

Living with Cutis Laxa: An Exploratory Study

by

Pooja Nitin Solanki

BS, University of California Los Angeles, 2017

Submitted to the Graduate Faculty of the

Department of Human Genetics

Graduate School of Public Health in partial fulfillment

of the requirements for the degree of

Master of Science

Master of Public Health

University of Pittsburgh

2020

UNIVERSITY OF PITTSBURGH

GRADUATE SCHOOL OF PUBLIC HEALTH

This thesis was presented

by

Pooja Nitin Solanki

It was defended on

May 27, 2020

and approved by

Andrea Durst, MS, DrPH, Assistant Professor of Human Genetics, Associate Director Genetic Counseling Program, Co-Director MPH in Public Health Genetics Program, Graduate School of Public Health, University of Pittsburgh

Martha Ann Terry, MA, PhD, Associate Professor of Behavior and Community Health Sciences, Director MPH in Behavioral and Community Health Sciences Program, Graduate School of Public Health, University of Pittsburgh

Thesis Advisor: Zsolt Urban, PhD, Associate Professor of Human Genetics, Graduate School of Public Health, University of Pittsburgh

Copyright © by Pooja Nitin Solanki

2020

Living with Cutis Laxa: An Exploratory Study

Pooja Nitin Solanki, MS, MPH

University of Pittsburgh, 2020

Abstract

Rare diseases, while individually uncommon, collectively may impact up to 10% of the population. This makes rare disease a major global public health issue. Most rare diseases have a genetic etiology. Cutis laxa is one such rare connective tissue disorder; people with the condition often face a high burden of disease but face challenges in finding well-informed and knowledgeable healthcare providers. To better understand the experiences and challenges that people with cutis laxa have while navigating their healthcare systems, six qualitative interviews were conducted amongst English speaking adults who have been diagnosed with cutis laxa. Participants were recruited through the Cutis Laxa Internationale Facebook page; interviews were recorded and conducted through Skype Business. The interviews focused on questions about the process of diagnosis, medical management and care, availability of resources, and sources of support for these participants. The interviews were transcribed and coded for thematic analysis. This study identified several themes, most notably, lack of knowledge amongst providers, concern for provider engagement, anxiety about potential symptoms, desire for coordinated care, and rare disease in the healthcare system. There have been no other qualitative studies that focus on the experiences of people with cutis laxa. This study helps fill this empty niche, provide more information about the experiences and challenges of those that have cutis laxa, offer insight for healthcare providers of patients with cutis laxa and other rare diseases, and contextualize how the needs of the cutis laxa community fit into the greater need for public health interventions with the rare disease population.

Table of Contents

Preface.....	x
1.0 Introduction.....	1
1.1 Specific Aims	2
2.0 Literature Review	3
2.1 Cutis Laxa	3
2.1.1 Autosomal Dominant Cutis Laxa	6
2.1.2 Autosomal Recessive Cutis Laxa	6
2.1.3 X-Linked Recessive Cutis Laxa	10
2.1.4 Acquired Cutis Laxa	10
2.1.5 Treatment for Cutis Laxa.....	11
2.1.6 Resources Associated with Cutis Laxa	12
2.2 Rare Diseases	13
2.2.1 Introduction to rare diseases.....	13
2.2.2 Epidemiology of rare diseases	14
2.2.3 Quality of life for patients and families with rare diseases	15
2.2.4 Measuring depression in patient with rare diseases	17
2.2.5 Challenges of having a disfiguring disorder	18
2.3 Objectives	21
3.0 Manuscript.....	22
3.1 Background	22
3.1.1 Cutis Laxa	22

3.1.2 Rare Diseases	23
3.2 Methods	24
3.2.1 Study Design	24
3.2.2 Recruitment	24
3.2.3 Data Analysis	25
3.3 Results.....	26
3.3.1 Participant Demographic Information	26
3.3.2 Themes	26
3.3.2.1 Rare Disease in Healthcare	28
3.3.2.2 Living with Uncertainty	35
3.3.2.3 Patient Response	41
3.4 Discussion	45
3.4.1 Future Research	51
3.4.2 Limitations	52
3.5 Conclusions	52
4.0 Significance to Genetic Counseling and Public Health	53
4.1.1 Significance to Genetic Counseling	53
4.1.2 Significance to Public Health	54
5.0 Public Health Essay: Analyses of Demographics and Beck Depression Inventory	
Scores of Participants in the Cutis Laxa Research Study	57
5.1 Background	57
5.1.1 Cutis Laxa & Rare Diseases	57
5.1.2 Rare Disease, Depression, and Quality of Life	58

5.1.3 Beck Depression Inventory and Self-Report Depression Scales	59
5.1.4 Rare Disease, Empowerment, and Resilience	60
5.2 Methods	61
5.2.1 Participant and Data Collection:	61
5.2.2 Data Analysis:.....	63
5.3 Results.....	64
5.4 Discussion	73
5.4.1 Demographics	73
5.4.2 Beck Depression Inventory Scores	75
5.4.3 Future Directions	76
5.5 Conclusions	77
Appendix A Institutional Review Board Approval (Thesis)	78
Appendix B Facebook Recruitment Script.....	79
Appendix C Interview Questions.....	80
Appendix D Demographic Questions	82
Appendix E Codebook.....	83
Appendix F Institutional Review Board Approval (Essay).....	85
Bibliography	87

List of Tables

Table 1 Monogenic Forms of Cutis Laxa.....	4
Table 2: Resources Associated with Cutis Laxa.....	12
Table 3 Theme Chart.....	27
Table 4 Categories of Data Downloaded from Progeny	63
Table 6 Participants a Diagnosis of Cutis Laxa with a Known Mutation	68
Table 7 Beck Depression Inventory (BDI) Scale	71
Table 8 Beck Depression Inventory Scores of Unaffected Versus Affected Individuals	71

List of Figures

Figure 1 Study Participants with a Diagnosis of Cutis Laxa: Age at Interview/Death	65
Figure 2 Study Participants with a Diagnosis of Cutis Laxa: Age at Interview/Death Boxplot	66
Figure 3 Study Participants with a Diagnosis of Cutis Laxa: Race (General)	67
Figure 4 Study Participants with a Diagnosis of Cutis Laxa: Causative Mutations.....	68
Figure 5 Distribution of Cutis Laxa Causing Genes Across Racial Groups	69
Figure 6 Distribution of Samples by Country (Count).....	70
Figure 7 Histogram of BDI Scores of Participants with a Diagnosis	72
Figure 8 Histogram of BDI Scores of Family Members	72

Preface

Thank you to my professors and mentors at Pitt Public Health for your guidance and wisdom, particularly Dr. Gollin, Dr. Terry, Dr. Urban, Candy, Andrea, and Robin. Your support has been invaluable, and I hope to pay it forward in the future.

Thank you to cutis laxa community for your enthusiasm, engagement, and insight. I deeply appreciate the opportunity that you have given me to complete this project.

Finally, thank you to my family. There are no words.

1.0 Introduction

Cutis laxa is a rare connective tissue disorder that affects approximately 200 to 400 families around the world. There are several different subtypes of cutis laxa, including monogenic and acquired forms. While there has been research into the pathological mechanisms of the condition, there are no known studies that focus on the experiences of people living with cutis laxa specifically. As far as this researcher knows, this is the first qualitative study that directly asks people with cutis laxa about how they navigate and perceive their healthcare.

Cutis laxa can be a debilitating condition with severe symptoms that can impact quality of life (Berk, Bentley, Bayliss, Lind, & Urban, 2012). This can be exacerbated by the nature of having a rare disease, which can result in increased difficulty in finding knowledgeable providers and access healthcare (Schieppati, Henter, Daina, & Aperia, 2008). Furthermore, rare diseases can impact up to 10% of the global population (Pogue et al., 2018). Therefore, it is important to understand the experiences of people with cutis laxa and other rare diseases because they can impact a large proportion of the population and the population faces unique challenges. Thus, it is important to understand the experience of people cutis laxa in the context of the larger population with rare disease. Furthermore, it can help inform healthcare providers who treat people with cutis laxa how to best meet their needs and what resources are most needed by this population.

The main aim of this study is exploratory. No one has talked to this population exclusively and systematically about their needs and perceptions before. This project seeks to gain information that could potentially help guide future studies and creation of targeted resources for people with cutis laxa. To accomplish this, the study is comprised of semi-structured interviews over Skype for Business with English-speaking adults who have been diagnosed with cutis laxa. The

interviews were recorded and transcribed. Thematic analysis was used to identify common themes amongst the participants.

1.1 Specific Aims

The specific aims of this project are the following:

- Describe the experience of being diagnosed with cutis laxa, a rare disease with variability between and within subtypes.
- Describe the experiences and challenges that people with cutis laxa face as they try to obtain healthcare.
- Find areas in the experience of navigating healthcare that can be improved for people for cutis laxa. If no areas for improvement are identified, identify what has helped people with cutis laxa cope with their diagnosis and managing their healthcare.
- Identify differences between participants, particularly between participants with different subtypes.
- Suggest future directions that could improve the care and quality of life for people with cutis laxa and other rare diseases.

2.0 Literature Review

2.1 Cutis Laxa

Cutis laxa is a rare connective tissue disorder characterized by loose or inelastic skin as well as anomalies in the heart, muscles, joints, blood vessels, intestines, and lungs (Berk et al., 2012). The characteristic loose skin as a symptom, first recognized in 1832, was called dermatolysis and noted to be associated with congenital unspecified heart disease and kyphosis (Wigley, 1943). German doctor Otto Seifert and his assistant Du Mesnil were the first to coin the term cutis laxa in a scientific publication in 1890 ("Cutis Laxa," 1890). By 1972, the literature notes that there are several different modes of inheritance for the condition, starting with dominant and recessive forms (Beighton, 1972). Researchers discovered the first gene, *ELN*, to cause with cutis laxa in 1998; other genes were subsequently identified (Tassabehji et al., 1998).

There are several types of cutis laxa. There are various inherited subtypes linked to 11 different genes (Urban & Davis, 2014). Age of onset, severity of skin appearance, and associated symptoms vary within and between subtypes. There is also acquired cutis laxa, which has an unknown genetic etiology but is considered to be caused by an environmental trigger. Cutis laxa can be diagnosed through genetic testing or through skin biopsy using an elastin stain to identify fragmented or diminished elastic fibers.

There are 200 to 400 families documented worldwide affected with cutis laxa ("Cutis laxa," 2017). According to the latest census by the patient support foundation, Cutis Laxa Internationale, there are 385 known patients around the world as of January 19, 2019 ("Patients Worldwide," 2019). While most types of cutis laxa are not associated with a particular race or ethnicity,

autosomal recessive forms of cutis laxa can be common in populations with high rates of consanguinity, as is often the case with autosomal recessive genetic conditions (Kaiser, 2016). Certain forms of cutis laxa can be common in specific communities due to high consanguinity, founder effect, and reproductive isolation, like the Mappila ethno-religious community in the state of Kerala, India which has a higher incidence autosomal recessive cutis laxa type 1B (ARCL1B) compared to the general population (Kappanayil et al., 2012).

Table 1 Monogenic Forms of Cutis Laxa

Subtype	Gene	Mode of Inheritance	Characteristics
Autosomal dominant cutis laxa (ADCL)	<i>ELN</i>	Autosomal dominant	Loose skin folds, emphysema, aortic root dilation and rupture, inguinal hernia (Szabo et al., 2006)
Autosomal recessive cutis laxa type 1A (ARCL1A)	<i>FBLN5</i>	Autosomal recessive	Loose skin folds, emphysema, supraaortic stenosis, peripheral pulmonary artery stenosis, genitourinary diverticula, early mortality (B. Callewaert et al., 2013)
Autosomal recessive cutis laxa type 1B (ARCL1B)	<i>FBLN4</i>	Autosomal recessive	Milder loose skin folds, bone fragility, emphysema, diaphragmatic and inguinal hernia, vascular tortuosity and aneurysm, joint laxity, and pectus excavatum (Huchtagowder et al., 2006)
Autosomal recessive cutis laxa type 1C (ARCL1C)	<i>LTBP4</i>	Autosomal recessive	Loose skin, tachypnea, emphysema or hypoplastic lung, diaphragmatic hernia, umbilical hernia, inguinal hernia, pulmonary artery stenosis, intestinal dilation and tortuosity, joint laxity,

Table 1 Continued

			postnatal growth delay (Urban et al., 2009)
Autosomal recessive cutis laxa type 2A (ARCL2A)	<i>ATP6V0A2</i>	Autosomal recessive	Loose skin folds, general connective tissue weakness, growth delay, developmental delay, and neurological abnormalities (Kornak et al., 2008)
Autosomal recessive cutis laxa type 2B (ARCL2B)	<i>PYCR1</i>	Autosomal recessive	Loose skin folds, intrauterine growth retardation, congenital hip dislocation, hyperextensibility, hypotonia, developmental delay, intellectual disability, bone fragility, and dysgenesis or agenesis of the corpus collosum (Kariminejad et al., 2017)
Autosomal recessive cutis laxa type 3A (ARCL3A) (also known as de Barsy Syndrome A)	<i>ALDH18A1</i>	Autosomal recessive	Wrinkled skin that lessens with age, corneal clouding, intellectual disability, global developmental delay, joint dislocations, and seizures (Bicknell et al., 2008)
Autosomal recessive cutis laxa type 3B (ARCL3B) (also known as de Barsy Syndrome B)	<i>PYCR1</i>	Autosomal recessive	Thin and translucent skin, intrauterine growth restriction, corneal clouding, microcephaly, intellectual disability, and bone fragility (Dutta, Ekbote, Thomas, Omprakash, & Danda, 2016)
MACS Syndrome (Macrocephaly, Alopecia, Cutis laxa, and Scoliosis)	<i>RIN2</i>	Autosomal recessive	Macrocephaly, alopecia, cutis laxa, scoliosis, joint laxity, swollen facial appearance, mild intellectual disability (Aslanger et al., 2014)
Geoderma osteodysplasticum (GO)	<i>GORAB</i>	Autosomal recessive	Osteoporosis and prematurely wrinkly skin (Newman et al., 2008)

Table 1 Continued

Occipital Horn Syndrome (OHS)	<i>ATP7A</i>	X-linked recessive	Loose skin folds, occipital horns, short and broad clavicles (Tsukahara, Imaizumi, Kawai, & Kajii, 1994)
-------------------------------	--------------	--------------------	--

2.1.1 Autosomal Dominant Cutis Laxa

Autosomal dominant cutis laxa (ADCL) is usually caused by heterozygous mutations in the *ELN* gene (chromosome 7q11.23) (Tassabehji et al., 1998). ADCL can also be caused mutations in *FBLN5* (chromosome 14q32.12) (Markova et al., 2003). *ELN* codes for tropoelastin, a precursor which aggregates together to form an elastin polymer. Elastin is an essential structural component of elastic fibers that form the extracellular matrix of skin, lungs, and blood vessels (Baldwin, Simpson, Steer, Cain, & Kielty, 2013). The age of onset for ADCL ranges from birth to early adulthood, and it is rarely associated with a reduction in lifespan. ADCL is associated with loose skin folds that give the appearance of premature aging as well as other characteristic dysmorphic features including a long philtrum, large ears, a beaked nose, and a hoarse voice (B. Callewaert et al., 2011). While ADCL is generally considered to be more benign than the autosomal recessive forms of cutis laxa, it can be associated with internal organ anomalies such as emphysema, aortic root dilation and rupture, and inguinal hernia (Szabo et al., 2006).

2.1.2 Autosomal Recessive Cutis Laxa

FBLN5 is linked with autosomal recessive cutis laxa type 1A (ARCL1A). *FBLN5* codes for the fibulin-5 protein, which is an extracellular matrix protein that helps organize tropoelastin

to form elastic fibers (Wachi et al., 2008). The gene is typically expressed during fetal development in the great vessels, cardiac valves, lung, uterus, and skin (Kowal, Richardson, Miano, & Olson, 1999). ARCL1A is associated with severe skin folding, inelasticity, and early onset emphysema that results in early mortality. Valvular issues, supraaortic stenosis, peripheral pulmonary artery stenosis, and genitourinary diverticula can occur in ARCL1A. Dysmorphic features associated with ARCL1A include high forehead, broad and beaked nose, large dysplastic ears, and sagging cheeks (B. Callewaert et al., 2013).

Autosomal recessive cutis laxa type 1B (ARCL1B) is linked to *FBLN4* (chromosome 11q13.1). Mutations in *FBLN4* result in abnormal coding of the fibillin-4 protein, which interferes with the formation of elastic fibers, vascular patterning, collagen production, and skeletal function (Huchtagowder et al., 2006). Symptoms of ARCL1B include milder loose skin compared to other types of ARCL1, bone fragility, emphysema, diaphragmatic and inguinal hernia, vascular tortuosity and aneurysm, joint laxity, and pectus excavatum (Huchtagowder et al., 2006). Onset can occur during early childhood, or as early as the prenatal stage (Letard et al., 2018). Dysmorphic features include high forehead, hypertelorism, and Marfanoid skeletal features (B. Callewaert et al., 2013).

LTBP4 (chromosome 19q13.2) codes for latent transforming growth factor- β binding protein 4. Transforming growth factor- β (TGF β) is essential for proper elastic fiber formation; mutations which knock out the function of this protein interfere with TGF β signaling (Su et al., 2015). Loss-of-function mutations are associated with autosomal recessive cutis laxa type 1C (ARCL1C). ARCL1C typically presents at birth and results in early mortality in childhood. Features of ARCL1C include tachypnea, emphysema or hypoplastic lung, hernia (diaphragmatic, umbilical, and inguinal), pulmonary artery stenosis, intestinal dilation and tortuosity, joint laxity,

postnatal growth delay, as well as other anomalies and birth defects. Dysmorphic features associated with ARCL1C include long philtrum, wide fontanelles, hypertelorism, receding forehead, and flat midface as well as retrognathia, micrognathia, or mandibular hypoplasia (Urban et al., 2009).

Loss-of-function mutations in *ATP6V0A2* (chromosome 12q24.31) result in autosomal recessive cutis laxa type 2A (ARCL2A). *ATP6V0A2* has also been linked to one patient with de Barsy Syndrome, which is described later in this section (Leao-Teles, Quelhas, Vilarinho, & Jaeken, 2010). This gene codes for the $\alpha 2$ subunit of the vesicular ATPase H^+ pump; loss of this subunit results in impaired secretion and accumulation of tropoelastin, an elastin precursor, in Golgi vesicles (Huchtagowder et al., 2009). This type of cutis laxa is associated with general connective tissue weakness, growth delay, developmental delay, and neurological abnormalities. Dysmorphic features include large fontanelles with delay in closure and down-slating palpebral fissures (Kornak et al., 2008). This is a congenital form with a variable life expectancy (Kariminejad et al., 2017).

Autosomal recessive cutis laxa type 2B (ARCL2B) is caused by mutations in *PYCR1* (chromosome 17q25.3). *PYCR1* encodes pyrroline-5-carboxylate reductase 1, an enzyme, found in the mitochondria necessary for the synthesis of the amino acid proline; mutations in this gene do not cause proline auxotrophy, but do impair mitochondrial membrane potential and increase oxidative stress as well as apoptosis (Dimopoulou et al., 2013). This subtype has an onset during the prenatal period and is associated with intrauterine growth retardation, congenital hip dislocation, hyperextensibility, hypotonia, developmental delay, intellectual disability, bone fragility, and dysgenesis or agenesis of the corpus collosum. The distinctive facial dysmorphic

features include prominent forehead, long philtrum, and triangular face (Kariminejad et al., 2017; Noordam et al., 2009).

Autosomal recessive cutis laxa type 3A (ARCL3A), also known as de Barsy Syndrome A, is linked to *ALDH18A1* (chromosome 10q24.1). *ALDH18A1* codes for Δ^1 -pyrroline-5-carboxylate synthase (P5CS), which is necessary to produce amino acids proline, ornithine, and arginine. ARCL3A is another mitochondrial enzyme associated with corneal clouding, wrinkled skin that lessens with age, joint laxity, intellectual disability, global developmental delay, joint dislocations, and seizures. Symptoms present soon after birth (Bicknell et al., 2008).

Autosomal recessive cutis laxa type 3B (ARCL3B) is also called de Barsy Syndrome B. Like ARCL2B, mutations in *PYCR1* also cause this subtype. Like ARCL2A, this condition is also associated with corneal clouding, as well as joint laxity, thin and translucent skin, intrauterine growth restriction, microcephaly, intellectual disability, and bone fragility (Dutta et al., 2016). There has also been a reported case of aortic root dilation (Lin et al., 2011).

RIN2 (chromosome 20p11.23) is linked with RIN2 syndrome, also known as MACS syndrome (Basel-Vanagaite et al., 2009). *RIN2* encodes the Ras and Rab interactor 2 protein. RIN2 syndrome was initially called MACS syndrome due to its association with Macrocephaly, Alopecia, Cutis laxa, and Scoliosis. The condition is also sometimes associated with joint laxity, swollen facial appearance, mild intellectual disability. RIN2 syndrome is autosomal recessive and has onset during adolescence or adulthood (Aslanger et al., 2014).

Geoderma osteodysplasticum (GO) is caused by loss-of-function variants in *GORAB* (chromosome 1q24.2) (Hennies et al., 2008). Mutations in *GORAB* interfere with protein trafficking and glycosylation of secretory cargo protein (Witkos et al., 2019). GO is chiefly associated with osteoporosis and premature wrinkly skin, and can also include other dysmorphic

features like maxillary hypoplasia, drooping or sagging cheeks, and increased palmar creases (Kariminejad et al., 2017). Like RIN2 syndrome, GO is autosomal recessive. However, the onset of this condition can be as early as infancy (Newman et al., 2008).

2.1.3 X-Linked Recessive Cutis Laxa

Occipital Horn Syndrome (OHS) causes cutis laxa and is linked with mutations in *ATP7A* (chromosome Xq21.1), which encodes a type of ATPase involved in copper transport. Mutations in *ATP7A* that cause OHS typically do not result in total loss of protein product, but either partially functional protein product or reduced amount of functional protein (Tumer, 2013). *ATP7A* variants with little to no residual protein activity result in a more severe condition called Menkes disease (Tumer, 2013).

In addition to lax skin, OHS is characterized by occipital horns (calcium deposits on the occipital bone) and short, broad clavicles. OHS can also include distinctive facial features (hooked nose, long philtrum, high forehead, long neck), chronic diarrhea, genitourinary abnormalities, osteoporosis, and borderline intelligence (Tsukahara et al., 1994). Onset of OHS occurs in childhood and the long-term prognosis of the condition is unknown due to its low prevalence (Kaler, 2011).

2.1.4 Acquired Cutis Laxa

There are two types of acquired cutis laxa. Type I acquired cutis laxa typically has onset during adulthood and can be triggered by several different types of medications, diseases, or environmental exposure; the mechanism and genetic etiology for acquired cutis laxa remain

unclear (Paulsen, Bredgaard, Hesse, Steiniche, & Henriksen, 2014). Loose and inelastic skin usually appears on the face first. Like inherited types of cutis laxa, there can be nondermatological findings: emphysema, intestinal diverticula, hernias, and vascular dilations (Berk et al., 2012).

Type II acquired cutis laxa is also known as Marshall syndrome and typically has onset in early childhood. The condition initially presents with extensive inflammatory skin papules covering the body, which then gives away to the loose and wrinkled skin phenotype (Haider, Alfadley, Kadry, & Almutawa, 2010).

2.1.5 Treatment for Cutis Laxa

Currently, no cure for cutis laxa exists (Mohamed, Voet, Gardeitchik, & Morava, 2014). People are generally born with the amount of elastin that they need for their lifetime and generally do not produce more as they age (Duque Lasio & Kozel, 2018). Treatment for cutis laxa is mainly symptomatic. Cosmetic surgery is possible to address the distinctive skin appearance with cutis laxa, but it generally does not have a lasting impact. People with supraaortic stenosis or aortic root dilation can undergo surgery to manage the condition before it becomes life-threatening. Early onset emphysema is also treated on a symptomatic basis. People with cutis laxa can consult with a variety of specialists, including dermatologists, cardiologists, pulmonologists, geneticists, gastroenterologists, and more. There are currently no active clinical trials for people with cutis laxa, although one clinical trial was completed in 2020 in University of Warsaw to investigate the use of mesenchymal stem cells to treat the dermatological symptoms of cutis laxa.

2.1.6 Resources Associated with Cutis Laxa

There is one international patient support organization dedicated to individuals with cutis laxa, Cutis Laxa Internationale (<https://www.cutislaxa.org/en/>), which runs a private but active Facebook group. There are general overviews of cutis laxa on several major medical and genetic online resources: Medscape, Orphanet, Healthline, and Genetics Home Reference. The subtypes are summarized on Online Mendelian Inheritance in Man (OMIM) (OMIM, n.d.) as well as the webpages of National Organization for Rare Disorders (NORD) (NORD, n.d.) and the University of Pittsburgh Cutis Laxa Research Study (Zsolt, 2020). Despite these resources, there are major gaps. There are no ICD-10 codes specific to cutis laxa. UptoDate, a major resource for medical providers that aggregates literature reviews of diseases, does not have a page on cutis laxa. GeneReviews, another resource that provides literature reviews of genetic disorders, has specific pages for four different types of autosomal recessive cutis laxa, but not the other kinds.

Table 2: Resources Associated with Cutis Laxa

<p>Patient Organizations</p> <ul style="list-style-type: none">• Cutis Laxa Internationale ("Patients Worldwide," 2019) <p>Informational Websites (general overview of cutis laxa)</p> <ul style="list-style-type: none">• Genetics Home Reference ("Cutis laxa," 2017)• Healthline (Nall, 2017)• Medscape (Handler, 2017)• Orphanet (Orphanet, n.d.) <p>Informational Websites (reviews of specific subtypes of cutis laxa)</p> <ul style="list-style-type: none">• GeneReviews (incomplete)<ul style="list-style-type: none">○ <i>ATP6V0A2</i>-Related Cutis Laxa (Autosomal Recessive Cutis Laxa Type 2A) (Van Maldergem, Dobyns, & Kornak, 1993)○ <i>FBLN5</i>-Related Cutis Laxa (Autosomal Recessive Cutis Laxa Type 1A, Autosomal Dominant Cutis Laxa) (Van Maldergem & Loeys, 1993)

Table 2 Continued

<ul style="list-style-type: none">○ <i>LTBP4</i>-Related Cutis Laxa (Autosomal Recessive Cutis Laxa Type 1C) (B. L. Callewaert & Urban, 1993)○ <i>EFEMP2</i>-Related Cutis Laxa (Autosomal Recessive Cutis Laxa Type 1B) (Loeys, De Paepe, & Urban, 1993)● Online Mendelian Inheritance in Man (OMIM, n.d.)● National Organization for Rare Disorders (NORD, n.d.)● University of Pittsburgh Cutis Laxa Research Study (Zsolt, 2020)
--

2.2 Rare Diseases

2.2.1 Introduction to rare diseases

In the United States, the Orphan Drug Act defined an “orphan disease” (or rare disease) as a condition that affected less than 200,000 people in the U.S. (Wellman-Labadie & Zhou, 2010) or no more than 1 in 1250 people (Schieppati et al., 2008). The European Commission of Public Health defines rare diseases as debilitating conditions that have a prevalence of less than 1 in 2000 (Health, 2009). The majority of rare diseases are debilitating, chronic, and have an early onset (Mascalzoni, Petrini, Taruscio, & Gainotti, 2017). Mascalzoni et al. argue that solidarity amongst people with rare diseases, both with the same disease or phenotype and simply those who are bonded by the rare nature of the disease, is essential to driving further research across the board (2017). The paper argues that because by their very nature, rare diseases affect less people, and thus have less focus on drug research and undergo more difficulty in health policy development. Rare diseases consist of a heterogenous group of conditions, face delays in diagnosis, and have limitations in research and available treatments (Schieppati et al., 2008). This results in specific and unique challenges to the public health systems across different countries.

There have been several initiatives targeted towards the rare disease population. One of the earliest is the Orphan Drug Act of 1983 in the United States, which provided incentives to the pharmaceutical industry to create drugs for populations that impact fewer than 200,000 patients. Between 1983 and 2018, 503 new therapies for rare diseases have been developed (Thomas & Caplan, 2019). As of 2017, there are 23 countries across North America, Latin America, Europe, and the Asia-Pacific area with either a national plan, strategy, or program specifically for rare diseases (Khosla & Valdez, 2018).

There are also several organizations dedicated to rare disease populations, like the National Organization for Rare Diseases in the United States, and multiple databases to assist with diagnosis and management, like DataGenno, Eurodis, FindZebra, GeneReviews, OMIM, Orphanet, PatientsLikeMe, and Phenome Central (Pogue et al., 2018).

2.2.2 Epidemiology of rare diseases

Rare diseases, while individually uncommon, collectively may impact up to 10% of the population (Pogue et al., 2018). In total, they may impact nearly 400 million people worldwide (Jia & Shi, 2017). The prevalence of rare diseases in the general population has increased and is expected to continue to do so due to new discoveries of rare diseases every year and advancements of molecular technologies like whole exome sequencing and whole genome sequencing (Pogue et al., 2018) (Ferreira, 2019). Eighty percent of these diseases are genetic (Baynam et al., 2017). While estimates vary, researchers estimate there are between 5000 and 8000 unique rare diseases (Ferreira, 2019). In a review article that focused on childhood rare diseases, researchers found that nearly half of people with rare diseases in the United States had to travel more than 50 miles for medical services; in Europe, half of people with rare diseases had to travel to a different region to

access services or they could not access them at all (Zurynski, Frith, Leonard, & Elliott, 2008). Rare diseases are collectively highly prevalent because they affect hundreds of millions of people around the world, but there are barriers to appropriate medical care and services because of the distribution of these resources.

It can be difficult to ascertain the epidemiology of rare diseases. To use mitochondrial diseases as an example, many of these conditions have variable clinical presentations, non-specific features, invasive or highly specialized methods of diagnosis, and complex referral patterns; all of these factors make it difficult to conduct an epidemiology investigation (Chinnery & Turnbull, 2001). Many other types of rare diseases also share these qualities and thus face similar difficulties.

2.2.3 Quality of life for patients and families with rare diseases

In a French qualitative study based on semi-structured interviews, Caroline Huyard interviewed patients or parents of patients with six different rare diseases, which in this study were diseases with a prevalence of less than 5 in 10,000 (C. Huyard, 2009). Many of the participants stated that they understood limitations to diagnosis, information, and availability of a cure when it came to their specific rare disease. The source of their frustration arose from the inability of their medical providers to admit their limits and refer to another specialist, poor disclosure of the diagnosis by their medical provider, or feeling that their medical provider did not take their symptoms or perspectives seriously. Participants in the study also stated the importance of the medical providers providing actionable guidance about day-to-day living with a condition, even when knowledge about the disease is limited. The majority of participants also expressed the desire to meet other people in the same situation and emphasized the need for an association related to

their disease. The study found that patient experiences and expectations of medical providers were overall similar, despite the patients having different rare diseases (C. Huyard, 2009).

In a survey conducted on patients and caregivers of those with rare diseases by Network of Public Health Institutions on Rare Diseases (NPHIRD) across France, Italy, Romania, Spain, Turkey and the United Kingdom, respondents indicated that they perceived their access to healthcare to be lower than average (Kodra et al., 2007). NPHIRD also reported that the most common positive experience across all patients and caregivers was the helpfulness and kindness of medical providers. This emphasizes the importance of attitude and support of medical providers for people who have rare diseases.

A qualitative study conducted with organizational representatives of patient groups associated with inborn errors of metabolism (IEM) explored patient experience living with a particular subset of rare disease (Khangura et al., 2016). Inborn errors of metabolism are diseases associated with defects in key enzymes that process or break down essential biochemicals such as amino acids, lipids, and sugars or nucleotides. The study interviewed 18 representatives from Canada, United States, and the United Kingdom; 12 of these representatives were either people who had an IEM or were parents of a child who did. The participants described the great deal of uncertainty associated with diagnosis, prognosis, and mortality. While participants recognized that their medical providers could not be experts on all rare diseases, they stated that they perceived uncertainty and lack of knowledge from their providers. This in turn caused patients to find other ways to cope with their anxiety stemming from uncertainty, which included gathering knowledge about the disease from other sources, meeting with other affected families, and educating others. This indicates that patients with rare diseases have the burden of looking for resources outside of the scope of their medical providers or their healthcare system (Khangura et al., 2016).

Another study conducted by the Health Sciences Research Group from the University of Manchester conducted a qualitative study amongst U.K. patients with another group of rare diseases: progressive ataxias (Daker-White et al., 2015). Amongst its findings, the study noted that some patients did not find a diagnosis to be helpful when there was no treatment or cure available, and when it compounded the uncertainty surrounding potential symptoms. While other studies have shown that adult patients often have a sense of relief with a diagnosis after a long diagnostic odyssey, this is not always the case (Dudding-Byth, 2015). In addition, patients in this study expressed frustration with the lack of the information given by providers and the perceived lack of knowledge on ataxias even amongst expert specialists (Daker-White et al., 2015). The study noted that the “perceived failure of the medical system” increased the anxiety already present from the uncertainty associated with a rare, under-studied disease.

Some studies have also shown that medical providers feel that their education on rare diseases is lacking. In a study that surveyed 295 Belgian doctors, general physicians showed a lack of knowledge about rare diseases compared to specialists and that most doctors, regardless of specialties, had specific information needs for their rare disease patients (Vandeborne, van Overbeeke, Dooms, De Beleyr, & Huys, 2019). Another survey conducted among 169 physicians in Spain also demonstrated that both primary care physicians and specialists lacked training and knowledge in rare diseases (Ramalle-Gómara et al., 2020).

2.2.4 Measuring depression in patient with rare diseases

Quality of life and mental health are not synonymous, but rather mental health is a component of the larger definition of quality of life, which is a term that describes holistic physical, mental, and social well-being (Post, 2014). Therefore, measuring depression in people with rare

diseases can provide another window of insight into the overall quality of life of those populations despite not being a perfect proxy.

There have also been some limited studies on the relationship between rare diseases and depression. The first study, published in 2019, surveyed 300 patients with rare diseases in Germany and found that people with rare diseases and a high symptom burden were more likely to have depression or anxiety (Uhlenbusch et al., 2019). This study used the German version of the Patient Health Questionnaire-9 to measure depression.

There are several different survey tools to measure depression amongst participants. The Beck Depression Inventory is one such tool that has been validated with across different populations, including those with different medical conditions (Richter, Werner, Heerlein, Kraus, & Sauer, 1998) (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961). Other survey tools include the Patient Health Questionnaire-9 (Kroenke, Spitzer, Williams, & Löwe, 2010), Hospital Anxiety and Depression Scale (Snaith, 2003), Zung Self-Rating Depression Scale (Zung, 1965), and Center for Epidemiologic Studies Depression Scale (Radloff, 1977).

2.2.5 Challenges of having a disfiguring disorder

In addition to its rarity, cutis laxa is also notable for its distinctive facial appearance (loose or inelastic skin that looks prematurely aged). People who have a disfiguring disorder or a condition associated with an atypical physical appearance can face additional, unique burdens. In a survey of adults who were outpatients with appearance-altering conditions at an Italian dermatological hospital, researchers found the psychiatric morbidity of their condition to be approximately 25% amongst 2579 respondents, which is two to three times greater than the general population of Western countries (Picardi, Abeni, Melchi, Puddu, & Pasquini, 2000). A cross-

sectional study which looked at severity of symptoms and health-related quality of life amongst patients with a range of dermatological disorders found that the relationship between the severity of symptoms and psychosocial burden varied with the disorder, but generally increased with the severity of symptoms (Sampogna, Tabolli, Giannantoni, Paradisi, & Abeni, 2016). Overall, dermatologists have noted that because psychiatric comorbidity can be associated with at least 30% of their patients, dermatologists have a role in assessing psychopathology of their patients (Gupta, Gupta, Ellis, & Koblenzer, 2005).

The stress of having a “visible” disease can be seen with other patients who also have rare diseases in which there is an extra-dermatological burden. Neurofibromatosis type 1 (NF1) has a prevalence of 1 in 3000 and can be associated with visible plexiform neurofibromas. A study of 228 patients with NF1 given multiple surveys evaluating psychological stress, body image, and psychosocial burden. found that people with NF1 had more negative body-image issues and were more likely to have distress or lower quality of life compared to people with other dermatological disorders. This study in particular compared patients who have NF1 to patients who have psoriasis; researchers postulated that the poorer body image in patients with NF1 may be because NF1 is less well-known and thus less socially accepted compared psoriasis (Granstrom, Langenbruch, Augustin, & Mautner, 2012). This demonstrates the intersection of having a rare condition as well as a visible one; there are unique stressors like lack of societal acceptance.

People with a disease that modifies appearance can face social stigmatization, which can also lead to a reduced quality of life. The level of social stigmatization can vary depending on the type and location of the skin lesion as well cultural setting. In some societies, like in Afghanistan or Pakistan, people with visible skin disorders can be isolated to their own homes and rejected by their families (Dimitrov & Szepletowski, 2017). Dimitrov and Szepletowski also note that this

isolation can prevent people affected by skin disorders from obtaining jobs or being eligible for marriage, disrupting the typical expected life course of a person and resulting in a higher rate of psychiatric morbidity. In a survey conducted amongst people in the Netherlands who developed vitiligo, a condition that results in the loss of skin pigment in patches, people who developed the condition in their childhood had lower health-related quality of life (HRQL) compared to healthy controls, with negative childhood experiences showing an association with lower HRQL (Linthorst Homan et al., 2008).

This social stigmatization can be compounded by the feeling of not receiving adequate support from medical professionals. In another survey, the majority of respondents with vitiligo reported that they received most of their information about their condition from nonmedical resources rather than their own dermatologist (Elbuluk & Ezzedine, 2017). Medical providers may not choose to be purposely ignorant of or deny information to their patients about rare conditions, but this situation nevertheless results in perceived increased isolation and systematic challenges to already burdened patients.

In another study involving semi-structured interviews with people with systemic lupus erythematosus (SLE), participants discussed their dissatisfaction with their healthcare providers being unable to understand the psychosocial challenges that came with the disease and the perception that physicians felt uncomfortable discussing body image and their disease. Like other studies on people with similar conditions, appearance had an impact on depression and anxiety rates amongst people with SLE (Hale, Radvanski, & Hassett, 2015). The study indicated this could also impact the ability of patients and doctors to communicate effectively with one another and impact treatment adherence. This emphasizes the importance of having a trusting, open

relationship with the healthcare provider – both for medical treatment and for overall quality of life.

2.3 Objectives

Rare diseases are known to be a growing public health (Valdez, Ouyang, & Bolen, 2016). Cutis laxa is one of the 5000 to 8000 rare diseases that have been identified so far (Ferreira, 2019). The causes of cutis laxa are diverse, there is variety in presentation between and within subtypes, and there are limited resources specifically devoted to this population. Rare diseases and diseases which change appearance can sometimes have a major impact on mental health or quality of life (Uhlenbusch et al., 2019) (Picardi et al., 2000).

This project is a qualitative study that will consist of interviews with adults with cutis laxa. The interview questions will cover the following topics: the process of diagnosis, medical management and care, availability of resources, and sources of support for people who live with the disease. As far as this author knows, this will be the first qualitative study that will focus on experiences and quality of life of people with cutis laxa. There have been other studies of this kind that have involved people with different diseases.

3.0 Manuscript

3.1 Background

3.1.1 Cutis Laxa

Cutis laxa is a rare connective tissue disorder characterized by loose or inelastic skin as well symptoms in other body systems depending on the subtype (Berk et al., 2012). Cutis laxa is associated with 11 different genes as well as an acquired form with a typically later age of onset (Urban & Davis, 2014). There are about 200 to 400 families who are documented to have cutis laxa ("Cutis laxa," 2017). Most types of cutis laxa are not associated with a particular race or ethnicity, aside from specific communities that have a higher prevalence in some autosomal recessive subtypes due to high consanguinity and founder effect (Kaiser, 2016). Penetration can be variable and symptoms can vary between subtypes, ranging from being limited to inelastic skin to internal organ anomalies to early death in childhood. Cutis laxa can be diagnosed through skin biopsy or through genetic testing. Cutis laxa has no cure; treatment is principally symptomatic (Mohamed et al., 2014).

Cutis Laxa Internationale is the single associated international support organization for cutis laxa. This organization also moderates the online community through its Facebook group.

3.1.2 Rare Diseases

The definitions for rare disease vary across countries; the Orphan Drug Acts in the United States define it as a condition that affects less than 200,000 people or no more than one in 1250 people (Wellman-Labadie & Zhou, 2010). In total, rare diseases impact up to nearly 400 million worldwide (Jia & Shi, 2017). Eighty percent of rare diseases are genetic. The majority of rare diseases are debilitating, chronic, and have an early onset while their rarity limits health policy development and research (Mascalzoni et al., 2017). Furthermore, features of even individual rare diseases, like highly specialized diagnosis processes, complex referral patterns, variable and non-specific features can make it difficult to conduct epidemiological investigations (Chinnery & Turnbull, 2001). Rare diseases are difficult to diagnose, track, conduct research upon, and are collectively heterogeneous. However, together they impact a large portion of the global population.

Furthermore, people with rare diseases face limitations in getting a diagnosis, obtaining appropriate medical care, and finding knowledgeable medical providers (C. Huyard, 2009). Having a diagnosis does not always bring catharsis, particularly when there is no cure available, there is a dearth of information about the condition, and there is anxiety surrounding potential symptoms. People with rare diseases also desire and appreciate positive interactions, like a show of empathy, from their medical providers (Kodra et al., 2007). However, the lack of knowledge amongst their providers can result in uncertainty and anxiety. In turn, people with rare diseases often cope by gathering knowledge on their own and connecting with other people with the same condition (Khangura et al., 2016).

This in turn raises the question of whether people with cutis laxa share the same struggles and concerns of other people with rare diseases. There have been no studies thus far that explore

the experiences of people with cutis laxa. Thus, the goal of this study is to explore the concerns, challenges, and experiences of people with cutis laxa, particularly as they navigate their healthcare.

3.2 Methods

3.2.1 Study Design

The study was comprised of semi-structured interviews with people living with any subtype of cutis laxa. The prepared questions were focused on the participant's journey in diagnosis and treatment (see Appendix C for question list) The interviews were conducted and recorded through Skype for Business, using only audio. The audio was saved on the student researcher's university Box account and subsequently transcribed by the student researcher onto Microsoft Word Online on the same Box account. Skype for Business and Box were chosen based on the level of security and privacy they offered. The study was approved by the University of Pittsburgh IRB under the number PRO19100357 (See Appendix A).

3.2.2 Recruitment

Recruitment of participants was conducted through the Cutis Laxa Internationale Facebook community page, an online forum for people with cutis laxa and their family members from around the world. The Facebook group has 306 members as of the summer of 2020. The administrator of the group posted the study's recruitment script first on January 21, 2020 and again on March 9, 2020 (see Appendix B for recruitment script). Inclusion criteria for participation were the

following: over 18 years old, have a diagnosis of cutis laxa, ability to speak English, and ability to use Skype. Interested parties were able to reach out to cutislaxa@pitt.edu to enroll in the study. Appointments to review the consents and conduct the interview were agreed upon via email. Consents documents were then reviewed over the phone or through Skype Business upon appointment, and participants scanned and emailed back their signed documents. Recruitment was meant to end in mid-April, but the 2020 COVID-19 pandemic resulted in closure of the Pitt Public Health facilities, essentially terminating recruitment on March 20, 2020.

3.2.3 Data Analysis

The student researcher coded the transcripts and compiled a codebook on Microsoft Word Online. During the process of transcribing and coding, the student researcher took notes on findings and patterns that appeared to be recurrent. After coding, the student researcher compiled the quotes of each of the codes across the participants, along with notes taken during the process, into memos that provided an overview of each code. After reviewing the memos and taking further notes on each code and how they related to other codes, key patterns were identified through an inductive approach (Braun & Clarke, 2006). These patterns were then organized into a grid of themes and subthemes.

3.3 Results

3.3.1 Participant Demographic Information

After the posting the recruitments scripts on the Cutis Laxa Internationale Facebook group, 10 people expressed interest in participating. Two interested parties were lost to follow-up. Two more potential participants withdrew after expressing interest or completing the consent due to life circumstances that required immediate attention. Thus, in total, six participants were interviewed.

All the participants self-identified as Caucasian and reside in the United States. Three of the participants were men and three were women. The ages of the participants ranged from 18 to 73. All except one were over the age of 40 and diagnosed in adulthood. Two of the participants had acquired cutis laxa. One participant had autosomal dominant cutis laxa. One participant had autosomal recessive but did not recall which subtype because they had undergone genetic testing as a young child. Another participant had been diagnosed by skin biopsy; they have another genetic condition and suspected to have Occipital Horn Syndrome. The final participant is currently in process of being diagnosed; their genetic testing identified variants in *LTBP4* and *RIN2*, each associated with ARCL1C and MACS syndrome respectively. Of the four with monogenic form or suspected monogenic forms of cutis laxa, three have undergone genetic testing. The fourth was diagnosed via skin biopsy.

3.3.2 Themes

Based on the six interviews, the researcher identified three overall themes related to the participants' experiences living with cutis laxa. The first theme is rare disease in healthcare,

covering their interactions with and perceptions of their medical providers and their healthcare system as patients with a rare disease. The second theme is living with uncertainty, which includes concerns about their health and their responses to those concerns. The third theme is patient response, which encompasses the actions and responses the participants have undertaken as a result of living with cutis laxa.

Table 3 Theme Chart

Themes	Subthemes
Rare disease in healthcare	Lack of knowledge and coordination amongst providers
	Concern about having symptoms taken seriously
	Provider engagement or lack thereof
	Ill-designed for rare disease patients
	Genetics
Living with uncertainty	Anxiety about potential symptoms
	Greater awareness of health
	Desire for preventative and consolidated care
	Comfort in good facilities
	Comfort in community
Patient Response	Willingness to travel further to see providers
	Educating others, including providers
	Self-advocacy
	Interest and engagement in research

Note that direct quotations are in italics. Quotations in bold italics refer to when the interviewer is speaking. Phrases in brackets are edits or inserted clarifications made by the researcher. The identification following the quotes distinguishes the participant. Some quotations do not have an identification code to obfuscate the identity or potentially distinguishing characteristics about the participants.

3.3.2.1 Rare Disease in Healthcare

The participants discussed how being a patient with a rare disease impacts how they navigate and perceive their medical care. They recognized that these experiences as typical of people with rare diseases and distinct from people who do not have a rare disease.

The first, and most ubiquitous, subtheme was the lack of knowledge and coordination amongst the participants' medical providers as well as lack of resources in their healthcare systems due to the rarity of cutis laxa. Every participant discussed having medical providers with limited or no understanding of cutis laxa.

Even very specialized dermatologists may have seen...they told me they may have read about one case in medical school, never having even seen it. If you look at the stats of the patients versus the general population, that would be totally be true. QCL8

There's not too many people at all even in the world that understand this. I mean, I think probably Dr. Urban and some of the group. They're one of the very few. QCL1

For individual, for more specific issues, they've always been incredible, but I think it has been a little bit hard with finding somebody who understands cutis laxa and other issue that they're working on, can be hard because it's just so rare. I think my primary care doctor is phenomenal but definitely doesn't have much of any knowledge about it. I think I have often explained to her what it is, and the best to my knowledge of what it affects. QCL5

Participants contextualized cutis laxa amongst other less rare, but still uncommon, connective tissue disorders. They spoke about cutis laxa being rare even amongst the rare.

And there aren't many physicians that understand rare diseases in general and certainly in connective tissue disorder cutis laxa would not be on their radar anyway. They would know about Marfan probably but that will probably be the most common one that they would know about. QCL4

The only connective tissue that anyone seems to know about is Marfan and anything else no one seems to know anything about it. [laughs]. QC9

This lack of knowledge is compounded by the lack of coordination between specialists. This is a concern for patients with cutis laxa, who can have issues in multiple body systems, and therefore require some guidance on which providers they should see. This lack of coordination can limit the ability of a person with a rare disease to have a comprehensive view of their own health and resulted in a more fragmented understanding.

You know, really it would more of a question, 'is there any consolidated resource available that I could point providers to before my appointment. QCL10

I think healthcare system, it would be nice to have things a bit more connected. So, like, I don't know, sometimes it feels a little bit disjointed where something like, like might fall under the purview of two different doctors and I have to just guess which one I go to. It might be helpful in an ideal medical system to be more connected so you're not trying to figure things out in multiple different sources. QCL5

Participants also described having a dearth of resources within the medical system.

Okay. Are there any particular resources or services? So not necessarily a doctor, but a resource or service within your healthcare system that you have found helpful?

[laughs]

It's okay if the answer is no.

Yeah, really, not a whole lot. QCL9

Despite expressing these frustrations, participants also recognized that this lack of knowledge is tied to the rarity of cutis laxa and that this is a challenge for their healthcare systems.

And what are your expectations for an ideal medical provider and/or healthcare system?

You know, I...I don't know. I feel like, you know, like I've said that nobody knows anything about it. But at the same time I don't know, is it reasonable to, you know, to have physician trained to identify this. I don't even know if that's reasonable with it being so rare. I mean I do understand that maybe it's not, you know, spent any time or a lot of time spent on it because most people will never see it. It's hard. I do, I kind of understand it. For my own sake, I wished more people did QCL9

The concern about having their symptoms taken seriously was another major subtheme. In addition to the challenge of finding knowledgeable and experienced providers, the majority of

participants spoke either about the stress of not being taken seriously by their medical provider or emphasized the importance of being taken seriously as patients.

Like sometimes I'm worried that I'm just like being a hypochondriac or exaggerating an issue but I think ultimately the most important thing they can do is take whatever fear it is seriously and understand it can, it could be the bad route or like the bad expectation and I think that taking whatever concern it is seriously. QCL5

This concern is tied to the next subtheme, provider engagement or lack thereof. While they may expect that their providers might have a lack of knowledge or experience, participants also appeared to judge their medical providers on their willingness to learn about cutis laxa, listen to their concerns, or help them in their diagnostic journey. When discussing poor impressions of their medical provider providers, participants discussed their providers outright dismissing their diagnosis or symptoms, as well as being unwilling to learn or lumping all connective tissues disorders together.

A doctor wants to be the one to find something and if they didn't find it, they still question it. And since this is something not many doctors know about, I think it causes not so much maybe confusion, but I think they're very hesitant to make any diagnosis or any ... pretty much have any involvement because they don't know enough to put their two cents in. QCL10

Yet from that point forward, she said that "I have no experience with this.

You're going to have to find someone who does and work with a

rheumatologist.” So, my relationship has not been good with the medical provider QCL8

But at the same time, they just kind of like - “oh you know, there’s all those connective tissue disorders. There’s a million of them.” They don’t really pay a lot of attention to that piece of it. QCL9

On the other hand, participants had positive opinions about medical providers who were willing to learn about the condition or appeared to make any effort, even if they were not knowledgeable.

When I originally started seeing all my doctors, my parents had to explain what it was and when I became a regular patient, a lot of them took it upon themselves to learn more about it. QCL5

He didn’t even sound like he knew an awful lot about it but at least he tried. QCL1

I give a lot of credit to the dermatologist who did excuse herself from the appointment and actually go and google these, this elastin loss issues. She started mid-dermal elastosis and followed the word elastolysis and only then she ordered her pathologist to do the correct stain. So, the relationship I have with her, I have some respect for her. QCL8

The next subtheme, the healthcare system not being designed for patients with rare disease, represents the participants’ perspectives on their medical care on a systemic level. One common

point was simply how short most appointments are and how little time they have to communicate with the physicians face-to-face, which is not conducive for patients with multiple or complicated concerns.

I guess they try to be supportive and uh...it's...it's...they usually allocate 15 minutes to half an hour per person. And I used to go in for a visit and it's like...I'd say this, this, and this problem. And they're like, "well let's focus on this one thing first." [coughs] It's like that-that doesn't work with people that have a whole bunch of problems. It really doesn't. They end up – they let my cholesteatoma go so long. They...you know...[coughs] pardon me. I mean, sure, that works with the average Joe, it doesn't really work with rare patients. QCL1

They don't really have-it's the typical 10- or 15-minute visit. You're in, you're out. I can tell it's not something they're comfortable spending a lot of time on.

QCL4

Another common point amongst participants was the feeling that the healthcare was routine and like an “assembly-line”. This is meant to be efficient and economical for a broad scale of patients, but not suited for patients with unique needs.

Ideally, it would be somebody that I be in contact with without having to see them face to face. So I could send them a text or email and get a reply back.

Someone that genuinely makes me feel that that their whole purpose being in the medical profession is to make sure that I live the best life I can by being as medically sound as possible. I think I feel more like a spoke in the wheel, or a

piece of a part of the assembly line that they just have to get through instead of feeling like they want to help me be the healthiest I can be. QCL10

It's just hard to get anybody to understand that things aren't going to work the same way on me as they do other people. [...] Just, you know people just want to do robot factory work and you know, they've got this one thing that works for the majority of the patients and they do that. Yeah, they're just not knowledgeable about this. QCL9

As it gets closer, I will want to spend a lot more time with the surgeon who gets assigned to me to educate them on the connective tissue since I have very soft tissue. I'm not going to be like anyone else. That doesn't mean the surgery won't go the normal way but I just know that from having soft skin and having all the things - and all the things from the last sixteen, they need to do a little more research. QCL4

Conversely, a participant who had positive interactions with their medical providers describes and emphasizes the importance of being seen as a person.

I think that medical provider is caring a lot about the people they are treating more than just the disease and disorder so I don't know, remembering things about patients and knowing where they are at in life and stuff like that. QCL5

The final subtheme is genetics. Some of the participants discussed their interactions with medical genetics providers. This is related to the patient-provider relationship, but because the medical genetics professionals are more likely to interact with people with rare diseases, the researcher chose to place these interactions in a separate category. Two of the participants, one

with a monogenic form with cutis laxa and one with an acquired form of cutis laxa, described feeling dismissed when encountering medical genetics professionals. While a medical genetics professional may have had limited suggestions, particularly for someone with an acquired form of cutis laxa, both participants focused on how they were made to feel by the genetics departments.

And the genetic departments just dug their heels and said that we'll wait-well, you're in this study [another cutis laxa research study], we'll wait for the study. They didn't want to do anything at all because I guess...I'm not...like one of those little kids that are falling over or something. They don't want to do anything. QCL1

I even went to see a geneticist. I don't know there's any genetic link to my condition, yet he was extremely dismissive. QCL8

Only one participant, one with a monogenic form, brought up genetic counselors and described them as an informative resource.

If you want to get more detailed information, you pretty much have to go to a genetic counselor. They'll take the time to work with you to figure out what's going on. But most people don't know to go there. And a lot of hospitals don't even have genetic counselors. QCL4

3.3.2.2 Living with Uncertainty

When participants discuss living with cutis laxa, they characterize it by a feeling of uncertainty and anxiety. The main source of this anxiety comes from potential symptoms. Participants expressed concern and uncertainty about potential symptoms that could arise due to

cutis laxa. Some of the participants related these negative feelings to past or ongoing medical issues.

I think I sometimes get nervous that they are going to do a checkup and find something bad. I think that that's probably an area where cutis laxa has impacted my life a lot. I just get nervous that there's always something bad that can come next. I think that before I see them, I get anxious about it, but I don't think that's so much their fault as a memory of times when the diagnoses were not good and being afraid that will come again. QCL5

Do you think your life is different because you have cutis laxa or nothing really has changed since you've gotten cutis laxa?

Not yet, but I fear it's going to be. I've had some, a lot, of issues over the past several months. And now with the cutis laxa diagnosis some of the stuff falls into place. I'm really worried, I'm waiting on test results to come back from an oncologist. But I've been coughing up blood and a lot of mucous. The blood has stopped but-I now worry about COPD, emphysema, lung issues, so, um, yeah. So as far nothing in the immediate right now has changed other than just taking it day by day. QCL10

Another participant echoed this anxiety and uncertainty when discussing their diagnostic journey. Even in the absence of major medical crises related to their diagnosis, the potential for major symptoms were still a concern.

But I think for a lot of cutis laxa patients, there's the obvious appearance of aging. That's not a really big thing with me. It's more of the process of finding

why my skin is changing to this degree and why I'm feeling off and is there is a much larger medical concern driving this or not. So that was really took me down psychologically during that time period. QCL9

This anxiety about symptoms is related to another subtheme, which is a greater awareness of the participants' own health, including perceiving themselves to be different in some way.

I've been going to [another syndrome] conferences for years and meeting lots of other women with [another syndrome], I could see differences. I always felt a little different and looked a little different QCL1

You've got this mysterious skin condition. You know that something's wrong and there's no confirmation of that. And it's a very uneasy way to live daily life.

QCL8

Two of the participants mentioned feeling almost as if they were “hypochondriacs” due to having multiple health issues.

It feels like these things kind of snowball. I've got multiple things happening at the same times. That's kind of a frustrating issue. It makes you feel, kind of like a hypochondriac when multiple seemingly different, wholly different things are going on at the same time. QCL9

As a response, some participants mention making general lifestyle changes to improve their overall health.

So I would say that I've tried to eat better, stay away from outside toxins and uh I would try and reduce my stress once I got a handle on what's going on with me medically. My stress level has been up and down because of all this. QCL10

Anxiety about potential symptoms is also connected to another subtheme: the desire for more preventative care and more consolidation of care that they have. This was a concern for people who were new to their diagnosis as well as living with their diagnosis throughout their lives.

I need more suggestions and more evaluation and more ideas of what I can do to improve my condition QCL1

I do not feel supported at all. I am, I literally am running from one specialty to the next to fix the immediate problem causing me the most pain or is the most symptomatic. Nobody's treating me as a whole or doing consolidated healthcare for me. I have been my own advocate for my entire life. QCL9

I would hope that there would be some kind of, almost like algorithm or something that once you get a diagnosis, it will kick something back to your doctor, "okay this person needs to be seen by a pulmonologist, cardiologist, dot dot dot." These are things that will need to be monitored and kept a close eye on so I don't have to go and chase this stuff down and keep an eye on it myself. Of course I would, I care more about me than anyone else. But I just wish there was some better protocols or outlined procedures that need be maintained or met, I guess. QCL10

When asked about what resources patients with cutis laxa should have, participants specifically suggested things that would provide more guidance in their care and increase accessibility to preventative care.

If they had a rare condition desk or nurses that were devoted to that, helping the patients you may have. QCL1

I think, I think it might be kind of helpful if they had a list of here's the type of doctors that you'll probably need to see and it's helpful to get set up with them early because I had, I feel like I have found most of my doctors as an issue comes up, I think have to find someone and get scheduled with them and all of that. I think it may have been helpful to have an understanding of all the things that could come up so I could like preemptively know that like this might affect my lungs rather than it being a surprise and I have to scramble to find a doctor to check in on that. QLC5

One participant pursued receiving an official diagnosis to ensure they would receive appropriate management for symptoms they had been living with for years. Before this, one of their doctors gave them an unofficial diagnosis of “mixed connective tissue disorder.”

Just this last year I had my primary send me for referral for genetics so I can get something. I had to get heart surgery two years ago so after having that I thought it was important to have a real diagnosis in my chart so I can get proper follow up and proper surveillance. With these connective tissue disorders, the biggest, probably scariest, complication is an aortic dissection. And so, I wanted to, since I had my mitral valve, my regurgitating prolapsed mitral valve

repaired, my cardiologist is like “there’s no reason to do any more echoes because you’re fixed.” And so that’s what really prompted me to get a real diagnosis in my chart so I can have proper surveillance QCL9

The participants brought up several things that helped alleviate this uncertainty. One was categorized into the subtheme of confidence with good facilities. Several of the participants mentioned that good hospital facilities instill confidence upon them, although the limited knowledge and experience are still frustrating.

I mean I get confidence from a really well-run hospital, like [named] hospital system. Obviously if I needed a blood draw and we were going to look at my immune system, they were really efficient at that. So that gives me more confidence, getting more data like that. How it’s interpreted, then, no. Because the lack of experience just doesn’t give me a whole lot of hope.

Then they just built a new health park. I really like the health parks. So instead of having to go the big hospitals with all the parking, pay to park, all the ton of people, they built a – some satellite health parks around my area and one’s right next to my house. So it’s brand new, super nice. I went there for my CT scans. I go there for my bloodwork. I think that having a local, new, clean, easy, accessible facility makes the – my patient anxiety and the whole process of it much friendlier, much less anxiety, and so, um, yeah. I don’t know. I think that – I like the fact that I got this really good facility so close to me. QCL9

Finding comfort in community is another subtheme relevant to the response of living with uncertainty. Participants also discussed finding support through the Facebook group. Specifically,

it was the knowledge that they were not the only one to undergo the same experiences and that they are not alone that they have found reassuring. It should be noted that all the participants were recruited from the Facebook group dedicated to the cutis laxa community, and therefore all had interactions with a cutis laxa social network.

And today I'm not so stressed about it because I understand a lot more. The community on social media helps a lot. And they all follow the same process. I'm not alone here. Everyone has gone through this. And everyone with rare diseases has to go through this investigative path. QCL8

3.3.2.3 Patient Response

Answers categorized under the “patient response” theme describe how participants have responded to living with cutis laxa. This includes what actions they have taken or are willing to take, as well as how having a rare disease has shaped their interests and behaviors.

In response to challenges in finding knowledgeable medical professionals, participants discuss traveling or being willing to travel longer distances.

I've traveled hours to see doctors, and those are just in my own state. This diagnosis, or you know, working to get this diagnosis, is so new, you know. I'd be interested in traveling further to be able to find somebody who can, you know, who knows what they're dealing with and how to actually help properly. QCL9

Participants also discuss educating their providers about their conditions and their needs. Some saw it as a source of frustration while others saw it as an opportunity.

I think that growing up it was very common to walk through it, what it impacts, how it's manifested for me, with every urgent care doctor who I would see. I think that a lot of the times they would bring in extra doctor who are around but not seeing anybody that day so they could hear it. They would kind of use it as an educational experience when I would come in and bring in the training doctors or the people who currently weren't seeing anyone so I could explain and they could see what rare diseases look like.

How was that experience, with being an example case?

I think that I never really got that bothered by it. I think that sometimes it would feel a little bit weird but I was never really worried about it. I kind of thought that it was not such a big deal because it seemed like a good way to make sure that future people would know how to deal with something similar or dealing with a different rare disease so yeah, I guess it didn't really bother me." QCL5

I don't feel stressed so much that...it's just that...I don't think I feel stressed or anxiety in any way. I think I'm pretty...I've always think I've got a calm and collected - but it is frustrating because I know that I - I know that I'm taking a deep breath and just trying to go through the entire explanation of all the stuff that I've had and all the stuff I've had done. QCL9

In response to the question if they had seen medical providers who were unfamiliar with cutis laxa:

Most of them. I switched to [new physician] two years ago and before that I had another doctor, [former physician], and I had to educate all of them. QCL4

This particular participant continues:

I'm pretty close to what's going so it's really affected me in that way. Since nobody else had the answers I took it upon myself to see if we could find a better way to educate the general population, including physicians and nurses, about these rare diseases. QCL4

Both of these subthemes, a willingness to travel farther and educating others, is a response to limitations outlined under the theme of rare disease in healthcare.

Increased self-advocacy is another subtheme under patient response. The three female participants described becoming more willing to speak out or advocate for themselves both within and outside their healthcare. The three male participants did not explicitly mention having this experience. The following quotes do not have identifiers attached to preserve anonymity.

You know, it's...it's...in a lot of areas it's the same way. It's easy to get...what can you say...sour or...cynical about it. But I try not to let it but I think my...my experiences have made me more...action-orientated in some cases. Making me more willing to go up and bang my head against the door or suggest something.

I think it has helped me be less afraid to say if I need help or need something. I think that a lot of anything that has not worked with doctors has been partly out of fear of saying you need help with something or saying that you need more or like, I guess, open, and so I think it has helped me be more open that things I need in general in life and just like being more open about talking about serious issues as well.

I'd say that the fact I've been my own healthcare advocate probably relates to my entire life as a whole that I've kind of always had to push for myself in every other aspect of my life. So I think I'm used to being my own advocate not only in my own healthcare, but in work. I think that becomes almost a personality trait. You've got to fight for yourself and the things that you need out of healthcare.

Finally, participants showed interest in engaging in research and tracking the progress of research in cutis laxa.

I was happy, I was happy that I found a clinic.” [referencing the University of Pittsburgh cutis laxa study] *QCL1*

I'm fairly in the middle of it. I actually just finishing up my certification to be a PI [principal investigator] so I'm actually starting this study with a pharmaceutical company as a PI in the next month or so. QCL4

While the sample is naturally skewed because people more interested in research are more likely to volunteer for a research study, participants connected this to their experience with rare diseases. One participant explicitly stated it as the most important thing that the healthcare system can do for them as a person living with cutis laxa.

Well, keep researching. Keep performing studies and trying to gain funding and traction. It's just all of the same things that are applicable to any rare disease. With the lack of the numbers would be the lack of pursuit, so yeah. They can just pursue. QCL8

3.4 Discussion

To the best of the researcher's knowledge, this is the first study that directly worked with people with cutis laxa to understand their personal experience with the disease. The study interviewed six people with different subtypes of cutis laxa about their experiences with finding and receiving health care for their condition. The primary goals were to begin to identify the experiences, concerns, and priorities of people living with cutis laxa and to understand how these findings align with existing literature on patient experience and patients with rare disease. Asking individuals' opinion in an open manner can help define future aims for research, healthcare, and education that are the most important for the community.

One of the most common challenges that the participants described, as well as what appeared to be the most frustrating, was the lack of knowledge and resources. Every participant described encounters with providers unfamiliar with cutis laxa and nearly every patient discussed the difficulty of finding a provider with some knowledge or expertise. This fits into the larger scope of literature describing rare diseases; a review article of 21 studies on living with rare diseases, 14 papers discussed the lack of knowledge amongst healthcare providers (Khangura et al., 2016). The participants themselves recognized that this is the result of the rarity of the condition and are sympathetic to the difficulty that providers face. In fact, some noted that cutis laxa is rare even in the context of other rare diseases, contextualizing it with other connective tissue disorder to emphasize how few providers have heard of it. This is in contrast to the findings of Khangura et al., which found that six out of 21 studies identified negative feelings in response to this lack of knowledge (Khangura et al., 2016).

Traditionally, the provider-patient relationship is characterized by expertise possessed by the provider, which the provider will then use to dictate, guide, or discuss medical decision-making

for the patient (Emanuel & Emanuel, 1992). These roles are set by culture; the provider and patient hold these expectations before they even first interact. Having a condition as uncommon as cutis laxa skews this dynamic. At times, a person with rare disease may be an “expert patient” and take on the role of educating the provider about not only their symptoms, but about the condition in general (Anderson, Elliott, & Zurynski, 2013). Meanwhile, healthcare providers may feel that they do not have adequate training or access to resources to best help their patients (Vandeborne et al., 2019).

The participants in this study discuss educating or attempting to educate their providers. Some of them talk about the willingness or reluctance of their providers to listen to them and learn about the condition, which was a source of frustration for them. Some of the participants expressed teaching their providers sometimes caused unease for them, while also acknowledging the importance of educating providers for both themselves and for others with cutis laxa. The reluctance of providers to engage and unease of patients corroborate with existing literature about the patient-provider relationship; some providers may be unwilling to cede control while patients feel a burden that they generally do not expect to have in a provider-patient relationship (Budych, Helms, & Schultz, 2012). It can also result in providers showing reluctance to treat or dismissal of their patients’ experiences. This is reflected by some of the observations that the participants in this study made regarding provider engagement.

The experiences of patients with cutis laxa have parallels to the experiences of people with unexplained medical symptoms, such as dealing with frustration and being met with skepticism by their providers (Stone, 2014). This may point to the limitations of a rare disease diagnosis in some ways. The literature on people with unexplained medical symptoms shows how a diagnosis helps provide clarity and justification for providers, society, and themselves (De Sanctis et al., 2018).

This is also true amongst people with rare disease; the desire for and difficulty of identifying a diagnosis for person with a rare disease is often so prolonged to such an extent that it has a name: the diagnostic odyssey. Cutis laxa is a diagnosis, but one with which medical providers are rarely familiar. Theoretically, a diagnosis should translate to knowing what the issue is and connecting the patient to appropriate management and treatment. For people with cutis laxa, this is not always the case.

In fact, a diagnosis can widen the scope of issues that the patients are concerned with. Whether it was a recent diagnosis or one that the participant has lived with for years, most of the participants expressed some degree of concern or uncertainty about the potential future symptoms, which is linked to the desire for appropriate management and coordination. Additionally, even a diagnosis of a specific subtype of cutis laxa does not necessarily define all the manifestations that affected individuals or providers might expect because cutis laxa can show variable expression and because their frequencies are still being defined for many types of cutis laxa. This was the cause of increased expectations or anxiety amongst the participants. In turn, this makes the provider-patient relationship all the more critical. In another survey among 346 medical students in Poland, the majority of respondents stated that their perceived their knowledge of rare diseases was limited (Domaradzki & Walkowiak, 2019). More studies are needed to explore the knowledge, or lack thereof, about rare diseases among medical providers.

Despite this shift in the traditional provider-patient dynamics, participants discuss other aspects of their interactions with providers that are also important. The participants mentioned that they sometimes feared their healthcare providers would not take their concerns seriously. Subsequently, they spoke positively about providers who listened, took their concerns seriously, and attempted to help connect the participants to appropriate tests and specialists. Having a positive

patient-provider relationship is associated with good health outcomes (Gallagher & Levinson, 2004). For people with rare diseases in particular, providers such as primary care physician can play an important role as an advocate (Dudding-Byth, 2015). These findings show that providers who are not experts on cutis laxa can still do basic things to help people with cutis laxa without needing further training or expertise. This does not eliminate the need for access to knowledgeable providers, which has been emphasized by the participants, but it would reduce the undue burdens that people with cutis laxa face on top of having a rare disease.

Again, participants recognized that the healthcare system imposes limitations on providers that prevent them from having a fulfilling relationship. They specifically commented on the limited time they have with providers as well as the factory-like nature of the healthcare system, which attempt to maximize efficiency and standardization. Participants recognize that this is caused by the system in which their providers operate, but it still can make them feel dehumanized and further weaken their view of and relationship with their provider.

Moreover, while these are not new findings for the general population, they can pose particular challenges for this one (Sofaer & Firminger, 2005). It is at odds with the needs of people with a rare disease like cutis laxa. Participants spoke about needing time to discuss their symptoms, management, and questions but not having it. They also talked about how standard procedures may need to be modified or simply given more consideration because of their cutis laxa. This directly affects their healthcare because they cannot safely assume that what works for the general population will work for themselves and they need to convince their providers of this. This study shows that in a system that does not provide the resources that they need, patients with cutis laxa still expect the basic dignity of being treated as human beings rather than cogs in a machine.

The participants also brought up a lack of coordination as an issue with receiving health care. One participant described not knowing they should see a pulmonologist until almost two decades after their diagnosis. Two others expressed frustration that their providers did not appropriately communicate with each other or fail to do so at all, leaving the burden to the participants. Lack of communication between specialties can be typical with patients with multiple morbidities or conditions that affect multiple body systems, and this disjointed care can result in poorer outcomes (WHO, 2016).

Participants suggested ways to address this issue. One suggested having a “rare condition nurse” or some kind of care coordinator. Another suggested that there should be an official list of which specialties a person with cutis laxa should consult with. Guidelines often exist for rare conditions, but, as mentioned previously, cutis laxa is rare even amongst rare conditions. Clinical guidelines exist as GeneReviews for some subtypes, but not all. In addition, GeneReviews are written for healthcare providers so patients may not be able to understand a GeneReviews page even if they found it. This is a project that physicians and researchers studying cutis laxa can tackle for the community in the future.

Participants also discussed what they found helpful or comforting as people living with cutis laxa. As mentioned earlier, participants positively viewed providers who are willing to engage with the participants, learn about cutis laxa, and treat them as a whole person rather than simply their disease. Two participants also mentioned that having well-run, accessible facilities was comforting, which is in accordance with views of patients in the general population (Grondahl et al., 2018). Participants also discussed finding comfort in the cutis laxa community because they could learn about other people who shared their experiences and know that they are not alone. This is also a common finding amongst the rare disease community; people with different types of

diseases, including Wilson's disease, Fragile X syndrome, and cystic fibrosis, have sought out people going through the same experience (Caroline Huyard, 2009) (von der Lippe, Diesen, & Feragen, 2017). This also makes sense in the context of the difficulties that the participants expressed about navigating their health care. They discussed worrying about potential symptoms and feeling that their providers and the healthcare systems are unable to meet their needs. It follows that solidarity with others with cutis laxa is comforting when other arenas are lacking.

As in other rare disease communities, the participants also demonstrated ways they took initiative to address living with cutis laxa. It can be on a personal level, such as being willing to travel farther to find qualified medical providers. Sometimes it is the willingness to educate their providers, both for their own sake and for the sake of others the provider might see in the future. Some of the participants also thought in terms of the bigger picture through research. Like other people with rare diseases, the participants were interested in research about their condition because they saw it as directly related to potential care for themselves and their community (Picardi et al., 2000). They expressed the need for more research, discussed being happy when they found research studies to participate in, and suggested future directions and potential studies. One expressed interest in creating a disease registry while another mentioned that they were preparing to help conduct a study themselves. While people who volunteer to participate in research may already have a positive bias towards interest, this level of interest is echoed in the larger rare disease community, which has been active in both participating in and driving research studies. (Ayme, Kole, & Groft, 2008). Even in a community, especially in one as small as the cutis laxa community, participants understand that research is tied to their care and deeply care about pushing forward.

In addition, the female participants discussed how living with cutis laxa made them more active and vocal in other arenas of life, which male participants did not explicitly mention. The literature shows that women can be met with more skepticism by healthcare providers (Blanchard & Lurie, 2004). This may be exacerbated by having a rare condition, which can sometimes result in even more skepticism and dismissal. As a result of undergoing these experiences, women may self-advocate in the non-medical sectors of their lives. Because of the nature of rare diseases, it can be challenging to find gender and cultural differences in how people respond to and experience rare disease. This is a topic that should further explored in the future.

Also of note, aside from that gender difference, participants discussed how their lives had not changed or how they tried to make sure it did not change outside of the medical sphere. This may demonstrate the resilience that comes from living with a rare disease.

3.4.1 Future Research

The goal of this study was to speak directly to people with cutis laxa to begin to understand their experiences and needs. Future studies should continue to gather data through interviews. Because most subtypes of cutis laxa have onset in childhood, it is also important to incorporate parents of children with cutis laxa as well. It would also be beneficial to gain insight from providers who treat patients with cutis laxa. In addition, future studies should also seek out people with cutis laxa who are not Caucasian or who live outside of the United States to gain a more comprehensive picture of the experience of living with cutis laxa. It may also be helpful to create a survey based on findings of these interviews to see if they are generalizable to the larger cutis laxa community. Finally, it is important to push for resources like care guidelines for all subtypes to help people with cutis laxa navigate their care.

3.4.2 Limitations

There were some limitations to this study. Only people who had access to the Facebook group, spoke English, and had access to Skype for Business could participate in the study. All the participants were Caucasian and from the United States, but cutis laxa is not known to be limited to any particular ethnicity or region. Therefore, this study may have skewed toward people who already have a greater access to resources, care, and community comparatively speaking. In addition, because recruitment was done amongst a community interest group and respondents self-selected, participants were anticipated to have stronger opinions about their experiences with cutis laxa. Finally, the interviews were transcribed by only one person.

3.5 Conclusions

This study identified several themes about people's experiences living with cutis laxa: the lack of knowledge amongst their healthcare providers, the dynamic of the patient-provider relationship, overall issues with the healthcare system, the uncertainty of living with symptoms, what they have found helpful, and how they have responded proactively. These themes are consistent across multiple subtypes of cutis laxa and fit into the larger literature about people living with rare diseases as well as overall patient experience with their providers and the healthcare system. In the future, there should be more collaboration with the cutis laxa community.

4.0 Significance to Genetic Counseling and Public Health

4.1.1 Significance to Genetic Counseling

Most rare diseases have a genetic basis (Baynam et al., 2017). Genetic counselors routinely have patients who have rare disorders. People with cutis laxa are an underserved and under-studied population. It is important to discuss their experiences to understand how cutis laxa fits into the greater literature on people with rare diseases to provide new insight and propose new solutions. These findings may give insight to genetic counselors about people with cutis laxa and their specific needs. It may also add further insight about people with conditions that are extremely rare, even in comparison to other diseases. This knowledge could help genetic counselors fulfill their roles as advocates and educators for patients.

The study also explored the effectiveness and accessibility of personal health services for this population. The participants discussed wanting healthcare providers who were knowledgeable about the condition, put in effort on their behalf to help them, treated them as human beings, and had enough time for them. Genetic counselors have the skillset and professional training to fulfill these needs. Genetic counselors can further help their patients by advocating for them within healthcare systems and reaching out to their other providers. In fact, one participant explicitly stated that the best person to talk to understand a diagnosis of cutis laxa is a genetic counselor, but many places do not have them.

If you want to get more detailed information, you pretty much have to go to a genetic counselor. They'll take the time to work with you to figure out what's

going on. But most people don't know to go there. And a lot of hospitals don't even have genetic counselors. QCL4

However, two other participants discussed feeling dismissed by medical geneticists. While medical genetics professionals, particularly genetic counselors, have the knowledge and skills to be a uniquely helpful asset to patients in the rare disease community, it is still essential for medical genetic professionals to prioritize the patient interaction. Even in a situation where a healthcare provider cannot offer a great deal of information or guidance, they can still try to ensure that their patient does not feel dismissed and abandoned. The participants emphasized the basic need to be heard. This may require more psychosocial investment on the part of the medical provider, but it would not require a massive investment of resources and would go far in addressing a basic issue.

Furthermore, genetic counselors can also try to deliberately perform outreach for rare disease communities. Genetic counseling students and practicing counselors can reach out to specific rare disease groups, whether online or local chapters, to build awareness and foster relationships. In addition, NSGC can pursue partnerships with rare disease organizations to further the same goals. This would help expand the impact of genetic counselors to beyond the clinic and laboratory.

4.1.2 Significance to Public Health

Worldwide, as many as 400 million people may have rare diseases (Jia & Shi, 2017). People have already recognized that rare diseases are a major public health concern (Valdez et al., 2016). However, participants in this study tied the lack of expertise and the negative experiences they had with their medical providers to the overall healthcare system. They stated outright that

the healthcare system is designed so that the provider is pressured to see as many patients as possible, does not have time for them, and does not know how to connect them to other providers with expertise. Half of the participants directly stated that the healthcare system is designed to meet the needs of the average patient, but that does not work for a person with a rare disease. They recognized the limitations and that they themselves were outliers. Still, because of the number of people worldwide with rare diseases, healthcare systems still need to have the flexibility to appropriately care for patients with rare diseases. Monitoring the system in which people receive healthcare, creating policies to help people with cutis laxa and other rare diseases, and assuring a competent workforce are all essential public health services that can support providing the best care possible to patients with rare diseases.

These findings once again emphasize the need for a healthcare system that is flexible, well-connected, and centered on patients. The World Health Organization has already recognized the need for this for the general population in an initiative called “Framework on integrated people-centred health services” (WHO, 2016). Patients with rare diseases may be on the extreme end of the spectrum and thus some of their challenges are magnified versions of preexisting problems for the general population. This emphasizes the need for changes on a policy and systematic level.

Because the rare disease community is dispersed across countries and the world, the most effective strategy may be to start at the federal or country level. Some governments around the world have already created plans, strategies, or programs to begin to address the needs of the rare disease community (Khosla & Valdez, 2018). These government agencies should continue to invite collaboration with patient organizations. Public health professionals can also help patient organizations with designing policies that in turn can be presented to politicians, which patient organizations have already been doing for years (Ayme et al., 2008).

This study collected data from people with an extremely rare disease that highlight the need for the vital skills that genetic counselors can offer to people with rare diseases as well as the need to reform the healthcare system to be flexible to the needs of complex patients.

5.0 Public Health Essay: Analyses of Demographics and Beck Depression Inventory Scores of Participants in the Cutis Laxa Research Study

5.1 Background

5.1.1 Cutis Laxa & Rare Diseases

Cutis laxa is a connective tissue disorder with both genetic and acquired subtypes. The condition is characterized by loose, inelastic skin and can be associated with intestinal, cardiac, and pulmonary issues. Age of onset, symptoms, and modes of inheritance can vary across different subtypes. There is one autosomal dominant form, caused by pathogenic variants in the gene *ELN*. There are also nine autosomal recessive subtypes, each linked with different genes. No cure exists for cutis laxa; management is symptomatic (Mohamed et al., 2014). Because cutis laxa can impact multiple body systems, patients with cutis laxa can follow with a variety of medical specialists, including dermatologists, cardiologists, pulmonologists, geneticists, and gastroenterologists. There are no centers with expertise in cutis laxa; the two most well-known experts on cutis laxa in the United States are researchers Dr. Zsolt Urban at the University of Pittsburgh and Dr. Morava-Kozicz at the Mayo Clinic.

Cutis laxa has been documented in between 200 and 400 families worldwide, with 395 known patients around the world according to the Cutis Laxa Internationale census ("Patients Worldwide," 2019). This makes it one of the rarest conditions in the world. There are varying definitions of rare disease, but the Orphan Drug Act in the United States defined rare disease (specifically "orphan disease") as a condition that affects fewer than 200,000 people in the United

States (Wellman-Labadie & Zhou, 2010). Most rare diseases are debilitating and chronic (Mascalzoni et al., 2017). In addition, while rare diseases are individual rare, all rare diseases taken collectively may impact up to 10% of the global population (Pogue et al., 2018). For this reason, rare diseases have been recognized to be a public health concern (Valdez et al., 2016).

5.1.2 Rare Disease, Depression, and Quality of Life

Several studies have been done to look at depression and quality of life in individuals with rare diseases. Uhlenbusch et al. published the first study to investigate the relationship between rare disease and depression in 2019 (Uhlenbusch et al., 2019). This cross-sectional study used a German version of the Patient Health Questionnaire-9 to assess depression and anxiety amongst 331 participants with different rare chronic diseases. The study found that people with more severe symptom burden have increased levels of depression.

There are a dearth of studies about the relationship between rare disease and depression, but the literature has shown that people with chronic illness are more likely to have depression than the general population (Clarke & Currie, 2009). Furthermore, depression has been shown to sometimes worsen a chronic condition and that treating depression can improve management and experience of the condition (DeJean, Giacomini, Vanstone, & Brundisini, 2013).

There have been more studies on the relationship between rare disease and quality of life. People with mental illness like depression are more likely to have a lower quality of life (Papakostas et al., 2004). The literature has also shown that people with rare diseases are more likely to have a lower quality of life. Bogart et al. showed in a cross-sectional survey of 1218 people with different rare diseases that this population had a poorer health-related quality of life compared to both the general population and the population with chronic illness (Bogart & Irvin,

2017). Amongst these findings, having a higher income was associated with a greater health-related quality of life and the researcher hypothesized that having a higher income would allow better access to quality healthcare and better ability to seek out qualified experts. Furthermore, the frustration and experience of having a rare disease can extend beyond health and affect general quality of life (von der Lippe et al., 2017).

The literature has shown rare disease can be connected to both depression and lower quality of life, and that depression and quality of life can impact each other. This raises questions of how all three of these factors interact and compound each other and their effects.

5.1.3 Beck Depression Inventory and Self-Report Depression Scales

Beck et al. created the Beck Depression Inventory (BDI) as a self-rating questionnaire for people over 13 years old as a way to assess depression in a standardized way for research and clinical psychiatry (Beck et al., 1961). The test is based on rating self-descriptive sentences on a scale of 0 to 3; the scores are then added together to give a score that indicates if the person taking the test has depression and how severe the condition is (Metcalf & Goldman, 1965). Since 1961, the Beck Depression Inventory has been used in thousands of studies and has been shown to have internal consistency across sample populations, can detect changes in individuals over time, has validity with other depression scales, and can distinguish between people with and without depression (Richter et al., 1998).

Other self-report depression scales exist as well: the Patient Health Questionnaire-9 (Kroenke et al., 2010), Hospital Anxiety and Depression Scale (Snaith, 2003), Zung Self-Rating Depression Scale (Zung, 1965), and Center for Epidemiologic Studies Depression Scale (Radloff, 1977). All of these, along with the Beck Depression Inventory, have been translated into multiple

languages and used with populations around the world (Gelenberg, 2010). There is no evidence that any self-report questionnaire is superior to another, but the Beck Depression Inventory and Patient Health Questionnaire-9 are used most commonly (Zimmerman, 2018).

The drawback of the Beck Depression Inventory and other similar tools is that they are self-reported and thus the people taking the tests may exaggerate or underreport answers (Richter et al., 1998). However, these tests can be useful as screening tools to direct high-risk patients to diagnosis and support (Gelenberg, 2010).

5.1.4 Rare Disease, Empowerment, and Resilience

People with rare diseases have been shown to face more challenges, which can leave them vulnerable to depression and poorer quality of life. However, the lack of resources, information, and support has also driven empowerment among populations with rare disease to push for progress in research and policy, including funding research and helping to design policies (Ayme et al., 2008). The World Health Organization recognizes empowerment as important for improving health outcomes and quality of life (Neuhauser, 2003).

While the definitions of resilience can differ, it is generally defined as adapting to adverse and stressful circumstances and that there are multiple factors including health, personality, culture, and biology that can influence resilience (Southwick, Bonanno, Masten, Panter-Brick, & Yehuda, 2014). Amongst a cohort of 3324 people with different rare diseases, researchers found that resilience, scored by the number of fewer-than-expected impaired days based on a regression model, was associated with better outcomes for physical and emotional functioning (Schwartz, Michael, & Rapkin, 2017). The literature has also shown that the development of coping strategies and resilience is common amongst people with rare conditions (Schwartz et al., 2017).

Thus, with rare diseases, individuals may have a higher chance for experiencing depression and poor quality of life as well as empowerment and resilience. Literature amongst all of these factors in relation to rare disease is still growing, particularly the connection between depression and rare disease. Looking at the Beck Depression Inventory scores of affected people and their family members can add to growing base of knowledge and suggest future directions of study. This is important for both the cutis laxa community and the larger rare disease community; understanding the intersection between rare disease and depression can contribute to improving the quality of life for a vulnerable population. This study aims to study the demographics of the participants of the Cutis Laxa Research Study and analyze the results of the Beck Depression Inventory scores of people with cutis laxa to contribute to the literature on cutis laxa and rare diseases.

5.2 Methods

5.2.1 Participant and Data Collection:

The data for this study were provided by the Cutis Laxa Research Study, which is based out of the University of Pittsburgh Graduate School of Public Health. The goal of this study is to explore the genetic and biological basis of cutis laxa to gain a better understanding of diseases of the extracellular matrix as well as to contribute to better diagnosis and treatment of those with cutis laxa.

People can reach out to the Cutis Laxa Research Study if they are interested in participating. Most subjects become a part of the study through self-referral by finding the cutis laxa website

through their own research, referral by their medical providers who have heard of this study through their own research of their patient's condition, or referral by patient groups like Cutis Laxa Internationale. Participants from around the world and varying ages are recruited into the study.

The study collects data from participants through clinical questionnaires and annual cutis laxa clinics, in which participants who are able travel to the University of Pittsburgh to complete a variety of medical tests (pulmonary function tests, skin elasticity tests, and echocardiograms) and a genetics evaluation. Participants are also asked to complete a Beck Depression Inventory test if they attend a clinic. These Beck Depression Inventory tests were added to the self-administered questionnaires that participants are asked to fill out during the cutis laxa clinics in the fall of 2010. Participants complete the questionnaires, including the Beck Depression Inventory test, on their own or opt out by not completing them. Because the Beck Depression Inventory is designed for people above the age of 13, only teenagers and adults are invited to complete them. Clinical questionnaires (which do not include the Beck Depression Inventory tests) can be filled out by a participant's physician or remotely via the research team. This information as well as the family pedigree of participants are then inputted into Progeny.

The Cutis Laxa Research Study also looks at anonymized samples from National Institute of General Medical Sciences (NIGMS) Human Genetic Cell Repository, which includes cells from people who have cutis laxa or other connective tissue disorders, and sometimes includes demographic information. The study was approved by the University of Pittsburgh IRB under the number PRO19100357 (See Appendix F).

5.2.2 Data Analysis:

The researcher downloaded a Microsoft Excel spreadsheet of the data of affected (n=236) and unaffected participants (n=23) involved in the study from Progeny. These data included affected status, age, mutation, and more. A complete list is in bullet point form in Table 4. Some of these categories overlap or are redundant. Many of these categories had blank fields and therefore while there were a total of 249 participants for which there was data, some of the data was limited in such a way that they could not be included in analyses.

Table 4 Categories of Data Downloaded from Progeny

- CL Affection Status
- CL Diagnosis Comments
- CL Phenotype
- Other Anomalies Not Listed
- Type of Cutis Laxa
- Gene
- Genotype
- Genotype Comments
- Carrier?
- Patient ID
- Age
- Age at Diagnosis
- Age at Onset
- BDI Valid?*
- Significance of Mutation/Variation
- Race: General
- Race: Hispanic
- Race/Ethnicity: Specify
- Current Age
- Contact: Country
- Anonymous?
- Age symptoms began (Onset)
- Age at Death
- Age at Interview/Age at Death
- Refer: Dr. Country**
- Mutation: Table.Gene
- Mutation: Table.Causative Mutation?
- Mutation: Table.Mutation: Status

*Beck Depression Inventory

**country of origin of referring provider

Unaffected people who are included in the study have a family member in the study or a known case of cutis laxa in their family. For the data analysis, people who were affected with another connective tissue disorder (n=9) and people whose affected status was labeled as “indeterminate” (n=23) were excluded.

The Beck Depression Inventory scores were not included on Progeny. The researcher reviewed the paper records of study participants who attended a cutis laxa clinic and recorded their Patient ID, affected status, and Beck Depression Inventory score. There were Beck Depression Inventory scores for 12 unaffected participants and 26 affected participants. Several participants chose not fill out the questionnaires. Some filled out the questionnaires midway but did not complete them and were thus not included.

Microsoft Excel was used create histograms, box plots, and bar charts to organize and present demographic and descriptive information drawn from the data. The researcher also used Stata SE (Version 15.1) to conduct further data analysis on the Beck Depression Inventory scores. This was done to investigate the hypothesis that the Beck Depression Inventory scores would differ between affected and unaffected participants. A nonparametric test, the two-sample Wilcoxon rank-sum test, was used given the limited number of data points and the lack of confidence that the data fit the rules of the Central Limit Theorem. The alpha value was set as 0.05.

5.3 Results

There was a total of 236 participants with a diagnosis of cutis laxa in the data set. One hundred sixty (67.8%) had a recorded age at interview or death, the age at which the participant was enrolled in the study. The distribution of ages is shown in Figures 1 and 2. The mean age of

the individuals in this study was 24 years, while the median age was 17.5 years. The range of ages were 0 (indicating that they were younger than a year old) and 82 years.

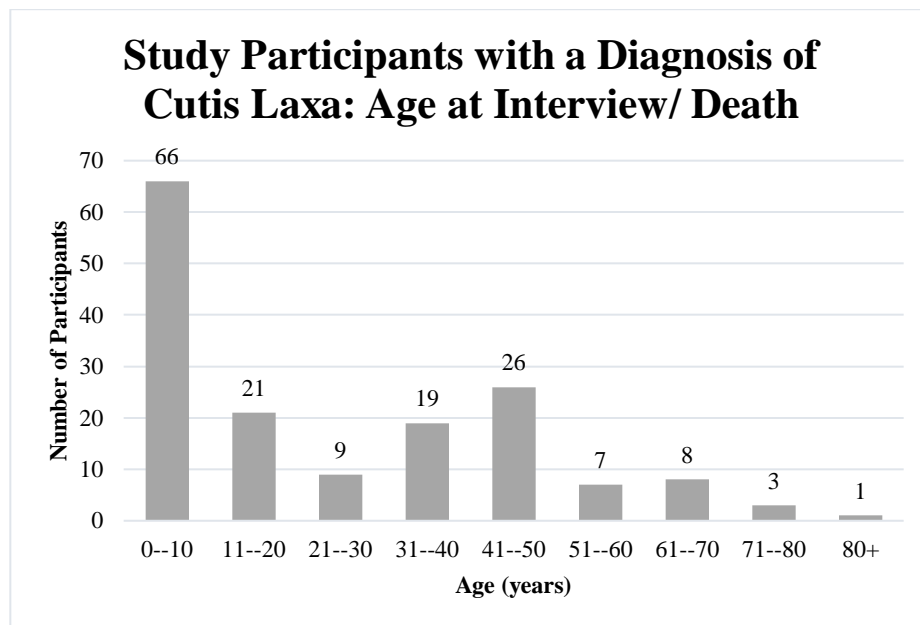


Figure 1 Study Participants with a Diagnosis of Cutis Laxa: Age at Interview/Death

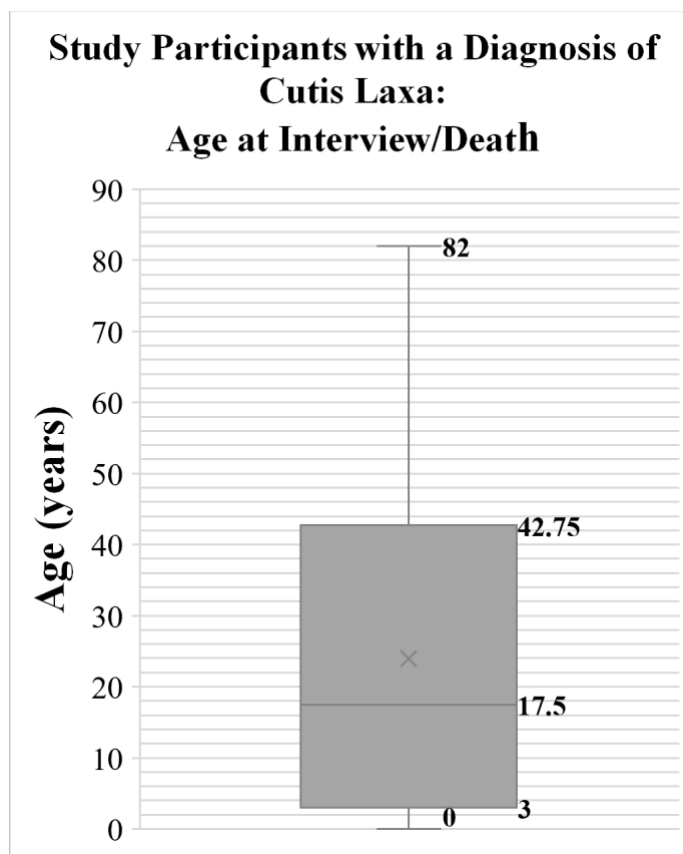


Figure 2 Study Participants with a Diagnosis of Cutis Laxa: Age at Interview/Death Boxplot

A total of 136 (57.6%) participants with a diagnosis had a recorded race (see Figure 3). Two study participants were American Indian or Alaskan, 18 participants were Asian, six were Black or African American, 101 were White or Caucasian, and nine were two or more races. Of the 101 White/Caucasian affected participants, 20 were Latino or Hispanic. Because the ethnicity was not consistently recorded, the researcher chose not to include ethnicity in this analysis.

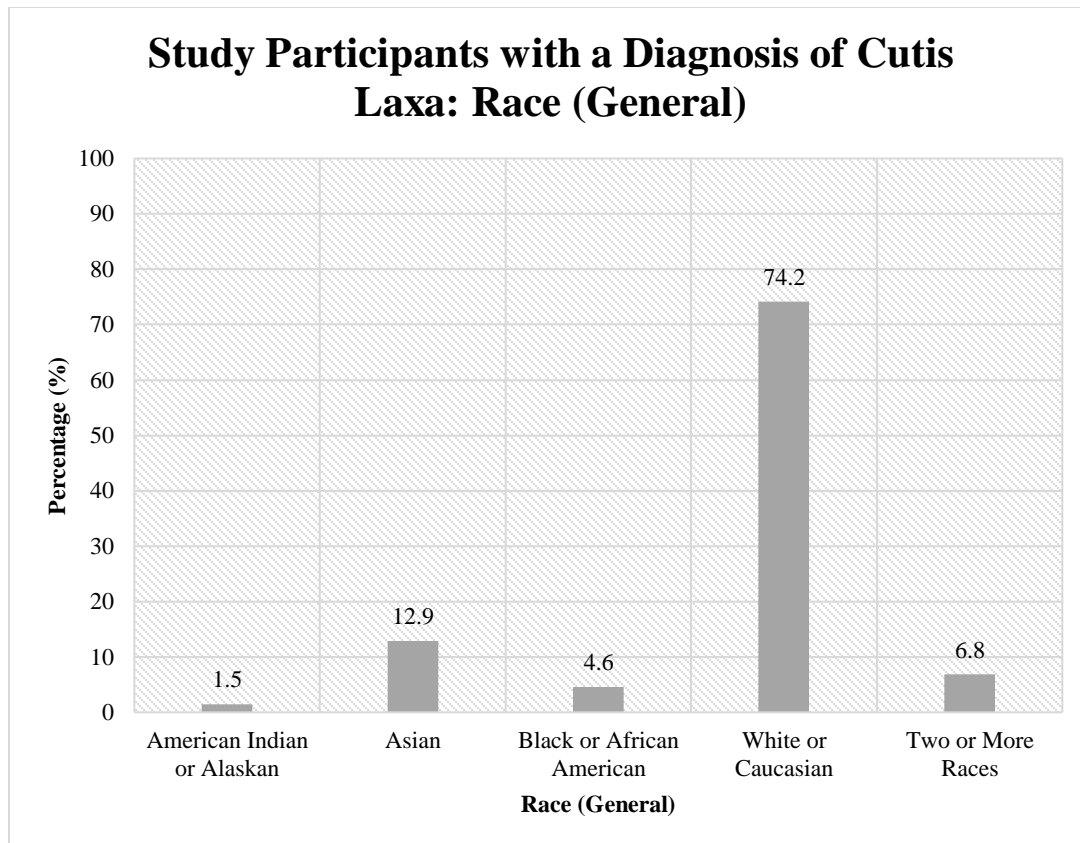


Figure 3 Study Participants with a Diagnosis of Cutis Laxa: Race (General)

The Cutis Laxa Research Study also recorded causative mutations in 74 (31.4%) of the 236 participants with a diagnosis (see Figure 4). Amongst the participants, 32 people (43.2%) carried pathogenic variants in *ELN*, which causes autosomal dominant cutis laxa. The rest of the group have a form autosomal recessive cutis laxa: there were four people (5.4%) with variants in *FBLN5* (linked to ARCL1A), two people (2.7%) with variants in *FBLN4* (linked to ARCL1B), 14 people with variants in *LTBP4* (linked to ARCL1C) 15 people with variants in *ATP6V0A2* (linked to ARCL2A), three people with variants in *PYCR1* (linked to ARCL2B), and four people with variants in *GORAB* (linked to GO).

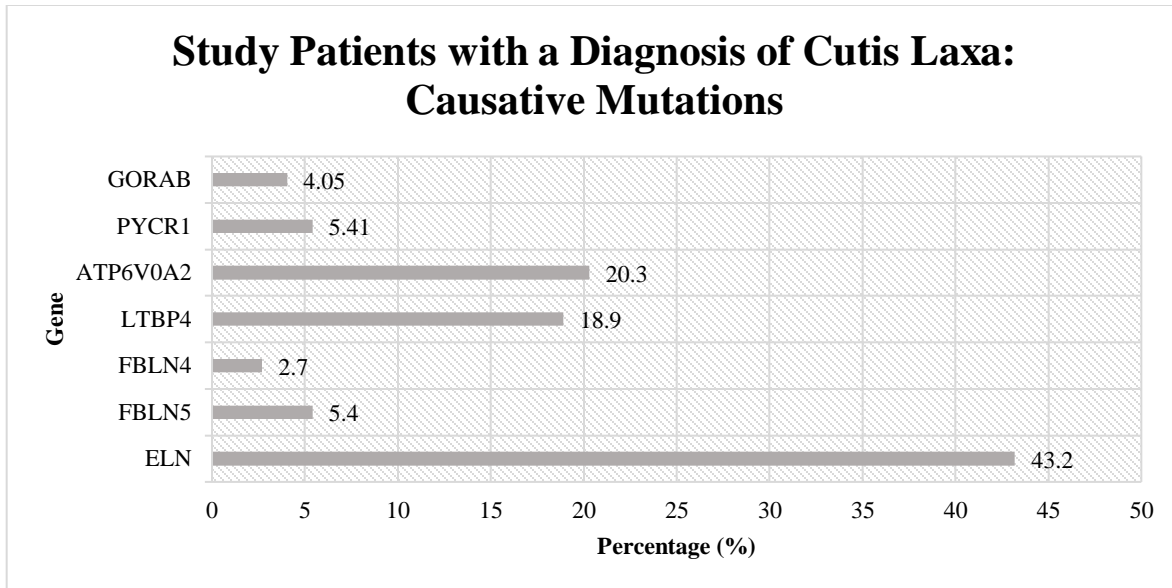


Figure 4 Study Participants with a Diagnosis of Cutis LAXa: Causative Mutations

Of the 74 participants with a known causative mutation, 56 had a recorded race. Of these, 41 (73.2%) were Caucasian/White, nine (16.1%) were Asian, three were Two or More Races (5.3%), two (3.6%) were American Indian or Alaskan, and one was Black (1.8%). Table 3 details the percentage of people who had a known mutation amongst their own race.

Table 5 Participants a Diagnosis of Cutis Laxa with a Known Mutation

Race (General)	Number with a Known Mutation	Percentage with Known Mutation Amongst Own Race
American Indian or Alaskan	2	100%
Asian	9	52.9%
Black	1	16.7%
Caucasian/White	41	40.2%
Two or More Races	3	33.3%

Figure 5 represents the distribution of cutis laxa causing genes in Caucasian and non-Caucasian groups. In the Caucasian population, six out of seven subtypes are represented. In the non-Caucasian group, five out of seven subtypes are represented.

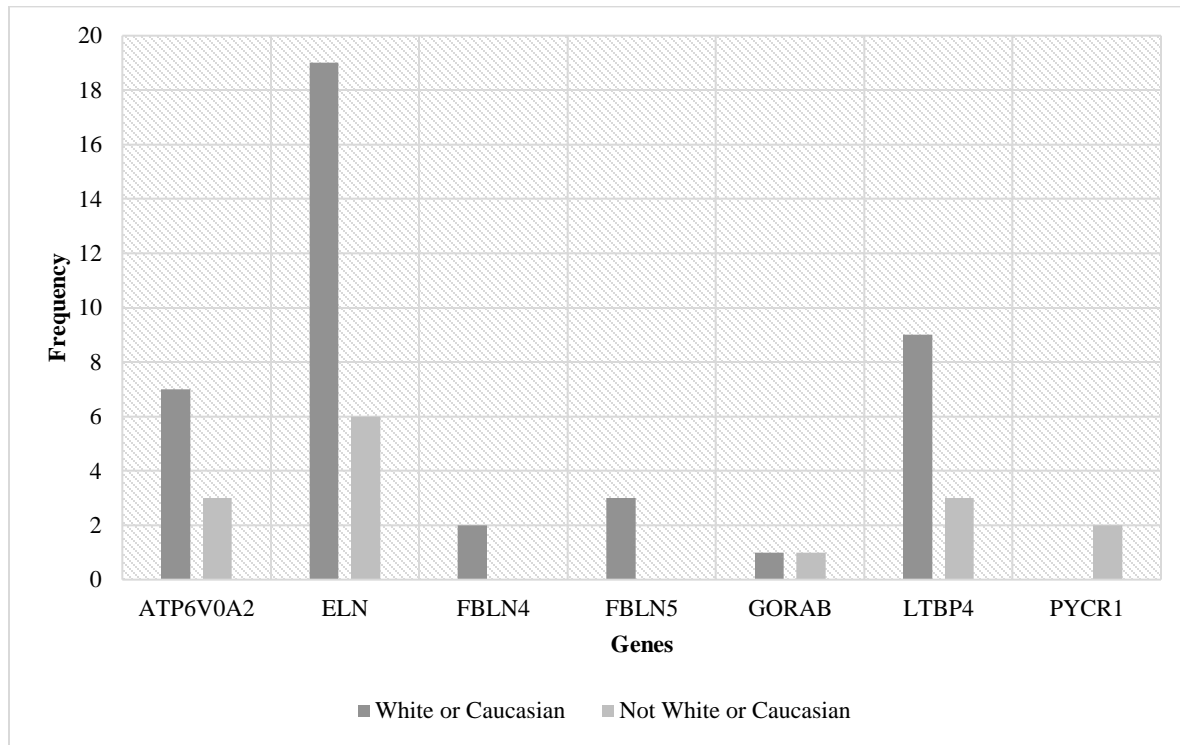


Figure 5 Distribution of Cutis Laxa Causing Genes Across Racial Groups

Among the participants with a diagnosis, there were 128 with known countries of origin: 12 (9.4%) were from Asia, 31 (23.4%) were from Europe, 79 (62.2%) were from North America, and 5 (4.0%) were from other continents. Because some of the participants were the only ones involved in the study from their specific country of origin, the breakdown is by continent rather than country.

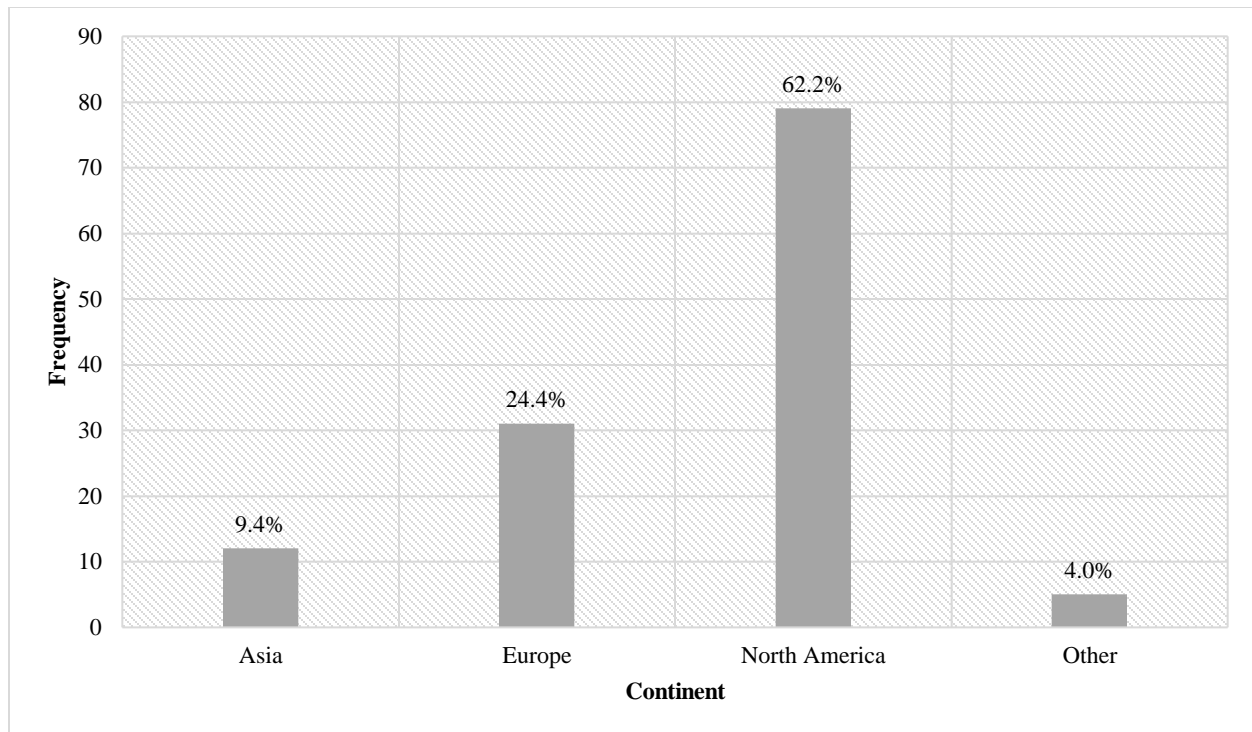


Figure 6 Distribution of Samples by Country (Count)

A total of 38 people, 26 with a diagnosis and 12 family members without a diagnosis, had Beck Depression Inventory scores available. Scores on the Beck Depression Inventory for affected individuals were compared to those of their unaffected family members. The Wilcoxon rank-sum test returned a z-value of 1.820 and p-value of 0.0687. Based on an alpha value of 0.05, this test fails to reject the null hypothesis and does not show a difference in the Beck Depression Inventory scores between individuals with a diagnosis and without a diagnosis. Furthermore, the mean scores of family members and participants with a diagnosis were 4.75 and 7.96 respectively, both of which are categorized as “typical ups and downs” in the Beck Depression Inventory (BDI) Scale (see Tables 6 and 7).

Table 6 Beck Depression Inventory (BDI) Scale (Beck et al., 1961)

BDI Score	Levels of Depression
0-10	Typical ups and downs
11-16	Mild mood disturbance
17-20	Borderline clinical depression
21-30	Moderate depression
31-40	Severe depression
40+	Extreme depression

Table 7 Beck Depression Inventory Scores of Unaffected Versus Affected Individuals

	n	Mean	SD	Median	IQR
Unaffected	12	4.75	6.86	3	6.5
Affected	26	7.96	6.81	7	10

Figures 7 and 8 show the distribution of the scores across participants with a diagnosis and family members. Figure 7 shows that all the unaffected family members had scores of less than 10, with one outlier at a score of 23.

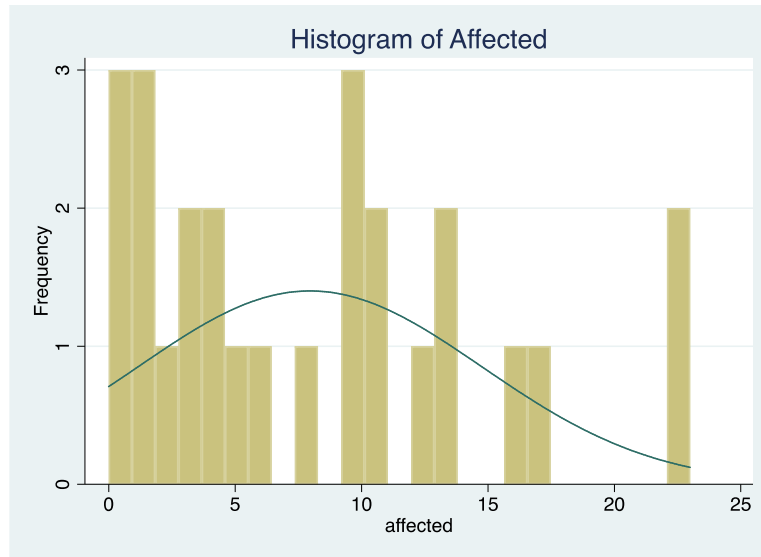


Figure 7 Histogram of BDI Scores of Participants with a Diagnosis

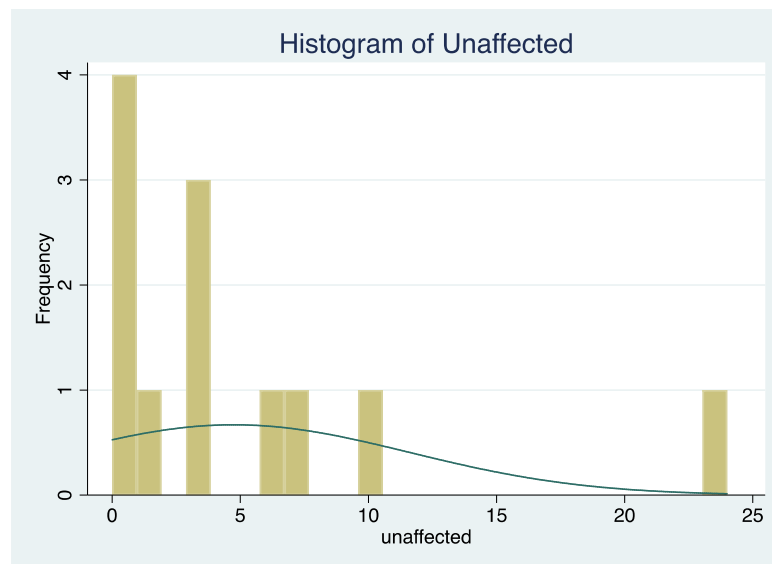


Figure 8 Histogram of BDI Scores of Family Members

5.4 Discussion

The results of this study show the first overview of the demographics and distribution of monogenic subtypes of the participants in the Cutis Laxa Research Study. This study also analyzes the differences between BDI scores of affected participants and unaffected family members. Analysis found that there were no significant differences between the groups and that the average scores of each group did not indicate depression in either group.

5.4.1 Demographics

In regard to demographics, the results show that the mean age of the individuals in this study was 24 years and the median age was 17.5 years. This shows that at least half of the patients enrolled in the study were under 18 years old at the time of enrollment. Most subtypes of cutis laxa have an onset during infancy and childhood and some subtypes result in a shorter lifespan. In addition, 56.8% of the participants with known causative mutations had autosomal recessive subtypes, which tend to present earlier and more severely. This may explain the age distribution amongst study participants during the time of their enrollment.

The majority of participants in the study are Caucasian (74.2%) and from North America (66.2%). This is unsurprising given that the study is based out of the United States, the website is in English, and the percentage of Caucasian people in the United States is 76.5% (census.gov, 2019). In combination, 85.4% of participants with known countries of origins were from either Australia, Canada, Europe, or the United States: all of these countries have some form of rare disease policy and regulatory structure in place (Dharssi, Wong-Rieger, Harold, & Terry, 2017). Among European participants, 10 were from France; Cutis Laxa Internationale, the patient

organization, is based out of France. As indicated in the introduction, there is no evidence that cutis laxa is concentrated amongst the Caucasian or Western populations. Therefore, this may be an issue of access and healthcare infrastructure, which is already recognized as a public health concern for rare diseases (Valdez et al., 2016). For example, there are a limited number of known medical centers that have treated patients with acquired cutis laxa: University of Pittsburgh Medical Center (Pittsburgh, PA), Washington University Medical Center (St. Louis, MO), Mayo Clinic (Rochester, MN), Johns Hopkins Medical Center (Baltimore, MD), and University of Texas Southwestern Medical Center (Dallas, TX) (Harlow). While there may be more medical centers and individual providers that have treated patients with cutis laxa, a person with a complex and rare disorder may have greater access to potential diagnosis and treatment in larger medical centers where experts are located. This means that people who live closer to these medical centers have the ability to reach them or have resources to obtain care are more likely to receive a diagnosis.

Only a portion of participants with a recorded race have a recorded causative mutation. White or Caucasian participants comprised the majority of study participants and participants with known causative mutations. However, over half (59.8%) of White or Caucasian participants were not identified to have a known causative mutation. In addition, only one out of six Black participants were identified to have a known causative mutation while of the two American Indian or Alaskan participants, both (100%) carried identified causative mutations. Diagnostic testing (which can be a skin biopsy or genetic test) for a rare disorder such as cutis laxa can be limited to the resources to which the participants have access. However, given that all groups outside of White or Caucasian people had fewer than ten affected people with known mutations, it can be difficult to ascertain if there are constraints in access to resources or if it is more difficult to identify

variants in some racial groups than others because the original research initially conducted studies on a single racial group.

5.4.2 Beck Depression Inventory Scores

Amongst participants with Beck Depression Inventory scores available, the mean scores in each group indicated them to be in “normal ups and downs” range according to the Beck Depression Inventory scale. The statistical analysis did not find a significant difference between the scores of the two groups. There are several key considerations. First is that the unaffected participants were not true controls, but family members of affected individuals. Family members of affected individuals have their own stresses and frustrations that can affect their quality of life, so their scores may have been higher than individuals from the general population (C. Huyard, 2009). In addition, the BDI scores were taken from people who were able to travel to Pittsburgh to participate in the Cutis Laxa clinic, which implies that they may have more socioeconomic capital and access to resources in general. This in turn may be a source of bias for these results because the study would not include people who do not have the resources or ability to travel to the clinic. The BDI questionnaire is also self-administered and several people did not fill out the questionnaire or left it incomplete. This may have skewed the results in either direction. Finally, this was a small sample size; this alone necessitates reanalysis when there are more BDI scores available.

These results contrast other studies found in the literature regarding quality of life and prevalence of depression when living with a rare disease. These studies have shown that people living with rare diseases generally have worse quality of life outcomes compared to the general population. However, these studies used different survey tools to measure depression and quality

of life, including the Patient-Reported Outcomes Measurement Information System (PROMIS) and Patient Health Questionnaire-9 (PHQ-9) (Uhlenbusch et al., 2019) (Bogart & Irvin, 2017). Both of these studies also had cohorts with multiple different types of rare diseases, rather than focusing on a group with one specific rare disease. These studies were also conducted through online surveys, with larger sample sizes and more outreach. In addition, Uhlenbusch et al.'s 2019 study specifically mentioned that people with a higher symptom burden were more likely to have depression. This may warrant further exploration of symptom burden and its connection to depression or quality of life amongst cutis laxa participants. People living with rare diseases can also have a greater resilience capability, which allows them to better cope with the challenges they face on a regular basis (Pulciani, Nutile, & Taruscio, 2018). This in turn can act as a protective factor against depression and promote mental health. Future research in this area should look at resilience capability in conjunction with depression and quality of life.

5.4.3 Future Directions

The Cutis Laxa Research Study should continue to collect standardized demographic information. It may be helpful to include further demographic details, like level of education and family income, to further understand how social determinants of health may play a role in receiving a diagnosis, obtaining healthcare, and participating in research studies.

There is the potential to reanalyze the Beck Depression Inventory scores of this cohort with more robust statistic tests to ascertain differences. However, it is notable that both people with a diagnosis and their unaffected family members scored low on the Beck Depression Inventory tests. In the future, it would be important to continue gathering data and conducting these tests among people with cutis laxa, attempting to reach out to people with cutis laxa who cannot come to a

research clinic in Pittsburgh, and perform further analysis with more information. Because this test is self-administered, it is possible to include the Beck Depression Inventory as a part of the set of questionnaires that participants are asked to fill out when first enrolling in the study. This would increase the number of individuals taking the Beck Depression Inventory to beyond those with the means to come to a research clinic. This can help understand how these initial findings may fit with the larger cutis laxa community. If the findings continue to show low rates of depression and lack of significant differences between affected and unaffected populations, this would contrast the literature that already exists about rare disease and depression. This should prompt further investigation in what distinguishes the cutis laxa community and what lessons they may carry for other rare disease populations.

5.5 Conclusions

This was first demographic overview of affected participants in the Cutis Laxa Research Study at the University of Pittsburgh and the first analysis of self-rated depression tests among people with cutis laxa and their unaffected relatives. The demographics of the participants skewed towards people under the age of 18, from Western populations, and White/Caucasian ancestry. There were no significant differences between the Beck Depression Inventory scores between affected participants and their unaffected relatives. These findings have the potential to drive further studies and analysis to understand how the cutis laxa community fits in with the larger rare disease community.

Appendix A Institutional Review Board Approval (Thesis)

University of Pittsburgh Institutional Review Board

Human Research Protection Office
3500 Fifth Avenue, Suite 106
Pittsburgh, PA 15213
Tel (412) 383-1480
www.hrpo.pitt.edu

APPROVAL OF SUBMISSION (Expedited)

Date:	January 15, 2020
IRB:	STUDY19100357
PI:	Pooja Solanki
Title:	Patient Experience with Cutis Laxa

The Institutional Review Board reviewed and approved the above referenced study. The study may begin as outlined in the University of Pittsburgh approved application and documents.

Approval Documentation

Review type:	Initial Study
Approval Date:	1/15/2020

Finalized Documents:	• Consent Form, Category: Consent Form;
----------------------	---

As the Principal Investigator, you are responsible for the conduct of the research and to ensure accurate documentation, protocol compliance, reporting of possibly study-related adverse events and unanticipated problems involving risk to participants or others. The HRPO Reportable Events policy, Chapter 17, is available at <http://www.hrpo.pitt.edu>.

Continuing review (CR) can be submitted by clicking "Create Modification/CR" from the active study at least 5 weeks prior to the expiration date.

Clinical research being conducted in an UPMC facility cannot begin until fiscal approval is received from the UPMC Office of Sponsored Programs and Research Support (OSPARS).

If you have any questions, please contact the University of Pittsburgh IRB Coordinator, [Carolyn Ivanusic](#).

Please take a moment to complete our [Satisfaction Survey](#) as we appreciate your feedback.

Appendix B Facebook Recruitment Script

Hello, my name is Pooja Solanki. I am the study coordinator for the Cutis Laxa Research Study and a second-year genetic counseling student at the University of Pittsburgh Graduate School of Public Health. I am currently working on my master's thesis, which is called "Patient Experience with Cutis Laxa: A Qualitative Study."

My thesis focuses on understanding the unique experiences and challenges that patients with cutis laxa undergo when trying to navigate their medical care, both before and after their diagnosis. The goal of this study is to find information that can help healthcare professionals provide better care to patients with cutis laxa and other rare diseases.

To carry out this study, I will be conducting interviews with people with any type of cutis laxa. These interviews will take approximately 30 minutes and will be conducted over Skype. These interviews will be recorded, but I will not collect any identifying information (your name, your address, or other information that could help someone else figure out if you are participating in the study).

If you are over 18 years, can communicate in English, and are interested in participating, please contact me at cutislax@pitt.edu. To protect your privacy and preserve anonymity, please do not post your interest in participating in the comments of the post.

Thank you for taking the time to read my message and have a lovely day!

Appendix C Interview Questions

- Tell me about how you learned about your diagnosis.
 - If you were a child at the time, how was it explained to you?
 - Do others in your family have cutis laxa?
- Where did you and your family go to get information about cutis laxa?
 - How did you learn about those resources?
- Do you think your life is different because you have cutis laxa?
 - If **yes** – can you tell me how your life is different?
- **For those with acquired cutis laxa:** do you think your life has changed since getting cutis laxa?
 - If **yes**, tell me how your life has changed?
- Do you have any medical providers you regularly see or services that you regularly use? If so, can you tell me about them?
- Tell me about the medical providers you see.
 - How often? What services do you use? How often?
 - How did you find these medical providers?
 - Was finding qualified and knowledgeable doctors a challenge?
 - Do you have to travel far or struggle in other ways to see your doctors?
- Tell me about your relationship with your doctors or regular medical providers.
- Do you feel stressed when you see your medical providers? If so, for what reasons?
- Do you think that your medical providers have a good understanding of cutis laxa? Tell me why you say that.

- Have you ever seen a medical provider who was not familiar with cutis laxa? Tell me about your experience.
- Tell me about ways you feel supported by medical providers and by the healthcare system.
 - Are there particular resources or services within your healthcare system that you have found helpful?
- Tell me about some times that you have not felt supported or you have faced barriers in getting what you need because of your medical providers and your healthcare system?
 - What are some resources or services that you think your healthcare system should have for people with cutis laxa or a rare disease?
- How have your experiences in the healthcare system impacted how you navigate other parts of your life?
 - If you have had poor experiences with the healthcare system, do you think that it has impacted other parts of your life negatively? If so, how?
- What are your expectations for an ideal medical provider and/or healthcare system?
- What is the most important thing that your medical providers/healthcare system can do for you as a person living with cutis laxa?

Appendix D Demographic Questions

- What is your age?
- What is your gender?
- What is your race/ethnicity?
- What country do you live in?
- What type of cutis laxa do you have?
- How old were you diagnosed with cutis laxa?
- Have you ever had genetic testing?
 - If so, what were the results?

Appendix E Codebook

CODE	ORIGIN WORDS	DEFINITION
FAM	Family	Discuss family, including communication, disclosure of results, other asymptomatic
SYM	Symptoms	Discuss symptoms or lack thereof
MPKNOWCL	Medical Provider Knowledge Cutis Laxa	Discuss medical providers' knowledge of cutis laxa, include lack thereof
MPKNOWCD	Medical Provider Knowledge Connective Tissue Disorder	Discuss medical providers' knowledge or expertise in connective tissue disorders
GENET	Genetics	Discuss genetics, including testing, counseling
RESCH	Research	Discuss research process, providers being part, want for more research
MANAGCL	Management Cutis Laxa	Discuss management or treatment of symptoms, including wishes, and which providers they saw
MANAGNCL	Management Not Cutis Laxa	Discuss management or treatment of health outside of cutis laxa
DX	Diagnosis	Discuss process of diagnosis
LFNOTMED	Life Not Medical	Discuss life changes outside of medical sphere
ACCESS	Access	Discuss access or lack thereof, including barriers, like cost
RESOUR	Resources	Discuss resources they have found helpful; this includes information
RELATMP	Relationship Medical Providers	Discuss relationship/interaction with medical providers, including how they think they are perceived by the medical providers and how they perceive the medical providers

RD	Rare Disease	Discuss rare disease – having one, how cutis laxa is a rare disease, being a unique patient
HCSYS	Healthcare System	Discuss healthcare system in general, not focusing on providers – how they feel within it, their perception, and what they want
APP	Appearance	Discuss changes to appearance or lack thereof
EDU	Education	Discuss educating medical providers or other people
SELFEDU	Self Education	Discuss educating themselves about cutis laxa
PREV	Prevention	Discuss preventive or preemptive care
OTH	Other	Discuss other people dealing with health issues, whether with cutis laxa or other disease
FINDMP	Finding Medical Providers	Discuss process of finding providers
SELFPERCEP	Self Perception	Discuss specifically perceiving something about their own body or their health
INSUR	Insurance	Discuss or mention insurance
NEGEM	Negative Emotions	Explicitly bring up negative emotions or having negative reactions (fear, doubt, anxiety, unhappiness)
UNCODED	Uncoded	Uncoded

Appendix F Institutional Review Board Approval (Essay)



University of Pittsburgh Institutional Review Board

3500 Fifth Avenue
Pittsburgh, PA 15213
(412) 383-1480
(412) 383-1508 (fax)
<http://www.irb.pitt.edu>

Memorandum

To: Zsolt Urban MD
From: Frank Lieberman MD, Vice Chair
Date: 8/25/2010
IRB#: [PRO10020125](#)
Subject: Genetics of Extracellular Matrix in Health and Disease

At its full board meeting on 8/11/2010, the University of Pittsburgh Institutional Review Board, Committee E, reviewed the above referenced research study and approved it pending minor modifications. Your responses to these comments have been reviewed and the research submission, in its currently modified form, adequately addresses the concerns of the IRB and is therefore approved.

Please note the following information:

The risk level designation is Greater Than Minimal Risk.

Approval Date: 8/25/2010
Expiration Date: 8/10/2011

For studies being conducted in UPMC facilities, no clinical activities can be undertaken by investigators until they have received approval from the UPMC Fiscal Review Office.

Please note that it is the investigator's responsibility to report to the IRB any unanticipated problems involving risks to subjects or others [see 45 CFR 46.103(b)(5) and 21 CFR 56.108(b)]. The IRB Reference Manual (Chapter 3, Section 3.3) describes the reporting requirements for unanticipated problems which include, but are not limited to, adverse events. If you have any questions about this process, please contact the Adverse Events Coordinator at 412-383-1480.

The protocol and consent forms, along with a brief progress report must be resubmitted at least one month prior to the renewal date noted above as required by FWA00006790 (University of Pittsburgh), FWA00006735 (University of Pittsburgh Medical Center), FWA00000600 (Children's Hospital of Pittsburgh), FWA00003567 (Magee-Womens Health Corporation), FWA00003338 (University of Pittsburgh Medical Center Cancer Institute).

Please be advised that your research study may be audited periodically by the University of Pittsburgh Research Conduct and Compliance Office.

University of Pittsburgh
Institutional Review Board

3500 Fifth Avenue
Pittsburgh, PA 15213
(412) 383-1480
(412) 383-1508 (fax)
<http://www.irb.pitt.edu>

Memorandum

To: [Zsolt Urban](#), PhD
From: [Judith Martin](#), MD, Vice Chair
Date: 1/7/2019
IRB#: [REN18110296](#) / PRO10020125
Subject: Genetics of Extracellular Matrix in Health and Disease

The Renewal for the above referenced research study was reviewed and approved by the Institutional Review Board, Committee D, which met on 1/3/2019.

Please note the following information:

Note, the modification that was submitted with this renewal (MOD10020125-19) was reconsidered, due to insufficient justification. **As a reminder, no further enrollment can occur until the increase has been reviewed and approved.**

The risk level designation is Greater Than Minimal.

Approval Date: 1/3/2019
Expiration Date: 1/2/2020

This study is supported by the following federal grant application:
R01 Genetics of Extracellular Matrix in Health and Disease

Please note that it is the investigator's responsibility to report to the IRB any unanticipated problems involving risks to subjects or others [see 45 CFR 46.103(b)(5) and 21 CFR 56.108(b)]. Refer to the IRB Policy and Procedure Manual regarding the reporting requirements for unanticipated problems which include, but are not limited to, adverse events. If you have any questions about this process, please contact the Adverse Events Coordinator at 412-383-1480.

The protocol and consent forms, along with a brief progress report must be resubmitted at least **one month** prior to the renewal date noted above as required by FWA00006790 (University of Pittsburgh), FWA00006735 (University of Pittsburgh Medical Center), FWA00006600 (Children's Hospital of Pittsburgh), FWA00003567 (Magee-Womens Health Corporation), FWA00003338 (University of Pittsburgh Medical Center Cancer Institute).

Please be advised that your research study may be audited periodically by the University of Pittsburgh Research Conduct and Compliance Office.

Bibliography

- Anderson, M., Elliott, E. J., & Zurynski, Y. A. (2013). Australian families living with rare disease: experiences of diagnosis, health services use and needs for psychosocial support. *Orphanet J Rare Dis*, 8, 22. doi:10.1186/1750-1172-8-22
- Aslanger, A. D., Altunoglu, U., Aslanger, E., Satkin, B. N., Uyguner, Z. O., & Kayserili, H. (2014). Newly described clinical features in two siblings with MACS syndrome and a novel mutation in RIN2. *Am J Med Genet A*, 164a(2), 484-489. doi:10.1002/ajmg.a.36277
- Ayme, S., Kole, A., & Groft, S. (2008). Empowerment of patients: lessons from the rare diseases community. *Lancet*, 371(9629), 2048-2051. doi:10.1016/s0140-6736(08)60875-2
- Baldwin, A. K., Simpson, A., Steer, R., Cain, S. A., & Kielty, C. M. (2013). Elastic fibres in health and disease. *Expert Rev Mol Med*, 15, e8. doi:10.1017/erm.2013.9
- Basel-Vanagaite, L., Sarig, O., HersHKovitz, D., Fuchs-Telem, D., Rapaport, D., Gat, A., . . . Sprecher, E. (2009). RIN2 deficiency results in macrocephaly, alopecia, cutis laxa, and scoliosis: MACS syndrome. *Am J Hum Genet*, 85(2), 254-263. doi:10.1016/j.ajhg.2009.07.001
- Baynam, G., Bowman, F., Lister, K., Walker, C. E., Pachter, N., Goldblatt, J., . . . Dawkins, H. J. S. (2017). Improved Diagnosis and Care for Rare Diseases through Implementation of Precision Public Health Framework. *Adv Exp Med Biol*, 1031, 55-94. doi:10.1007/978-3-319-67144-4_4
- Beck, A. T., Ward, C. H., Mendelson, M., Mock, J., & Erbaugh, J. (1961). An inventory for measuring depression. *Arch Gen Psychiatry*, 4, 561-571. doi:10.1001/archpsyc.1961.01710120031004
- Beighton, P. (1972). The dominant and recessive forms of cutis laxa. *J Med Genet*, 9(2), 216-221. doi:10.1136/jmg.9.2.216
- Berk, D. R., Bentley, D. D., Bayliss, S. J., Lind, A., & Urban, Z. (2012). Cutis laxa: a review. *J Am Acad Dermatol*, 66(5), 842.e841-817. doi:10.1016/j.jaad.2011.01.004
- Bicknell, L. S., Pitt, J., Aftimos, S., Ramadas, R., Maw, M. A., & Robertson, S. P. (2008). A missense mutation in ALDH18A1, encoding Delta1-pyrroline-5-carboxylate synthase (P5CS), causes an autosomal recessive neurocutaneous syndrome. *Eur J Hum Genet*, 16(10), 1176-1186. doi:10.1038/ejhg.2008.91
- Blanchard, J., & Lurie, N. (2004). R-E-S-P-E-C-T: patient reports of disrespect in the health care setting and its impact on care. *J Fam Pract*, 53(9), 721-730.
- Bogart, K. R., & Irvin, V. L. (2017). Health-related quality of life among adults with diverse rare disorders. *Orphanet J Rare Dis*, 12(1), 177. doi:10.1186/s13023-017-0730-1
- Braun, V., & Clarke, V. (2006). Using thematic analysis in psychology. *Qualitative research in psychology*, 3(2), 77-101.
- Budysh, K., Helms, T. M., & Schultz, C. (2012). How do patients with rare diseases experience the medical encounter? Exploring role behavior and its impact on patient-physician interaction. *Health Policy*, 105(2-3), 154-164. doi:10.1016/j.healthpol.2012.02.018
- Callewaert, B., Renard, M., Huchtagowder, V., Albrecht, B., Hausser, I., Blair, E., . . . Urban, Z. (2011). New insights into the pathogenesis of autosomal-dominant cutis laxa with report of five ELN mutations. *Hum Mutat*, 32(4), 445-455. doi:10.1002/humu.21462

- Callewaert, B., Su, C. T., Van Damme, T., Vlummens, P., Malfait, F., Vanakker, O., . . . De Paepe, A. (2013). Comprehensive clinical and molecular analysis of 12 families with type 1 recessive cutis laxa. *Hum Mutat*, 34(1), 111-121. doi:10.1002/humu.22165
- Callewaert, B. L., & Urban, Z. (1993). LTBP4-Related Cutis Laxa. In M. P. Adam, H. H. Ardinger, R. A. Pagon, S. E. Wallace, L. J. H. Bean, K. Stephens, & A. Amemiya (Eds.), *GeneReviews*(®). Seattle (WA): University of Washington, Seattle
- Copyright © 1993-2020, University of Washington, Seattle. GeneReviews is a registered trademark of the University of Washington, Seattle. All rights reserved.
- census.gov. (2019). United States Census Bureau QuickFacts. Retrieved from <https://www.census.gov/quickfacts/fact/table/US/PST045219>
- Chinnery, P. F., & Turnbull, D. M. (2001). Epidemiology and treatment of mitochondrial disorders. *American journal of medical genetics*, 106(1), 94-101.
- Clarke, D. M., & Currie, K. C. (2009). Depression, anxiety and their relationship with chronic diseases: a review of the epidemiology, risk and treatment evidence. *Med J Aust*, 190(S7), S54-60.
- Cutis Laxa. (1890). *Hospital (Lond 1886)*, 7(180), 362.
- Cutis laxa. (2017). Retrieved from <https://ghr.nlm.nih.gov/condition/cutis-laxa>
- Daker-White, G., Kingston, H., Payne, K., Greenfield, J., Ealing, J., & Sanders, C. (2015). 'You don't get told anything, they don't do anything and nothing changes'. Medicine as a resource and constraint in progressive ataxia. *Health Expect*, 18(2), 177-187. doi:10.1111/hex.12016
- De Sanctis, V., Soliman, A. T., Canatan, D., Elsedfy, H., Karimi, M., Daar, S., . . . Kattamis, C. (2018). An ICET- A survey on Hypoparathyroidism in Patients with Thalassaemia Major and Intermedia: A preliminary report. *Acta Biomed*, 88(4), 435-444. doi:10.23750/abm.v88i4.6837
- DeJean, D., Giacomini, M., Vanstone, M., & Brundisini, F. (2013). Patient experiences of depression and anxiety with chronic disease: a systematic review and qualitative meta-synthesis. *Ont Health Technol Assess Ser*, 13(16), 1-33.
- Dharssi, S., Wong-Rieger, D., Harold, M., & Terry, S. (2017). Review of 11 national policies for rare diseases in the context of key patient needs. *Orphanet J Rare Dis*, 12(1), 63. doi:10.1186/s13023-017-0618-0
- Dimitrov, D., & Szepietowski, J. C. (2017). Stigmatization in dermatology with a special focus on psoriatic patients. *Postepy Hig Med Dosw (Online)*, 71(0), 1115-1122. doi:10.5604/01.3001.0010.6879
- Dimopoulou, A., Fischer, B., Gardeitchik, T., Schroter, P., Kayserili, H., Schlack, C., . . . Kornak, U. (2013). Genotype-phenotype spectrum of PYCR1-related autosomal recessive cutis laxa. *Mol Genet Metab*, 110(3), 352-361. doi:10.1016/j.ymgme.2013.08.009
- Domaradzki, J., & Walkowiak, D. (2019). Medical students' knowledge and opinions about rare diseases: A case study from Poland. *Intractable Rare Dis Res*, 8(4), 252-259. doi:10.5582/irdr.2019.01099
- Dudding-Byth, T. (2015). A powerful team: the family physician advocating for patients with a rare disease. *Aust Fam Physician*, 44(9), 634-638.
- Duque Lasio, M. L., & Kozel, B. A. (2018). Elastin-driven genetic diseases. *Matrix Biol*, 71-72, 144-160. doi:10.1016/j.matbio.2018.02.021

- Dutta, A. K., Ekbote, A. V., Thomas, N., Omprakash, S., & Danda, S. (2016). De Barsy syndrome type B presenting with cardiac and genitourinary abnormalities. *Clin Dysmorphol*, 25(4), 190-191. doi:10.1097/mcd.0000000000000142
- Elbuluk, N., & Ezzedine, K. (2017). Quality of Life, Burden of Disease, Co-morbidities, and Systemic Effects in Vitiligo Patients. *Dermatol Clin*, 35(2), 117-128. doi:10.1016/j.det.2016.11.002
- Emanuel, E. J., & Emanuel, L. L. (1992). Four models of the physician-patient relationship. *Jama*, 267(16), 2221-2226.
- Ferreira, C. R. (2019). The burden of rare diseases. *Am J Med Genet A*, 179(6), 885-892. doi:10.1002/ajmg.a.61124
- Gallagher, T. H., & Levinson, W. (2004). A prescription for protecting the doctor-patient relationship. *Am J Manag Care*, 10(2 Pt 1), 61-68.
- Gelenberg, A. J. (2010). Using assessment tools to screen for, diagnose, and treat major depressive disorder in clinical practice. *J Clin Psychiatry*, 71 Suppl E1, e01. doi:10.4088/JCP.9058selc.01gry
- Granstrom, S., Längenbruch, A., Augustin, M., & Mautner, V. F. (2012). Psychological burden in adult neurofibromatosis type 1 patients: impact of disease visibility on body image. *Dermatology*, 224(2), 160-167. doi:10.1159/000337548
- Grondahl, V. A., Kirchhoff, J. W., Andersen, K. L., Sorby, L. A., Andreassen, H. M., Skaug, E. A., . . . Helgesen, A. K. (2018). Health care quality from the patients' perspective: a comparative study between an old and a new, high-tech hospital. *J Multidiscip Healthc*, 11, 591-600. doi:10.2147/jmdh.S176630
- Gupta, M. A., Gupta, A. K., Ellis, C. N., & Koblenzer, C. S. (2005). Psychiatric evaluation of the dermatology patient. *Dermatol Clin*, 23(4), 591-599. doi:10.1016/j.det.2005.05.005
- Haider, M., Alfadley, A., Kadry, R., & Almutawa, A. (2010). Acquired cutis laxa type II (Marshall syndrome) in an 18-month-old child: a case report. *Pediatr Dermatol*, 27(1), 89-91. doi:10.1111/j.1525-1470.2009.01052.x
- Hale, E. D., Radvanski, D. C., & Hassett, A. L. (2015). The man-in-the-moon face: a qualitative study of body image, self-image and medication use in systemic lupus erythematosus. *Rheumatology (Oxford)*, 54(7), 1220-1225. doi:10.1093/rheumatology/keu448
- Handler, M. Z. (2017). Cutis Laxa (Elastolysis). Retrieved from <https://emedicine.medscape.com/article/1074167-overview#:~:text=Background,of%20inheritance%20show%20considerable%20heterogeneity>.
- Harlow, L. Acquired Cutis Laxa. Retrieved from <http://cutislaxa.pitt.edu/acquired.php>
- Health, E. C. o. P. (2009). *Council Recommendation of 8 June 2009 on an action in the field of rare diseases*. Retrieved from Office Journal of the European Union:
- Hennies, H. C., Kornak, U., Zhang, H., Egerer, J., Zhang, X., Seifert, W., . . . Mundlos, S. (2008). Geroderma osteodysplastica is caused by mutations in SCYL1BP1, a Rab-6 interacting golgin. *Nat Genet*, 40(12), 1410-1412. doi:10.1038/ng.252
- Huchtagowder, V., Morava, E., Kornak, U., Lefeber, D. J., Fischer, B., Dimopoulou, A., . . . Urban, Z. (2009). Loss-of-function mutations in ATP6V0A2 impair vesicular trafficking, tropoelastin secretion and cell survival. *Hum Mol Genet*, 18(12), 2149-2165. doi:10.1093/hmg/ddp148

- Huchtagowder, V., Sausgruber, N., Kim, K. H., Angle, B., Marmorstein, L. Y., & Urban, Z. (2006). Fibulin-4: a novel gene for an autosomal recessive cutis laxa syndrome. *Am J Hum Genet*, 78(6), 1075-1080. doi:10.1086/504304
- Huyard, C. (2009). What, if anything, is specific about having a rare disorder? Patients judgments on being ill and being rare. *Health Expectations: An International Journal of Public Participation in Health Care & Health Policy*, 12(4), 361-370. doi:<http://dx.doi.org/10.1111/j.1369-7625.2009.00552.x>
- Huyard, C. (2009). What, if anything, is specific about having a rare disorder? Patients' judgements on being ill and being rare. *Health Expect*, 12(4), 361-370. doi:10.1111/j.1369-7625.2009.00552.x
- Jia, J., & Shi, T. (2017). Towards efficiency in rare disease research: what is distinctive and important? *Sci China Life Sci*, 60(7), 686-691. doi:10.1007/s11427-017-9099-3
- Kaiser, J. (2016). Saudi gene hunters comb country's DNA to prevent rare diseases. *Science*.
- Kaler, S. G. (2011). ATP7A-related copper transport diseases-emerging concepts and future trends. *Nat Rev Neurol*, 7(1), 15-29. doi:10.1038/nrneurol.2010.180
- Kappanayil, M., Nampoothiri, S., Kannan, R., Renard, M., Coucke, P., Malfait, F., . . . De Paepe, A. (2012). Characterization of a distinct lethal arteriopathy syndrome in twenty-two infants associated with an identical, novel mutation in FBLN4 gene, confirms fibulin-4 as a critical determinant of human vascular elastogenesis. *Orphanet J Rare Dis*, 7, 61. doi:10.1186/1750-1172-7-61
- Kariminejad, A., Afroozan, F., Bozorgmehr, B., Ghanadan, A., Akbaroghli, S., Khorram Khorshid, H. R., . . . Morava, E. (2017). Discriminative Features in Three Autosomal Recessive Cutis Laxa Syndromes: Cutis Laxa IIA, Cutis Laxa IIB, and Geroderma Osteoplastica. *Int J Mol Sci*, 18(3). doi:10.3390/ijms18030635
- Khangura, S. D., Tingley, K., Chakraborty, P., Coyle, D., Kronick, J. B., Laberge, A. M., . . . Potter, B. K. (2016). Child and family experiences with inborn errors of metabolism: a qualitative interview study with representatives of patient groups. *J Inherit Metab Dis*, 39(1), 139-147. doi:10.1007/s10545-015-9881-1
- Khosla, N., & Valdez, R. (2018). A compilation of national plans, policies and government actions for rare diseases in 23 countries. *Intractable Rare Dis Res*, 7(4), 213-222. doi:10.5582/irdr.2018.01085
- Kodra, Y., Morosini, P. R., Petrigliano, R., Agazio, E., Salerno, P., & Taruscio, D. (2007). Access to and quality of health and social care for rare diseases: patients' and caregivers' experiences. *Ann Ig*, 19(2), 153-160.
- Kornak, U., Reynders, E., Dimopoulou, A., van Reeuwijk, J., Fischer, B., Rajab, A., . . . Mundlos, S. (2008). Impaired glycosylation and cutis laxa caused by mutations in the vesicular H⁺-ATPase subunit ATP6V0A2. *Nat Genet*, 40(1), 32-34. doi:10.1038/ng.2007.45
- Kowal, R. C., Richardson, J. A., Miano, J. M., & Olson, E. N. (1999). EVEC, a novel epidermal growth factor-like repeat-containing protein upregulated in embryonic and diseased adult vasculature. *Circ Res*, 84(10), 1166-1176. doi:10.1161/01.res.84.10.1166
- Kroenke, K., Spitzer, R. L., Williams, J. B., & Löwe, B. (2010). The Patient Health Questionnaire Somatic, Anxiety, and Depressive Symptom Scales: a systematic review. *Gen Hosp Psychiatry*, 32(4), 345-359. doi:10.1016/j.genhosppsych.2010.03.006
- Leao-Teles, E., Quelhas, D., Vilarinho, L., & Jaeken, J. (2010). De Barsy syndrome and ATP6V0A2-CDG. *Eur J Hum Genet*, 18(5), 526; author reply 526. doi:10.1038/ejhg.2009.218

- Letard, P., Schepers, D., Albuissou, J., Bruneval, P., Spaggiari, E., Van de Beek, G., . . . Guimiot, F. (2018). Severe Phenotype of Cutis Laxa Type 1B with Antenatal Signs due to a Novel Homozygous Nonsense Mutation in EFEMP2. *Mol Syndromol*, 9(4), 190-196. doi:10.1159/000489838
- Lin, D. S., Chang, J. H., Liu, H. L., Wei, C. H., Yeung, C. Y., Ho, C. S., . . . Lin, S. P. (2011). Compound heterozygous mutations in PYCR1 further expand the phenotypic spectrum of De Barsy syndrome. *Am J Med Genet A*, 155a(12), 3095-3099. doi:10.1002/ajmg.a.34326
- Linthorst Homan, M. W., de Korte, J., Grootenhuys, M. A., Bos, J. D., Sprangers, M. A., & van der Veen, J. P. (2008). Impact of childhood vitiligo on adult life. *Br J Dermatol*, 159(4), 915-920. doi:10.1111/j.1365-2133.2008.08788.x
- Loeys, B., De Paepe, A., & Urban, Z. (1993). EFEMP2-Related Cutis Laxa. In M. P. Adam, H. H. Ardinger, R. A. Pagon, S. E. Wallace, L. J. H. Bean, K. Stephens, & A. Amemiya (Eds.), *GeneReviews*(®). Seattle (WA): University of Washington, Seattle
- Copyright © 1993-2020, University of Washington, Seattle. GeneReviews is a registered trademark of the University of Washington, Seattle. All rights reserved.
- Markova, D., Zou, Y., Ringpfeil, F., Sasaki, T., Kostka, G., Timpl, R., . . . Chu, M. L. (2003). Genetic heterogeneity of cutis laxa: a heterozygous tandem duplication within the fibulin-5 (FBLN5) gene. *Am J Hum Genet*, 72(4), 998-1004. doi:10.1086/373940
- Mascalzoni, D., Petrini, C., Taruscio, D., & Gainotti, S. (2017). The Role of Solidarity(-ies) in Rare Diseases Research. *Adv Exp Med Biol*, 1031, 589-604. doi:10.1007/978-3-319-67144-4_31
- Metcalf, M., & Goldman, E. (1965). VALIDATION OF AN INVENTORY FOR MEASURING DEPRESSION. *Br J Psychiatry*, 111, 240-242. doi:10.1192/bjp.111.472.240
- Mohamed, M., Voet, M., Gardeitchik, T., & Morava, E. (2014). Cutis Laxa. *Adv Exp Med Biol*, 802, 161-184. doi:10.1007/978-94-007-7893-1_11
- Nall, R. (2017). Cutis Laxa. Retrieved from <https://www.healthline.com/health/cutis-laxa>
- Neuhauser, D. (2003). The coming third health care revolution: personal empowerment. *Qual Manag Health Care*, 12(3), 171-184; discussion 185-176. doi:10.1097/00019514-200307000-00007
- Newman, W. G., Clayton-Smith, J., Metcalfe, K., Cole, R., Tartaglia, M., Brancati, F., . . . Black, G. C. (2008). Geroderma osteodysplastica maps to a 4 Mb locus on chromosome 1q24. *Am J Med Genet A*, 146a(23), 3034-3037. doi:10.1002/ajmg.a.32564
- Noordam, C., Funke, S., Knoers, N. V., Jira, P., Wevers, R. A., Urban, Z., & Morava, E. (2009). Decreased bone density and treatment in patients with autosomal recessive cutis laxa. *Acta Paediatr*, 98(3), 490-494. doi:10.1111/j.1651-2227.2008.01145.x
- NORD. (n.d.). Cutis Laxa. Retrieved from <https://rarediseases.org/rare-diseases/cutis-laxa/>
- OMIM. (n.d.). Phenotypic Series - PS123700 - Cutis Laxa. Retrieved from <https://omim.org/phenotypicSeries/PS123700>
- Orphanet. (n.d.). Cutis Laxa. Retrieved from https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=209
- Papakostas, G. I., Petersen, T., Mahal, Y., Mischoulon, D., Nierenberg, A. A., & Fava, M. (2004). Quality of life assessments in major depressive disorder: a review of the literature. *Gen Hosp Psychiatry*, 26(1), 13-17. doi:10.1016/j.genhosppsych.2003.07.004
- Patients Worldwide. (2019). Retrieved from <http://www.cutislaxa.org/en/patients-worldwide/>

- Paulsen, I. F., Bredgaard, R., Hesse, B., Steiniche, T., & Henriksen, T. F. (2014). Acquired cutis laxa: diagnostic and therapeutic considerations. *J Plast Reconstr Aesthet Surg*, 67(10), e242-243. doi:10.1016/j.bjps.2014.06.010
- Picardi, A., Abeni, D., Melchi, C. F., Puddu, P., & Pasquini, P. (2000). Psychiatric morbidity in dermatological outpatients: an issue to be recognized. *Br J Dermatol*, 143(5), 983-991. doi:10.1046/j.1365-2133.2000.03831.x
- Pogue, R. E., Cavalcanti, D. P., Shanker, S., Andrade, R. V., Aguiar, L. R., de Carvalho, J. L., & Costa, F. F. (2018). Rare genetic diseases: update on diagnosis, treatment and online resources. *Drug Discov Today*, 23(1), 187-195. doi:10.1016/j.drudis.2017.11.002
- Post, M. W. (2014). Definitions of quality of life: what has happened and how to move on. *Top Spinal Cord Inj Rehabil*, 20(3), 167-180. doi:10.1310/sci2003-167
- Pulciani, S., Nutile, E., & Taruscio, D. (2018). Patient Associations: a driving force for Rare Diseases research. Resilience: a driving force for Patient Associations. *Ann Ig*, 30(4), 307-316. doi:10.7416/ai.2018.2222
- Radloff, L. S. (1977). The CES-D scale: A self-report depression scale for research in the general population. *Applied psychological measurement*, 1(3), 385-401.
- Ramalle-Gómara, E., Domínguez-Garrido, E., Gómez-Eguílaz, M., Marzo-Sola, M. E., Ramón-Trapero, J. L., & Gil-de-Gómez, J. (2020). Education and information needs for physicians about rare diseases in Spain. *Orphanet J Rare Dis*, 15(1), 18. doi:10.1186/s13023-019-1285-0
- Richter, P., Werner, J., Heerlein, A., Kraus, A., & Sauer, H. (1998). On the validity of the Beck Depression Inventory. A review. *Psychopathology*, 31(3), 160-168. doi:10.1159/000066239
- Sampogna, F., Tabolli, S., Giannantoni, P., Paradisi, A., & Abeni, D. (2016). Relationship Between Psychosocial Burden of Skin Conditions and Symptoms: Measuring the Attributable Fraction. *Acta Derm Venereol*, 96(1), 60-63. doi:10.2340/00015555-2094
- Schieppati, A., Henter, J. I., Daina, E., & Aperia, A. (2008). Why rare diseases are an important medical and social issue. *Lancet*, 371(9629), 2039-2041. doi:10.1016/s0140-6736(08)60872-7
- Schwartz, C. E., Michael, W., & Rapkin, B. D. (2017). Resilience to health challenges is related to different ways of thinking: mediators of physical and emotional quality of life in a heterogeneous rare-disease cohort. *Qual Life Res*, 26(11), 3075-3088. doi:10.1007/s11136-017-1633-2
- Snaith, R. P. (2003). The Hospital Anxiety And Depression Scale. *Health Qual Life Outcomes*, 1, 29. doi:10.1186/1477-7525-1-29
- Sofaer, S., & Firminger, K. (2005). Patient perceptions of the quality of health services. *Annu Rev Public Health*, 26, 513-559. doi:10.1146/annurev.publhealth.25.050503.153958
- Southwick, S. M., Bonanno, G. A., Masten, A. S., Panter-Brick, C., & Yehuda, R. (2014). Resilience definitions, theory, and challenges: interdisciplinary perspectives. *Eur J Psychotraumatol*, 5. doi:10.3402/ejpt.v5.25338
- Stone, L. (2014). Blame, shame and hopelessness: medically unexplained symptoms and the 'heartsink' experience. *Aust Fam Physician*, 43(4), 191-195.
- Su, C. T., Huang, J. W., Chiang, C. K., Lawrence, E. C., Levine, K. L., Dabovic, B., . . . Urban, Z. (2015). Latent transforming growth factor binding protein 4 regulates transforming growth factor beta receptor stability. *Hum Mol Genet*, 24(14), 4024-4036. doi:10.1093/hmg/ddv139

- Szabo, Z., Crepeau, M. W., Mitchell, A. L., Stephan, M. J., Puntel, R. A., Yin Loke, K., . . . Urban, Z. (2006). Aortic aneurysmal disease and cutis laxa caused by defects in the elastin gene. *J Med Genet*, 43(3), 255-258. doi:10.1136/jmg.2005.034157
- Tassabehji, M., Metcalfe, K., Hurst, J., Ashcroft, G. S., Kielty, C., Wilmot, C., . . . Jones, C. J. (1998). An elastin gene mutation producing abnormal tropoelastin and abnormal elastic fibres in a patient with autosomal dominant cutis laxa. *Hum Mol Genet*, 7(6), 1021-1028. doi:10.1093/hmg/7.6.1021
- Thomas, S., & Caplan, A. (2019). The Orphan Drug Act Revisited. *Jama*, 321(9), 833-834. doi:10.1001/jama.2019.0290
- Tsukahara, M., Imaizumi, K., Kawai, S., & Kajii, T. (1994). Occipital horn syndrome: report of a patient and review of the literature. *Clin Genet*, 45(1), 32-35. doi:10.1111/j.1399-0004.1994.tb03986.x
- Tumer, Z. (2013). An overview and update of ATP7A mutations leading to Menkes disease and occipital horn syndrome. *Hum Mutat*, 34(3), 417-429. doi:10.1002/humu.22266
- Uhlenbusch, N., Lowe, B., Harter, M., Schramm, C., Weiler-Normann, C., & Depping, M. K. (2019). Depression and anxiety in patients with different rare chronic diseases: A cross-sectional study. *PLoS One*, 14(2), e0211343. doi:10.1371/journal.pone.0211343
- Urban, Z., & Davis, E. C. (2014). Cutis laxa: intersection of elastic fiber biogenesis, TGFbeta signaling, the secretory pathway and metabolism. *Matrix Biol*, 33, 16-22. doi:10.1016/j.matbio.2013.07.006
- Urban, Z., Huchtagowder, V., Schurmann, N., Todorovic, V., Zilberberg, L., Choi, J., . . . Davis, E. C. (2009). Mutations in LTBP4 cause a syndrome of impaired pulmonary, gastrointestinal, genitourinary, musculoskeletal, and dermal development. *Am J Hum Genet*, 85(5), 593-605. doi:10.1016/j.ajhg.2009.09.013
- Valdez, R., Ouyang, L., & Bolen, J. (2016). Public Health and Rare Diseases: Oxymoron No More. *Prev Chronic Dis*, 13, E05. doi:10.5888/pcd13.150491
- Van Maldergem, L., Dobyns, W., & Kornak, U. (1993). ATP6V0A2-Related Cutis Laxa. In M. P. Adam, H. H. Ardinger, R. A. Pagon, S. E. Wallace, L. J. H. Bean, K. Stephens, & A. Amemiya (Eds.), *GeneReviews*(®). Seattle (WA): University of Washington, Seattle
- Copyright © 1993-2020, University of Washington, Seattle. GeneReviews is a registered trademark of the University of Washington, Seattle. All rights reserved.
- Van Maldergem, L., & Loeys, B. (1993). FBLN5-Related Cutis Laxa. In M. P. Adam, H. H. Ardinger, R. A. Pagon, S. E. Wallace, L. J. H. Bean, K. Stephens, & A. Amemiya (Eds.), *GeneReviews*(®). Seattle (WA): University of Washington, Seattle
- Copyright © 1993-2020, University of Washington, Seattle. GeneReviews is a registered trademark of the University of Washington, Seattle. All rights reserved.
- Vandeborne, L., van Overbeeke, E., Doms, M., De Beleyr, B., & Huys, I. (2019). Information needs of physicians regarding the diagnosis of rare diseases: a questionnaire-based study in Belgium. *Orphanet J Rare Dis*, 14(1), 99. doi:10.1186/s13023-019-1075-8
- von der Lippe, C., Diesen, P. S., & Feragen, K. B. (2017). Living with a rare disorder: a systematic review of the qualitative literature. *Mol Genet Genomic Med*, 5(6), 758-773. doi:10.1002/mgg3.315
- Wachi, H., Nonaka, R., Sato, F., Shibata-Sato, K., Ishida, M., Iketani, S., . . . Seyama, Y. (2008). Characterization of the molecular interaction between tropoelastin and DANCE/fibulin-5. *J Biochem*, 143(5), 633-639. doi:10.1093/jb/mvn014

- Wellman-Labadie, O., & Zhou, Y. (2010). The US Orphan Drug Act: rare disease research stimulator or commercial opportunity? *Health Policy*, 95(2-3), 216-228. doi:10.1016/j.healthpol.2009.12.001
- WHO. (2016). *Framework on integrated, people-centred health services*. Retrieved from Sixty-Ninth World Health Assembly: https://apps.who.int/gb/ebwha/pdf_files/WHA69/A69_39-en.pdf
- Wigley, J. E. (1943). Dermatolysis (Cutis Laxa). *Proc R Soc Med*, 36(6), 294-295.
- Witkos, T. M., Chan, W. L., Joensuu, M., Rhiel, M., Pallister, E., Thomas-Oates, J., . . . Lowe, M. (2019). GORAB scaffolds COPI at the trans-Golgi for efficient enzyme recycling and correct protein glycosylation. *Nat Commun*, 10(1), 127. doi:10.1038/s41467-018-08044-6
- Zimmerman, M. (2018, 12/4/2019). Using scales to monitor symptoms and treat depression (measurement based care). Retrieved from <https://www-uptodate-com.pitt.idm.oclc.org/contents/using-scales-to-monitor-symptoms-and-treat-depression-measurement-based-care#H184319686>
- Zsolt, U. (2020). Cutis Laxa Research Study FAQs. Retrieved from <http://cutislaxa.pitt.edu/>
- Zung, W. W. (1965). A SELF-RATING DEPRESSION SCALE. *Arch Gen Psychiatry*, 12, 63-70. doi:10.1001/archpsyc.1965.01720310065008
- Zurynski, Y., Frith, K., Leonard, H., & Elliott, E. (2008). Rare childhood diseases: how should we respond? *Arch Dis Child*, 93(12), 1071-1074. doi:10.1136/ad.2007.134940