<td>Sandra O. and pregnancy</td>
<td>34</td>
</tr>
<tr>
<td>Susan G. and pain, surgery and familial stress</td>
<td>37</td>
</tr>
<tr>
<td>Ana R. and social exclusion</td>
<td>39</td>
</tr>
<tr>
<td>Suggestions to improve quality of life for NF1 Patients</td>
<td>41</td>
</tr>
<tr>
<td>METHOD OF EVIDENCE ACQUISITION</td>
<td>44</td>
</tr>
<tr>
<td>REFERENCES</td>
<td>45</td>
</tr>
<tr>
<td>CURRICULUM VITAE</td>
<td>52</td>
</tr>
</tbody>
</table>
# LIST OF TABLES

<table>
<thead>
<tr>
<th>Table</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Prevalence of neurofibromatoses vs. other genetic mutations</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>Progression pattern of neurofibromatosis type 1</td>
<td>6</td>
</tr>
<tr>
<td>3</td>
<td>Clinical diagnostic criteria for Nf1</td>
<td>7</td>
</tr>
<tr>
<td>4</td>
<td>Major complications of Nf1 by system</td>
<td>19</td>
</tr>
<tr>
<td>5</td>
<td>Types of mutations</td>
<td>21</td>
</tr>
<tr>
<td>6</td>
<td>Quality of life aspects impacted by Nf1</td>
<td>33</td>
</tr>
</tbody>
</table>
# LIST OF FIGURES

<table>
<thead>
<tr>
<th>Figure</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>The Elephant Man and severe neurofibromatosis type 1</td>
<td>5</td>
</tr>
<tr>
<td>2</td>
<td>Mild manifestations of neurofibromatosis type 1</td>
<td>7</td>
</tr>
<tr>
<td>3</td>
<td>Plexiform vs. cutaneous neurofibromas</td>
<td>9</td>
</tr>
<tr>
<td>4</td>
<td>Lisch nodules of the iris</td>
<td>11</td>
</tr>
<tr>
<td>5</td>
<td>Pseudarthrosis and bowing of the limb</td>
<td>15</td>
</tr>
<tr>
<td>6</td>
<td>Neurofibromin’s role in regulatory pathways</td>
<td>23</td>
</tr>
</tbody>
</table>
## LIST OF ABBREVIATIONS

ADD ................................. Attention Deficit Disorder
CNS .................................... Central Nervous System
GAP ..................................... GTPase Activator Protein
GTP ..................................... Guanosine Triphosphate
JMML .................................. Juvenile Myelomonocytic Leukemia
MPNST ................................ Malignant Peripheral Nerve Sheath Tumor
NF1 ..................................... Neurofibromatosis Type 1
NF2 ..................................... Neurofibromatosis Type 2
MPNST ................................ Malignant Peripheral Nerve Sheath Tumor
PNS ..................................... Peripheral Nervous System
QoL ..................................... Quality Of Life
INTRODUCTION AND HISTORY

Neurofibromatosis historically was a general term used to describe the combined symptomatic manifestations of certain skin and bone pathologies, including benign tumors of nervous tissue origin termed neurofibromas.\(^1,2\) Certain cases of neurofibromatosis confused physicians and researchers alike, who noticed that the tumors manifested either mostly peripherally, or mostly within the vestibule of the ear and within the CNS.\(^1\) In 1987, the disease was split definitively by the National Institute of Health into Neurofibromatosis type 1 (NF1) and Neurofibromatosis type 2 (NF2), recognizing NF1 as the classic, peripherally-expressed disorder, and NF2 as the intracranial and CNS-affecting disorder.\(^1\) Although NF1 is often described as a rare disease, its rate of 1 in 3,000 births makes it more common than many other well-known genetic mutations including Cystic Fibrosis, Tay-Sachs and Huntington’s Disease (Table 1).

**Table 1. Prevalence of neurofibromatoses vs. other genetic mutations.**

<table>
<thead>
<tr>
<th>Genetic Disorder</th>
<th>Estimated Occurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurofibromatosis Type 1</td>
<td>1 in 3,000</td>
</tr>
<tr>
<td>Neurofibromatosis Type II</td>
<td>1 in 40,000</td>
</tr>
<tr>
<td>Schwannomatosis</td>
<td>1 in 40,000</td>
</tr>
<tr>
<td>Cystic Fibrosis</td>
<td>1 in 2,000 (white ethnicity)</td>
</tr>
<tr>
<td></td>
<td>1 in 90,000 (other ethnicity)</td>
</tr>
<tr>
<td>Tay-Sachs disease</td>
<td>1 in 2,500 (Ashkenazi Jewish ethnicity)</td>
</tr>
<tr>
<td></td>
<td>1 in 250,000 (other ethnicity)</td>
</tr>
<tr>
<td>Huntington’s disease</td>
<td>1 in 20,000</td>
</tr>
</tbody>
</table>

Neurofibromatosis type 1 (NF1) is caused by a genetic mutation in the \textit{Nf1} gene which encodes neurofibromin, a protein that is essential in regulating the growth pathways of various cells.\textsuperscript{2} Mutations in this gene are found in populations all over the world, regardless of ethnicity or gender, and is passed down in an autosomal dominant fashion.\textsuperscript{2} Although many cases are of hereditary origin, about half of the reported cases are from spontaneous mutations in individuals with no familial history of NF1.\textsuperscript{3} It was first officially recognized and described in medical literature by von Recklinghausen in 1882, and for that reason is sometimes called von Recklinghausen syndrome.\textsuperscript{3} However, case reports for patients with neurofibromatosis type 1 date as far back as 1785, when a physician reported about a “wart man”, with symptoms aligning with a severe case of NF1.\textsuperscript{4}

Neurofibromatosis has since popped up in literature with varying medical impact. Perhaps the most historic (and misrepresentative) case of NF1 is the story of Joseph Merrick in London in 1844 who resembled having, and was misdiagnosed with, an extreme form of NF1 (Figure 1).\textsuperscript{5} He was then paraded around Europe in circuses as “The Elephant Man.”\textsuperscript{5} Merrick had many severe deformities, including an enlarged skull, enlarged limbs, and many tumorous protrusions from the skin.\textsuperscript{5} Merrick was posthumously re diag nosed with Proteus syndrome, a rare genetic mutation that may phenotypically resemble NF1 but has a different etiology.\textsuperscript{5a} This famous case contributed greatly to the social stigma around NF1, and the disease colloquially being termed “the elephant man’s” disease.\textsuperscript{6} The stigma still persists today, in part due to a Hollywood box office hit under the same name.\textsuperscript{6} The fact that Merrick did not have NF1 has done little to
abate the social stigma of patients with NF1 by people who describe them as having “the elephant man’s disease” but are unaware of its offensive history.⁶

On the one extreme on the spectrum of manifestation, it is possible for people with neurofibromatosis type 1 to live healthy, complication-free lives. In fact, despite having a near 100% penetrance, the level of symptoms of NF1 in individual patients is highly variable.³,⁷ It is stressed in the literature that neurofibromatosis is at first a disorder and not a disease.⁷ The difference between the two is that having a disorder does not necessarily lead to the development of medical problems; NF1 may even go undiagnosed by an unassuming physician.⁷

Neurofibromatosis type 2, like type 1, is also an autosomal dominant genetic disorder; however, the mutation occurs on a different chromosome and occurs much less frequently than NF1 (Table 1).¹ NF2 stems from a mutation on chromosome 22, whereas NF1 stems from a mutation on chromosome 17.⁷ Typically, NF2 manifests intracranially within the ear canal, or in the meninges, and demonstrates different diagnostic symptoms than that of NF1.¹

A third type of neurofibromatosis has recently been described in the literature, termed Schwannomatosis.⁷ It is believed to occur at the same rate and stem from the same chromosome as NF2; however, it manifests itself differently than either NF1 or NF2. These manifestations often include pain (not usual in NF1 and NF2) and schwannomas, tumors of specifically Schwann cell origin (also seen in NF2) instead of neurofibromas, tumors of both Schwann cell and other nerve-associated cells’ origin.⁷ NF2 and Schwannomatosis often have a delayed onset of symptomatic expression
(usually not appearing until adulthood), whereas a diagnosis of NF1 can be made on an infant, based on characteristic symptomatic manifestations that are discussed later.\textsuperscript{7}

This thesis seeks to present in detail the impacts on quality of life that neurofibromatosis causes, and discuss current management and treatment strategies that exist and what can be done further to improve these people’s lives. Indeed, the quality of life for people with neurofibromatosis type 1 can be quite poor. There is yet no gene therapy that exists to repair the mutation. Instead, clinicians mainly focus on treating each symptomatic manifestation separately.\textsuperscript{7} The disorder, once it becomes a disease, manifests itself clinically in many ways including: neurofibromas (on the skin and within the body), cardiovascular problems such as hypertension, vessel obstruction or hemorrhage, Lisch nodules in the eyes, hyperpigmented macules on the skin termed café-au-lait spots, learning disabilities such as a reduced IQ or mental capacity for certain types of cognitive function, and more.\textsuperscript{2,7,13} In addition, there is a large psychosocial impact on patients who fear how their disabilities may impact their status in the minds of others.\textsuperscript{7} There is also a constant fear that their condition can become malignant and progress into one or more forms of cancer (which occurs in NF1 patients at around a frequency of 5\%).\textsuperscript{8}

Based on the prevalence of each type of neurofibromatosis, this thesis focuses primarily on the impact on quality of life for patients affected with NF1. However, many of these symptoms also affect patients with the other types of neurofibromatosis. Thus in focusing on the following cases, this thesis will emphasize the need to increase the quality of life for patients suffering from all types of neurofibromatosis.
Figure 1. The Elephant Man and severe neurofibromatosis type 1. (a) Joseph Merrick, exhibited as The Elephant Man, was misdiagnosed with an extreme case of NF1, and only recently rediagnosed with Proteus syndrome (British Medical Journal, 1890; Tibbles and Cohen, 1986). (b) A patient with an extreme case of NF1, with many cutaneous neurofibromas and one large sacral plexiform neurofibroma (Antônio et al., 2013).
MANIFESTATION AND PROGRESSION

Neurofibromatosis type 1 has a nearly 100% genetic penetrance, but is also highly variable in respect to its manifestation, with a spectrum of extremely mild to extremely severe cases. The complications arise due to a lack of expression of the protein neurofibromin. Neurofibromin is mostly expressed in neurons and cells that support them such as Schwann cells, oligodendrocytes and astrocytes, but is also expressed in leukocytes, the adrenal medulla, and smooth muscle in the vasculature. NF1 is a progressive disease, and symptoms tend to manifest or worsen as the patient ages (Table 2). There is no known treatment for neurofibromatosis type 1.

Table 2. Progression pattern of neurofibromatosis type 1.

<table>
<thead>
<tr>
<th>Age of Patient</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth</td>
<td>Café-au-lait spots, Pseudoarthrosis, External, Cognitive disabilities, Visible plexiform neurofibroma</td>
</tr>
<tr>
<td>Childhood</td>
<td>Freckling, Optic glioma, Severe scoliosis</td>
</tr>
<tr>
<td>Teenage/Young adult</td>
<td>Cutaneous neurofibroma, Lisch nodules, Short stature, Precocious puberty</td>
</tr>
<tr>
<td>Adult</td>
<td>Malignancy, Pheochromocytoma, Paraspinal plexiform neurofibroma</td>
</tr>
</tbody>
</table>


Because of the many types of mutations that can occur in patients with NF1, most clinicians today forego genetic testing in favor of a clinical diagnostic criteria that requires examining the whole body and the patient presenting with at least two symptoms to make a positive NF1 diagnosis (Table 3). Not every known manifestation of NF1 happens to every patient. Some manifestations, such as the neurofibromas and café-au-
lait spots, are highly common among all NF1 patients and occur in over 95% of cases (Figure 2).\textsuperscript{12} Certain manifestations, such as scoliosis and malignancy, are much rarer and occur in 10% or less of total cases.\textsuperscript{12}

**Table 3. Clinical diagnostic criteria for NF1**

| 6 or more café-au-lait spots, >5 mm before puberty, > 15 mm after puberty |
| Axillary, groin or neck freckling (non-sun exposed freckling) |
| 2 or more cutaneous neurofibromas |
| 1 plexiform neurofibroma |
| 2 or more iris Lisch nodules |
| Optic glioma |
| NF1 characteristic bony lesion (pseudarthrosis, scoliosis, etc…) |
| First degree relative with NF1 |

►2 or more of the above are required for a diagnosis of NF1.

**Adapted from:** Tonsgard JH. Clinical Manifestations and Management of Neurofibromatosis Type 1. *Seminars in Pediatric Neurology.* 2006;13(1):3

**Figure 2. Mild manifestations of neurofibromatosis type 1.** Mild manifestations of NF1 include spots of discoloration termed café-au-lait spots, and benign tumors termed neurofibromas, both of which are depicted above. The neurofibromas are tumors caused by nerve and nerve-associated cells. (Accrochoc, 2000)
Neurofibroma

One of the hallmark manifestations of NF1, a neurofibroma is a dysplastic growth of peripheral nerve and nerve-associated cells, including Schwann cells, fibroblasts, perineural cells, mast cells, axons, and blood vessels. A neurofibroma can present itself in four different ways. 1) Superficial cutaneous neurofibromas present as circular, buttonous outgrowths on the skin, originating from superficial nerves (Figure 3). 2) Subcutaneous or dermal neurofibromas are localized nerve tumors that begin in the dermis, deeper than the superficial counterpart, and closer to pain receptors; therefore they sometimes induce localized pain. 3) Nodular plexiform neurofibromas and 4) diffuse plexiform neurofibromas are less localized, and more sheet-like forms of outgrowth, derived from the uncontrolled growth along the nerve or from multiple nerve fascicles instead of just on one part of the nerve (Figure 3). Nodular plexiform neurofibromas present subcutaneously or on the skin, whereas diffuse plexiform neurofibromas affect all layers of the skin, can be entirely internal, and can even affect the dorsal spinal roots, the sympathetic network of nerves, and nerves in muscle, bone and the viscera.

Neurofibromas usually start at puberty and increase in number with age, ensuring that almost all adults with NF1 have at least one. Over 95% of NF1 patients have neurofibromas. The cutaneous, buttonous form is the most common form; fortunately this form is usually benign and can be removed surgically. The cutaneous neurofibromas’ impact on the patient is mostly psychological and cosmetic. One-third of NF1 patients develop the plexiform variant of neurofibroma. The diffuse subtype of plexiform
neurofibroma is usually congenital, but can be difficult to detect in infants due to its deep and often asymptomatic manifestation. This variant can be more damaging to the patient, with its greater difficulty to be surgically removed due to its depth within the skin or healthy tissue, its ability to influence underlying bone growth leading to limb asymmetry, and its greater chance at becoming malignant.

The danger of malignancy is much higher in patients with the plexiform neurofibromas. Around 10% of plexiform neurofibroma, or 3% of total NF1 patients, patients develop a specific type of malignancy termed a malignant peripheral nerve sheath tumor (MPNST). The greatest risk of developing this type of malignancy is in patients between the age 15-40 years old. This tumor is highly malignant, associated with a lot of pain, and metastasizes quickly to other tissues, particularly the lungs. Chemotherapy and radiation therapy do not work very effectively against MPNST and survival rates are estimated to be less than a year for patients with MPNST.

Figure 3. Plexiform vs. cutaneous neurofibromas. (a) A plexiform neurofibroma demonstrating the sheet-like outgrowth along the length of the nerve or neural network (Antônio et al., 2013). (b) A cutaneous neurofibroma demonstrating its localized, buttonous appearance (Al Bisher et al., 2011).
**Café-au-lait spots and freckling**

Café-au-lait spots, like neurofibromas, are a hallmark manifestation of NF1 and also occur in over 95% of patients.\(^{12}\) They are usually present at birth and are often the first diagnostic measure that a clinician uses to diagnose NF1. Some healthy patients may develop café-au-lait spots and not have neurofibromatosis type 1, but the presence of 6 or more spots is suggestive of NF1. Patients with NF2 can present also with café-au-lait spots, but never more than 6, which is one characteristic for a clinician to use to be sure he is dealing with NF1.\(^7\) Café-au-lait spots present as hyperpigmented round or oval-shaped spots and must be at least 0.5 cm in diameter in children or greater than 1.5 cm in adults to be considered a café-au-lait spot (Figure 2).\(^{12}\) These spots do not become neurofibromas. Similar to neurofibromas, the number (and size) of spots increase with age.\(^{12}\) They are not necessarily caused by an increase in melanocytes within the spot; instead some studies suggest the melanocytes within the spot are producing giant pigment granules.\(^{21}\) One knockout gene study explores the development process of melanocytes, since both Schwann cells and melanocytes share a precursor cell of neural crest origin, and are both impacted in neurofibromatosis.\(^{22}\) They discovered a certain developmental window for precursor cells fated to become melanocytes, wherein insufficient neurofibromin protein from the mutated *Nf1* gene causes a change in melanocyte colonization within the dermis and epidermis.\(^{22}\)

Similar to café-au-lait spots, diffuse freckling of the skin, and freckling of the axilla and groin region, is common in NF1 and presents as many small, hyperpigmented spots on the skin.\(^{12}\) Freckling usually begins in childhood, around the age 5-7.\(^{12}\)
Optical complications

The development of Lisch nodules within the iris is a manifestation unique to neurofibromatosis type 1 and is therefore a useful diagnostic measurement for clinicians.\(^7\) Very rarely do Lisch nodules present unaccompanied by NF1, although it is possible.\(^22\) Lisch nodules are present in 90 to 100\% of patients with neurofibromatosis.\(^23\) They begin to form during the teenage years, and are non-vision impairing.\(^12\) They are benign tumors, specifically melanocytic hamartomas, and their origin can be traced to the same precursor cells impacted by the lack of neurofibromin that also generate the melanocytes involved in café-au-lait spots.\(^23\) They present as reddish-brown spots, usually in the bottom half of the iris (Figure 4).\(^12\) There is a correlation between age and the number of Lisch nodules present, suggesting that more nodules develop with age.\(^23\) Although the largest Lisch nodules can be perceived with the naked eye, often a slit lamp exam is needed to detect the earliest cases of Lisch nodules.\(^23\)

Figure 4. Lisch nodules of the iris. Visible in the iris of this patient are the Lisch nodules: reddish-brown spots aggregated mostly in the bottom half of the iris. More nodules appear with age, and are benign and asymptomatic. (Adams et al., 2011)
Other common optical complications beyond Lisch nodules include optical gliomas, which occur in 15 to 20% of NF1 patients. These gliomas are of astrocytic origin, due to unregulated astrocytic growth, again stemming from the lack of the protein neurofibromin in cellular growth regulation. The mean onset-age of these tumors is quite young, occurring on average in children 4.2 years old. Although neurofibromin regulates cellular growth in astrocytes through a different pathway than in other tumorous cell types involved in neurofibromatosis, the result is the same: a benign tumor that increases in size with age. Although the optical glioma can occur along any part of the optic nerve, and most tumors are asymptomatic. The most problematic places that optical gliomas can occur are close to the eyes, causing proptosis, or close to the hypothalamus where it can influence hypothalamic function and cause precocious puberty and short stature. Optical gliomas can also lead to visual loss, with the greatest risk being between 15 months and 7 years old; children between these ages with NF1 should be checked regularly by an ophthalmologist. Plexiform neurofibromas in the orbit is associated with optical gliomas.

**Learning disabilities**

It was once feared by parents that children with NF1 have a much greater chance to develop mental retardation, due primarily to sample bias by older studies on institutionalized patients with NF1. It is now known that people with NF1 do on average have lower IQs than the normal mean (one IQ study found an average of 88.6 SD±14.6 in people with NF1 vs 101.6 SD±14.2 in the control group) but the average IQ
of patients with NF1 is still much greater than what is considered intellectual impairment (IQ < 70).\textsuperscript{28} Furthermore studies show that there are children with NF1 who possess average or above-average IQ, and that the IQ distribution is bimodal, with a peak in the normal range and a peak in impairment range.\textsuperscript{12,27} There is a slightly higher incidence of mental retardation in patients with NF1, but the incidence of mental retardation in patients ranges in various studies from the normal 3% found in the general population to 8% at the greatest.\textsuperscript{27,28}

Besides a slightly lower average IQ, other types of cognitive impairments do often manifest themselves in patients with NF1, presenting in up to 65% of patients with NF1.\textsuperscript{29} These impairments can alter the ability to think and learn properly, due to the lack of a key brain function. There is no specific learning disability that manifests in patients with NF1, but various learning disabilities can present in patients.\textsuperscript{29} For instance, lacking the ability to process written or spoken language can lead to speech or educational deficiencies; lacking the ability to integrate visual signals into motor movements can lead to poor coordination and clumsiness.\textsuperscript{7} Some rat model studies support the hypothesis that NF1 impairs spatial learning, leading to a decreased ability for the patient to navigate and orient his or herself with the surroundings, or perform tasks that involve substantial hand-eye coordination.\textsuperscript{30} Attention deficit disorder is another common manifestation in patients with NF1.\textsuperscript{7} These disabilities are often found more in males than females and often persist into, or manifest in, adulthood.\textsuperscript{7} It should be reemphasized that these impairments are usually specific to certain brain functions and do not impair a patient’s innate intelligence.\textsuperscript{7,27} However, should impacted patients not undergo proper management and
therapy for the presenting learning disability, the impairments may impact patients’ educational and professional career as well as self-esteem and happiness.

**Orthopedic manifestations**

Deep diffuse plexiform neurofibromas’ that grow in limbs, and their effects on underlying bone growth, can be the cause of many of the orthopedic problems seen in patients with NF1. Diffuse plexiform neurofibromas are often congenital, and can grow rapidly during adolescence and infancy; they may displace, erode or demineralize the adjacent bone by increasing pressure or increasing the surrounding vasculature. The most common orthopedic problems include scoliosis, congenital pseudarthrosis of an extremity, asymmetric overgrowth of an extremity, or short stature.

Scoliosis is seen in about 10% of NF1 patients, and can range from mild to severe curvatures of the spine. It is believed that scoliosis is secondary to an adjacent spinal diffuse plexiform neurofibroma inducing vertebral dysplasia or erosion. Mild scoliosis can be treated with a brace that is worn underneath clothing. A small subset of patients with scoliosis can develop a severe form termed dystrophic scoliosis, manifesting in childhood, forming a sharp angle of the spine and untreatable with a normal brace; surgery is the preferred treatment method for dystrophic scoliosis.

Pseudarthrosis occurs in 3% of NF1 cases, often present at birth or shortly after, and mostly affects the tibia or forearm. Pseudarthrosis is a bone fracture that the body believes to be two independent bones and thus does not attempt to fuse the fracture, and abnormal bowing of the limb can occur (Figure 5). Pseudarthrosis is difficult to treat
surgically and prophylactic bracing is recommended; in the most severe cases where surgery does not help, limb amputation may improve the quality of life of the patient.\textsuperscript{7,12} Bone overgrowth of one limb can also occur, possibly induced by an adjacent plexiform neurofibroma, and it most notably affects the legs.\textsuperscript{7} Asymmetry can be prevented if treated early enough with methods to destroy growth plates or delay the growth of the abnormal limb to allow the other limb to catch up in length.\textsuperscript{7}

An average shorter stature is common in patients with NF1, even when they present with normal growth hormone levels and without any hypothalamic-influencing optical gliomas; the etiology for this is yet unknown, but in some cases can be treated with growth hormone therapy.\textsuperscript{33}

\textbf{Figure 5. Pseudarthrosis and bowing of the limb.} Congenital pseudarthrosis can present itself in patients with NF1, often shortly after birth, and most often in the tibia. It is caused by a failure of regular bone formation or a fracture in the bone that the body does not act to fuse. Continued dysplastic bone growth or subsequent fractures can lead to the bowing of the limb as seen above. (Kalra and Agarwal, 2012)
Vascular manifestations

The lack of neurofibromin as a regulator for various cells’ growth affects many other places in the body besides the hallmark skin and brain manifestations discussed above. The body’s vasculature is surrounded by nerves and neurofibromatosis can affect these as well. Although vasculopathy overall is not very common, the most common manifestation of NF1 in the vasculature is hypertension, with renal artery stenosis or dysplasia being the primary cause.\textsuperscript{34,35} The frequency of renal artery dysplasia is 1\% in NF1 patients.\textsuperscript{34} Blood vessels of any size can be susceptible to stenosis or occlusion due to NF1, and most patients with symptomatic conditions present with multiple affected vessels.\textsuperscript{11} Pregnancy can increase the risk of vasculopathy with NF1.\textsuperscript{11}

Cerebrovascular stenosis or occlusion is another possible vasculopathy caused by NF1, manifesting most commonly in the carotid arteries. It is less common than renal artery stenosis, but can ultimately lead to aneurysm formation, hemorrhage and early mortality in patients with NF1.\textsuperscript{36} Statins are useful in reducing vascular inflammation and treating early signs of aneurysm.\textsuperscript{36}

Congenital heart defects (CHD) have been found in 0.4-6.4\% of patients with NF1, and may stem from developmental problems related to a lack of neurofibromin in key developmental cells of the endo and myocardium.\textsuperscript{11} These defects include pulmonary valve stenosis and tetralogy of Fallot, cardiovascular problems which can lead to cyanosis if left untreated. Tetralogy of Fallot refers to a combination of 4 anatomical malformations of the heart, including ventricular septal defect, biventricular connection of the aortic root, obstruction of the right ventricular outflow tract, and right ventricular
Complete heart repair surgery is usually performed on neonates with tetralogy of Fallot with an 85% long-term survival rate. In general, CHDs are rarer NF1 manifestations, and are usually found in severe cases of the Nf1 gene mutation.

**Malignancy**

Malignancy is another fear of patients with neurofibromatosis type 1. Excluding neurofibromas and optical gliomas, which are relatively common in NF1 patients as discussed above, one study found the overall risk of a malignant neoplasm in patients to be 6.9%. The frequency of non-CNS tumor formation (4.9%) was slightly higher than the frequency of CNS tumors (2%), with the frequency of a neoplasm in general higher for patients with NF1 than in their relatives (3.2% for non-CNS and 1.2% for CNS tumors in relatives). Another study found the overall malignancy risk in NF1 patients slightly lower at 4.4%, with non-CNS tumors (2.9%) still more common than CNS tumors (1.5%), excluding neurofibromas and optic gliomas.

The most common non-CNS tumor, besides neurofibromas, that appear in patients with NF1 are the malignant peripheral nerve sheathe tumors (MPNST) discussed earlier and which carry a high mortality risk. In addition, NF1 patients have higher frequencies of leukemia, including chronic myeloid leukemia, acute lymphoblastic leukemia, non-Hodgkin’s lymphoma, and juvenile myelomonocytic leukemia (JMML). JMML is a rare form of leukemia affecting children. In one study 14% of cases were children with NF1. Sarcomas, specifically rhabdomyosarcoma, also have increased frequencies in patients with NF1. Rhabdomyosarcomas are usually aggressive, developing from the
precursor cells to muscle, and mainly manifest in the head and neck, urinary and reproductive organs, or extremities.\textsuperscript{7,39} They can cause problems if they start to occlude the bladder or put pressure on the eye.\textsuperscript{7} Pheochromocytomas are also more common in patients with NF1; a pheochromocytoma can lead to an excess of circulating epinephrine, and causing excess sweating, high blood pressure and heart rate, and poor blood sugar management.\textsuperscript{7,39}

CNS tumors in patients with NF1 include the relatively common optical gliomas discussed above caused by an overgrowth of astrocytes; these are referred to as Grade I astrocytomas and are usually benign and asymptomatic. They can cause vision or endocrine problems if the tumor grows near eyes or hypothalamus respectively.\textsuperscript{12} Other astrocytomas, termed grade III and IV astrocytomas, can arise and grow in any part of the brain or spinal cord, but most commonly occur in the cerebellum, cerebrum or brain stem.\textsuperscript{12,39} These tumors can be aggressive and symptomatic, causing seizures, headaches, fainting, comas.\textsuperscript{7} Chemotherapy or invasive surgery may be required to treat the brain tumor if the patient’s health is compromised, but a positive outcome is not always guaranteed and the tumor can return.\textsuperscript{12}

\textbf{Other manifestations}

Macrocephaly is a common condition in patients with neurofibromatosis type 1, believing to affect between 30 to 40\% of patients with NF1.\textsuperscript{7} The cause for macrocephaly is still unknown. Both the skull and the brain are usually enlarged, with no other correlating physical symptoms nor any correlation between the skull and brain size and
any learning disabilities.\textsuperscript{7} It is believed the enlargement could be due to a larger presence of white matter around the grey matter in the brains of NF1 patients.\textsuperscript{41}

Hydrocephalus affects about 1-2\% of NF1 patients, causing an excess buildup of fluid in the ventricles of the brain.\textsuperscript{7,38} This can compress parts of the brain and lead to headaches, visual complications or seizures.\textsuperscript{7} A ventricle shunt inserted surgically is the common treatment.\textsuperscript{7}

Headaches and seizures, independent of any underlying brain tumor, are also common in patients with NF1; they affect about 10 to 20\% of patients, with headaches (including migraines) being more common than seizures.\textsuperscript{12,38} Medication used to treat headaches and seizures in the general population are also effective in patients with NF1.\textsuperscript{12}

Table 4 provides a review of the major complications that may be found in the patient due to Nf1.

\textbf{Table 4. Major complications of NF1 by system.}

<table>
<thead>
<tr>
<th>SYSTEM</th>
<th>COMPLICATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>SKIN</td>
<td>Cosmetic (cutaneous neurofibroma)</td>
</tr>
<tr>
<td>CNS</td>
<td>Learning disability; Glioma; Seizures; Spinal cord compression by tumor</td>
</tr>
<tr>
<td>PERIPHERAL NERVES</td>
<td>Neurofibroma; Malignant peripheral nerve sheath tumor (MPNST)</td>
</tr>
<tr>
<td>CARDIOVASCULAR</td>
<td>Hypertension (renovascular), Vascular stenosis; Hemorrhage</td>
</tr>
<tr>
<td>GASTROINTESTINAL</td>
<td>Lumenal obstruction; Constipation</td>
</tr>
<tr>
<td>ENDOCRINE</td>
<td>Pheochromocytoma</td>
</tr>
<tr>
<td>SKELETAL</td>
<td>Skeletal dysplasia; Bone cysts; Scoliosis</td>
</tr>
<tr>
<td>GROWTH</td>
<td>Short stature; Macrocephaly</td>
</tr>
<tr>
<td>HEMATOLOGICAL</td>
<td>Nonlymphatic leukemia</td>
</tr>
</tbody>
</table>

\textit{Adapted from:} Korf BR. Malignancy in Neurofibromatosis Type 1. The Oncologist. 2000;5(6):478.
PATHOGENESIS OF NF1 AND THE IMPORTANCE OF NEUROFIBROMIN

Genetics introduction

Most people have two functional copies of any gene, noted shorthand as +/+, and which typically ensures the proper amount of a protein is being expressed by the cells. When one copy of the gene is aberrantly expressed or not expressed at all, it is termed haploinsufficiency and written as +/- . In haploinsufficiency, depending on the type of mutation, either a mutated, nonfunctional form of the protein is produced alongside the normal version, or simply less of the normal protein is produced. If both functional copies of the gene are compromised, it is written as -/- and the gene is deemed homozygously inactivated. Various types of mutations exist which may or may not compromise a gene’s function (Table 5). These mutations happen at the level of nucleotides, which are the building blocks of the genome. Groups of 3 nucleotides, termed a codon, code for any 1 of 20 amino acids, and different mutations to the codon can alter the desired amino acid, or even terminate protein synthesis early.

In addition, there exists variability between cell types as to the level of expression for any given gene. This leads to predictable symptomatic manifestations for certain genetic disorders based on which cell types are most dependent on the mutated gene. At given time within a person’s lifetime, expression of a certain gene by the various cell types can increase or decrease; the signals for these changes in expression of a gene falls underneath the term “epigenetics”, and these signals can be transmitted by hormones or various other stimuli.
Table 5. Various types of mutations.

<table>
<thead>
<tr>
<th>Type of Mutation</th>
<th>Effect on Protein</th>
</tr>
</thead>
<tbody>
<tr>
<td>Silent mutation</td>
<td>A substitution of one type of nucleotide for another in the gene, but which does not change the coded for amino acid. Leads to no change to the protein.</td>
</tr>
<tr>
<td>Insertion mutation</td>
<td>An insertion of new nucleotides into the genetic code. If the insertion was not in a multiple of 3 nucleotides, it could fundamentally shift the reading frame of the gene, vastly altering the protein. If insertion is 3n nucleotides, it will lead to a larger and possibly nonfunctional protein.</td>
</tr>
<tr>
<td>Deletion mutation</td>
<td>A deletion of a certain number of nucleotides in the gene, or possibly the entire gene itself. If the deletion is not in a multiple of 3 nucleotides, it could fundamentally shift the reading frame of the gene, vastly altering the protein. If deletion is 3n nucleotides, it will lead to a smaller and possibly nonfunctional protein. If the entire gene is deleted, none of the protein will be expressed.</td>
</tr>
<tr>
<td>Missense mutation</td>
<td>A substitution of one nucleotide for another which changes the coded for amino acid. This may or may not lead to a change in the folding structure of the protein, and may or may not alter the protein’s function.</td>
</tr>
<tr>
<td>Nonsense mutation</td>
<td>A substitution of one type of nucleotide for another, which changes the codon from coding for an amino acid to coding for a stop signal. This leads to a smaller and possibly nonfunctional protein.</td>
</tr>
</tbody>
</table>
Neurofibromin

The gene for neurofibromin is found on chromosome 17. Specifically, it is located at 17q11.2. In this nomenclature, the “q” refers to the long arm of the 17th chromosome, and the “11.2” references how far away from the centromere the gene is.2,42 On the other hand, NF2 is caused by a mutation of a gene found on chromosome 22 for a protein dubbed “Merlin” or “Schwannomin”.7 Although found on separate chromosomes, both neurofibromin and merlin have a similar primary function which is cellular growth suppression; for this reason, both proteins are known as tumor suppressor proteins.7 In addition to regulating various cellular division pathways, additional functions for both of these proteins have recently been discovered: neurofibromin has been found to have other cytoplasmic roles such as stabilizing microtubules, and merlin has been found to be an important signaling protein in cell-to-cell and cell-to-ECM interaction.7,43 The many functions of these proteins are yet to be fully understood, and may explain why so many complications beyond tumor growth occur when a patient presents with NF1 or NF2.

Neurofibromin’s primary function as a tumor suppressor protein is performed by its regulatory role in two pathways: the Ras-GAP pathway and the cAMP-PKA pathway.7 Most of the research on neurofibromin’s role as a regulator involves its role in the Ras-GAP pathway.7 The Ras-GAP pathway is an important pathway for cell proliferation, beginning when a receptor is triggered by certain growth factors.44 Ras has two main conformations: bound to GTP or to GDP. Ras is a GTPase, albeit a slow one on its own: it will hydrolyze a GTP molecule into GDP given enough time.44 NF1 is considered a GTPase Activating Protein (GAP), and will expedite the ability of Ras to hydrolyze GTP
to GDP. When Ras is in its GTP bound state, which it assumes after growth factor activation, it becomes the gas pedal to cell proliferation.\textsuperscript{44} Ras-GTP will lead to the activation of many downstream proteins that in turn lead to cell proliferation and cell survival (Figure 6).\textsuperscript{44} Neurofibromin acts as the brakes on cell proliferation, by inducing Ras to hydrolyze GTP to GDP, rendering it to its inactive state.\textsuperscript{44} Because Ras-induced cell proliferation is so prevalent among all cell types, it is easy to picture the dire consequences of unchecked, widespread cellular growth by the absence of neurofibromin, which is meant to keep growth in check.\textsuperscript{44} Neurofibromin’s importance as the key GAP, vs. other GAPs, for Ras regulation varies between certain cell types, leading to the manifestations of unregulated growth of specific cell types seen in NF1.\textsuperscript{45}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{neurofibromin_regulatory_pathways.png}
\caption{Neurofibromin’s role in regulatory pathways.} Neurofibromin acts as a regulator on the Ras-GAP pathway and the cAMP-PKA pathway. Neurofibromin downregulates cell proliferation by inducing the Ras-GDP inactive state. Neurofibromin also upregulates adenylate cyclase, leading to higher intracellular cAMP levels, greater PKA activity, and ultimately less cellular growth. (Williams et al., 2009).
\end{figure}
The cAMP-PKA pathway is another important part of neurofibromin’s role in cellular cytoplasmic function and growth regulation. Neurofibromin acts as an upregulator to adenylate cyclase, a protein activated by extracellular signals binding to their respective receptors. Adenylate cyclase forms cAMP from ATP molecules, and cAMP goes on to activate PKA, an important cytoplasmic kinase with many functions, one of which is to regulate the growth of certain cell types. High cAMP also activates a protein named Rap1, which has anti-Ras activity. This cAMP-PKA growth regulation pathway with respect to neurofibromin is most studied in astrocyte growth and function, where a lack of neurofibromin can have consequences of unchecked astrocytic growth, glioma formation, and learning disabilities. However, other cell types are also known to rely on cAMP-PKA signaling for normal function and growth as well. For example, some studies show that neurofibromin’s absence in respect to cAMP-PKA signaling, in addition to any Ras-GAP abnormalities, plays a role in Schwann cell cytoplasmic dysfunction and abnormal growth seen in NF1 manifestations.

Pathogenesis

All individuals that have NF1 are born with one functional copy of the neurofibromin gene and one mutated or deleted copy of the gene. If in gestation there had been two nonfunctional copies, the embryo would have many developmental issues stemming from the lack of neurofibromin as a regulator for key developmental cells. These developmental cells include the neural crest cells, which have shown particular sensitivity to neurofibromin levels, and which are known to orchestrate development of
key tissue such as bones, neurons, smooth muscle, endocrine, and adipose tissue among others.\textsuperscript{46,47} In mouse models, studies have demonstrated that embryos homozygously missing the gene for neurofibromin, termed “\textit{Nf1} knockout mice”, cannot complete the development of key parts of the heart which are neural crest cell induced, including the myocardial structure and the right ventricle cardiac outflow tract, and that the embryo terminates at day 14 of gestation.\textsuperscript{11}

The gene sequence for neurofibromin is 335,000 base pairs long with 59 exons: 3 of which are alternatively spliced to create related but also distinct forms of neurofibromin.\textsuperscript{48} These variant forms of neurofibromin add complexity to the understanding of the \textit{Nf1} gene mutations, with the possibility of a mutation affecting only one spliced form of neurofibromin over another.\textsuperscript{7} This variability would explain some of the differences in form and degree of manifestation seen among patients with NF1 but with different forms of mutation. Indeed, over 500 different mutations have been noted in subjects with NF1, ranging over all the types explained in Table 5; however, the most common mutations result in a shorter, nonfunctional form of neurofibromin.\textsuperscript{7}

The many forms of mild to severe types of mutations found in the genome of people with NF1 can play a large role into the wide range of manifestations seen among patient populations with NF1.\textsuperscript{7,49} Indeed, some researchers have found that in the most severe manifestations of NF1, the entire \textit{Nf1} gene and even some adjacent genes have been deleted.\textsuperscript{49} Between 5-20\% of subjects present with this full gene deletion, and have more severe manifestations such as dysmorphisms, cardiac abnormalities, mental retardation, developmental delays, early on-set neurofibromas, and increased risk of
MPNST formation.\textsuperscript{49,50} In addition, epigenetic factors may also contribute to the variability of manifestations seen in patients.\textsuperscript{42} Epigenetic factors are factors separate from any changes to the actual neurofibromin genetic code, but which can influence the expression of the gene. These include, but are not limited to: cellular responses to various hormones, epistasis with other genes, gene methylation, and exposure to environmental or infectious agents.\textsuperscript{42} The relative uncontrollability of these epigenetic factors plays a role in the diverseness and age-relatedness of manifestations. It may also explain why identical siblings with NF1 can present with different manifestations.\textsuperscript{7,42}

**Haploinsufficiency**

As noted earlier, patients with NF1 are almost all born with cells heterozygous for one normal gene and one mutated or deleted gene. Haploinsufficiency causes lower levels of functional cytoplasmic neurofibromin.\textsuperscript{44} This in turn leads to less regulation of the Ras-GAP and cAMP-PKA pathways, and higher sensitivity by cells to external stimuli that activate these pathways, such as growth factors.\textsuperscript{44} Haploinsufficiency is enough to cause cytoplasmic abnormalities, loss of proper cellular function, and lead to many characteristic manifestations in NF1. Some cell types are more sensitive to neurofibromin haploinsufficiency than others, affecting their development and function and leading to common manifestations seen in NF1.\textsuperscript{51} These cell types include, but are not limited to, the neural crest and neural crest derived cells, neural tube derived cells, and some mesoderm derived cells.\textsuperscript{51}
Neural crest cells seem particularly sensitive to changing neurofibromin levels. Haploinsufficient neural crest cells (+/-) and their many derivatives lead to a plethora of the non-tumorous manifestations seen in NF1. These include abnormal pattern of colonization by melanocytes in the dermis during a key developmental window, leading to general hyperpigmentation, as well as abnormal melanocytic cells in the iris leading to Lisch nodules. Schwann cells and neurons of the PNS which are derived from neural crest cells are at higher risk of forming neurofibromas. Cardiac problems may arise if these neural crest cells do not properly form the endocardial cushion, a key step in heart development, and lead to congenital heart defects or contribute to other cardiovascular disease. Bone deformities may arise if the neural crest cells do not properly form the craniofacial bones, which can contribute to facial dysmorphisms seen in severe cases.

In the CNS, haploinsufficiency can contribute to the loss of connections in the brain: specifically, patients with NF1 under MRI exhibit reduced anterior-posterior connectivity, and differences in local nerve connectivity, the latter correlating with IQ. This can be attributed to haploinsufficient oligodendrocytes which, like the Schwann cells of the PNS, display abnormalities in the presence of low neurofibromin. Specifically, oligodendrocytes in patients with NF1 demonstrated split, decompacted myelin, which can alter the transmittance speed and efficiency of signals between neurons. Hypertrophic, non-tumorous astrocytic growth, caused by a lack of sufficient growth regulation in astrocytes by neurofibromin, can also contribute to the learning disorders seen in patients with NF1.
In the vasculature, some NF1 patients exhibit symptoms of chronic inflammation resulting in arterial aneurysm formation and possible mortality.\textsuperscript{36} Researchers have found that the reduced neurofibromin levels in a NF1 +/- myeloid cells is sufficient to recreate the conditions for aneurysm formation \textit{in vivo}.\textsuperscript{36} This is attributed to the lack of regulation on pathways such as the Ras-GAP pathway, which make the myeloid cells more sensitive to growth factors and other stimuli, causing them to not only proliferate but become hyperactive and secrete their own growth factors and cytokines.\textsuperscript{36} These secreted cytokines can be responsible for arterial stenosis, hypertension, and aneurysm formation once myeloid cells begin to infiltrate the vessel walls.\textsuperscript{36}

\textbf{“Second hit” tumor formation}

Loss of the second, normal gene for neurofibromin in cells of patients with NF1 can happen seemingly randomly over a patient’s lifetime, and leads to the other manifestations seen in NF1 such as tumor formation.\textsuperscript{7} This loss of heterozygosity, termed a “second hit” of mutation, parallels other types of cancer that usually only begin after multiple mutations in the genome.\textsuperscript{55} Many NF1 tumors can be traced to neural crest origin such as those involving Schwann and chromaffin cells. The origin of some other cancers can be traced to other developmental tissue, such as leukemia from mesodermal myeloid cells, or astrocytomas from ectodermal neural tube tissue.\textsuperscript{56} In patients with NF1, researchers have found that the loss of the second gene in Schwann cells leads to the tumorous neurofibromas, both cutaneous/dermal and plexiform variants, as well as the more aggressive MPNST.\textsuperscript{56} Although Schwann cells make up the bulk of a
neurofibroma, other cell types such as fibroblasts, mast cells and perineural cells, are found in greater amounts in the neurofibromas.\textsuperscript{57} Evidence suggests that a neurofibroma only forms when the other cell types around the Schwann cells are also haploinsufficient; healthy surrounding cells seem to prevent neurofibroma growth.\textsuperscript{56,57} Loss of heterozygosity in melanocytes leads to the café-au-lait spots that are so prominent in patients with NF1; heterozygosity in melanocytes can explain the subtle general hyperpigmentation that patients have in comparison to their relatives or parents.\textsuperscript{56} In astrocytes, loss of heterozygosity leads to the formation of astrocytomas, whether they are benign and on the optic nerve or malignant and in other parts of the CNS.\textsuperscript{56} In the vasculature, myeloid cells. Chromaffin cells with “double hit” mutations can lead to pheochromocytomas and the endocrine and cardiovascular problems that follow suit.\textsuperscript{44}

**Potential Future Therapies**

The Ras-GAP pathway, which is hyperactive in these tumorous tissues, provides many downstream proteins that are ideal targets for current and future therapies. Anti-Ras drugs such as farnesyl transferase inhibitors have demonstrated some efficacy in fighting these tumors in clinical trials.\textsuperscript{44} Because the protein mTOR (mammalian target of rapamycin) is involved in the downstream effects of the Ras pathway, targeting this protein with rapamycin or similar drugs has also shown efficacy in fighting certain tumors, such as the plexiform neurofibroma.\textsuperscript{2,56}

More research is currently underway for therapies targeting the Ras pathway and other cellular growth pathways.\textsuperscript{2} Further research into predictive tests that can identify
patients at high-risk for specific abnormalities, and research into more variety of targeted biological therapies is needed. In all situations, the earlier that cancer is found and treatment begins, the better the chance for a positive prognosis for the patient.
QUALITY OF LIFE

There are many ways to measure the quality of life (QoL) impact for patients suffering from a condition or disease. Some of the most popular ways include detailed surveys or questionnaires that patients or physicians fill out based on their own experiences. The aggregation is run through statistical tests to determine the average impact on various factors. For NF1, these surveys include the SF36 Health Survey Questionnaire (see appendix), which contains 36 questions covering 8 lifestyle and health categories. The patient chooses the best answer to each question, and each answer has a value between 0-100. The averages of the answer values to certain question numbers (e.g. #20 and 32 averaged together measures social functioning) can determine the impact of the disease on specific variables. Other surveys include the Skindex survey, which exists specifically to measure the QoL impact by skin diseases. Various answers to this 29-item questionnaire are ranked and averaged, similar to the SF-36, to determine the impact on QoL for a range of aspects including emotions, physical symptoms, and functioning.

Patient population studies using the SF-36 and Skindex surveys demonstrate a negative impact by neurofibromatosis type 1 on all aspects of a patient’s life. Some studies suggest breaking down NF1’s impact on QoL into two categories: the disease’s severity and thus its effect on physiology, and its cosmetic impact and thus the disease’s effect on psychology. Patients overwhelmingly report a lower QoL in both categories, but the emotional impact due to NF1’s effect on the patient’s perceived social value and self-esteem was the greatest. Studies show that even if the majority of NF1 cases
fortunately contain mild internal manifestations and are non-severe in respect to pathophysiology, a patient’s own perception of the severity of his disease is directly related to the amount of cosmetic discordance which unfortunately is quite common in NF1.\textsuperscript{59} This can add unneeded fear to patients, in addition to the psychological impact already affecting patients in social settings due to the cosmetic detriment of the disease.\textsuperscript{59} Physicians can use the knowledge from these studies in their future treatment of patients with NF1, by making fixing deformities a higher priority to help ease the mental health of the patients.

A specific questionnaire exists for the impact to QoL on children with disabilities, termed the Behavior Assessment System for Children (BASC), which relies on the self-reporting by children, teachers and parents to determine how they perceive a disability impacts the behavior of the child.\textsuperscript{60}

Patient population studies utilizing the BASC, specifically the second edition, found that children with NF1 are greatly impacted socially and emotionally, particularly in school. Some studies suggest that these impacts may be due to underlying leaning disorders common in people with NF1 which can also affect their social skills; however, cosmetic appearances may also contribute to social exclusion and teasing by peers.\textsuperscript{61} In particular, children with NF1 tested low in “Leadership and Functional Communication” implying unpopularity and fewer reciprocated friendships.\textsuperscript{61} Social problems such as bullying, and behavioral problems such as depression, anxiety or aggression, were common in children with NF1. Researchers attribute the lack of social skills to
underlying neurocognitive defects and the stresses of school. Thus, therapy targeting a patient’s learning disorders can be effective in improving a child’s social status in school.

The level of impact on the quality of life for patients with neurofibromatosis type 1 varies greatly based on the level of expression of the mutation in the affected individual. There are many aspects of the patients’ and the patients’ families’ lives that can be affected when dealing with the management and treatment of neurofibromatosis type 1 (Table 6). These aspects can range from physical and emotional burden to financial burden, as health or life insurance providers may charge high deductibles or choose not to cover the patient at all due to expected high medical costs.

Table 6. Quality of life aspects impacted by NF1.

<table>
<thead>
<tr>
<th>Aspects that can impact quality of life include:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Academic challenges and learning disorders</td>
</tr>
<tr>
<td>Discrimination for employment</td>
</tr>
<tr>
<td>Discrimination for health insurance/life insurance coverage</td>
</tr>
<tr>
<td>Disfigurement</td>
</tr>
<tr>
<td>Fear of malignancy</td>
</tr>
<tr>
<td>Lack of physical activity (if bone deformities are present)</td>
</tr>
<tr>
<td>Out-of-pocket expenses by patient or family</td>
</tr>
<tr>
<td>Orthopedic problems and having to wear corrective brace</td>
</tr>
<tr>
<td>Pain</td>
</tr>
<tr>
<td>Pregnancy complications and the risk of passing NF1 onto child</td>
</tr>
</tbody>
</table>
Psychosocial issues due to lack of self-esteem and confidence
Social exclusion and stigmatization
Time consuming, repetitive clinical visits for check-ups or removing neurofibromas
Vision loss


The following are cases of people with neurofibromatosis type 1 demonstrating how the disease has impacted their life. As the following individual cases are discussed, the impacting factors on the patient’s life will be discussed more fully.

**Sandra O. and pregnancy**

Sandra was diagnosed with neurofibromatosis type 1 shortly after birth. The diagnosis was made primarily due to the many café-au-lait spots present on her skin. As she grew older, cutaneous neurofibromas began to form as well. Up until adulthood, her manifestations were relatively mild. The greatest impact on the quality of life in her childhood and teenage years were psychosocial. She would feel the need to often wear long sleeve clothing to cover her skin, would be afraid to participate in activities such as swimming or beach days with friends, felt depressed at times, and would often take trips to the dermatologist to remove any cutaneous neurofibromas (sometimes flying to different cities to do so). A deep tumor formed in her foot during teenage years, causing pain when walked upon, and requiring excision with surgery. Fortunately, she suffered no apparent learning disorders. With her endearing personality and the positive support of her family and friends, she overcame any academic or social challenge posed to her by
NF1 to live a successful adult life. As an adult she wished to have children but was warned against doing so by physicians who worried that hormonal imbalances from pregnancy may aggravate her condition. After trying and failing to have a child, her condition did indeed worsen. Malignant glioblastoma tumors began forming in her brain, specifically grade III or IV astrocytomas, and which have a poor prognosis. Sandra kept a positive outlook on life, an important aspect to fighting cancer, but after much surgery, radiation, and chemotherapy, the cancer persisted and she ultimately succumbed to her disease at 39 years of age.

The information on the relationship between pregnancy and neurofibroma is still quite limited. Because NF1 is an autosomal dominant mutation, there is a 50% chance that an offspring will have the mutation as well. Genetic counseling exists to help potential parents with NF1 to understand their disease and the risk factors involved. This knowledge factors into the decision-making by patients on whether or not to have children, with some patients opting out of childbirth altogether. In one study 44% of subjects stated that the knowledge of the risk of NF1 factored into their pregnancy decision, with another 34% expressing that it would have influenced their decision had they known about the risk beforehand.

Parental age may also play a role in the chance of sporadic mutations in NF1 patients with no familial history. One study reviewing two decades of the general Czech population found that, as the mean parental age of the Czech population has increased, so too has the incidence of NF1. They concluded that advanced parental age can affect sporadic mutations, with more bearing on paternal rather than maternal age. They found
that the mean paternal age of sporadic NF1 patients was 3.7 years older than the general population, versus 1.7 years older than the general population for mothers.\textsuperscript{64}

In respect to hormone imbalances due to pregnancy, some studies suggest that the increase in hormone levels from pregnancy can aggravate symptomatic manifestations and lead to an increase in the number and size of cutaneous or subcutaneous neurofibromas developing on the skin and elsewhere.\textsuperscript{65} Pelvic or uterine neurofibroma development, or pelvic bone deformity, can cause pain during pregnancy, block the descent of the child, and require a caesarian section. In one population study for NF1 women bearing children, the rate of caesarian section, at 36.1\%, was much higher than the general population average of 9-20\%.\textsuperscript{65} Over 80\% of women subjects also reported new or further growth of existing neurofibromas during pregnancy.\textsuperscript{65} This may be due to an increased expression of progesterone receptors, found on 75\% of neurofibroma cells, and to a lesser extent estrogen receptors, found on 5\% of neurofibroma cells.\textsuperscript{66} In contrast, no normal nerve samples showed progesterone receptor expression.\textsuperscript{67} Interestingly, the plexiform variant of neurofibromas may be less susceptible to growth based on raised hormone levels than the cutaneous and dermal variants; however, malignant peripheral nerve sheathe tumors (MPNST) were still susceptible to increased growth from these hormones.\textsuperscript{67} Progesterone receptors are also found expressed in astrocytomas in the brain, while normal astrocytes do not express such receptors, suggesting an influence of raised progesterone levels on increased brain tumor frequency as well.\textsuperscript{67} Due to these steroids’ role as stimulatory agents of neurofibroma growth, future therapeutics may target the level of these steroids to treat neurofibromas.\textsuperscript{66}
**Susan G. and pain, surgery and familial stress**

Susan was born with NF1 manifestations such as café-au-lait spots that doctors initially just believed were birthmarks.\(^7\) However as a newborn she cried incessantly, demonstrating signs of pain. At 16 months, Susan had blood in her urine, leaving the toilet bowl red.\(^7\) Doctors discovered a mass blocking the ureter, a neurofibroma, and diagnosed Susan with NF1. The tumors that began early for Susan would become the cause of significant pain for her, and the beginning of many stresses the family would have to bear. As Susan’s mother, Dolores, described it “it’s not that one person in the family has NF; it’s that the whole family has NF.” These familial stresses included feelings of guilt, and blame shifting by Dolores and her husband, and their respective parents, on whose genetics may have contributed to the disease.\(^7\) Dolores also felt Susan’s sisters, who were not diagnosed with NF1, may have felt neglected in respect to how much attention Susan received. Over Susan’s lifetime, she required over 40 surgeries both major and minor, and the time and expenses for these contributed to the familial stress.\(^7\) Dolores would schedule surgeries on holidays so Susan could miss the least amount of school. Susan also suffered from learning disorders, including poor handwriting and poor math skills, and required private tutoring and enrollment in private school, both of which added to the financial burden of the family.\(^7\)

Susan suffered from neurofibromas all over her body, including the feet, arms, scalp, above the eye, and eyebrows. The cranial neurofibromas caused a lot of headaches, and required invasive surgery that caused scars and more pain during recooperation. Plexiform neurofibromas developed internally and led to further internal pain; for
instance, a persistent tumor on the bladder made urination difficult and required extensive bladder surgery.\textsuperscript{7} Susan required multiple prescription medications to manage the pain. She was very resilient in overcoming the physical and academic challenges that came her way, insisting on going to college despite her guidance counselor’s advice against it. She married and lived a happy life until her NF1 complications overwhelmed her. She ultimately passed away at 34.\textsuperscript{7}

Pain, other than from headaches and migraines, is relatively uncommon in NF1 but can manifest itself in various ways.\textsuperscript{12} Headaches and migraines, which affect about 20\% of NF1 patients, can be treated with the usual prophylactic medication.\textsuperscript{12} Cutaneous neurofibromas can be painful when they are erupting, or when traumatized once full grown. Paraspinal plexiform neurofibromas can cause spinal root and back pain.\textsuperscript{12} Orthopedic problems such as scoliosis or pseudarthrosis, along with the corrective surgery or brace, can also lead to pain.\textsuperscript{68} Neurofibromas that grow in the fingers or feet and pinch nerves or are constantly exposed to trauma can lead to extreme pain and need to be removed surgically.\textsuperscript{68} Finally, sudden pain can be due to the formation of a malignant peripheral nerve sheath tumor, which is highly aggressive and associated with invariable severe pain. MPNST needs to be diagnosed early before it quickly metastasizes, as it does not respond well to chemotherapy or radiation and must be excised surgically.\textsuperscript{12} Due to the lethality and spontaneity of MPNST, NF1 patients complaining about pain should be examined carefully by their physician for signs of MPNST through ultrasound or X-Ray.\textsuperscript{15}
Ana R. and social exclusion

Ana was born in Mexico with a red mark on her face she describes as looking “like a bee sting”: an early neurofibroma. As she grew older, it too grew in size, and began to slowly encompass an entire side of her face. Her parents moved to the U.S. to find Ana better health care for her condition and she was diagnosed with NF1 and treated for her tumors at Loma Linda University Medical Center. However, her facial tumor rapidly grew back, and more developed all over her body with age.

Ana suffered from depression as a child, stating that kids her age would ask her why she looked the way she did, how she just wished she looked like her friends, and wished to know as a child “why God was so mean? I felt like I did something wrong.” She became reluctant to go to school out of fear for how she would be treated. She remembers how some other kids would cry when they saw her. Other times, she would be stopped on the street and blessed by strangers; although she felt mentally and physically normal, her treatment by others made her feel shy and isolated. Ana ultimately selected not to finish her college coursework, feeling discriminated against by administration who offered her disabled services. She also tried to get a job but felt discriminated by employers based on her appearance. She was likened to the elephant man, Joseph Merrick, by people who saw her. Ultimately, Ana secluded herself from public as much as possible and left the house about once a month. At age 22 when the tumor was so big it started impacting her vision and causing headaches, she visited a team of doctors who began a series of 5 reconstructive surgeries to remove the tumor and improve Ana’s appearance. The cosmetic improvement that occurred to Ana
following surgery changed her life. She felt as if the world opened up to her. She developed confidence and now leaves the house often, no longer feeling threatened by strangers. She has made new friends and began dating, returned to school, and is working towards becoming a cosmetologist.\textsuperscript{70} She is unwilling to have children, however, out of fear of passing on her disease. She now wishes to help others who may be sheltering themselves from society.\textsuperscript{69}

Stories of psychosocial issues and societal exclusion are common among patients with visible manifestations of NF1. Psychological issues develop even in patients with mild manifestations, and some studies show that a greater severity of skin manifestations does not correlate to a greater level of emotional problems impacting the patient.\textsuperscript{71} The number of symptoms for anxiety and depression are higher in patients with NF1 than the general population, and even higher than in patients with other chronic diseases, such as various forms of cancer.\textsuperscript{71} Patients may not feel comfortable wearing certain clothing, and may feel traumatized in social settings whether making new friends at school, interviewing for jobs, or trying to date. Unfortunately, the stigma for NF1 being “the elephant man’s disease” still persists today, even among some physicians who may be uneducated on the difference between Proteus Syndrome and NF1.\textsuperscript{72} The on-going stigmatization only makes it harder for patients and their families to feel and be treated as normal. Patients and family members aware of Joseph Merrick’s story, but unaware of the difference between NF1 and Proteus Syndrome, can become worried that mild NF1 manifestations will degenerate into something more disfiguring.\textsuperscript{72}
Suggestions to improve quality of life for NF1 Patients

The best way to improve the quality of life for patients with mild and non-life threatening manifestations is by educating the public on NF1 and destigmatizing the condition. There are still limits to the amount of cosmetic improvement that can be bestowed onto patients, and removing the negative stigma from society through education will go a long way in helping these patients feel comfortable acquiring jobs and socializing, without the fear of alienation or scaring others way. Teachers who are educated about NF1 will understand that a student with the condition may have learning disabilities and not a lack of intelligence, and employers who are educated would understand that the condition is not contagious and will not spread to customers. Patient and family education about the condition can also help; the participation in support groups that focus on alleviating any psychological issues or stress related to the disease can help patients feel more comfortable within their own body, and more understanding of the severity (or lack-there-of) of their condition to help alleviate fear.

Beyond public education, physicians should treat, to the best of their ability, the various patient-specific manifestations that occur with NF1. The goal of management should be to improve not only the patient’s physiological health, but also the patient’s psychological health, which can do wonders to alleviate the many of the stresses that patients carry. For manifestations that affect quality of life through physiological debility such as scoliosis, vision loss or pain from neurofibromas, corrective bracing or appropriate surgical procedures should be used to alleviate the debilitating symptoms and allow the patient to function normally. Cosmetic manifestations should not be ignored,
and neurofibromas should be surgically removed when possible to prevent visible outgrowths from causing psychological or social damage, as well as treating the café-au-lait spots with hydroquinone or laser therapy to correct the hyperpigmentation. Research shows that improving the patient’s cosmetic look helps them lead more fulfilling lives with respect to their social and occupational settings.

Learning disabilities such as depression should be treated with the appropriate therapy and programs to prevent patients from feeling inferior amongst their peers and leave them capable of academic and occupational success. If possible, families should opt for tutoring and/or enroll the patient in programs designed to overcome the specific learning disorder. Psychosocial issues such as depression may be secondary to other problems, such as feelings of inferiority due to a learning disability or cosmetic feature, and may be remedied by fixing the primary cause. Therefore, along with therapy, researchers should develop medications that can ameliorate the primary causes of a learning disabilities. For example, lovastatin has shown efficacy in treating specific learning disabilities, such as spatial and behavioral learning deficits, in mice. However, studies in children with similar statin, simvastatin, have yet to demonstrate the same cognitive improvements in human trials.

Finally, the quality of life for patients can be improved by scheduling routine check-ups with knowledgeable physicians who can detect early signs of symptoms such as learning disorders or malignancies. It is particularly important to detect any learning disorders early on in children, such as ADD or speech problems, as that can greatly help a child’s academic and social life. Check-ups are also important for
catching MPNSTs early, which can develop from plexiform neurofibromas and metastasize rapidly, as well as cause severe pain.\textsuperscript{15} Annual eye exams are important for monitoring vision and preventing vision loss, headaches, or endocrine imbalances, should a tumor begin developing along the optic nerve.\textsuperscript{7,12} Catching other types of tumors early, such as pheochromocytomas should a patient present with excessive sweating and irregular blood pressure, or grade III or IV astrocytomas should a patient present with abnormal headaches, would provide a great advantage in cancer therapy and may prevent these tumors from becoming lethal.\textsuperscript{12}
METHOD OF EVIDENCE ACQUISITION

I performed PubMed and Google Scholar searches of the English-language literature (from 1968 to 2016) using the terms neurofibromatosis, neurofibromatosis management, neurofibromatosis quality of life, neurofibromatosis pathogenesis, neurofibromatosis history, neurofibromatosis review, neurofibromatosis and pregnancy, clinical neurofibromatosis, elephant man, neurofibromatosis family and more. I searched textbooks and articles online about people living with neurofibromatosis to represent cases for quality of life. Relevant bibliographies of literature were manually reviewed for additional resources.
REFERENCES


CURRICULUM VITAE

Zaidal Aseel Obagi
Zaidal8@gmail.com
Year of Birth: 1993
Place of Birth: Los Angeles, California, USA
Languages spoken: English, French, Arabic

Education:
B.A. Biology, Boston University, May 2015
B.A. Economics, Boston University, May 2015
M.S. Medical Sciences, Boston University, September 2016

Honors
AP Scholar with Distinction, Spring 2011 Received a “4” on five or more AP exams.
Dean’s List, Spring 2013 – Spring 2015 Received a 3.5 or above GPA during the semester.
UROP Grant for Melanoma Research at BU Med School, Fall 2014 Applied for and received a UROP grant for research at BU School of Medicine Dermatology Department.
UROP Presentation on Progeria Research at 17th Annual UROP Symposium, Fall 2014 Presented a poster on my clinical research work on progeria performed at Brigham and Women’s Hospital.
Alpha Epsilon Delta Pre-Health Honor Society, Spring 2015 Membership is given to academically qualified pre-health focused students and requires constant volunteer work.
Cum Laude Biology and Economics, Spring 2015 Graduated in the top 30% of the class.

Paid Employment Positions
Co-founder of RZProductions (Beverly Hills, CA, June 2010-August 2011)
I managed the website development company with my friend Raj Vir during our senior year of high school.

School-related Extracurricular Activities
Peer Health Exchange Mentor (Boston, MA, September 2011- May 2012)
I traveled to high schools in the Greater Boston area that cannot afford a quality health-education program, and taught the freshmen class the PHE health curriculum and proper decision making.. My group focused on the negative effects of drug usage as a teenager.
Member of L’Association Française de Boston University (Boston, MA, September 2014 – May 2015)

The AFBU met at various times throughout the semester to practice French amongst each other as we dined, watched a movie or met for other activities.

Tennis Club BU (Boston, MA, September 2014 – May 2015)

The tennis club met weekly for members to practice tennis, play matches with each other, and compete in tournaments held by the club.

Alpha Epsilon Delta Pre-Health Society (Boston, MA, January 2015 – May 2015)

As a member of AED, I volunteered in various community service events around Boston and attended health-oriented lectures held by professors or doctors on current issues and challenges that health care faces in the US and globally.

Wizards Volunteer (Boston, MA, January 2015 – May 2015, January 2016-May 2016)

As a wizards volunteer, I traveled to schools or YMCAs around Boston and performed science experiments with young kids to inspire their interest in science. The program assists children who are in communities that may otherwise not foster an appreciation for science in children.

Clinical Experiences

Assistant to Dr. Zein E. Obagi in Obagi Skin Health Institute (Beverly Hills, CA, September 2007-August 2015)

I often watch Dr. Zein Obagi work on patients and learn all I can about dermatology, doctor-patient contact, behind-the-scenes operations of a clinic, and running a global skin care company. Other types of doctors such as plastic surgeons often come into his clinic to perform procedures in the surgery room, and I watch these procedures as well.

Shadowed anesthesiologist Dr. Alex Zaks (Beverly Hills, CA, July-August 2011)

I shadowed Dr. Zaks in his surgery center and observed a wide variety of different surgeries, including knee reconstruction surgery and plastic surgeries.

Assisted and shadowed otolaryngologist Dr. Shawn Nassiri (Beverly Hills, CA, June-July 2012)

I assisted Dr. Nassiri in his clinic set up rooms for patients and observed procedure such as laryngoscopies.

Shadowed Dr. Marie Gerhard-Herman at Brigham and Women’s Hospital, Harvard Medical School (Boston, MA, May 2013–May 2014)
I shadowed cardiologist Dr. Marie Gerhard-Herman into patient rooms at Brigham and Women’s Hospital and learned more about patient care in a hospital setting.

**Research Experiences**

**Research Assistant in the Cardiovascular Department Vascular Lab of Brigham and Women’s Hospital, Harvard Medical School** *(Boston, MA, May 2013 – May 2014)*

I performed clinical research work on children with progeria, in which I studied ultrasound pictures of carotid arteries looking for plaque development and other abnormalities.

**Research Assistant in the Alani Lab at the BU School of Medicine Dermatology Department** *(Boston, MA, September 2014 – May 2015)*  
**Supervisor: Dr. Rhoda Alani**

I performed lab work on melanoma involving managing and lysing cells and performing western blot assays on different melanoma cell lines.

**Other experiences:**

**Campaign intern for Zein Obagi Jr. for Congress, 33rd. District of CA** *(Los Angeles, CA, May 2012- August 2012)*

As a campaign intern, I learned a lot about economic issues facing the average constituent, especially in relation to healthcare and the disparity that exists between cost and quality treatment.

**Walk for Warriors 5k** *(Los Angeles, CA, May 2014, May 2015, and May 2016)*

I run the 5k to raise funds for veterans annually.

**Textbook Editor and Reviewer for Dr. Zein E. Obagi’s Dermatology Textbook, 2nd Edition** *(Beverly Hills, CA, June-July 2014)*

I reviewed chapters written by Dr. Zein E. Obagi for his new dermatology medical textbook. In doing so, I learned a lot about dermatology.

**Film Producer** *(Los Angeles, CA, September 2010-Current)*

As a film producer hobbyist, I help make films with friends in LA who aspire to become directors and actors. I have produced two feature-length films, **One Night in LA** and **Home Video**, along with various short-films such as **Akal** and **The Dreamer**, as well as various YouTube clips.