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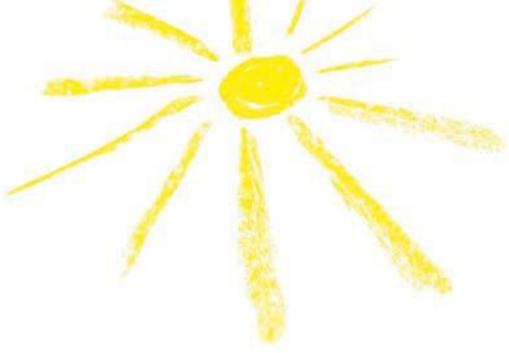
The Progeria Handbook

2nd Edition

2019 Interim Version

A Guide
for Families
& Health Care
Providers
of Children
with Progeria

 Progeria
Research Foundation®



The Progeria Handbook

A Guide for Families
& Health Care Providers
of Children with Progeria
2nd Edition – 2019 Interim Version

The mission of The Progeria Research Foundation is to discover the cause, treatment, and cure for Hutchinson-Gilford Progeria Syndrome and its aging-related conditions, including heart disease.

Together we *WILL* find the cure!



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The information in this book is the most current available and is subject to change. This book and updates to this book will be available online at <https://www.progeriaresearch.org/patient-care-and-handbook/>

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This book is dedicated to all children with Progeria:
For your endless courage, enduring beauty, and undaunted spirit.
You are our inspiration.



My Philosophy for a Happy Life

- #1 Be OK with what you ultimately can't do,
because there is so much you CAN do
- #2 Surround yourself with people you want to be around
- #3 Keep moving forward
- #4 Never miss a party if you can help it

**Presented By Sam Berns at
TEDxMidAtlantic
October 26, 2013**

<http://www.youtube.com/watch?v=36m1o-tM05g>

For Sam

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A Message from the Medical Director

Since its inception in 1999, The Progeria Research Foundation has been working towards discovering the cause, treatments, and cure for Progeria. We've seen Progeria move from obscurity, to gene finding, to treatment trial, to our first-ever treatment for Progeria. Each day that passes, families and their health care providers search for guidance on how to help improve the lives of children with Progeria. With their beautiful smiles and their incredible personalities, we all want children with Progeria to live their lives to the fullest. I sincerely hope this guide provides some assistance with that common goal.

I am extremely proud to present this second edition of *The Progeria Handbook: A guide for families and health care providers of children with Progeria*. We've learned a tremendous amount about dealing with health and disease in Progeria since our first edition. This is all due to the dedication of the world's experts on Progeria who contributed to this edition, and to the courageous children and families who enter into The Progeria Research Foundation programs.

Since the first edition was published, over 100 children with Progeria from 47 different countries have been cared for by the Progeria experts who contributed to this edition. This has allowed us all to grow and learn about Progeria, and how to help care for these amazing children.

Thank you to all who devoted their time and expertise so that this handbook could be developed. Most of all, thank you to the children who inspire the rest of us every day.

This handbook is intended to help families of children with Progeria at all ages and stages of development and disease. There are sections that speak directly to families, and there are more technical recommendations for health care providers. These are intermingled within each chapter.

The Progeria Research Foundation strives to be the driving force worldwide to:

- Discover the cure for Progeria
- Develop treatments for children with Progeria
- Provide programs that push the field of Progeria research forward every day towards the cure
- Be a valuable resource for families living with Progeria and their health caretakers

Together we *WILL* find the cure!



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1. Progeria: Frequently Asked Questions

What is Hutchinson-Gilford Progeria Syndrome?

What is PRF's history and mission?

Is there a treatment or a cure for Progeria?



What is Hutchinson-Gilford Progeria Syndrome (HGPS or Progeria)?

Progeria is also known as Hutchinson-Gilford Progeria Syndrome (HGPS). It was first described in 1886 by Dr. Jonathan Hutchinson and in 1897 by Dr. Hastings Gilford.

Progeria is a rare, fatal, “premature aging” syndrome. It’s called a syndrome because all the children have very similar symptoms that “go together”. The children have a remarkably similar appearance, even though Progeria affects children of all different ethnic backgrounds. Although most babies with Progeria are born looking healthy, they begin to display some characteristics of Progeria in the first year of life. Sometimes one of the earliest signs of Progeria is tightness or bulging of the skin in the abdominal and/or thigh area. Other signs of Progeria include growth failure, loss of body fat and hair, skin changes, stiffness of joints, hip dislocation, generalized atherosclerosis, cardiovascular (heart) disease, and stroke. Children with Progeria die of atherosclerosis (heart disease) or stroke at an average age of 14 years (with a range of about 8-21 years). Remarkably, the intellect of children with Progeria is unaffected, and despite the physical changes in their young bodies, these extraordinary children are intelligent, courageous, and full of life.

Progeria is a rare genetic disease that is not usually passed down from parents, because it is a chance occurrence (mutation) in the DNA (see Genetics Section). There is a genetic test for Progeria and PRF has a genetic testing program. Progeria affects all races and both girls and boys equally. Children with Progeria are found all over the world, and PRF's mission is to help every child worldwide.

What is PRF's history and mission?

The Progeria Research Foundation (PRF) was established in the United States in 1999 by the parents of a child with Progeria, Drs. Leslie Gordon and Scott Berns, and many dedicated friends and family who saw the need for a medical resource for the doctors, patients, and families of those with Progeria and for funding of Progeria research. Since that time, PRF has become a driving force for promoting advances in the field, including the historic discovery of the Progeria gene and the discovery of the first treatment for Progeria. (See, Diagnosis, Genetics and Genetic Counseling Section and Treatment Trials Section) PRF has developed a comprehensive network of programs (see PRF *Programs & Services*) to aid those affected by Progeria and those researchers who want to conduct Progeria research. PRF is the only non-profit organization worldwide solely dedicated to finding treatments and the cure for Progeria and its aging-related disorders including heart disease.

Is there a treatment or a cure for Progeria?

There is currently no cure for Progeria. There is a treatment for Progeria that helps some, but not all aspects of disease (see Treatment Trials Section). Lonafarnib is a drug that is available only through clinical treatment trials. Doctors cannot prescribe this from their offices because it is not available by prescription. Lonafarnib helps with cardiovascular disease and bone disease in Progeria. It does not help with skin, joints or hair. It is taken orally, as either a capsule or a liquid. Its main side effects are diarrhea, nausea and loss of appetite, which often lessen or go away after a few weeks to months. To learn more about lonafarnib, contact The Progeria Research Foundation. The Progeria Research Foundation funds research to find new treatments and a cure for Progeria.

2. Diagnosis, Genetics, and Genetic Counseling

For Families

What causes Progeria?

After an intense scientific search, the gene for HGPS was discovered in April 2003 by a group of researchers working together through The Progeria Research Foundation Genetics Consortium, as well as by a French group of researchers. The gene responsible for HGPS is called LMNA (pronounced “lamin-a”). One tiny spelling mistake in the DNA sequence of LMNA is responsible for Progeria. This type of gene change is called a point mutation. The LMNA gene normally makes a protein called lamin A, which is an important protein for most cells in our bodies. Lamin A is found in the cell nucleus (the part of each cell that contains the DNA) and helps maintain the shape and function of the cell.

In Progeria, the LMNA mutation causes the gene to produce an abnormal lamin A protein called **progerin**. In children with Progeria, many cells in the body – such as the blood vessels, skin, and bones – make the progerin protein. As the children age, progerin builds up in these cells causing progressive disease. The discovery of this new protein called progerin has allowed us to understand why children with Progeria grow old before their time, and has led us down a pathway to the first-ever drug treatment trials for Progeria (see *Drug Treatment Trials*). We also now know that everyone’s body makes progerin, although in much lower amounts compared to children with Progeria. Therefore, by working to help children with Progeria, we may have discovered a brand new protein that affects heart disease and aging in all of us (See *Aging & Progeria*).



Genetic testing for Progeria can be performed from a small sample of blood (1-2 tsp) or sometimes from a sample of saliva

How is Progeria diagnosed?

Progeria is best diagnosed by using both clinical examination and genetic testing. When a physician or a family member suspects that a child has Progeria, he or she may consult with a geneticist and/or genetic counselor about this possibility. Genetic testing in the United States should be performed through a CLIA- approved* testing laboratory. Testing can be achieved through The PRF Diagnostic Testing Program, provided at no cost to families (see *PRF Programs & Services*, section 20). The genetic test is done by coordinating a blood sample submission by mail through home physicians, from anywhere in the world, to PRF. Less often, saliva is tested. Once the sample is received, the test results are usually completed in 2 to 4 weeks, depending on the extent of genetic testing that is required. Results are provided to families through their local physicians, who can discuss results, answer questions, and provide a care plan with families in person. PRF is always available for questions and follow-up with both the physicians and the families.

Are there different types of Progeria?

In this handbook, we refer to the typical or classical HGPS as Progeria. Classical Progeria is caused by a particular genetic change in a particular location on the LMNA gene. Therefore, when we are searching only for classical Progeria, we test one section of the LMNA gene, and not the entire gene. There are other closely related genetic diseases that are called “progeroid laminopathies” or “progeroid syndromes”. These diseases can be more or less severe than classical Progeria, and they are typically even rarer than classical HGPS. When we are searching for progeroid syndromes, we test the entire LMNA gene and often other genes as well.

The guidelines in this handbook focus on children with classic Progeria, because we know more about the disease process and treatment strategies for classic Progeria. Applying that knowledge to nonclassic progeroid syndromes may be helpful to families and home caretakers, but good judgment must be applied, by local caretakers since children with nonclassic progeroid syndromes will have different needs and problems.

*Clinical Laboratory Improvement Amendments (CLIA) is a body of industry regulations ensuring quality laboratory testing.

Is Progeria contagious or inherited?

HGPS is not contagious and is not usually passed down in families. The gene change is almost always a chance occurrence that is extremely rare. Children with other types of progeroid syndromes which are not HGPS may have diseases that are passed down in families. However, HGPS is a “sporadic autosomal dominant” mutation – sporadic because it is a new change in that family, and dominant because only one copy of the gene needs to be changed in order to have the syndrome.

For parents who have never had a child with Progeria, the chances of having a child with Progeria are 1 in 4 million. But for parents who have already had a child with Progeria, the chances of it happening again to those parents is much higher – about 2-3%. Why the increase? This is due to a condition called “mosaicism”, where a parent has the genetic mutation for Progeria in a small proportion of their cells, but does not have Progeria. Mosaicism occurs a small percentage of the time (2-3%) in many genetic diseases. If some of the parental eggs or sperm have the genetic mutation, then those parents could have another child with Progeria. Prenatal testing is available to look for the LMNA genetic change. Each family’s doctor or genetic counselors should be consulted about prenatal testing.

For Health Care Professionals

(adapted from GeneReviews 2018, Gordon et al.)

Diagnosis/testing

The diagnosis of classic or nonclassic genotype HGPS is established in a proband with characteristic clinical features, along with identification of a heterozygous pathogenic variant in *LMNA* that results in production of the abnormal lamin A protein, progerin. Individuals with **classic genotype HGPS** are heterozygous for pathogenic variant [c.1824C>T](#), (~90% of individuals with HGPS). Individuals with **nonclassic genotype HGPS** have the characteristic clinical features of HGPS and are heterozygous for another *LMNA* pathogenic variant in exon 11 or intron 11 that results in production of progerin (identified in ~10% of individuals with HGPS).

Suggestive Clinical Findings

Hutchinson-Gilford progeria syndrome (HGPS) **should be suspected in** individuals with severe growth failure, areas of sclerodermatous skin, partial alopecia that progresses to total alopecia by age 2 years, generalized lipodystrophy, retrognathia, x-ray findings including distal clavicular and terminal phalangeal resorption as well as coxa valga, and delayed/ incomplete primary tooth eruption, all in the setting of normal intellectual development.

Genetic counseling

Almost all individuals with HGPS have the disorder as the result of a *de novo* autosomal dominant pathogenic variant. Recurrence risk to the sibs of a proband is small (as HGPS is typically caused by a *de novo* pathogenic variant) but greater than that of the general population because of the possibility of parental germline mosaicism. Once the *LMNA* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk is possible. The risk to the sibs of a proband is small. However, 3/110 (3%) currently living individuals with classic genotype HGPS identified through the PRF International Registry are caused by an apparent somatic or germline mosaicism in a parent. Because of the (unlikely) possibility of recurrence as a result of germline mosaicism in one of the parents, prenatal testing is possible.

Incidence and Prevalence

The estimated birth incidence for HGPS is one in four million births with no observed differences based on ethnic background [Hennekam 2006].

The prevalence of children with HGPS per total population is one in 20 million [Gordon et al 2014].

Categories of Progeroid Diseases

There are five major categories that help to define *LMNA*-related disorders. The first two define HGPS, while the latter 3 are not considered HGPS:

1. Progerin-producing classic genotype HGPS
2. Progerin-producing non-classic genotype HGPS
3. Non-progerin-producing progeroid laminopathies
 - Due to heterozygous *LMNA* pathogenic variant that does not result in progerin production
 - Due to pathogenic variants in other genes (e.g., *ZMPSTE24*)
4. Non-progeroid laminopathies (see Differential Diagnosis)
5. Non-laminopathy progeroid syndromes (see Differential Diagnosis)

The diagnosis of **classic genotype HGPS is established in** a proband with the above Suggestive Findings and identification of a heterozygous [c.1824C>T](#) pathogenic variant in *LMNA* by molecular genetic testing (see Table 1).

The diagnosis of **nonclassic genotype HGPS is established in** a proband with Suggestive Findings similar to classic genotype HGPS and identification of an autosomal dominant progerin-producing pathogenic variant in either the exon 11 splice junction or intron 11 of *LMNA* (see Table 1).

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing, multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing).

Single-gene testing.

- Targeted analysis for *LMNA* pathogenic variants [c.1824C>T](#) (identified in 90% of individuals with HGPS), can be performed first in individuals with Suggestive Findings of HGPS.
- Sequence analysis of *LMNA* can be performed if no pathogenic variant is found on targeted analysis. Sequence analysis of intron 11 should be included if this was not already completed with targeted analysis.

Note: *LMNA* deletions and/or duplications have not been reported in individuals with HGPS.

A **multigene panel** that includes *LMNA*, *ZMPSTE24*, and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition at the most reasonable cost while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype.

When the phenotype is indistinguishable from many other inherited disorders characterized by progeroid phenotype, **comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are likely involved) is the best option. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

Genotype-Phenotype Correlations

Table 1. Classic Genotype HGPS and Nonclassic Genotype HGPS: Causative *LMNA* Variants and Comparative Clinical Phenotypes

Genotype	<i>LMNA</i> Pathogenic Variant	Phenotypic Features compared to Classic HGPS	# Identified	Reference
Classic HGPS	c.1824C>T; p.G608G	See footnote 2	113	Eriksson et al, [2003], De Sandre-Giovannoli et al, [2003]
Nonclassic HGPS	<u>c.1822G>A</u> p. G608S	Moderate	5	Eriksson et al, [2003], PRF
	c.1821G>A p. V607V	Severe; neonatal progeria	3	Moulson et al [2007], Reunert et al [2012], PRF
	c.1968G>A p.Q656Q	Very mild	2	Hisama et al [2011], Barthelemy et al [2015]
	<u>c.1968+1G>C</u>	Severe	2	Iqbal & Iftikhar [2008], PRF
	<u>c.1968+1G>A</u>	Severe	4	Moulson et al [2007], Navarro et al, [2004], PRF
	<u>c.1968+2T>A</u>	Mild	2	Bar et al [2017], PRF
	<u>c.1968+2T>C</u>	Mild	1	PRF
	<u>c.1968+5G>A</u>	Very mild	2	Hisama et al [2011], PRF
	<u>c.1968+5G>C</u>	Moderate	3	PRF

PRF = Progeria Research Foundation Diagnostic Testing Program
 1. There is a spectrum of severity for classic genotype HGPS, and most individuals with nonclassic genotype HGPS fall within that spectrum. Comparisons with classic genotype HGPS are based on the mid-range of severity for classic genotype HGPS. Please note that it is possible for a listed pathogenic variant to yield a spectrum of disease severity among different affected individuals.
 2. Individuals with *LMNA* pathogenic variant [c.1824C>T](#) appear remarkably similar in phenotype [Eriksson et al 2003].

Mode of Inheritance

Hutchinson-Gilford progeria syndrome (HGPS) is typically caused by a *de novo* autosomal dominant pathogenic variant. Penetrance is Complete.

Risk to Family Members

- Almost all individuals with HGPS have the disorder as the result of a *de novo* pathogenic variant.
- Approximately 3% of currently living individuals with the classic HGPS genotype identified through The Progeria Research Foundation Diagnostics Program have HGPS as the result of apparent germline (or somatic and germline) mosaicism in a parent.
- Parents of probands are not affected.
- Because HGPS is typically caused by a *de novo* pathogenic variant, the recurrence risk to the sibs of a proband is small. Currently there are 3 non-twin sibling cases of HGPS among a total of 113 classic cases identified (2%). The number of unaffected siblings among the 113 total cases is unknown. Thus, the recurrence risk for subsequent pregnancies after one individual has been genetically diagnosed with HGPS is significantly higher than the 1 in 8 million incidence for the general population, though still low.
- **Offspring of a proband:** Individuals with classic and nonclassic HGPS are not known to reproduce.

Prenatal testing and Preimplantation Genetic Diagnosis

Once the *LMNA* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk (because of the rare possibility of germline mosaicism in a parent) or preimplantation genetic diagnosis are possible.

Molecular Basis of Disease

For the *LMNA* pathogenic variant c.1824C>T, the C to T transition does not change the translated glycine amino acid), but activates a cryptic splice site, resulting in a transcript with a deletion of 150 base pairs in the 3' portion of exon 11. Translation followed by post-translational processing of this altered mRNA produces a shortened abnormal prelamin A protein with a 50 amino-acid deletion near its C-terminal end, henceforth called "progerin." The 50 amino-acid deletion removes the recognition site that leads to proteolytic cleavage of the terminal 18 amino acids of prelamin A, along with the phosphorylation site(s) involved in the dissociation and re-association of the nuclear membrane at each cell division.

A key component of disease in HGPS is the presumably persistent farnesylation of progerin, which renders it permanently intercalated into the inner nuclear membrane where it can accumulate and exert progressively more damage to cells as they age. That the failure to remove the farnesyl group is at least in part responsible for the phenotypes observed in HGPS is strongly supported by studies on both cell and mouse models which have either been engineered to produce a non-farnesylated progerin product or treated with a drug that inhibits farnesylation, rendering a non-farnesylated progerin product.

Other *LMNA* variants that do not result in the production of progerin protein, result in abnormal lamin A proteins with variable abnormalities in their structure and function, including interactions with the nuclear membrane, lamin-associated proteins, all of which produce cellular and organismal diseases with varying phenotypes that overlap with HGPS in some aspects.

Genetically Related Disorders

Some 12 distinguishably different genetic conditions with nucleotide variants in *LMNA* have been identified. See OMIM [150330](#). In addition, pathogenic variants in *ZMPSTE24*, which encodes zinc metalloproteinase, an enzyme involved in the post-translational processing of LMNA can cause excess prelamin A proteins and a related phenotype (OMIM 606480)

Non-progerin-producing Progeroid laminopathy can be used to describe phenotypes that have overlap with but are obviously different from classic and nonclassic genotype HGPS. Various pathogenic variants in *LMNA* identified through [The Progeria Research Foundation Diagnostic Testing Program](#), [International Progeria Registry](#), and/or [Medical and Research Database Program](#) result in a variety of lamin A abnormalities, resulting in various phenotypes

Non-progeroid laminopathies caused by pathogenic *LMNA* variants that result in abnormal lamin A protein

- Autosomal dominant [Emery-Dreifuss muscular dystrophy](#) (AD-EDMD)
- Autosomal recessive [Emery-Dreifuss muscular dystrophy](#) (AR-EDMD)
- Autosomal dominant familial dilated cardiomyopathy and conduction system defects (see [Dilated Cardiomyopathy](#))
- Autosomal dominant Dunnigan-type familial partial lipodystrophy (FPLD) (OMIM 151660)
- Autosomal dominant [limb-girdle muscular dystrophy 1B](#) (LGMD1B) (see [Limb-Girdle Muscular Dystrophy](#))
- Autosomal recessive axonal neuropathy [Charcot-Marie-Tooth disease 2B1](#) (CMT2B1)

- Autosomal recessive mandibuloacral dysplasia (MAD) [Cao & Hegele 2003].
- Single case reports of individuals with *LMNA* variants and unique clinical phenotypes [Caux et al 2003; Kirschner et al 2005].

Differential Diagnosis

Non-laminopathy progeroid syndromes. The following are other syndromes that include some features of premature aging:

- Neonatal progeroid syndrome (Wiedemann-Rautenstrauch syndrome) (OMIM [264090](#))
- Acrogeria (OMIM [201200](#))
- [Cockayne syndrome](#)
- Hallermann-Streiff syndrome (OMIM [234100](#))
- Geroderma osteodysplastica (OMIM [231070](#))
- [Berardinelli-Seip congenital lipodystrophy](#) (congenital generalized lipodystrophy)
- Petty-Laxova-Weidemann progeroid syndrome (OMIM [612289](#))
- Ehlers-Danlos syndrome, progeroid form (OMIM [130070](#))
- [Werner syndrome](#) (OMIM: 277700)
- Mandibuloacral dysplasia (See [Genetically Related Disorders](#)) (OMIM [248370](#))
- Nestor-Guillermo syndrome (OMIM [614008](#))
- Penttinen Syndrome (OMIM 601812)
- Other (POL3RA and PYCR1 mutations)

3. Heart Health: Cardiology

Monitoring cardiovascular health

Unique issues across the lifespan

Aspirin for heart health

Overview of Cardiovascular Features in Progeria

Children with Progeria develop progressive changes of their heart and vessels over time. While they are at a high risk for heart attacks and strokes at any age, there may be signs of stiffness of the heart and blood vessels which cause few, if any, noticeable symptoms. With age, children with progeria most commonly develop progressive abnormalities including heart muscle thickening (ventricular hypertrophy) and calcification of vessels and left-sided heart valves with or without obstruction.

Annual testing is often the best way to detect any changes in heart health, and this is particularly important for children with progeria, with or without known cardiovascular issues.

Premature, progressive atherosclerosis leading to cardiovascular failure causes over 80% of deaths in HGPS. It is believed that cardiovascular disease is caused by a combination of vascular stiffening, plaques, and cardiac abnormalities including valvular stenosis and/or regurgitation, valvular calcification, left ventricular hypertrophy, and eventual left-sided failure.

Left ventricular diastolic dysfunction is the most prevalent echocardiographic abnormality, seen in all age groups, but its prevalence increases with age. Other cardiac abnormalities, including mitral and aortic valve stenosis or regurgitation and Left ventricular hypertrophy are seen primarily during the second decade of life.



Blood lipids such as cholesterol are very often normal in Progeria

For the Family: Risks and Recommendations

Your child's cardiologist or other caregiver will recommend annual screenings for blood pressure, cholesterol and heart function tests including an ECG (electrocardiogram) and an Echocardiogram (cardiac ultrasound) with additional testing if appropriate. Blood pressure and ECG are often in the normal range until a child is older. Careful, repeat measurements are recommended because the best way to detect a problem is by asking if there has been a change over time. Here is a list of common tests and recommendations:

- Annual doctor's visit, ideally with a pediatric cardiologist
- Electrocardiogram (ECG) at least annually
- Measurement of fasting lipids and glucose annually
- Maintaining appropriate hydration
- Low dose aspirin therapy may be prescribed by your child's doctor to help prevent strokes and heart attacks

For the Healthcare Professional: Risks and Recommendations

Monitoring cardiovascular health

Children with HGPS are at high risk for heart attacks and strokes at any age, however recent observations suggest that cardiovascular disease in Progeria is characterized by progressive vascular stiffness with variable patterns of vascular occlusion, particularly affecting vessels of the head and neck. Frank hypertension appears less common than blood pressure lability,, and measuring blood pressure in both arms and leg in calm setting is particularly important for this population.

Most children have normal or hyperdynamic left ventricular function, though do display diastolic dysfunction starting in early childhood. Mitral and/or aortic valve calcification with obstruction typically occurs later in childhood, and may be accompanied by ventricular hypertrophy, atrial enlargement or valve insufficiency.

The following testing should be considered

- Cardiology visit with physical examination, including attention to pulses and four extremity blood pressure with manual appropriately sized BP cuff.
- Echocardiogram - including anatomic assessment with attention to LVOT, valve gradients, tissue Doppler and, LV function
- Echocardiography
- Carotid duplex ultrasound*, if available
- Pulse wave velocity*, if available

*Note, carotid duplex ultrasound and/or pulse wave velocity are available in some centers, but are not yet routinely performed on pediatric patients

Cardiovascular Treatments

Studies in adults and children with risk of vessel occlusions have shown benefits of low dose aspirin therapy, for both stroke and heart attack prevention.

Low dose aspirin, dosed by weight at 2-3 mg per kg body weight, is often recommended. Low dose aspirin should be considered for all children with HGPS at any age, regardless of whether the child has exhibited overt cardiovascular abnormalities or abnormal lipid profiles. Low dose aspirin may help to prevent thrombotic events, including transient ischemic attacks (TIAs) stroke, and heart attacks, by inhibiting platelet aggregation. Aspirin dosage is determined by patient weight, and should be 2-3 mg/kg given once daily or every other day. Platelets may become “stickier” (i.e., more likely to form clots) at times of stress with illness, fever, etc. While these recommendations are guidelines, individuals may make adjustment in aspirin dosing based on clinical course.

Once a child develops signs or symptoms of vascular decline, such as hypertension, TIA, strokes, seizures, angina, dyspnea on exertion, ECG changes, echocardiogram changes, or heart attacks, a higher level of intervention may be warranted. Antihypertensive or heart failure medications, anticoagulants, anti-seizure, and other medications may be prescribed. All medication should be dosed according to weight, and carefully adjusted according to accompanying toxicity (negative side effects) and efficacy (effectiveness).

> Aspirin Management

Aspirin may rarely cause stomach discomfort. If excessive bleeding or bruising is detected, stop aspirin therapy and consult your physician. Aspirin therapy will probably need to be discontinued 1 week prior to any surgery; consult your physician if any surgery is being planned.

If your child becomes ill with chickenpox, stop the aspirin therapy (see below).

> Reye's Syndrome

There is a weak association between aspirin usage during Varicella (chickenpox) infection and Fatty Liver With Encephalopathy (Reye's Syndrome) in children under 15 years of age. The risk of Reye's syndrome is extremely small compared to the potential benefits of low dose aspirin treatment, , given the risk of cardiovascular events in HGPS.

4. Brain Health: Neurology / Strokes

Strokes and TIAs

Aspirin for stroke prevention

Headaches

Seizures

Imaging recommendations

Sedation

Special circumstances: Travel, hydration

Overview of Neurovascular Disease in Progeria

Strokes and cerebrovascular disease are common problems in Progeria. Although children do not usually die of strokes or bleeding in the head, these issues can cause serious life-changing medical problems.

For the family: Risks and Recommendations

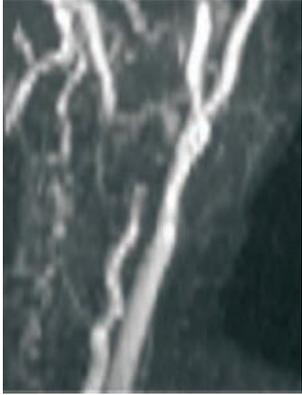
Strokes and Transient Ischemic Attacks (TIA's) are an increased risk for children with Progeria. It is recommended that children with Progeria undergo magnetic resonance imaging (MRI) and MR angiography (MRA) of the head and neck to determine the presence of arterial narrowing and stroke.

At the recommendation of your child's physician and/or neurologist, aspirin therapy is sometimes prescribed as a prevention therapy for future strokes

Headaches are frequently observed in children with Progeria. Headaches can be a single, one time occurrence, or happen repetitively. The headache may be localized (pain in one spot) or your child may complain of pain in multiple areas of the head and face. To stop the headaches from occurring, treatment may include rest in a quiet, dark environment, avoidance of some known triggers such as certain foods and beverages, lack of sleep, and fasting.



Good hydration is very important in Progeria to help keep demands on the heart and blood vessels low.



MRI of a 5 year old showing complete blood flow blockage in the carotid artery of the neck

The most common food and beverage triggers are chocolate, cheese, nuts, shellfish, Chinese food (commonly containing mono sodium glutamate (MSG)), sugar, caffeine, and alcohol. Medication treatments may be necessary to prevent and/or treat acute headaches if they occur frequently. It's important to keep children well hydrated, especially during long trips.

What to do in the event of a seizure: Some children experience seizures. Even if you feel frightened, it is important to stay calm and to stay with your child until the seizure stops. Notice when it starts and stops and what body parts are involved. If your child is sitting or standing, gently ease them to the floor and keep the head from falling backwards. Place your child on their side. It is important not to try to open the mouth or place anything between the teeth. Do not try to stop the movements or “shake” your child out of it. After the seizure, your child may have lost control of bowel or bladder function. And he/she may be more tired or experience headache or soreness. Contact a doctor if at any time the seizure is prolonged (more than 5 minutes), if there is change in the skin color, and/or if the child has trouble breathing. It is common for children

to be sleepy after a seizure; contact a doctor if the seizure is a new event for the child, if he/she cannot be fully awakened after 10-15 minutes, or if there are any additional concerns.

For the Healthcare Professional: Risks and Recommendations

Strokes and Transient Ischemic Attacks (TIAs)

Strokes and cerebrovascular disease are one of the leading causes of morbidity in children with Progeria. The earliest published incidence of stroke is at the age of 4 years. In one case, seizures were the presenting symptom of the stroke.

In an effort to provide some clues into the increased susceptibility to developing strokes, a series of children with Progeria have been studied to evaluate the types of changes that occur in the blood vessels of the head and neck with increasing age. Although there are a number of changes that are being newly characterized, it is clear that there are some similarities among the children as a group. The most frequent of these is narrowing of the largest of the blood vessels in a region where blood flow from the neck transitions into the portion that enters the skull at the base of the brain. Blood flow is slowed by this narrowing or constriction of the blood vessels and, potentially, by blood clots.

4.3 | Brain Health: Neurology/Stroke

Gradually the blood flow to the brain is slowed, which increases the likelihood of strokes and TIAs. The blood vessels, in an attempt to compensate for the blockage, form collateral vessels, or “side roads” to help with blood flow and to try to supply oxygen to the areas of the brain that were once served by the narrowed arteries. However, these new blood vessels are smaller and more fragile than normal blood vessels. In addition, these newer blood vessels are susceptible to shifts in blood pressure and hydration.

In children with Progeria, the first symptom of cerebrovascular disease is often a stroke or recurrent ischemic attacks (TIAs, also called “mini-strokes”, frequently accompanied by headaches, muscular weakness or paralysis affecting one side of the body, and/or seizures). Based on our experience, by the time the children present with neurologic symptoms from a stroke, there is often evidence of prior so-called “silent” strokes that have occurred in the past. Silent strokes are those that occur in brain regions that may not produce any clinical symptoms, but over time may accumulate and cause more permanent symptoms. If a stroke with new clinical symptoms occurs, then management of blood pressure is imperative. In the case of a larger stroke, monitoring in an ICU is often indicated until the child’s condition is stabilized. Medication treatments such as anticoagulation are often considered at that time.

Aspirin for stroke prevention

Drugs such as antiplatelet agents (like aspirin) are often given to prevent future strokes from occurring, especially in the areas where there is some narrowing of the blood vessels or partial blockage. Some doctors believe that all patients with this type of narrowing should be on a medication permanently as a preventative step. The decision to start aspirin and/or to add another type of medication to the aspirin should always be made by speaking to the medical team and/or consultation with a neurologist to guide appropriate care. Safety of many of these medications and guidelines for use are not well-established in pediatric patients and, therefore, careful evaluation and on-going monitoring is needed.

Headaches

Headaches are frequently observed in children with Progeria. This is likely at least in part to some of the changes in the blood vessels that are observed. Headaches can be isolated or recurrent in nature, and localized to one or more areas of the head and face. The exact causes of headaches are not completely understood. It is thought that many are the result of tight muscles and dilated, or expanded, blood vessels in the head.

Seizures

Seizures are brief, temporary disturbances within the electrical system of the brain. The most easily recognized seizure involves shaking movements of the body and a period of decreased awareness. Other, less obvious forms of seizures may affect a person's awareness, muscle control, or sensory perception.

Often, family members who witness a seizure will be asked to record details like the time of day that a seizure occurs, how long it lasts, what parts of the body are affected, and what the mental awareness is immediately before and after. This information can be quite helpful to determine the type of seizure present.

Doctors may recommend an electroencephalogram (EEG), which is a test where tiny electrode wires are attached to the head in order to record brain waves. An EEG can sometimes show changes in the electrical activity of the brain. A normal EEG does not exclude the diagnosis of seizure and patients may need additional monitoring as part of the evaluation. If the EEG is abnormal, the results can be used to determine if medications are necessary to prevent future seizures and, if so, may guide the choice of medication.

Strokes can occur, even in the absence of known cardiac problems. Childhood stroke symptoms are similar to those of adult stroke. In particular, watch for speech difficulties, eye movement problems, or weakness / numbness in one region of the body.

Imaging recommendations

It is recommended that children with Progeria undergo magnetic resonance imaging (MRI) and MR angiography (MRA) of the head and neck to determine the presence of arterial narrowing and stroke. In children with progeria, strokes are often clinically silent and the identification of infarct is unexpected. MRI may also identify small, abnormal vessels along the surface of the brain that form in response to the arterial narrowing and provide alternative pathways for blood flow and brain perfusion. Because children with arterial narrowing may benefit from daily aspirin and require proper hydration, it is important to know whether cerebrovascular disease exists.

Sedation

Many young children will require sedation in order to get imaging studies of the brain or the body. Children with Progeria who are known to have cardiovascular or blood pressure abnormalities will require special attention when undergoing sedation or anesthesia. An evaluation by a qualified provider, such as an anesthesiologist or intensivist, is recommended prior to any planned sedation to discuss fluid and blood pressure management plans. See Airway Management & Anesthesia for additional recommendations.

Special circumstances: Travel, hydration

Sudden onset of neurologic symptoms are often brought on by activities that involve over-breathing (hyperventilation), reduction in blood pressure, or dehydration. For these reasons, it is very important that children remain very well hydrated at all times. This is particularly crucial during times of illness and/or travel. Children who plan to travel should increase their hydration and fluid intake in the 24-48 hours prior to the start of the trip. As a rough estimate, minimum fluid requirements are about one liter daily, with a goal closer to 1.5 liters.

5. Emergency Care / Critical Care

Serious Medical Emergencies
Other considerations



Overview of Emergency Care/Critical Care

- Children with Progeria are at an increased risk of having a more “adult” type emergency such as chest pain (angina), a heart attack or a stroke

For the Family: Risks and Recommendations

- Many children with Progeria experience significant bruising for long periods of time even after a minor incident
- Due to the lack of subcutaneous fat, some children’s veins are difficult for healthcare providers to access
- Learn the signs and symptoms for a heart attack or stroke so you can recognize if your child is having a true emergency
- Heart attack symptoms: pain in chest, pain radiating down the arm or in the jaw, shortness of breath, sensation of crushing weight on the chest, light headedness
- Stroke symptoms: sudden numbness or weakness in the face, arm or leg, especially on one side of the body, sudden confusion, trouble speaking or difficulty understanding speech, sudden trouble seeing in one or both eyes, sudden trouble walking, dizziness, loss of balance or lack of coordination; severe headache with no known cause

Vascular access may be difficult in children with Progeria. A vein may appear prominent, but be inelastic and difficult to cannulate.

For the Healthcare Professional: Risks and Recommendations

Serious Medical Emergencies

Children affected by Progeria are at increased risk of more typically adult conditions such as angina, arrhythmias, myocardial infarction, transient ischemic attacks (TIA's), and strokes. The child with Progeria who presents with chest pain or pressure should be assumed to have ischemic heart disease until proven otherwise. Treatment is largely supportive, including supplemental oxygen and careful administration of IV fluids to correct hypovolemia, if present. If the child is not taking prophylactic aspirin at baseline, he/she should be encouraged to chew one-half to one baby aspirin (40.5 - 81mg). In general, avoid medications such as nitrates that can acutely drop blood pressure, due to risk of stroke. Treat pain and anxiety as needed to mitigate the effects of tachycardia on myocardial oxygen demands. If an arrhythmia develops, standard Pediatric Advanced Life Support (PALS) algorithms are recommended.

The cerebrovascular disease in Progeria can be significant. A history of seizures, severe headaches, or one – sided weakness may signify a prior transient ischemic attack or small stroke. Many children who suffer a clinically- recognized stroke are found to have evidence of prior “silent” strokes by MRI. Management of suspected TIA or stroke is largely supportive, such as supplemental oxygen and IV fluids to improve hydration status. If the child is hypertensive, avoid a rapid drop in blood pressure as this can worsen cerebral ischemia. Seizures are treated according to usual guidelines for pediatric patients. Chest pain can be a sign of a serious problem and should always be evaluated by a clinician.

Other considerations

Other considerations for children with Progeria with emergency medical conditions include the following:

- Vascular access: Although peripheral veins may appear prominent due to the paucity of subcutaneous fat, the vessels are typically less elastic and more difficult to cannulate than they would appear.
- Trauma: Children with Progeria may experience significant bruises that are present for long periods of time, even with minor trauma. Large hematomas of the scalp are not uncommon, especially if the child is taking prophylactic aspirin. Less commonly, but more serious in nature, children with Progeria appear to be at higher risk of subdural hematomas following relatively minor head trauma.
- Joint symptoms: Joint pain is a common complaint in children with Progeria, especially in the hips and knees. Most joint symptoms can be treated with over-the-counter analgesics; more significant pain should prompt referral to an orthopedic specialist due to the increased risk of hip subluxation or dislocation. Persistent hip pain should be evaluated due to the risk of avascular necrosis of the femoral head (AVN).

6. Airway Management / Anesthesia

Challenging airway features in Progeria Airway management Anesthesia and Sedation



Overview

Children with Progeria are at a higher risk of complications during anesthesia due to their small size and their risk for a heart attack. Special considerations should be used when and if your child needs surgery

For the Family: Risks and Recommendations

- Children with Progeria have small mouths, jaws and heads which needs to be taken into consideration if they should need anesthesia for surgery
- Talk with the anesthesiologist and your child's physician if you have any concerns.
- Share this section of the Progeria Handbook with your child's healthcare team

Nasal intubation may be challenging due to small nares and unusual glottic angle. For children who cannot be intubated by direct visualization, fiberoptic intubation may be necessary.

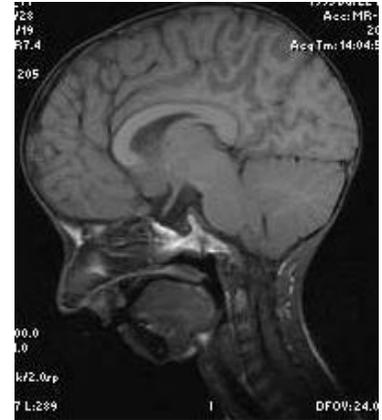
For the Healthcare Professional: Risks and Recommendations

➤ Challenging airway features in Progeria

Improvements in the practice of pediatric anesthesia have enhanced the safety of sedation and general anesthesia for purposes of diagnostic, interventional, or surgical procedures in children. Children with Progeria, however, are at higher risk of complications during sedation or anesthesia, related to their challenging airway anatomy as well as to the potential for cardiovascular events. Even an experienced pediatric anesthesiologist may not have had the opportunity to care for a child with Progeria, so this section discusses the special considerations for anesthesia and airway management.

The typical airway features of children with Progeria include the following:

- Mandibular hypoplasia
- Micrognathia and/or retrognathia
- Small mouth opening
- Abnormal dentition (delayed eruption, crowding)
- High-arched palate
- Decreased flexibility of neck and temporomandibular joints
- Skeletal contractures and decreased neck mobility
- Decreased subcutaneous fat
- Narrowed nose and small nares



Retrognathia in Progeria: Be prepared to use smaller than expected equipment and endotracheal tube size

Airway management

The physical features associated with Progeria may cause difficulty with patient positioning, mask seal, and visualization of the larynx. As such, the clinician must be prepared to utilize techniques for the difficult airway, including laryngeal mask airways (LMAs) and fiberoptic intubation techniques. For children who cannot be intubated by direct visualization, fiberoptic intubation may be necessary. For most diagnostic tests and minor surgery, if the procedure can be safely accomplished without endotracheal intubation, use of bag-mask ventilation or an LMA should be considered. However, the use of procedural sedation without a secure airway should be carefully performed by clinicians with expertise in airway management due to the risk of obstruction with sedating medications.

Nasal intubation may be challenging due to small nares and unusual glottic angle. Children with Progeria are proportionally smaller for age than their age-matched peers, thus selection of airway equipment sizes may be more accurate if based on height rather than on age. Moreover, there is an increased risk of hypothermia due to alopecia and the paucity of subcutaneous fat.

Anesthesia and Sedation

During sedation or anesthesia, the provider must be aware of the cardiovascular and cerebrovascular disease that characterize Progeria. Most young children with Progeria have normal ECGs and echocardiograms. As disease progresses, they may develop systemic hypertension, left ventricular hypertrophy, and mitral or aortic valve abnormalities. Unfortunately, studies such as stress tests may not be helpful to predict the risk of intra-operative events.

The coronary and cerebral vasculopathy associated with Progeria results in loss of vessel elasticity and increased risk of cardiac or cerebral ischemic events during states of hypovolemia or hypoperfusion. Children should remain well hydrated prior to and following planned procedures, and medications that may increase myocardial oxygen consumption or produce hypotension should be avoided. Many children with Progeria are advised to take prophylactic aspirin; the risks and benefits of stopping aspirin therapy prior to planned surgery should be discussed with the surgeon, cardiologist, and/or neurologist involved in the patient's care.

7. Eye Care

Overview of Ocular Features in Progeria
Risks and recommendations for the family
Recommendations for the eye care professional



Overview of Ocular features in Progeria

Most children with Progeria have tight skin and lack subcutaneous fat. These elements likely play a role in the following:

- Eyes slightly open when sleeping, likely due to tight skin and a lack of subcutaneous fat
- Eyes tear frequently; this is probably a reaction to the “dry eye” that is caused by tightened skin and a scant fat pad for the eyeball to sit in
- No eyebrows and scant eyelashes can decrease protection from dust and other irritants
- Photophobia, which is excessive sensitivity to light and the aversion to sunlight or well-lit places

Sleeping with eyes slightly open can cause “dry eye”.

Keeping eyes moist decreases the chances of exposure keratitis.

Risks and recommendations for the family

An eye exam at the time of diagnosis and then yearly is recommended. If eye disease is detected, patients might require more frequent eye exams.

There may be an increased risk of needing eyeglasses, as many (but not all) of the children are wearing glasses for farsightedness at a young age. It is unknown why this occurs.

It is important to incorporate annual eye examinations by a qualified ophthalmologist into the health regimen of children with Progeria, and to see an ophthalmologist if any questions about eye health arise.

Dry eye increases the risk of exposure keratitis and infections of the cornea. This is seen as a clouding of the eye and starts very small but can grow with time and block sight. This is a serious event and needs immediate attention by an ophthalmologist. To decrease the risk of keratitis, keep the eye moist.

- Here are some strategies that the ophthalmologist may recommend:
 - Administer artificial tears as many times per day as possible. Artificial tears are available as over the counter in any drug store. However, if you are using them more than 4 times per day you should use artificial tears that are preservative free. Preservative free artificial tears come in individual vials that have to be used within one day once they are opened.
 - At night, lubricating ointment can be placed into the eye to moisten and protect the opening
 - Skin tape can be used to close the eyelids gently at night

➤ Photophobia

Most children with Progeria do not need special treatment for their mild photophobia. However, if needed, sunglasses, dark clips for prescription glasses, or lenses that darken in bright light can all assist with sensitivity to bright light.

Recommendations for the eye care professional

- Typical Ophthalmic Findings
 - Mild to moderate hyperopia
 - Accommodative insufficiency
 - Decreased orbital fat leading to “shallow orbits”
 - Lack of brow hair
 - Madarosis

- Lagophthalmos
- Exposure keratopathy
- Corneal scarring
- Pterygia

Most patients with Progeria have ocular surface disease secondary to exposure keratopathy. They can present with photophobia, discomfort and decreased vision. Aggressive management of the ocular surface disease is recommended with the use of sunglasses, artificial tears, tape tarsorrhaphy at night, and the use of punctal plugs. In severe cases one could consider temporal tarsorrhaphy and the use of scleral lenses. The potential benefits of surgical management of the ocular surface disease should be carefully weighed against the risks of anesthesia.

Most patients with Progeria have mild to moderate hyperopia, as well as decreased accommodation. It is recommended that near visual acuity is evaluated, as well as dynamic retinoscopy and if reduced consider prescribing glasses to address the refractive error and decreased accommodation.

Patients with Progeria have not been found to develop glaucoma, cataracts or retinal degenerations that are typically associated with normal aging.

A comprehensive ophthalmologic evaluation is recommended at the time of diagnosis and yearly after that. If corneal disease is present then more frequent follow-ups might be required.



Figure 1. Note the lack of brown hair.



Figure 2. Madarosis worse for the upper than the lower eyelid



Figure 3. Inferior corneal scarring from exposure keratopathy



Figure 4. Aggressive pterygium involving the visual axis

8. Audiological Evaluation

The external ear of the child with Progeria

Behavioral testing for assessing hearing thresholds

Objective electrophysiologic tests of auditory function

Summary



Children with Progeria often develop low frequency conductive hearing loss. In general this does not lead to functional impairment.

Overview of Ear and Audiology in a child with Progeria

This section describes the typical hearing profile of children with Progeria, as well as a guide for the audiological evaluation and potential management strategies.

For the Family: Risks and Recommendations

- Due to the shape of the ear and the loss of skin flexibility, the outer ear can be very sensitive to pressure
- Families report that children with Progeria often have wax build up in their ears. Talk to your child's healthcare provider about using products to soften the wax.

- Children with Progeria frequently have mild to moderate low frequency hearing loss. Your child's healthcare provider should routinely test your child's hearing and refer you to a specialist should it be needed.

For the Healthcare Provider: Risks and Recommendations

- The external ear of the child with Progeria

In the typical ear, the pinna and lateral 1/3 of the ear canal are comprised of cartilage that is compliant, and subcutaneous fat allows the transducers (earphones) used in behavioral and electrophysiological tests of hearing to fit snugly and comfortably in the ear. The status of the external ear in children with Progeria poses a special difficulty in conducting hearing assessment, as the ear canals in children with Progeria are characterized by loss of compliance of the cartilage and loss of skin flexibility. The result is that the ear can be markedly sensitive to pressure applied by transducers applied to the pinna (such as the supra-aural ear-phones often used for air-conduction testing) and to the ear canal (such as tympanometry probes for performing acoustic emittance or insert earphones used for air-conduction testing or otoacoustic emissions). See Figures 1 and 2 below for photographs of ears of two children with Progeria. To the touch, the pinna is obviously more rigid than are the pinnae of children who don't have Progeria. Those engaged in hearing testing should manually apply pressure to the pinna and ask the child if that pressure causes discomfort before placing TDH supra-aural earphones.

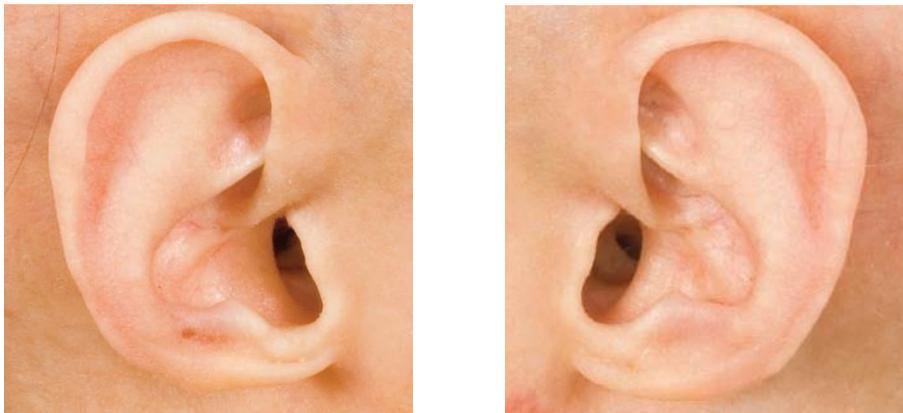


Figure 1. The right and left ears of children with Progeria. Note the large size of the entrance of the external auditory canal relative to the pinna.

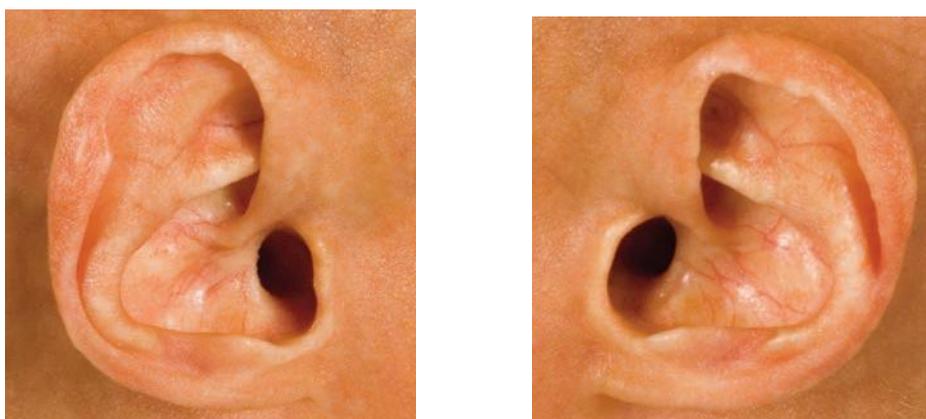


Figure 2. The right and left ears of a child with Progeria. Note the obviously smaller diameter of the ear canal in the deep (bony) portion of the ear canal, compared to the more shallow (cartilaginous) portion of the ear canal, most easily seen in the left ear.

The cartilaginous portion of the ear canal often has an appearance of a general loss of cartilage, resulting in a diameter significantly larger than the bony portion that comprises the medial 2/3 of the ear canal. This difference in the size of the soft tissue vs. bony portion of the ear canal can be confusing to the clinician who is attempting to place an earphone in the canal.

Usually, an earphone or tympanometry probe tip is coupled manually to the cartilaginous portion of the ear canal. The significant size discrepancy can make it difficult to obtain an airtight seal when attempting tympanometry and middle-ear muscle reflex testing. While potentially easier to obtain that airtight seal by coupling the eartip to the bony portion of the canal (rather than the cartilaginous portion), that bony part of the canal is *very* sensitive in everyone, and so it may be difficult for the patient with Progeria to tolerate placement of eartips for audiometric testing. Engage the patient in the testing process by introducing them to the next test and explaining that the eartips are made with assumptions (that is, the appropriate size and rigidity of the eartips) that don't necessarily apply to a child with Progeria. Children should also be uniformly given full license to suspend any test at any time, which may also increase their trust in the examiners and perhaps their tolerance of mild discomfort.

Cerumen impaction is often reported by families to be problematic in children with Progeria. The earwax is often very dry and adheres to the ear canal wall at the bony-cartilaginous juncture. Children with Progeria should routinely be seen by a physician to examine ears for cerumen impaction and follow physician recommendations for using liquid solutions (such as mineral oil and hydrogen peroxide) to try to soften wax prior to manual extraction by a physician.

Behavioral testing for assessing hearing thresholds

Measuring pure-tone hearing detection thresholds by behavioral audiometry is the gold-standard for the clinical assessment of hearing function.

Patients with Progeria are, by-and-large, cognitively typical for age, so their language is appropriate for a child their age. A child's language age is a good indicator for which behavioral test technique is most appropriate for determining pure-tone hearing thresholds, or if the child can be tested behaviorally at

all. Given that this disorder presents around age 18 to 24 months, hearing can be assessed in children with Progeria at the earliest age of diagnosis by visual reinforcement audiometry; this pediatric test technique is valid for typically-developing children ages 8 months to roughly 30 months. Children with Progeria ages 2 to 5 years can usually be tested by conditioned play audiometry. Children ages 5 years and older can usually be tested by conventional “hand-raising” audiometry.

8.6 | Audiological Evaluation

Children with Progeria almost uniformly have some degree of low-frequency conductive hearing loss. See Figure 3 for a typical audiogram (hearing test results) in a child with Progeria. Hearing loss is not always bilateral, nor is it always symmetrical when hearing loss exists in both ears. But, the configuration of the hearing loss has been seen consistently in children with Progeria: low-to-mid frequency upsloping to better (and perhaps normal) hearing in the higher frequencies.

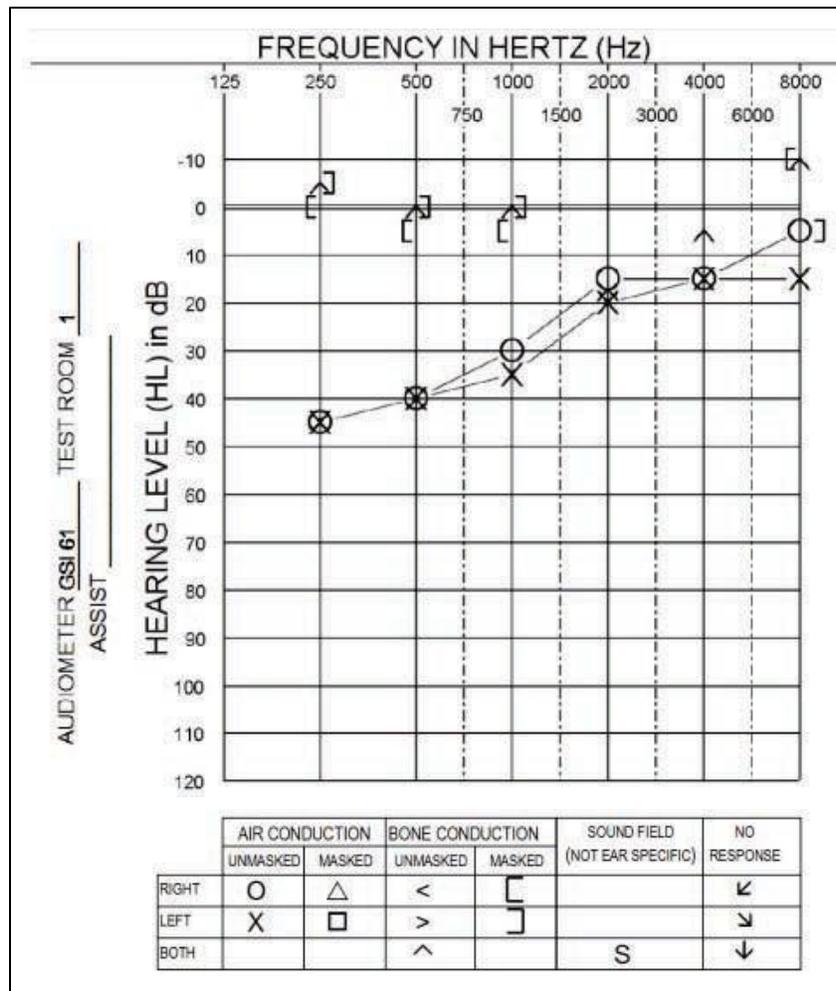


Figure 3. Typical audiogram of a child with Progeria: mild to moderate low-frequency conductive hearing loss.

Objective electrophysiologic tests of auditory function

➤ **Tympanometry**

Tympanometry is a test to assess the gross function of the middle-ear. It is performed by manually applying or inserting a rubber tipped probe that is intended to hermetically seal the ear canal. A low frequency tone (226 Hz) is presented in the ear canal while air pressure is changed from +200 daPa to -400 daPa. This change in air pressure is quite gentle and usually is completed in seconds. The change in the sound pressure level of the low frequency tone in the ear canal is a result of sound being transmitted more or less efficiently through the middle-ear system as a function of the air pressure in the ear canal. There are normative data for equivalent ear canal physical volume, peak pressure, static compliance, and tympanic width. Findings on tympanometry are essentially normal in many children with Progeria (regardless of hearing test results). When abnormal, static compliance is usually reduced and tympanic width is consequently wider than normal. This would suggest a “stiffening” of the eardrum and/or the ligaments connecting the 3 bones of the middle-ear. Physical ear canal volume and peak pressure is typically normal. Otologic examination in a few patients by a pediatric otolaryngologist did not reveal middle-ear effusion in any of these patients with reduced static compliance. Definitive reasons for abnormally reduced compliance on tympanometry remain unknown at this time.

➤ **Acoustic reflex (middle-ear muscle reflex) threshold**

Middle-ear muscle reflex threshold is a gross measure of middle-ear function that incorporates a reflex arc ascending from the 8th cranial nerve to the level of the superior olivary complex and descending the 7th cranial nerve both ipsilateral and contralateral to the stimulus. The test is conducted much the same way as tympanometry, making use of the same probe tip used in tympanometry. A hermetic seal is necessary to complete this testing, which can usually be completed within a few minutes. A low frequency probe tone (226 Hz) is presented in the ear canal and the ear canal air pressure is kept stable. A stimulating tone of varying frequencies (typically 500 Hz, 1000 Hz, and/or 2000 Hz) is presented in the ear canal at relatively high intensity (normal reflex thresholds are 85-90 dB HL). A stimulating tone sufficient to engage the middle-ear muscle reflex causes the stapedius muscle to contract, stiffening the middle-ear system. This stiffening can be detected in much the same way as it is with tympanometry. When there is middle-ear dysfunction, middle-ear muscle reflexes are typically elevated (> 90 dB HL) or absent (no reflex elicited using a maximum stimulus intensity level of 110 dB HL). Children with Progeria almost uniformly have elevated or absent middle-ear muscle reflexes, regardless of findings on tympanometry.

➤ **Otoacoustic emissions**

Otoacoustic emissions are a measure of the functional integrity of the cochlea, up to the level of the outer hair cell. These “ear sound” emissions are thought to arise from the electromotility of healthy outer hair cells, and so are a by-product of the normal hearing mechanism. People with sensorineural hearing loss, such as that caused by age (“presbycusis”) or noise (“noise-induced hearing loss”), have absent otoacoustic emissions. These ear sound emissions can be evoked by an external sound stimulus, such as a click or a pair of pure tones, and the resulting response from the cochlea can be measured in the ear canal with a very sensitive microphone if the ambient noise (in the room as well as from the patient) is quiet enough that the emission can be measured. This test, then, requires the placement of an earphone in the ear canal, which houses both a transducer for generating sound as well as recording sound. It does not require an airtight seal, but does require a reasonably good coupling to the walls of the ear canal so that sound does not leak out of the ear. Children with Progeria almost uniformly have normal otoacoustic emissions in the mid to high frequencies. It is known that otoacoustic emissions are typically affected (are either reduced or absent) by conductive transmission loss in the middle-ear due to middle-ear dysfunction. Otoacoustic emissions in children with Progeria are typical of what one would expect based on their audiogram: At frequencies where a conductive hearing loss exists (in these patients, usually low-to-mid frequencies), the otoacoustic emissions are reduced or absent. Of specific note, high frequency otoacoustic emissions (as high as 10k Hz) are uniformly present in children with Progeria as long as the conductive hearing loss does not extend to these higher frequencies. It would then seem that the cochlea of a child with Progeria does not decline in a way that would suggest “age-related” hearing loss. Their cochleas appear to maintain good function (at least through teenage years).

➤ **Auditory Brainstem Response (also known as Brainstem Auditory Evoked Response)**

Auditory Brainstem Response measures the far field electrical potentials evoked by a sound stimulus from the auditory brainstem nuclei through the level of the lateral lemniscus. Testing is typically used to estimate hearing thresholds in children too young or too developmentally impaired to participate in behavioral audiometry, or in cases where there is suspicion for a lesion of the ascending auditory neural pathway (such as a tumor on the 8th cranial nerve). As this test requires the passive participation of the patient, sleep is often desired during this testing (either natural or through the use of sedation). Similar concerns regarding placement of a transducer in the ear canal continue here, as the transducers used for Auditory Brain stem Response are the same as those used in behavioral audiometry. An additional concern is that the evoked response is recorded far field, using three or four scalp electrodes which must have low (< 5k ohm) and well-balanced skin

impedance (all within 5k ohm). Usually, a mild abrasive is used to exfoliate the skin and remove dead skin cells. Given the extremely thin skin of the patient with Progeria, care must be taken to not compromise skin integrity should this testing be conducted.

Interventions

A patient with a mild low frequency hearing loss has little functional impairment with communication. Consequently, parents usually report that their child with Progeria hears very well; often a low-frequency hearing loss was found that was not previously diagnosed. Audiological interventions are usually limited to annual monitoring of hearing for progressive worsening of hearing into the speech frequencies, or perhaps preferential seating in the classroom. Occasionally, based on parent report of the child with low-frequency hearing loss having difficulty attending to the teacher's voice, FM educational amplification is recommended to help the child hear the teacher's voice preferentially over the ambient sound in the classroom.

On occasion, a child with Progeria has significant hearing loss that is severe enough to interfere with understanding others. Given the anatomical changes of the external ear described earlier in this chapter, coupling a hearing aid to the ear via personal custom earmold could be challenging. The process of making an earmold for a hearing aid requires placing a cotton block on a string down the ear canal, and mixing two-part silicone together and injecting this silicone into the ear canal and ear, which then cures (hardens) within a few minutes; this is called an "earmold impression." Placing the cotton block deeply is often uncomfortable in a person with normal ear anatomy; in a child with Progeria, it is reasonable to expect greater discomfort. An approach that might lessen the discomfort during earmold impression is to lubricate the cotton block and ear canal with a water-based lubricant or with mineral oil prior to injecting the silicone. Prognosis for use of hearing aids is very good, as the type of hearing loss is conductive and there is no expected loss of clarity of the signal, as there can be when there is greater than a moderate degree of cochlear (i.e., sensorineural) hearing loss.

Summary

Children with Progeria have low-to-mid frequency conductive hearing loss that is usually mild, but can be moderate (or greater) in degree. The pathophysiology of this hearing loss is not clear at this time. Some children have grossly abnormal tympanometry with hearing thresholds that were relatively normal, while other patients with normal tympanometry have significantly impaired hearing. This conductive hearing loss exists even in the absence of cerumen and middle ear

effusion. Middle-ear muscle reflexes are almost uniformly elevated or absent. Otoacoustic emissions are almost uniformly normal at frequencies where the conductive hearing mechanism is normal to near normal (in the mid-to-high frequencies). The site-of-lesion then would appear to be some dysfunction in the middle-ear system that is not related to an ear infection/middle-ear effusion. This dysfunction results in a stiffening of the system and thus loss of sound transmission properties of the middle-ear.

When needed, audiological interventions are successful at helping the child with Progeria hear well. These interventions include assistive listening devices (such as FM systems) and hearing aids. It is not common for hearing loss to require the use of such devices, but if these are warranted, their benefit is immediate and, likely, obvious.

9. Dental Recommendations

For the families

For the medical and dental professional

Overview

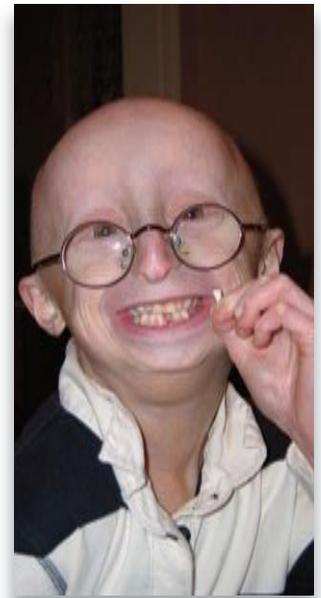
Good dental hygiene is important for all children, especially those with Progeria as they are at increased risk for dental disease.

For Families: Risks, Recommendations

There are many dental findings that are prevalent in children with Progeria:

- ✓ Crowding of the dentition
- ✓ Delayed eruption and/or failure of eruption of baby and adult teeth
- ✓ Insufficient space for permanent teeth
- ✓ Gum disease
- ✓ High rate of cavities
- ✓ Small, underdeveloped jaws
- ✓ Attrition (wear) of the primary teeth

One of the most important things you can do is establish a relationship with a dentist early in your child's life. By age 1, or by the time your child's first tooth erupts, your child should see a dentist – preferably a pediatric dentist. Due to your child's increased risk for dental disease, it is recommended that your child visit the dentist at least twice per year, for routine checkups, cleanings, and fluoride treatment, and more frequently if the dentist finds dental issues that need attention. This will not only enable frequent oral assessments, but also help your child feel comfortable in the dental setting.



Delayed eruption of baby teeth is extremely common in Progeria. Secondary teeth may eventually erupt behind primary teeth, but some may never erupt.

For the Medical and Dental Professional: Risks, Recommendations

- Typical dental findings in Progeria
 - Severe crowding
 - Malocclusion
 - Ectopic tooth eruption
 - Delay and failure of eruption of primary and permanent dentition
 - Insufficient space for secondary dentition
 - Tooth size/arch length discrepancies
 - Permanent molars often located in the ramus
 - Gingivitis and periodontal disease
 - Localized gingival recession
 - High caries rate (cavities)
 - Attrition of primary dentition
 - Hypodontia
 - Agenesis of permanent teeth, especially second premolars
 - Ankyloglossia
 - Palatal pseudocleft

- Craniofacial findings in Progeria
 - Alopecia
 - Prominent scalp veins
 - Perioral cyanosis
 - Convex profile
 - Limited range of motion
 - Hypoplastic maxilla and mandible
 - Micrognathia
 - Retrognathic maxilla and mandible
 - Class II skeletal malocclusion

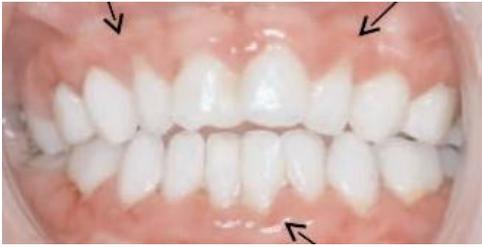
- Things to consider
 - Early visits to the dentist
 - More frequent recalls; consider 6-month recalls for exam, prophylaxis, and fluoride treatment
 - Establish a relationship with a dentist by age 1 or when first tooth erupts
 - Establish a dental home by the first birthday

- Importance of educating parents
 - High cavities rate in this population
 - Education on oral hygiene instructions
 - Education on etiology of cavities
 - Education on ways to prevent cavities
 - Discourage use of sippy cup and bottle with cariogenic beverages
 - water only in the cup or bottle
 - Begin brushing the teeth as soon as they erupt using a small smear of fluoride toothpaste
 - Early implementation of fluoride toothpastes, rinses, and in-office application of fluoride
 - Obstructive sleep apnea may be increased due to micrognathia/ retrognathia
 -

- Orthodontic consideration
 - Severe crowding and eruption disturbances may necessitate extraction therapy
 - Susceptibility to periodontal disease and limited opening often contraindicates conventional orthodontic therapy

- Tooth Extractions
 - Although there are no reports in this population to bisphosphonate usage and medication related osteonecrosis of the jaw (MRONJ), some consideration should be given when weighing the risks and benefits of removing teeth.
 - Low dose aspirin taken for stroke prevention may affect clotting, thus the risks and benefits of holding the aspirin versus the use of local measures for hemostasis (sutures/hemostatic agents) must be weighed.

➤ Figures demonstrating typical dental findings



Crowded teeth, with areas of gum recession (see arrows)



Cavities



Crowding with malposition of permanent teeth



Attrition (wear) of primary teeth



Attrition of primary central incisors and ectopic eruption of permanent mandibular incisors



Palatal pseudocleft



Ankyloglossia

10. Skin / Dermatology

Common skin findings in Progeria Hair and nails



Hair is lost gradually (not in large clumps) over several months to years.

Overview of Dermatology

This section describes the skin changes found in children with Progeria

Risks and Recommendations for the Family

- Changes in the skin can be the first symptom parents notice that their child may have a medical problem. This could be in the form of restrictive, tight skin, dark spots or a soft bulging on the stomach
- Skin can get dry and itchy – gentle cleansers and creams are recommended
- All children with Progeria lose their hair
- Nails can become dry and cracked or split. Be vigilant for in grown nails as they can become infected
- See a dermatologist for any concerns regarding your child's skin or hair loss

Risks and Recommendations for the Healthcare Professional

Common skin findings in Progeria

Skin changes can be the very first indication that there is a problem in children with Progeria. Skin abnormalities can sometimes be seen at birth, but the changes are most often noticed in the first year of life. Skin findings at birth include tight skin and may restrict motion. Skin tightening can be almost absent in some children, or can be severe and restrict chest wall motion and gastric capacity in others.

Skin findings vary in severity and include dark spots on the skin, tight skin, and small areas (1-2 cm) of soft bulging skin, particularly on the abdomen.

Skin can get dry and itchy. Gentle cleansers and over the counter creams sometimes help with this. It is recommended that families see a dermatologist for dryness and itching. Calluses are common on the feet due to loss of fat.

Hair and nails

Hair is often normal-looking at birth, but begins to fall out gradually within the first two years of life. The pattern of hair loss usually starts at the back or edges of the scalp hair. The top is usually the last to go. All mature hair is lost on the head and thin, sparse “downy” hair remains.

Eyebrows are lost in the first few years as well, leaving very slight blonde eyebrows behind. Eyelashes are usually not lost. Fingernails and toenails eventually become abnormally shaped, grow slowly, and at times crack. This does not generally cause functional problems, but watch for ingrown nails that can become infected.

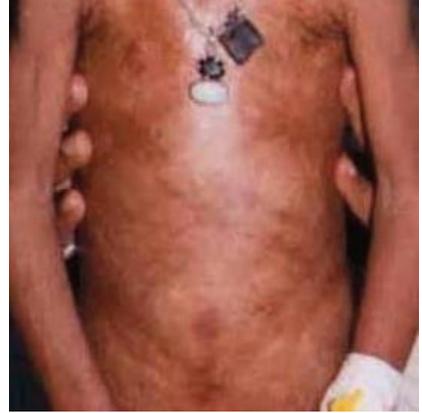
There is no specific treatment that prevents these dermatologic changes.

Fingernails and toenails eventually become abnormally shaped, grow slowly, and at times crack. This does not generally cause functional problems, but watch for ingrown nails that can become infected.

There is no specific treatment that prevents these dermatologic changes.



Hair loss starts at the periphery of the scalp; the top is often the last hair to go



Tight skin and small areas of bulging skin are evident on the abdomen

Nail dystrophy in children with Progeria



11. Bones / Orthopedics

- Bone structure
- Radiographic findings in children with Progeria
- Osteoarthritis of the hip



Though low bone density may develop, rate of bone fracture is no higher than in the general pediatric population.

Overview:

Children with Progeria face many problems with bone growth and development. Skeletal abnormalities can sometimes be seen at birth, but often develop as the children age.

Risks and Recommendations for the Family

Bone Structure

- Children with Progeria have smaller bones and are therefore relatively weaker than healthy children
- Weight bearing activities such as walking, running, jumping etc are encouraged to maintain bone density
- It's important for good bone health, that children receive

adequate Vitamin D and calcium in their diets. Ask a registered dietician, your child's primary care doctor or orthopedic specialist for recommendations

Bone Health as Your Child Grows

- An annual bone density screening – tracks your child's bone health
- Bone resorption: certain areas (fingertips, clavicles) are typical sites for bone to be resorbed back into the body. Fingertips may take on a bulbous look.
- Children with Progeria have very small jaws (see Dental section)
- Hip dislocation: some children with Progeria experience hip dislocation as they get older. This is due to changes in the shape of the leg bones in the hip socket and changes to the shape of the hip socket itself.
- Osteoarthritis of the hip: many children with Progeria develop osteoarthritis of the hip – your child's health care team will be able to determine the best course of treatment and pain management

For the Healthcare Professional: Risks and Recommendations

Bone structure

- Children with Progeria have smaller bones compared to their age-matched peers, but their bone mineral density is usually mildly low to low-normal after accounting for differences in bone size. However, because their bones are smaller, they are relatively weaker than age-matched children without Progeria. Spontaneous bone fractures are unusual and these children do not appear to suffer from broken bones any more frequently than children without Progeria. When fractures do occur, the bones heal appropriately.

In general, weight-bearing activities (i.e., walking, running, jumping) are good for maintaining bone mineral density and should be encouraged. Reasonable care should be taken when playing with larger peers, since friends who weigh more than children with Progeria could inadvertently cause an injury during play.

In order to maintain the best possible bone health, it is important that children receive adequate calcium and vitamin D in their diets. The goal for calcium intake is 1000-1200 mg per day (3-4 cups of milk or other calcium-rich foods or beverages). To facilitate the absorption of dietary calcium for proper bone growth, it is recommended that children ingest at least 400 IUD of vitamin D per day. Since it can be difficult to get adequate vitamin D in food alone, supplementary vitamin D (e.g., children's multi-vitamin tablet or vitamin D supplement) is recommended by the American Academy of Pediatrics. Please note that we do not recommend calcium supplementation, due to the concern that, unlike when getting calcium through the diet, calcium supplements can promote vascular calcification.



Child on the DXA scanner; this machine measures bone density and body composition

> Dual energy x-ray absorptiometry

Yearly bone density measurements by dual energy x-ray absorptiometry (DXA) are recommended to track progress of bone status. Scans of the spine (for density) and whole body provide the most helpful measurements in a child. A whole body scan is particularly helpful because it provides an assessment of body composition in addition to the bone measures. Hip measures are less reliable for bone density, due to the unusual femoral bone findings in Progeria. However, sometimes doctor's order DXA scans of the hip to understand how differences in hip development may affect a child's gait. DXA is available at most hospitals. For accuracy, adjust bone density Z-scores for small size. The Z-scores that are automatically generated are for larger age-matched children and will appear deceptively low, often in the osteoporotic range. When adjusted for size (i.e., using height-age), Z-scores increase, usually to the osteophytic or even the normal range.

> Quantitative computed tomography

Quantitative computed tomography (QCT) may be performed to assess bone structural geometry to assess fracture risk. QCT is not available in many hospitals, but is a three-dimensional analysis of bone structure that can aid in assessing bone status regardless of bone size. There is little pediatric normal control data in the literature at present, so following changes over time (i.e., annually) for a particular child is most helpful to assess skeletal status.

Radiographic findings in children with Progeria

> **Abnormal findings**

- **Acroosteolysis** -resorption of bone at the distal phalanges. This is usually not seen in every digit. Externally the fingertips become bulbous. This is seen as early as infancy, but it is not observed in all children until later years. It becomes progressively more severe with increasing age. There is typically no pain associated with acroosteolysis. This is the earliest radiographic manifestation of progeria.
- **Maldevelopment of the mandible** - the mandible is small , and the angle of the mandible is abnormally obtuse.
- **Clavicular resorption** – there is osteolysis at the distal ends of the clavicles.
- **Thinning and tapering of ribs** – the ribs are thin in caliber and tapered at their ends.
- **Bell-shaped Thorax** - the ribs have a “drooped” appearance and the thoracic apex is tapered. This gives the chest a bell shaped or pyramidal configuration.
- **Coxa valga deformity** – the femoral neck-shaft angle is abnormally increased (>125 degrees). This leads to a “horseriding” stance with a wide based gait and predisposes to hip joint instability and subluxation.
- **Coxa breva deformity** – the femoral neck is shortened
- **Coxa magna deformity** – the femoral head has a broad configuration
- **Acetabular dysplasia** – the acetabulum is abnormally shallow. This may lead to pain with weight bearing, hip subluxation, loss of range of motion, and osteoarthritis.

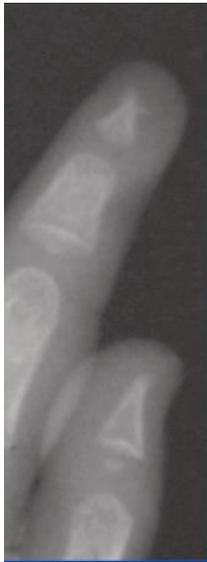
- Avascular necrosis of the femoral head – the femoral heads may lose proper blood supply, leading to flattening, fragmentation, and subchondral collapse.
- Long bone abnormalities - the diaphyses have a gracile appearance, the metaphyses are flared (proximal humerus, distal femur, proximal tibia), and the epiphyses are large and broad. Mineralization of the diaphyses may appear normal, while the metaphyses and epiphyses appear relatively demineralized.
- Enlarged capitellum of the distal humerus – the growth center at the lateral aspect of the distal humerus is atypically large.
- Cardiovascular and soft tissue calcifications – calcifications may be seen in a cardiovascular distribution or in the soft tissues of the abdomen or extremities, commonly surrounding the tufts of the digits of the hands.

Many x-ray findings develop later in life, so most are not used for diagnosis. The earliest finding is usually acroosteolysis

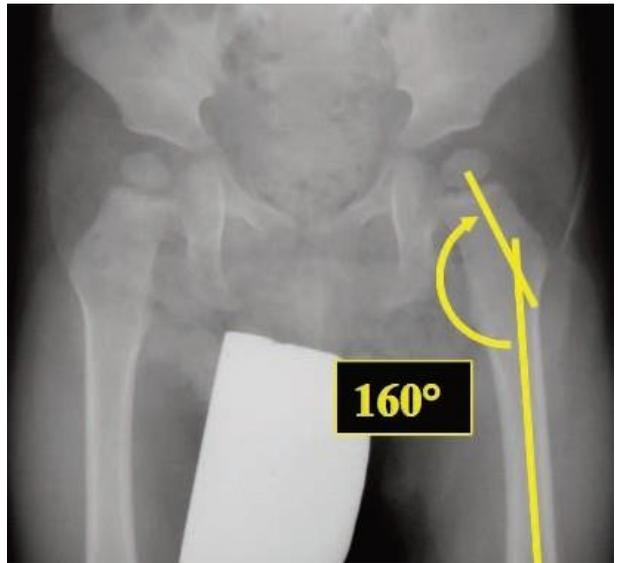
> Normal findings

- Bone age is variable; it can be normal, slightly advanced, or slightly delayed for chronological age
- Physes are normal – the growth plates at the ends of long bones are normal
- Elbow, wrist, knee and ankle joints are normal.
- Cranial sutures are normal – the spaces between the bones of the skull are normal.

> Radiographic findings



Acroosteolysis



Coxa valga



Clavicular resorption

Osteoarthritis of the hip

Osteoarthritis (OA) is a painful, chronic, incurable, non-inflammatory arthritis that affects diarthrodial joints by progressively breaking down hyaline cartilage. The syndrome is characterized clinically by pain, deformity, and limitation of motion, and pathologically by focal erosive lesions, cartilage destruction, subchondral bony sclerosis, cyst formation, and marginal osteophytes. While many etiologic factors have been postulated, the pathologic changes observed in patients with OA result from some form of mechanical injury. In children with Progeria, OA is likely the result of joint instability from anatomic misalignment and persistent articular surface incongruity related to dysplasia both of the femoral head (coxa magna) and acetabulum. There is a mismatch between the oversized femoral head trying to articulate with the undersized socket resulting in mechanical instability, impingement with range of motion, focal joint space narrowing, and subchondral sclerosis.

MRI using Thor or Gadolinium can be used to diagnose the earliest changes of osteoarthritis before irreversible changes are evident radiographically.

Treatment for osteoarthritis can help relieve pain and stiffness, but cartilage degradation may continue to progress. Initial treatment includes physical therapy to restore range of motion, muscle strength, and anti-inflammatory medications to relieve pain. To facilitate ambulation, children with advanced hip OA may require augmentative supports such as walkers. When children are unable to ambulate independently, they often require a wheelchair. As arthritic changes progress, surgical alternatives to reconstruct the involved joint, to create a stable, congruent joint may be considered. There have been at least 3 successful surgical reconstruction surgeries performed in children with Progeria. It is important to consider associated risk (i.e., complicated intubation, anesthesia) and medical conditions (i.e., cardiovascular disease) when considering these or any procedures in this high risk population.

Although most children eventually have radiographic evidence of OA, only a minority develop persistent, significant pain or permanent subluxation within their lifespans.

12. Physical Therapy (PT)

Clinical presentation Interventions

Precautions

Activity guidelines

Swimming

Overview of Physical Therapy for Children with Progeria

Generally, physical therapy (PT) promotes health with a focus on gross motor skills.

This chapter presents general recommendations for children with Progeria. Children vary widely in their presentation. Therefore, evaluation by appropriate health care professionals is necessary to address individual needs.

Please also refer to *Going to School*, section 17, for additional advice on physical adaptations from parents of children with Progeria.

For the Family: Risks and Recommendations

Children with Progeria develop contractures of their joints and associated boney deformities early in life. These impairments are progressive and impact their ability to perform activities of daily living and to fully participate in the typical activities of similarly-aged peers. Rate and degree of progression is highly variable. Children with Progeria are also at risk for strokes which can be subclinical. The effects of these strokes on development and function has not yet been determined.

There have been no studies to determine the effectiveness of physical therapy interventions on physical activity with this population. The recommendations in this handbook are based on clinical observations and discussion with patients and their health care providers.



Joint contracture occurs in all children with Progeria. Physical therapy and activity may positively impact progression.

Most children with Progeria should receive physical therapy. Physical therapy includes evaluation, direct and consultative services by a qualified professional, and a home exercise program. All are integral parts of the whole plan of care. A frequency of three times a week is generally recommended for direct treatment. If direct service is not available, home care by care-takers – with twice yearly evaluations – is necessary to revise the physical therapy plan of care.

A physical therapy evaluation should include the following assessments: range of motion and muscle length, muscle performance, posture, pain, gait, locomotion, balance, self-care and home management, neuromotor development, sensory integrity, community participation, the need for assistive, and adaptive devices, and orthotics.

Interventions include developmental and functional activities, therapeutic exercises, and prescription of adaptive equipment and orthotics. Physical therapists can also assist with locating appropriate programs for physical activity, such as local swimming classes with qualified instructors.



> Global joint contractures



Activity guidelines

Children with Progeria should be encouraged to participate in physical activities. Participation is important as it enhances peer interaction, contributes to physical fitness, and may minimize impairments and functional limitations as the disease progresses.

Children can engage in a wide variety of physical activities, such as walking, dancing, hiking, and swimming. They may not be able to participate in some team sports as they are significantly shorter and have less body mass than their peers, therefore safety may be an issue. Bony deformities may also be a limiting factor for some physical activities. High impact activities and trampolines should be avoided due to the possibility of hip dislocation.

If in doubt, ask for advice from a physician and/or physical therapist who is familiar with your child.

Children and families may need assistance from a therapist in order to find appropriate physical activities or programs. They may also need assistance finding appropriate sized toys or adapted toys (i.e., tricycles) in order to engage in physical activities.

Swimming

Swimming is great for joint flexibility; however, children with Progeria face several challenges with swimming. Because they have a severe lack of body fat, they are not well insulated. Pool water may feel extremely cold; if the water can be heated to a higher degree then the pool will be better tolerated. The ocean or ponds will be more of a challenge. We recommend a wetsuit, fitted to the child if possible. Standard children's wetsuits are too large in the legs and arms, and will not be able to properly insulate the body. In addition, fat is important for the ability to swim because it floats. Therefore, it is much more difficult for children with Progeria to swim without flotation devices. All swimming activities should be supervised by an adult who is qualified in water safety a rescue.

For the Health Care Professional: Risks and Recommendations

Clinical presentation

Children with Progeria develop contractures in all joints of the body. Additionally, changes to the bones including resorption of the distal clavicles and distal phalanges of both the hands and feet contribute to the children's functional impairments. Coxa valga, skeletal dysplasia and acetabular dysplasia are found in virtually all children. Progression to unilateral or bilateral hip dislocation can also occur . and can significantly impair ambulation. If severe, the child may lose the ability to ambulate.

Characteristic patterns of limited range of motion have been observed in the hip joint, flexion, rotations in both flexion and extension, and abduction. In the knee joint, motion is limited in both flexion and extension. Hamstring length is relatively preserved with popliteal angles not differing significantly from knee extension. In the ankle joint, the subtalar joint becomes fixed in eversion at an early age. Plantar flexion beyond neutral is often limited.

Gait is characterized by a crouched appearance in the sagittal plane and significant calcaneal position at the ankle with hindfoot valgus and midfoot pronation. Segmental transverse plane motion during ambulation is very limited.

Hip and foot pain are common features in children with Progeria, but can occur in other areas as well. Hip pain can be sudden or have an insidious onset and may or may not be associated with trauma. Pain in the hip may be a symptom of a serious bony problem including hip dislocation and should always be evaluated by a physician.

Foot pain appears to be related to the calcaneovalgus position of the foot and ankle, and the lack of subcutaneous fat under the calcaneus. These factors cause increased weight-bearing on the poorly padded calcaneus. Foot pain can be significant enough that children cannot walk barefoot and ambulation becomes limited.

Younger children with Progeria have demonstrated delay in their balance responses which may result in injury. Assessment of both dynamic and static balance is indicated. The precise mechanism of the balance dysfunction is unknown, although contractures and subclinical strokes may play a role.

Interventions

> Therapeutic exercise

Range of motion exercises may be of some benefit in preserving joint range. Exercises should be done several times a week and stretches should be maintained at end range. Activities which cause the child to move through the full excursion of joint range of motion are more functional and more enjoyable for the children and should be encouraged.

Aerobic conditioning is not necessarily indicated, as function is limited more often by joint contractures and pain and less by the secondary effects of cardiovascular impairment. However, it appears the more active the children are, the more functional they remain.

Muscle strengthening may be beneficial for strengthening the muscles opposing the areas of most common contractures such as gluteus maximus, quadriceps, and gastrocnemius complex to help maintain range of motion.

Orthotics may be necessary to provide support or improve alignment. Fabrication of a well-padded orthotic that distributes the child's weight more evenly over the entire plantar surface of the foot is helpful in improving tolerance to ambulation by decreasing pain.

> **Functional training in self-care and home management**

Functional limitations include the inability to assume certain positions such as side-sitting or perform activities such as squatting or climbing stairs. Transitional movements such as moving through kneeling may also be difficult. Limitations in range of motion appear to be the primary reason for these difficulties. Short stature may also impact their function.

Functional limitations will impact the child's ability to get on a school bus, negotiate playground equipment, and perform many self-care activities.

Assessment and provision of assistive devices to optimize independence is needed to allow the children to function similarly to their age-matched peers. Home modifications may also be necessary (refer to *Occupational Therapy (OT)*, section 13).

> **Functional training in work (job/school/play), community, and leisure integration**

Children with Progeria are generally socially and cognitively intact. Locomotor skills are limited due to contractures and short stature. Therefore, children with Progeria may have difficulty keeping up with their peers. Independent mobility is preferable to dependent forms of mobility such as being carried or using a commercial stroller. Provision of mobility devices to allow the children maximum participation in their environments is often necessary as the disease progresses.

Mobility devices allow children with Progeria independent, as well as more age- and developmentally-appropriate, access to their environment. The devices can be an adjunct to mobility, and be situation specific, such as long distance mobility. Whenever feasible, the child should be encouraged to be as active as possible to maintain overall level of function.

When available, power mobility (electric wheelchair) is preferable to manual wheelchairs due to the limitations in the upper extremities. Walkers may also

be of some use particularly in children who have had strokes or who have more severe contractures.

Precautions

Any sudden change in functional status, such as the loss of the ability to walk, or pain or significant change in range of motion should be evaluated by a physician even if there is no traumatic event.

Although gentle stretching is part of PT care, aggressive stretching should be avoided as the risk of fracture as a result of this intervention is unknown.

Due to the tendency towards the development of a calcaneal deformity, heel cord stretches should be avoided.

13. Occupational Therapy (OT)

Evaluation
Self-care
Education
Social participation
Physical findings
Treatment approach
Summary of environmental changes

Overview of Occupational Therapy for the child with Progeria

Generally, occupational therapy (OT) promotes health with a focus on life skills, adaptive equipment, and fine motor skills. Occupational and physical therapists often work together for optimal whole body treatment.

Please also refer to *Living with Progeria*, section 17, for additional advice on physical adaptations from parents of children with Progeria.

For the Family: Risks and Recommendations

Evaluation

Children with Progeria should have yearly assessments by a pediatric occupational therapist. The evaluation should include the following areas:

- Physical measures (range of motion, strength)
- Coordination skills
- Functional skills



As joint contractures progress, children use alternative methods or assistance devices to perform activities such as putting on socks. This helps to maintain independence.

- Visual perceptual skills
- Visual motor integration skills

There have been no studies on the effectiveness of occupational therapy interventions with this population and the recommendations in this hand- book are based on clinical observations and discussion with the patients and their health care providers. Any sudden change in range of motion, hand strength, or ability to participate in functional activities should be evaluated by an OT, and if one is not available, a physician even if there is no traumatic event.

Areas of occupational therapy include self-care, education, work, play, leisure, and social participation. Children with Progeria have a very large array of activities that they enjoy participating in. They do have some difficulty performing some tasks and there are a few patterns that were noted and reviewed below. The limitations appear in relationship to the child's physical findings from their occupational, physical, and medical examinations. Participation in functional activities requires a skilled therapist who should fully probe to ascertain what the child can do. If the child has limitations which hinder his or her participation, an occupational therapist can assist with equipment redesigns or adaptations.

The following sections review common areas of occupation in which these children have difficulty and/or limitations, and offer some intervention strategies to increase their participation:

Self-care

> Dressing

Children with Progeria often have difficulty with lower extremity dressing (putting on shoes, socks, and pants below the knees). This appears to be related to lower extremity joint contractures. Some children also have difficulty with mastering fasteners as quickly as other children their age. Reasons for this include limited exposure to fasteners due to the style of clothing

they wear, cultural/parenting style, decreased strength, and coordination. Children with Progeria often need assistance with the lower extremity dressing. They often develop adaptive dressing strategies such as positional changes or the use of adaptive equipment such as reachers that can help them to be independent with donning lower extremity clothing. A sock aid can be used to put on socks, while a long-handled shoe horn may assist with putting on their shoes independently.

>Hygiene

Most children with Progeria are independent with age-appropriate hygiene by the age of 4 or 5; however, they require some environmental adaptations to assist with height obstacles and with what appears to be postural instability (hesitant on step stool). In the bathroom, stools should be placed at the toilet and sink. Parents may assist or supervise when they are getting in and out of the tub or shower due to safety concerns. Rarely do the children require adaptive equipment to assist with hygiene tasks such as bathing. However, equipment such as long handle sponges may be used to assist with lower extremity washing. Some children are not able to wipe themselves after toileting due to range of motion limitations and difficulty with balance. Aides such as long handled tongs (tongs with toilet paper wrapped around them) or wet wipes to decrease the amount of wiping can be helpful. Toilet seat inserts may increase the child's comfort due to the child's size and balance difficulty. Padded toilet seats may also be used to address discomfort with prolonged sitting due to increased bony prominences. With grooming or oral hygiene, an electric or battery-operated toothbrush may be used as the children may fatigue with brushing due to decreased strength and range of motion limitations. Flossing sticks and automated hands-free toothpaste dispensers may also be helpful. Please refer to Dental Recommendations, section 9, for further information on tooth hygiene. Although it is important for the children to participate in brushing their own teeth, it is recommended that this activity be supervised and parents assist to ensure optimal hygiene.

> **Feeding**

Children with Progeria become independent self-feeders. Early signs of decreased motor coordination or the effects of joint limitations can be noted during feeding with a utensil but do not generally interrupt food intake. Use of a rocker knife may assist some children with cutting. Children with reduced hand strength or coordination often find a straight knife, such as the Amefa straight knife, very helpful and parents seem to feel safe with the use of this knife.

> **Meal preparation and eating**

Children with Progeria often have limited participation with basic meal preparation as compared to age-matched peers. This may be due to height limitations and parenting style. Some families have arranged a section where snack items can be at a height the child can reach. Snacks should be removed from original packaging and placed in easily opened containers.

Modifications can also be made to allow children to pour their own drinks, as standard drink containers are typically too heavy and are difficult to grasp due to range of motion limitations. These modifications include placing drinks in a small partially-filled container with a spout. Stool(s) placed in the kitchen also allow for access to counter tops and the sink. If the child is starting to cook and there are difficulties, seek out an OT assessment for further assistance with bowl and pan holders, electric peelers, and other cooking aides. Adapted seats such as tripp-trapp or right-height chairs with additional foot plates allow the children to sit at the dinner table with their families.

Encourage your child's independence by removing snacks from their original packaging and placing in easy-to-open containers, placing stools in the kitchen, and having adaptive kitchen utensils on-hand.

> **House management**

Some children have difficulty managing basic home functions due to height limitations. Recommendations include adapted light switches with hanging strings or plastic devices, adapted door knobs (due to difficulty with hand positioning and strength to open the door independently), and automatic doors, which may also assist with children getting out of their house in case of an emergency.

Education

> **Positioning**

Children often complain of pain while sitting for prolonged periods of time, which appears to be related to their bony prominences. Seat cushions and frequent rest breaks, allowing them to stand if needed, are recommended.

Chairs within the classroom setting should allow them to be at standard seat height with their feet supported. The use of chairs such as a tripp-trapp or right-height chair, with an additional foot plate to allow them to get in and out of the chair safely, are also recommended. These special chairs are important as they allow for the child to be an active participant and socialize with their peers within the classroom. Being at the same height as their peers also allows them to visually scan the classroom and see the chalkboard or whiteboard.

> **Handwriting**

Children with Progeria often complain of hand fatigue or pain during writing or coloring activities. The reasons for this are unclear, but appears to be related to joint limitations, reduced fatty pads, and the functional position of the carpometacarpal thumb joint (which remains fixed in mid abduction or extension) and their limited wrist positioning (neutral to slight palmar flexion). Some parents report reduced motor control during handwriting. Others report difficulty with mastering writing. In

most of the children, this appears to be a result of abnormal wrist and hand positioning and decreased strength rather than visual perceptual, visual motor integrative, and/or fine motor incoordination. OT intervention often helps children with Progeria master handwriting, with improved motor control. Children can benefit from an individualized strengthening program, including stretching exercises and activities to enhance in-hand manipulation skills along with dexterity skills. Some children also benefit from using unique crayons and pencils that are shorter and narrower, to assist with the structure of their hands and their decreased strength. Padded pencil grips or padded pens may be used to decrease the amount of finger pain that is often experienced from the pressure of the writing utensil, due to the lack of fat deposits in fingertips. The use of a vertical surface is recommended to improve wrist dorsiflexion (the ability to bend upwards) and strength. Slant boards should only be used at the recommendation of a therapist after full evaluation, due to possible contraindications. Many children report fatigue and hand pain with lengthy writing assignments. Early education and exposure to keyboarding may increase the amount of written output the child can produce. Older children may benefit from voice-activated software if they experience motor problems with keyboarding and writing.

Children with Progeria can successfully meet the demands of the school day with some accommodation in the areas of seating, classroom tools, and lunch room considerations.

> Scissors

Some children with smaller hand size demonstrate difficulty mastering scissor cutting, and benefit from a smaller size scissor proportional to their hand size.

> Carrying objects

Many children with Progeria are not able to carry their own school bag or books to and from school or during the school day.

Those with difficulty in this area require accommodations such as a second set of books (one set at home and the second set in the appropriate classroom). Bags can then be lightweight, as all they need to carry are their notebooks or paperwork. If the child does wear a backpack, the bag should be no more than 15% of their body weight and should be placed over both shoulders. Additional accommodations include use of a backpack bag with wheels. The school therapist should complete a cafeteria assessment for lunch room adaptations that keep the child actively involved with of their peers (for example, ways to access the table tops or carry lunch trays). The children also often have difficulty walking and carrying moderately weighted objects. Most frequently they are unable to carry objects up or down stairs and thus require help from a peer, teacher, or parent.

Social participation

Most children report participation in sports, playing on the playground, and other leisure activities. There is no evidence suggesting that these children should not participate in these activities unless it impacts their health. Activities such as contact sports, team sports, or leisure activities with their peers may require some adaptation to accommodate for their abilities and medical conditions. At times the activity demands may be too great or the child may need specialized equipment. Please refer to *Physical Therapy, (PT)* section 12, for further recommendations on physical activities.

Many children with Progeria experience fatigue when walking extended distances. In addition, they may not be able to keep up with their peers or family pace due to their shorter stride; this may impact their socialization. Use of functional mobility devices such as strollers, manual wheelchairs, or power wheelchairs may be needed in various environments. The child's therapist should complete a functional mobility assessment and provide the child and family with ways to allow the child to have optimal modes of mobility. For example, power wheelchair options (such as the Permobil which has a seat elevator and a

chair-to-floor option) allow for increased independence. This chair allows the child to get in and out of the chair safely and to reach items at different heights, as well as navigate within the classroom, home, and community.

For the Health Care Professional: Risks and Recommendations

Physical findings

Physical findings vary markedly within age groups and age spans among children with Progeria. Body functions and structures that affect upper extremity use and functional activities often include the following:

- Joint contractures of all upper extremity joints
- Upper extremity asymmetries
- Prone to shoulder dislocations (which should be taken into consideration with weight bearing and strengthening activities such as gymnastics)
- Reduced upper extremity strength
- Wrists typically have limited dorsiflexion (bending upward)
- Some children's thumbs do not go into carpometacarpal (CMC) extension plane
- Most children's thumbs are used with the thumb against the distal interphalangeal joint of the index finger (the joint closest to the tip of the finger)
- On occasion hyperextension of the thumbs' interphalangeal joints (joint closest to the tip of the finger) is seen
- Metacarpalphalangeal joints most often have limited flexion (joints closest to the hand)
- Distal and proximal interphalangeal joints (the middle joint and the joint closest to the tip of the finger) tend to have flexion contractures
- Resorption of the distal phalangeals

- Distal phalangeals are often painful with pressure
- Decreased fat deposits within the hand (most notably at the thumb and finger tips)
- Short in stature
- Increased bony prominences
- Difficulty tolerating extreme hot or cold temperatures (i.e., weather, water)
- Some have decreased fine motor coordination
- Some have visual perceptual and visual motor integration deficits



Maximum
finger
extension in a
child with
Progeria



Treatment approach

After completion of an occupational therapy evaluation, a treatment program should be recommended. This may include direct services, home programming with follow-up, or ongoing consultation. Many children with Progeria will not require weekly services, but will require ongoing treatment with parent and child education.

The occupational therapist should provide evaluation and treatment to assist the children in all areas of function (self-care, education, work, play, leisure, and social participation). Children under the age of 6 years should be seen twice a year for an assessment by an occupational therapist. Children 6 years and older should be seen yearly for an occupational therapy

evaluation. If there is a significant change in function or other concern, the family should contact the therapist sooner. The treating therapist should have current medical history and be aware of all precautions. Ongoing communication is needed between the occupational and physical therapist, and may require combined treatment sessions at times. Accommodation or environmental changes may require minimum intervention but provide the child with optimal independence. An occupational therapy treatment program should include use of traditional physical disabilities treatment approaches, including passive range of motion with particular emphasis on the thumb, wrist, and fingers. At this time it is unknown if hand static splinting will improve range of motion; this should not be tried without the child first being seen for assessment by a pediatric hand specialist (MD). The therapist should provide the pediatric hand specialist with a comprehensive hand assessment that includes range of motion, strength, functional grasping, dexterity items, and activities of daily living.

Children with Progeria enjoy a very large array of activities. Despite their unique body functions and structural differences, there are many ways to accommodate their environment and tasks with adaptive devices and other changes that allow them to increase their independence and participation in activities of self-care, education, work, play, leisure, and social participation. Their involvement in these areas with their peers and their increased independence is important, especially as they become pre-adolescent.

Summary of environmental changes to help children with Progeria

> House

- Steps for bathroom
- Adaptive toothbrush (i.e. benefit 3D clean) with different angle as needed
- Adapted switches and knobs
- Lower the placement of items for food preparation
- Amefa straight knife to assist with cutting

> Mobility

- Adaptations differ depending on environment: home vs. neighborhood vs. larger community

> Allow for functional mobility

- Ease of mobility from place to place
- Ability to keep up with peers
- Mobility allows for socialization

> Recreation

- Adjust for safety or parents' concern
- Bike and/or tricycle

> School

- See *Going to School*, section 17

> Hand held devices

- Tablets
 - Due to the hand span, the smaller tablets are easier to manipulate and hold (7 inches)
- Keyboards
 - Mini keyboards are ideal

> Dressing

- Clothes with hand held loops (i.e. EZ sox, EZ under, EZ Tees)
- Shirts with wider/stretchy necks

14. Podiatry

Podiatric problems in children with Progeria Shoe inserts



For the Family: Risks and Recommendations:

- Children with Progeria have challenging feet – they often lack the proper fat padding to cushion their bones against hard surfaces; they may have skin abnormalities, joint contractures or issues with their toenails
- An annual visit with a podiatrist is recommended

Feet become sensitive to hard surfaces and shoes. Shoe inserts and slippers help prevent pain, blisters, and calluses

For the Health Care Professional:

Podiatric problems in children with Progeria

Several factors contribute to the challenging foot care issues for children with Progeria. These include a lack of a proper fat padding, skin abnormalities, toenail dystrophy, and limited joint range of motion in the ankle. These issues result in calluses (corns), blisters, heel discomfort, and an inability to walk on hard surfaces without shoes or slippers. Annual evaluation by a podiatrist are recommended. Calluses can be treated with moleskin or other padding. Massaging gently with moisturizing lotions can help to alleviate pain.

Children with Progeria have a gait deviation that is typical of someone with limited foot motion. The normal foot is capable of adapting to terrain that is uneven as the soft tissues of the foot allow the hind foot, mid-foot, and forefoot to function independently from one another. Since children with

Shoe inserts

Upon clinical exam, the normal padding associated with the plantar surface of the foot is not present, so accommodating the length of the foot to a shoe tends to be a difficult task. The foot of a child with Progeria is very narrow. The lack of padding also makes walking painful because the bones of their feet absorb all of the shock of gait.

Custom shoe inserts are recommended. They are often arranged for through the child's podiatrist. A well-padded, soft but supportive material is used to help stabilize the foot. First, an impression is made using an impression cast. This is then used to make a positive mold of the child's foot. A trilaminate material is then heated to become flexible and vacuum formed over the molds. Since it helps to take some of the volume up within the shoe, very little material is cut away to fill the extra space so the feet do not slide within the footwear.

15. N u t r i t i o n

- Increasing calories
- Healthy, high calorie snacks
- Making healthy food choices
- Shakes & smoothies



Children with Progeria may be born in the normal weight and length range, but sometime within the first year of life, they fail to gain the appropriate weight and drop off of the typical “weight curve” and “length curve” that pediatricians use to measure overall growth. It is particularly disconcerting for parents to witness their children eating small meals or indicating they are not hungry, since the child is simultaneously failing to grow. It is important to remember that all children with Progeria go through this transition, and that they settle into a steady growth rate that is very different from their peers. They do gain weight and height, but at a very slow and steady rate.

Studies have shown that children with Progeria actually eat enough calories to grow, but the basic disease process in Progeria does not allow them to grow normally. Therefore, providing even more calories through a nasogastric or gastrostomy feeding tube is unlikely to lead to increased weight or height. Some parents report that the children tend to take in smaller, more frequent meals. Each family should consult its home medical team to assess the patient’s individual nutrition goals, but the general goal is for each child to eat nutritious, high calorie foods by mouth and drink supplements when his or her intake is not meeting estimated needs.

Food intake is one of the most powerful daily challenges for children with Progeria and their families. Frequent, small meals often work well.

➤ Blood Lipids

The heart disease in Progeria is probably not driven by lipids. Children with Progeria usually have normal levels of cholesterol, triglycerides, and other types of fats that are measured in blood tests to assess risk of heart disease in the elderly. They sometimes have lower than optimal HDL (the “good” blood fat). When cholesterol or triglycerides levels are found to be high, dietary measures or statins are sometimes be used to lower the levels.

➤ Dietary Supplements

Discuss with your Pediatrician or Registered Dietitian whether your child might benefit from a standard pediatric multivitamin. However, because children with Progeria have an abnormal calcium metabolism, calcium supplementation is not recommended unless necessary for immediate medical need. Dietary calcium is recommended instead of calcium supplements, when possible.

Increasing calories

Try these simple additions to increase calorie count:

- Add healthy oils (canola or olive) to rice, pasta, vegetables, and soups/casseroles
- Melt cheese on vegetables, add to pasta, or include in sandwiches
- Add avocado to sandwiches or salads; use as a chip dip
- Add milk powder to hot cereals, scrambled eggs, soups, casseroles, ice cream, yogurt, and mashed potatoes
- Mix fruit and granola and/or nuts into yogurt; add peanut butter to vanilla yogurt
- Add cooked meats, ham, poultry, tuna, shrimp to casseroles, cooked noodles, sauces or scrambled eggs

Healthy, high calorie snacks

- Peanut butter or cheese on whole grain crackers
- Whole wheat toast with peanut butter and banana cut up; add some honey for sweetness
- Peanut butter on fruit
- Trail mix with nuts, dark chocolate, dried fruit, and whole grain, high fiber cereals
- Make a fun smoothie with your child using whole milk, frozen fruits, and yogurt or ice cream (see shake recipes below).

Making healthy food choices

Supplements and high calorie foods are encouraged when appetite is decreased. However, for a balanced diet, follow these general guidelines:

- Choose lean cuts of meat and poultry, and include fish in your family's diet
- Incorporate healthy fats from oils such as olive and canola, nuts, and avocado
- Choose whole grains
- Eat lots of fruits and vegetables
- Try new foods; sometimes it takes many times of trying a new food before your child will decide they like it

Shakes & smoothies

A group of Dietitians at Boston Children's Hospital created and tested the smoothie/shake recipes below:

All shakes are 12 ounces unless otherwise noted

Chocolate Peanut Butter Milkshake	Oreo Milkshake
½ cup whole milk 3 Tablespoons peanut butter 3 Tablespoons chocolate syrup 1 ½ cups chocolate ice cream <i>1330 calories, 31 grams protein</i>	½ cup crumbled Oreos 2 Tablespoons chocolate syrup 1 ½ cups vanilla ice cream ¾ cup whole milk <i>940 calories, 16 grams protein</i>
Double Chocolate Milkshake	Chocolate Peanut Butter Banana Milkshake
1 cup chocolate milk 2 Tablespoons chocolate syrup 1 packet chocolate Carnation Instant Breakfast 1 cup chocolate ice cream <i>940 calories, 25 grams protein</i>	½ cup whole milk 3 Tablespoons peanut butter 1 Tablespoon chocolate syrup ½ cup vanilla ice cream ½ banana <i>600 calories, 19 grams protein</i>

<p>Orange Mango Smoothie</p> <p>1 cup frozen mango chunks ½ cup whole milk ½ cup orange sherbet ½ cup vanilla ice cream ½ cup orange juice</p> <p><i>500 calories, 9 grams protein</i></p>	<p>Purple Fruit Smoothie</p> <p>1 banana ½ cup blueberries 1 container vanilla yogurt 1 cup orange juice 1 teaspoon vanilla</p> <p><i>470 calories, 11 grams protein</i></p>
<p>Apple Berry Freeze</p> <p>1 box Enlive apple ½ cup frozen blueberries 1 cup canned pears Ice to blend</p> <p><i>370 calories, 9 grams protein</i> * Fat free, dairy free</p>	<p>Cappuccino Milkshake</p> <p>1 packet Sanka Decaf Instant Coffee 1 Tablespoon hot water 1 cup vanilla ice cream ½ cup whole milk</p> <p><i>360 calories, 9 grams protein</i></p>
<p>Hawaiian Smoothie</p> <p>1 ½ cups vanilla ice cream ¾ cup pineapple juice 1 banana Ice to blend</p> <p><i>310 calories, 4 grams protein</i></p>	<p>Creamsicle Shake</p> <p>1 cup orange sherbet ½ cup whole milk</p> <p><i>290 calories, 5 grams protein</i></p>
<p>Strawberry-Banana Smoothie (Makes 8 ounces)</p> <p>½ cup vanilla ice cream 1 cup whole milk 1 packet vanilla Carnation Instant Breakfast ½ banana 1 Tablespoon strawberry syrup 1 cup fresh strawberries Ice to blend</p> <p><i>280 calories, 8 grams protein</i></p>	<p>Soy Milk Fruit Smoothie</p> <p>8 ounces soy milk ½ cup frozen mango chunks ½ cup strawberries 1 Tablespoon honey</p> <p><i>280 calories, 9 grams protein</i> * Dairy free</p>
<p>Strawberry Smoothie</p> <p>1 container strawberry yogurt ½ cup strawberries ½ cup pineapple juice</p> <p><i>250 calories, 8 grams protein</i></p>	<p>Blue Raspberry Icee</p> <p>½ cup frozen blueberries ½ cup cranberry-raspberry 100% fruit juice 1 cup lemon Italian ice</p> <p><i>220 calories, 1 gram protein</i></p>

	* Fat free, dairy free
Strawberry-Banana Freeze	Orange-Pineapple Freeze
1 cup strawberries ½ banana ½ cup orange Italian ice ½ cup orange juice <i>220 calories, 3 grams protein</i> * Fat free, dairy free	6 ounces pineapple juice ½ cup orange Italian ice ½ cup pineapple chunks <i>210 calories, 1 gram protein</i> * Fat free, dairy free
Strawberry-Banana Fat Free Smoothie <i>(Makes 8 ounces)</i>	
6 ounces strawberry fat free Chobani yogurt ½ cup skim milk ½ banana ½ cup fresh strawberries 1 Tablespoon strawberry syrup Ice to blend <i>130 calories, 10 grams protein</i> * Fat free	

We recommend consulting a local Registered Dietitian to monitor growth and nutrition of your child over time. The Dietitian is able to recommend age-specific nutritional supplements if needed. There are many products on the market that may not be appropriate for your child's needs based on age, size, specific laboratory tests and current nutritional needs; it is ideal to have a professional make recommendations. The stress of mealtime may be eased by the use of nutritional supplements. Try these tasty tips:

- **Serve cold and covered:** Due to the fact that supplements contain a lot of added vitamins and minerals, they taste better than they smell. If you are serving the supplement to your child as a beverage, be sure it is cold. Serve it from the can with a straw or put it in a bottle or a cup with a cover.
- **Be creative!**
 - Use vanilla flavored products as a substitute for milk in baked products
 - Add fruit and crushed ice and place in the blender to make a “smoothie”
- **Vanilla:** Unless you know that your child has a preference for a particular flavor of a supplement, buying vanilla is recommended. It is the best flavor to use in recipes and flavored syrups or fruit can be added for flavor variety.
- **Powdered products:** When mixing the powdered supplements with liquid to make a beverage, be sure to let it sit in the refrigerator for some time to let the powder completely hydrate. If adding a powdered supplement in the dry state to food, do so after the food has been cooked.

16. Pubertal Changes in Adolescent Females with Progeria

For The Family

Females with Progeria may achieve sparse pubic hair and breast buds, but do not achieve full sexual development. Menarche (first period) is achieved in over half of adolescent girls with Progeria. They may continue to have periods, often not cycling monthly. Blood loss is variable. Some girls can experience high blood loss (menorrhagia) and anemia can occur. Blood volume and hydration are important to maintain in children with Progeria. If you become concerned about loss of blood, or detect weakness or exhaustion that may be due to menstruation, please contact your child's local doctor. In a few cases, adolescents with excessive menstrual bleeding have been prescribed a low dose birth control pill that decreases or stops menstrual bleeding.



For the Healthcare Professional

In healthy non-HGPS adolescent girls, menarche is typically a late pubertal event, following the gradual development of breasts and pubic hair, the pubertal growth spurt, and changes in body composition that are characterized by increasing body fat. Some previous studies have suggested menarche and regular menstrual function in healthy adolescents and women to be dependent on the maintenance of a minimal weight for height and a critical percentage of body fat. Study of adolescents with HGPS demonstrates that these typical events are not required for menarche to occur.

Growth and Body Fat: Children with HGPS exhibit lifelong failure to thrive beginning in the first year of life, with weight and height typically falling well below the 3% percentile by age 2 years. Generalized lipodystrophy ensues, with severely low subcutaneous fat and leptin levels.

Tanner Staging: Around 40% remain Tanner stage 1, and the remainder develop Tanner stage II characterized by sparse pubic hair and/or breast buds. Adolescent females with HGPS do not achieve Tanner stage III.

Menstruation: An estimated 60% of females with HGPS experience menarche. Mean age of menarche is not significantly different from established mean age of menarche in healthy females without HGPS (around 14.5 years of age). Cyclicity is highly variable, with some experiencing irregular, light bleeding and others experiencing heavy bleeding with increased flow (menorrhagia) causing anemia. When menorrhagia occurs, with risk of anemia, consider treatment with low dose oral contraceptive agents to arrest the menstrual bleeding.

Those who experience menarche and those who do not are not different with respect to size, body fat percentage, Tanner stage, or serum leptin concentrations.

17. Going to School

Advice on working with the school
Emergency care in school
School, classroom, medical, and
transportation

Many children with Progeria attend school with their peers, and require special accommodations so that they can comfortably participate in regular classes. This section includes recommendations and some examples of practical accommodations for the children.



Advice on working with the school to accommodate your child's needs

It is highly recommended that parents have meetings with the principal, school nurses, therapists, and all teachers involved with your child. It's a great opportunity to inform everyone about what Progeria is and what your child's needs may be. It's also an opportunity for the staff to help each other and parents by sharing strategies and advice about how to best serve the child. Start-of-year meetings allow staff to ask questions that pop up unexpectedly, and help staff to see that parents are available for continued discussion and questions. Throughout the year, parents may also choose to incorporate a "communication book" in which teachers, teacher's assistants, and other helpers can enter observations which can then be discussed with parents. End-of-year meetings allow sharing between current teachers and the following year's teachers. Often the parents or the current teachers can choose the following year's teachers.

Choices may center around emergency preparedness training, demeanor of a particular teacher, and classroom proximity to the nurse's office or building entrance. Bring copies of this handbook to

meetings; these are available from PROF. Everyone will be appreciative of the shared communication and optimal preparedness.

Emergency care in school

Any child who develops dyspnea (shortness of breath), angina (chest pain), or cyanosis (blue discoloration of lips and skin) during exertion should stop immediately. If symptoms do not rapidly resolve, the child should receive emergency medical care according to the school or facility's emergency plan. If oxygen is available it should be administered. Due to the risk for cardiac events, it is also desirable for school medical personnel to be trained in cardiopulmonary resuscitation (CPR) and to have access to an automated external defibrillator (AED) with pediatric capability. For more information on CPR training, emergency care in the schools, and automated external defibrillators, refer to the American Heart Association website at www.americanheart.org.

School, classroom, medical, and transportation

- Ensure proper seating height with feet touching the surface. If feet are hanging, legs become uncomfortable. Most desks and chairs can be lowered, or smaller desks and chairs can be brought in.
- Supply a soft cushion to put on hard chairs or supply a support and multi-position orthopedic chair.
- Allow the child to sit, stand, and move around at will. Sometimes for comfort, the children need to stand at the desk intermittently instead of sitting and can do this without interrupting their work.
- It often becomes difficult for children with Progeria to sit cross-legged or on a hard floor. Provide a rolling stool chair in each class.
- Stools in bathrooms are needed to reach sinks. Doors to bathrooms should be easily opened or remain open throughout the day.
- For younger children, supply a stroller to the school. For older children, access to a wheelchair may be useful, especially if the child has joint problems.
- Two sets of books should be supplied, one for home and one for school.
- Monitor writing fatigue in the classroom.

- Writing suggestions:
 - Scribe or keyboarding as needed for longer writing assignments.
 - A sloped drawing board to place on the desk can be far more comfortable than writing on a flat surface.
 - Large pencils or pencil grips similar to ones supplied to arthritis sufferers may be more comfortable for writing.
 - A laptop computer can reduce fatigue or “writer’s cramp”.
- A rolling book bag is advised.
- Assign a lower locker on the end so there is no student to at least one side next to him/her.
- Allow the child to wear a hat in school. Most schools do not allow children to wear hats, but it’s important to allow children with Progeria to wear caps or hats if this makes them more comfortable.
- Accommodations for standardized and state testing:
 - Arrange for the test to be administered in short periods with frequent breaks.
 - The child can use a word processor, and/or answers to open-response questions as needed.
 - Another option is Scribe ELA Composition, wherein the child dictates the compositions to a scribe or uses a speech-to-text conversion device to record the composition as needed.
- For physical education class, it is optimal if the teacher allows the child to try things that he/she wants to try, but also let the child rest whenever needed. Making sure the child is always involved (not feeling left out) with the activity is very important. The teacher should monitor cardiovascular activity closely. This can be self-limiting, as the children should play with peers as much as possible. Often the child can serve a central “important” role such as scorekeeper or “designated quarterback” so that contact is minimized but involvement is maximized.
- The physical education teacher should provide accommodations in gym class and the locker room as needed. If the class goes outside, monitor temperature. If the child is not going out due to severe temperature, he/she can stay in with a buddy.
- Children with Progeria should not be picked up by other children. Children love to pick each other up but because they often squeeze too tightly or fall with the child, this is never recommended.

- Arrange for physical therapy 3 times per week in school, for 20-30 minutes per session, and for occupational therapy 1-2 times per week in school, for 20 minutes per session. PT is often provided as part of the school day, and it helps to avoid after-school PT and OT appointments which can detract from quality of life.
- Allow the child to carry a lunch box with him/her to eat or drink at will. Often the children need small, frequent drinks and snacks, but school usually limits eating and drinking times. Children with Progeria should be allowed to eat and drink at will without disrupting the classroom. Make sure substitute teachers are aware of this as well.
- The child may need to go to the front of the lunch line so that he/she has enough time to get food and eat it. Children with Progeria often eat more slowly than their peers, but they need to maximize food and drink intake. Also, taking a “buddy” to the front of the lunch line helps with carrying trays and with comfort level. Be sure the lunch room attendant can help them carry trays or reach food items if necessary.
- Have an adult or student escort carry the child’s backpack at the beginning of the day and assist at dismissal.
- A student or adult should also assist in transition from class to class. A one-on-one teacher’s assistant to escort your child from classroom to classroom and dining areas, carry heavy items such as back packs and books, and reach items on high shelves as needed depending on the child’s age, health status, and school regulations. As the children get older, their peers can assist with these types of tasks, thus avoiding the need for an assigned adult assistant in school.
- The child should leave class 2 to 3 minutes earlier than the regular dismissal time in between classes and for the bus. Backpacks become “head height” and can easily hit the child. Also, hallways become crowded and unruly between classes. Early transition time is optimal.
- The child should have a parent or other school-approved adult accompany the child on all field trips.
- Arrange for a mini-bus for transportation to and from school, if possible. The regular school bus is the least well monitored area of school. Special bus accommodations are optimal.
- Seating in the classroom should be in close proximity to the teacher and near the door. All children with Progeria develop a low tone hearing deficit. Though this does not generally affect the speech tones, sitting at the front of classes is optimal. Sitting near the door also helps classroom to classroom transition without disruption.
- Classrooms should be chosen so they are close to the elevator, if the school has one.
- Allow the child to use the elevator with a buddy whenever traveling between floors.
- In the younger years, have a warm “quiet area” with a blanket and pillow where the child can relax if they feel tired. Rest periods at the nurse’s office may be needed as she/he gets older.
- Nursing staff should be directed to call parents whenever the child is seen at nurse’s office.
- Nursing staff should have a defibrillator available for treatment.

- In case of ambulance transfer to a hospital, arrangements should be made to be taken directly to a pre-determined hospital where the hospital staff knows the child best and/or is best equipped to take care of a child with Progeria. Progeria is rare and in most cases the staff will not know how to treat patients with Progeria. Ambulance staff will determine if the medical situation warrants transfer to the nearest hospital, regardless of whether they have experience with the child.
- Having close friends and reliable assistants to help in school is **KEY** to making everyone feel comfortable and happy.

18. Progeria and Aging

What Progeria and aging have in common and how they are different



Progeria is called a “segmental” premature aging syndrome. That is because it does not mimic aging completely. For example, children with Progeria do not experience Alzheimer’s disease, cataracts, or cancers typical of aging. Conversely, aging in the general population does not bring about some of the bone changes and balding patterns seen in Progeria. It is very important to determine where aging and Progeria overlap at the biological level, so that we can learn and help everyone as much as possible.

What Progeria and aging have in common and how they are different

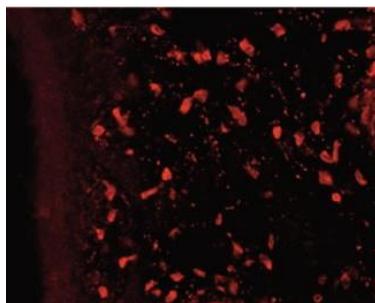
The discovery that Progeria is caused by a newly discovered protein called progerin raised entirely new questions: Is progerin produced by all of us? Does progerin have a role in aging and heart disease? Perhaps our most exciting new clue to the aging process is the discovery that the progerin protein is present at increasing concentrations in both Progeria and normal cells as they age. In addition, progerin is found in skin biopsies of older donors (see figure on next page), while young donors have less or no detectable progerin. The newly discovered relationship between Progeria and progerin has opened the doors of scientific exploration into how this molecule may play a role in heart disease and aging in the general population.

Understanding Progeria promises exciting new avenues for understanding the natural aging process. We all make a little bit of progerin, though much less than children with Progeria.

Children with Progeria are genetically predisposed to premature, progressive heart disease. Death occurs almost exclusively due to widespread heart disease, the number one cause of death globally¹.

As with any person suffering from heart disease, the common events for Progeria children are strokes, high blood pressure, angina, enlarged heart, and heart failure, all conditions associated with aging. Thus there is clearly a tremendous need for research in Progeria. Finding a cure for Progeria will not only help these children, but may provide keys for treating millions of adults with heart disease and stroke associated with the natural aging process.

Because the aging process is accelerated in children with Progeria, they offer researchers a rare opportunity to observe in just a few years what would otherwise require decades of longitudinal studies.



Skin biopsy showing progerin in a 93 year-old person without Progeria. The red dots are cells containing progerin.
(Photograph courtesy of K. Kjabali)

19. Drug Treatment Trials

The science behind the Progeria
clinical drug trials

Trial medications at a glance
Progeria clinical drug trials

The science behind the Progeria clinical drug trials

Background: There have been 3 clinical treatment trials funded and coordinated by The Progeria Research Foundation. In each trial, a drug or combination of drugs has shown positive results in the laboratory when tested on Progeria cells or on Progeria mice. PRF is focused on funding scientific research worldwide, so that scientists can discover new drugs that show promise in the laboratory. Once this is achieved, some of these drugs are ready to move into a human Progeria trial. We do not know if the drugs will work to help children with Progeria when we begin the trial, because only the trial itself will tell us whether the drug(s) have been effective. We examine trial results only after the trial is completed, usually 3-4 years after beginning the trial.

Finding the gene for Progeria was the key element to this entire avenue of exploration. This gene is called LMNA, and it normally encodes a protein called prelamin A (this protein is further processed and becomes lamin A). Children with Progeria have a mutation in LMNA which leads to the production of an abnormal form of prelamin A called “progerin.” Many years’ worth of basic research on prelamin A and lamin A gave us the ability to understand that the drugs administered in this trial may prevent progerin from damaging cells and thus reduce the severity of the disease Progeria.



The Progeria gene
discovery opened
the floodgates for
research into
Progeria that has
led to clinical drug
trials.

Trial medications at a glance

To date, the treatments that have been have all targeted different places along a common pathway that targets progerin. There are four drugs that have been studied in treatment trials for Progeria (see figure 1).:

- 1) A farnesyltransferase inhibitor (FTI) called lonafarnib
- 2) A statin called pravastatin
- 3) A bisphosphonate called zoledronic acid
- 4) An mTOR inhibitor called everolimus (similar to the drug rapamycin)

Lonafarnib

The protein that we believe is responsible for Progeria is called progerin. In order to block normal cell function and cause Progeria, a molecule called a “farnesyl group” must be attached to the progerin protein. There are a series of steps necessary for a cell to make the farnesyl group, and place it onto the progerin protein. Lonafarnib aim to block the attachment of the farnesyl group onto progeria, and therefore may make progerin less damaging to cells.

Treatment with lonafarnib has yielded a number of positive results. While a very slight increase in weight was observed in children with progeria taking the drug, the most important effect appeared to be an improvement in some of the function of the cardiovascular system, the part of the disease that causes death in most patients. Overall, blood vessels became more flexible with treatment. Lonafarnib also improved bone structure. Most importantly, lonafarnib may be increasing survival time. When comparing children who were treated with lonafarnib to those who were not, over a 2-year period there was one death in the treated group but 9 deaths in the untreated group. While the results were positive, it was also clear that lonafarnib alone was not enough to completely reverse the disease. We strive to

discover new drugs that will improve upon the benefits provided by lonafarnib. Lonafarnib is not approved by the U.S. Food & Drug Administration, and can only be given through approved clinical trials.

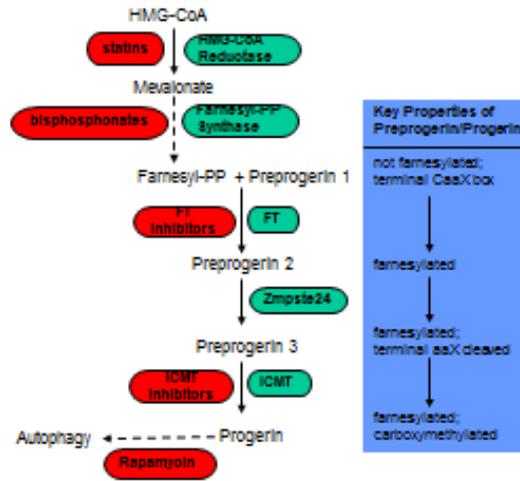
Pravastatin and zoledronic acid

The second trial combined pravastatin, zoledronic acid, and lonafarnib in the hopes that the three drugs together would be more effective than lonafarnib on its own. Pravastatin and zoledronic acid act by blocking (inhibiting) the production of the farnesyl group. However, the trial results showed that the three drug combination when compared with giving lonafarnib on its own were equally effective. Therefore, the three drug combination is not recommended as a replacement for lonafarnib on its own as a single therapy.

Everolimus

Everolimus (marketed under the trade names Afinator) is an oral mTOR inhibitor. This agent is used to prevent the rejection of transplanted organs such as heart, kidney and liver. In laboratory experiments, it can increase the breakdown of the abnormal molecule progerin. In this way, it functions differently from the other three drugs above, all of which attempt to reduce the production of the disease causing progerin. PRF is funding and co-ordinating a clinical trial at Boston Children's Hospital that administers everolimus plus lonafarnib to children with Progeria. Results of this trial are expected in 3-4 years.

Figure 1



Progeria clinical drug trials

Over the past 10 years, Progeria has gone from obscurity, to gene finding, and now to the completion of a number of clinical trials. This section will provide information on clinical trials in general, and where the Progeria clinical trials stand today. Websites where you can find more detailed information are provided.

> **Clinical Trials 101**

There is a vast amount of information about clinical trials available to you through the world wide web. Learning about clinical trials is very important, so that each family can decide whether to participate in any given study.

All clinical trials are considered research and are completely voluntary. The basic information for this section is derived from www.clinicaltrials.gov and modified for the Progeria clinical trials.

What is a clinical trial?

Broadly defined, a clinical trial is a health-related research study in which either or both health observation or intervention may be applied. For Progeria, we have embarked on research studies with both goals in mind. We study as many things as possible before, during, and after children are taking trial medications. Studying the “natural history” of Progeria helps us to define what is happening to the children, and develop treatment strategies for them in our efforts towards improving quality and longevity of their lives.

Why participate in a clinical trial?

Participants in clinical trials can play a more active role in their own health care, gain access to new research treatments before they are widely available, and help others by contributing to medical research.

Who can participate in a clinical trial?

All clinical trials have guidelines about who can participate. Using inclusion/ exclusion criteria is an important principle of medical research that helps to produce reliable results. The factors that allow someone to participate in a clinical trial are called “inclusion criteria” and those that disallow someone from participating are called “exclusion criteria”. For some of the Progeria trials, these criteria have included genetic confirmation of Progeria, age, record of weight gain over time, liver and kidney health status, previous treatment history, and other medical conditions. Before joining a clinical trial, a participant must qualify for the study. Inclusion and exclusion criteria are never used to reject people personally. Instead, the criteria are used to identify appropriate participants and keep them safe, since there is always a risk/benefit ratio to think about in research. The criteria help ensure that researchers will be able to answer the questions they plan to study.

What happens during a clinical trial?

The clinical trial team includes many types of researchers, such as doctors, nurses, therapists, statisticians, coordinators, laboratory technicians, and other health care professionals. They check the health of the participant at the beginning of the trial, give specific instructions for participating in the trial, monitor the participant carefully during the trial, and stay in touch after the trial is completed.

For the Progeria trials, each patient family periodically flies to the trial site for testing and drug supply. There is also some monitoring at home, so that any toxicities can be addressed immediately.

Reliable measures of disease improvement are essential for the clinical trials

Although studies with cells and mice are extremely encouraging, as with any experimental treatment, we must have measures of

disease improvement that we can rely on to tell us whether the drugs are helping the children, within the two-year time frame of the trials. This means that careful off- drug measures need to be taken prior to the start of drug treatment, so that we will be able to measure changes while on this drug. To this end, careful analysis of baseline clinical status of children with Progeria is performed, using their medical charts, the weighing-in program, and data from pre-drug studies performed at the trial site. The baseline measurements can then be compared to measurements taken periodically while on the treatment drug, so that we can determine as precisely as possible the exact impact of the treatment on the children.

What is informed consent?

Informed consent is the process of learning the key facts about a clinical trial before deciding whether or not to participate. It is also a continuing process throughout the study to provide information for participants.

To help someone decide whether or not to participate, the investigators involved in the trial explain the details of the study. The information is provided in the primary language of each family to ensure clear communication. Translation assistance is provided. Then the research team provides an informed consent document that includes details about the study, such as its purpose, duration, required procedures, and key contacts. Risks and potential benefits are explained in the informed consent document. The participant, or parents or legal guardians, then decide whether or not to sign the document. Children able to understand the major issues are usually asked to sign a form after the trial is explained to them in age appropriate terms. For a child under age 18, this is called assent. Informed consent is not a contract, and the participant may withdraw from the trial at any time.

What are the benefits and risks of participating in a clinical trial?

Benefits: Clinical trials that are well-designed and well-executed are the best approach for eligible participants to:

- Play an active role in their own health care
- Gain access to new research treatments before they are widely available
- Obtain expert medical care at leading health care facilities during the trial
- Help others by contributing to medical research

Risks: There are always risks to clinical trials:

- There are almost always side effects to experimental treatment. These are carefully monitored, but since the treatment drug has either never been given to children with Progeria, or the drug has not been given to many people in the world, we don't know all of the side effects that may occur. Side effects, especially newly identified side effects, are reported to participant families during the trial, whereas trial results about benefits cannot be reported until the trial has ended.
- The experimental treatment may not be effective for the participant. It is the clinical trial itself that asks whether the treatments are beneficial to children with Progeria. We do not know the answer until we finish the trial and analyze all of the data.
- The trial requires time and effort on the part of each family, including trips to the study site, more treatments, hospital stays or complex dosage requirements. Each family is a partner in the trial process.

It takes tremendous courage to travel far from home, to meet with people who often do not speak your language, and to entrust the care of your child to them.

Does a participant continue to work with a home primary health care provider while in a trial?

Yes. The clinical trials provide short-term treatments related to a designated illness or condition, but do not provide extended or complete primary health care. Testing is focused on changes that may occur on drug. Home health care is focused on the general health of the child. In addition, by having the health care provider work with the research team, the participant can ensure that other medications or treatments will not conflict with the trial medications.

Can a participant leave a clinical trial after it has begun?

Yes. A participant can leave a clinical trial at any time. When deciding whether to withdraw from the trial, the participant should discuss it with the research team, to ensure that stopping the drugs is done safely. The drugs will usually need to be returned; the cost will be paid by the people running the trial, not the family.

Where did the ideas for the trials come from?

Ideas for clinical trials came from researchers. After researchers test new therapies in the laboratory and in animal studies (called preclinical studies), the experimental treatments with the most promising laboratory results move into clinical trials. It is important to remember that, although treatments can look great in the laboratory, we will only know if and how well they work in patients by giving the treatments and then looking carefully at the results from the clinical trials.

Who sponsors clinical trials?

Clinical trials can be sponsored or funded by a variety of organizations or individuals. In the United States, Progeria treatment trials have been funded by The Progeria Research Foundation, by the National Institutes of Health (NIH), Boston Children's Hospital, and Dana-Farber Cancer Institute.

What is a protocol?

A protocol is a study plan on which all clinical trials are based. The plan is carefully designed to safeguard the health of the participants as well as answer specific research questions. A protocol describes what types of people may participate in the trial; the schedule of tests, procedures, medications, and dosages; and the length of the study. While in a clinical trial, participants following a protocol are seen regularly by the research staff to monitor their health and to determine the safety and effectiveness of their treatment.

What types of clinical trials are the Progeria trials?

Phase I trials determine drug dosage and toxicity in a small number of people.

Phase II trials determine both drug toxicity and the effectiveness of drugs on a disease in a small population.

Phase III trials determine the activity of a treatment by giving the real drugs to half the patients and placebo (sugar pills) or other therapy to the other half. These trials usually include a large number of people (1,000-3,000) to confirm its effectiveness, monitor side effects, compare it to commonly used treatments, and collect information that will allow the experimental drug or treatment to be used safely.

Phase IV trials are post-marketing studies that delineate additional information including the drug's risks, benefits, and optimal use.

To date, all of the Progeria trials are Phase I and Phase II trials, where both toxicity and effect on disease progression are studied. They are also “open label” trials, in which all of the children receive the same drug treatment (none of the participants receive placebo).

20. PRF Programs and Services

International Patient Registry
 Diagnostic Testing Program
 Medical & Research Database
 Cell & Tissue Bank
 Research funding
 Scientific workshops
 Public awareness
 Volunteers & fundraising



The Progeria Research Foundation (www.progeriaresearch.org) provides services for families and children with Progeria such as patient education and communication with other Progeria families. It serves as a resource for physicians and medical caretakers of these families via clinical care recommendations, a diagnostics facility, and a clinical and research database. It also provides funding for basic science and clinical research in Progeria and biological materials for the research, and brings researchers and clinicians together at scientific conferences.

This section describes the many programs and resources available through The Progeria Research Foundation. Through these programs, our work is paying off. Research on Progeria has soared! We have increased the rate of scientific publications by over 100%, and are still going strong. This is the research that will lead us to new treatments and the cure.

The courage of children and families participating in PRF programs is the key to new discoveries and progress in the field of Progeria.



International Patient Registry

Progeria is a very rare condition. PRF's International Patient Registry has been established to provide services and information to families of children with Progeria, treating physicians, and researchers, and to better understand the nature and natural course of Progeria. Entering a child with Progeria into the Registry serves to improve communication of ideas among interested researchers, and assures rapid distribution of new information that may benefit patients and/or their families.

Visit www.progeriaresearch.org/patient_registry.html for more information.

PRF serves as a resource for physicians and medical caretakers of these families via clinical care recommendations, a diagnostics facility, and a clinical and research database.

Diagnostic Testing Program

The PRF Diagnostic Testing Program offers genetic testing for children with Progeria, provided at no cost to families. In previous years, with so little information available on Progeria, families often suffered for months or even years in fear and frustration as they tried to get an accurate diagnosis and appropriate medical treatments for their child. A genetic test means earlier diagnosis, fewer misdiagnoses and early medical intervention to ensure a better quality of life for the children.

The first step is for our medical director to look at a child's clinical history and photographs. Then we will be in touch with the family and home physicians about having this blood test done. All personal information is kept strictly confidential.

We provide genetic sequence testing by a CLIA-approved* laboratory for either Exon 11 of the LMNA gene (only the portion of the gene where the classical HGPS mutation is found) or full LMNA gene sequencing (for other types of Progeria called progeroid laminopathies).

Visit www.progeriaresearch.org/diagnostic_testing.html for information.

Medical & Research Database

The PRF Medical & Research Database is a collection of medical records and radiological tests such as X-rays, MRIs, and CTs from children with Progeria from all over the world. The data is rigorously analyzed to determine the best course of treatments to improve the quality of life. Analysis of these medical records has provided new insights into the nature of Progeria and into the nature of other diseases such as heart disease, which in turn will serve to stimulate the advancement of new research projects. The information is invaluable for the health care provider and families. PRF has used the information to provide new analyses of Progeria to the medical and research worlds. Our medical care recommendation sheets and this care handbook are products of the PRF Medical & Research Database.

PRF is privileged to work with top quality academic centers on the PRF Medical & Research Database: Brown University Center for Gerontology & Health Care Research and Rhode Island Hospital.

The highest level of confidentiality is maintained in this and all PRF programs. The PRF Medical & Research Database is approved by the Institutional Review Board at Rhode Island Hospital.

Visit www.progeriaresearch.org/medical_database.html for information.

Cell & Tissue Bank

The PRF Cell & Tissue Bank provides medical researchers with genetic and biological material from Progeria patients and their families, so that research on Progeria and other aging-related diseases can be performed to bring us closer to finding the cure. Thanks to the participation of courageous children and their families, PRF provides over hundreds of cell lines and tissues from affected children and their immediate relatives to laboratories and researchers worldwide. This includes cells from blood, skin biopsies, teeth, hair, autopsy tissue and more. These essential research tools are provided worldwide. This helps assure not only that research into Progeria is maximized, but that children do not have to be asked to donate blood and skin biopsies multiple times. Researchers can simply apply to the PRF Cell & Tissue Bank for the biological materials they need to ask key questions about Progeria.

PRF is privileged to work with top quality academic centers and collaborators on the PRF Cell & Tissue Bank: Rhode Island Hospital, Brown University, Ottawa Hospital Research Institute and Rutgers University Cell & DNA Repository.

The highest level of confidentiality is maintained in this and all PRF programs. We remove names and all other identifying information and code all samples. The PRF Cell & Tissue Bank is approved by the Institutional Review Board of Rhode Island Hospital.

Visit www.progeriaresearch.org/cell_tissue_bank.html for information.

*Clinical Laboratory Improvement Amendments (CLIA) is a body of industry regulations ensuring quality laboratory testing.

Research funding

PRF's scientific grants have allowed innovative new research in Progeria to thrive through research projects performed throughout the USA and the world. Proposals are carefully evaluated by PRF's Medical Research Committee and Board of Directors. PRF solicits proposals worldwide in a continuing effort to encourage researchers to work in this intriguing and ever-growing field.

The PRF Medical Research Committee:

Bryan P. Toole, PhD, Chair
Professor Emeritus of Cell Biology and Anatomy,
Medical University of South Carolina

W. Ted Brown, MD, PhD
Director, New York State Institute for Basic
Research in Developmental Disabilities (Retired)

Judith A. Campisi, PhD
Professor of Biogerontology, Buck Institute for
Research on Aging

Maria Eriksson, PhD
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Monica Kleinman, MD
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Boston Children's Hospital

Tom Misteli, PhD
NIH Distinguished Investigator
Director, Center for Cancer Research, National
Cancer Institute, NIH

Marsha Moses, PhD
Director, Vascular Biology Program
Boston Children's Hospital

Scientific workshops

PRF organizes successful scientific conferences every 2-3 years. These meetings have brought together scientists and clinicians from all over the world to collaborate, sharing ideas and contributing their expertise in this lethal disease. The workshops are a cornerstone of inspiration for those in the scientific and medical communities who seek to understand Progeria and its relationship to aging and heart disease, and search for treatments and cure. Many generous organizations have co-sponsored these meetings, including the National Institutes of Health's Office of Rare Diseases; National Heart, Lung, and Blood Institute; National Cancer Institute; National Human Genome Research Institute; and National Institute on Aging, The Ellison Medical Foundation, Celgene Corporation, The Max and Victoria Dreyfus Foundation, and the American Federation on Aging Research.

Visit www.progeriaresearch.org/scientific_meetings.html for information.

Public awareness

Before PRF was formed, Progeria was virtually unknown to the general public and to many healthcare workers. Information about Progeria and our far-reaching message – that finding a cure may help those with heart disease and other aging-related conditions – has reached millions through PRF's web site, newsletters, educational materials, and the media. PRF's story has appeared on CNN, BBC, "Primetime", "Dateline", "Discovery", in Time and People magazines, The New York Times, The Wall Street Journal, and dozens of other widely-read media outlets. In 2013, the HBO documentary *Life According to Sam* reached millions more. <http://lifeaccordingtosam.com/#/home/> As awareness continues to spread throughout the world, more children come to PRF for diagnostic testing; more researchers apply to PRF for grant funding and cells to support their research; more scientists participate in PRF's scientific workshops; and more volunteers offer needed support.

Visit www.progeriaresearch.org/press_room.html for information.

Before PRF was formed, Progeria was virtually unknown to the general public. Now information has reached millions through our website, newsletters, educational materials, and the media.

Volunteers & fundraising

PRF relies on its chapters and other volunteers to help spread the word and raise funds for medical research. With the exception of the small staff, everyone involved with PRF, including its Board of Directors, committee members, and corporate officers generously give their time, energy, and talents to PRF for free so that we can spend less on administrative costs and more on raising awareness and finding a cure for Hutchinson-Gilford Progeria Syndrome.

Please visit www.progeriaresearch.org/get_involved.html to find out how you can be part of PRF's efforts.

Bibliography

Below is a listing of some recommended reading on Progeria. The list highlights many of the points made within the body of this handbook. It is by no means exhaustive. For additional reading, we recommend you go to PUBMED and search Progeria, lamin, or laminopathy. Some of the articles that your search finds will be free for downloading.

Websites

www.progeriaresearch.org/patient_care.html

The Progeria Handbook: A Guide for Families & Health Care Providers of Children with Progeria Clinical guidelines by system, psychosocial strategies, basic science and genetics

www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=gene&part=hgps

GeneReviews - A general clinical and genetics and basic science review

www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=176670

On Mendelian Inheritance in Man (OMIM) – Detailed high level genetics and landmark articles

www.clinicaltrials.gov/ct2/results?term=progeria

Clinical Trials Information

www.progeriaresearch.org/patient_registry.html

PRF International Patient Registry

www.progeriaresearch.org/diagnostic_testing.html

PRF Diagnostic Testing Program

www.progeriaresearch.org/medical_database.html

PRF Medical & Research Database

www.progeriaresearch.org/cell_tissue_bank.html

PRF Cell & Tissue Bank

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Merideth MA, Gordon LB, Clauss S, Sachdev V, Smith AC, Perry MB, et al. Phenotype and course of Hutchinson-Gilford Progeria syndrome. *N Engl J Med* 2008;358(6):592-604.

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Cardiac: Rivera-Torres J, Calvo CJ, Llach A, Guzmán-Martínez G, Caballero R, González-Gómez C, et al. Cardiac electrical defects in progeroid mice and Hutchinson-Gilford progeria syndrome patients with nuclear lamina alterations. *Proceedings of the National Academy of Sciences*. 2016

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