



The Progeria Handbook

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

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.

Together we *will* find the cure.



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Updates

The information in this book is the most current available and is subject to change. The Progeria Research Foundation, Inc. will maintain a list of handbook recipients and do its best to send updates.

Please refer to www.progeriaresearch.org/patient_care.html for handbook updates.

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



When things are difficult, the question we should
be asking is not, “why did this happen to us?”
but, “now that it has happened, what can we do
to make things better?”

from *When Bad Things Happen To Good People*
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by Rabbi Harold Kushner, Founding Board Member,
The Progeria Research Foundation, Inc.

Table of Contents

A Message from the Medical Director

Contributors

1. Progeria 101: Frequently Asked Questions
2. Cardiology
3. Neurology / Strokes
4. Emergency Care / Critical Care
5. Airway Management / Anesthesia
6. Nutrition
7. Eye Care
8. Audiological Evaluation
9. Dental Recommendations
10. Skin / Dermatology
11. Bones / Orthopedics
12. Physical Therapy (PT)
13. Occupational Therapy (OT)
14. Podiatry
15. Systems that Function Normally in Progeria
16. Going to School
17. Living with Progeria
18. Progeria and Aging
19. Drug Treatment Trials
20. PRF Programs & Services
 - International Patient Registry
 - Diagnostic Testing Program
 - Medical & Research Database
 - The Weighing-In Program
 - Cell & Tissue Bank
 - Progeria Family Network
 - Research funding
 - Scientific workshops

Bibliography

Clinical Care-at-a-Glance

Essential Phone Numbers



A Message from the Medical Director

For over a decade, The Progeria Research Foundation has been working towards discovering the cause, treatment, and cure for Progeria. We've seen Progeria move from obscurity, to gene finding, to treatment trial within that time. Each day that passes, families and their health care providers search for guidance on how to increase quality of life for 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 in that common goal.



With the input of many caring contributors, we've compiled this first edition information handbook. 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.

Concept

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. You will also note some repetition between sections. Because we are making each section available as a stand-alone document on the PRF website, some repetition is necessary.

Updates

Even as we write this first edition of the Progeria guide to clinical care, our understanding of Progeria and the needs of the children, their families, and health care providers is growing exponentially. We designed the handbook with a binding that allows you to add and replace information as new chapters are written in the future. In this way, you will be as up-to-date as possible on care recommendations and research programs for children with Progeria.

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 forward
- Be a valuable resource for families living with Progeria and their health caretakers

Together we *will* find the cure.

Handwritten signature of Leslie Gordon

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1. Progeria 101: Frequently Asked Questions

What is Hutchinson-Gilford Progeria Syndrome?

What is PRF's history and mission?

What causes Progeria?

How is Progeria diagnosed?

Are there different types of Progeria?

Is Progeria contagious or inherited?



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 many characteristics of accelerated aging by 18-24 months of age, or even earlier. Progeria signs 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 13 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.

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

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 has developed a comprehensive network of programs (see *PRF Programs & Services*, section 20) 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.

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 (PRF) 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 of 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 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 led us down a pathway to the first-ever drug treatment trials for Progeria (see *Drug Treatment Trials*, section 19). 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*, section 18).

How is Progeria diagnosed?

Progeria is best diagnosed by using both clinical examination and genetic testing. When a physician 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. Once the blood sample is received, the test results are usually provided in 10 days to 4 weeks, depending on the extent of genetic testing that is required. Results are provided to families through home 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.

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 more rare than classical HGPS. When we are searching for progeroid syndromes, we test the entire LMNA gene.

The guidelines in this handbook are written for children with classical Progeria, because we know more about the disease process and treatment strategies for classical Progeria. Applying that knowledge to nonclassical progeroid syndromes can be helpful to families and home caretakers, but good judgment must be applied, since children with nonclassical 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 definitely 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.

2. Cardiology

Monitoring cardiovascular health Aspirin for heart health



Monitoring cardiovascular health

Children with HGPS are at high risk for heart attacks and strokes at any age. Cardiovascular disease in Progeria is a gradual process. 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.

The following testing should be considered annually, and more often if home physicians recommend:

- Cardiology visit with physical examination
- Measurement of fasting lipids and glucose
- Blood pressures of arms and legs
- Electrocardiogram (ECG)
- Echocardiogram
- Carotid duplex ultrasound*, if available
- Pulse wave velocity*, if available

Blood lipids such as cholesterol are very often normal in Progeria.

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

Low dose aspirin, dosed by weight at 2-3 mg per kg body weight, is often recommended.

Aspirin Treatments

Studies in adults have shown that the benefits of low dose aspirin therapy increase with increasing cardiovascular risk. Recommendations here come from experience in adults and in children with diseases which predispose them to heart attacks and stroke.

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 their clinical course.

Once a child begins to develop 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 is warranted. Antihypertensive medication, anticoagulants, anti-seizure, and other medications usually administered to adults with similar medical issues have been given to children with HGPS. All medication should be dosed according to weight, and carefully adjusted according to accompanying toxicity (negative side effects) and efficacy (effectiveness).

> Aspirin for heart health

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.

3. Neurology / Strokes

Strokes and TIAs

Aspirin for stroke prevention

Headaches

Seizures

Imaging recommendations

Sedation

Special circumstances: Travel, hydration



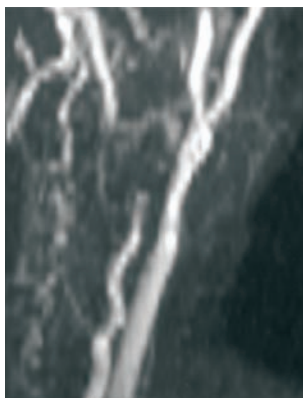
Strokes and cerebrovascular disease are one of the leading causes of morbidity and mortality in children with Progeria. The earliest published incidence of stroke is at the age of 4 years. In one case, seizures were the presenting cerebrovascular event. Importantly, stroke may occur while the child exhibits a normal ECG. As we continue to learn more about the types of neurological changes that occur in Progeria over time, we hope to positively influence clinical care of children with Progeria in the future.

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

Strokes and Transient Ischemic Attacks (TIAs)

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 largest of the blood vessels in the portion that enters the skull at the base of the brain. Blood flow is blocked by narrowing or constriction of the blood vessels and, potentially, by blood clots.

Gradually the blood flow to the brain is slowed, which increases the likelihood of blood clot formation and can lead to strokes and TIAs. The blood vessels, in an attempt to compensate for the blockage, form collateral vessels, or



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

“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 is often 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 such dramatic 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 clot formation and to prevent future strokes from occurring. The reasoning behind using these types of medications is to prevent future strokes, 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 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 single 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.

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. 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.

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.

> What to do in the event of a seizure

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

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.

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.

Imaging recommendations

It is recommended that children with Progeria undergo neuro-imaging studies to track disease progress and the presence of abnormalities such as silent strokes, new vessel formation in the brain, or vessel narrowing. This is best performed with a magnetic resonance imaging study (MRI) of the brain to screen for prior strokes. If possible, a magnetic resonance angiography study of the head and neck (MRA) should be done at the same time.

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*, section 5, 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.

4. Emergency Care / Critical Care

First response

Other considerations



First response

Children affected by Progeria are at increased risk of more typically adult emergencies such as angina, myocardial infarction, transient ischemic attacks, and strokes. The child with Progeria who presents with chest pain should be assumed to have ischemic heart disease until proven otherwise. Treatment is largely supportive, including supplemental oxygen and IV fluids. If the child is not taking prophylactic aspirin at baseline, he/she should be encouraged to chew a baby aspirin (81mg). In general, avoid medications such as nitrates that can acutely drop blood pressure. 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 algorithms are recommended.

The cerebrovascular disease in Progeria can be significant. A history of seizures, severe headaches, or 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 ischemic events by MRI. Management of suspected TIA or stroke is largely supportive, such as supplemental oxygen and IV fluids to improve hydration status. Seizures are treated according to usual guidelines for pediatric patients.

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

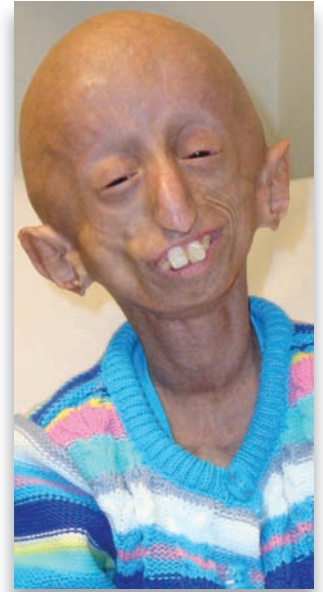
Other considerations

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.
- **Bruising:** 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.
- **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 and avascular necrosis of the femoral head.

5. Airway Management / Anesthesia

Challenging airway features in Progeria
Airway management
Anesthesia



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 temporo-mandibular joints
- Skeletal contractures and decreased neck mobility
- Decreased subcutaneous fat
- Narrowed nose and small nares

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.



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

Airway management

These features 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 non-oral procedures, if the procedure can be safely accomplished without endotracheal intubation, use of bag-mask ventilation or an LMA should be considered.

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 based on height than on age. Moreover, there is an increased risk of hypothermia due to alopecia and the paucity of subcutaneous fat.

Anesthesia

During sedation or anesthesia, the provider must be aware of the cardiovascular and cerebrovascular disease that characterizes 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 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.

6.Nutrition

- 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 some time 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. Some parents also report that the children tend to take in smaller, more frequent meals. Therefore, the goal is to give them nutritious and high calorie foods and supplements. Though each family should consult its home medical team, artificial feeding tubes such as nasogastric or G-tubes have not generally been more effective than oral nutritional supplementation for children with Progeria.

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

Discuss with your pediatrician or dietitian whether if your child might benefit from a standard pediatric multivitamin.

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

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

Making healthy food choices

Supplements and high calorie foods are encouraged. However, if given the opportunity to incorporate healthy foods into the diet, the following general guidelines apply:

- 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

Discuss with your pediatrician or dietician whether your child might benefit from a standard pediatric multivitamin.

Shakes & smoothies

The stress of mealtime may be eased by the use of nutritional supplements. Try these tasty tips when using nutritional supplement products:

- **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.
- **Powered 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.

On the following pages, we provide suggestions which will help to augment caloric intake by adding in healthy calories to everyday food items.

Recipes using these supplements can be found at:
www.pediasure.com/pdf/pediasure-recipes.pdf
www.nestle-nutrition.com/Recipes/
store.axcanscandipharm.com/recipes.php

PEDIASURE®

Manufactured by Abbott Nutrition
www.pediasure.com / www.abbott.com

Order on-line or call: 1 (800) 258-7677

Recommended age for use 1-13 years

Product specific information:

- Lactose-free, Gluten-free, Kosher
- Nutritionally Complete and can be used to supplement diet
- Flavors: Banana Crème, Berry Creme, Chocolate, Strawberry, Vanilla, Vanilla with Fiber
- 240 calories (1 calorie/ml) and 7g of protein per 8oz



PEDIASURE NUTRIPALS®

Manufactured by Abbott Nutrition
www.pediasure.com / www.abbott.com

Order on-line or call: 1 (800) 258-7677

Recommended age for use 1-13 years

Product specific information:

- Lactose-free, Gluten-free, Kosher
- Nutritionally balanced, used to supplement diet
- Flavors: Vanilla, Chocolate, Strawberry
- 150 calories and 7g of protein in 8oz



SCANDISHAKE®

Manufactured by Axcan Pharma Inc.
www.axcan.com/us_scandishake.php
www.axcan.com

Order on-line or call: 1 (800) 950-8085

Recommended age for use >1 year

Product specific information:

- Gluten-free, Kosher
- Flavors: Vanilla, Chocolate, Strawberry
- Not nutritionally complete, used to supplement diet
- Available in Lactose-free and Sugar-free
- 520-600 calories when mixed with 8oz of regular soy milk or whole milk



ENSURE®

Manufactured by Abbott Nutrition
www.ensure.com / www.abbott.com

Order on-line or call: 1 (800) 986-8502

Adult formula can be used under the guidance of pediatrician for children > 9 years



Product specific information:

- Lactose-free, Gluten-free, Kosher
- Nutritionally complete and can be used to supplement diet
- Flavors: Rich Dark Chocolate, Homemade Vanilla, Creamy Milk Chocolate, Strawberries and Cream, Butter Pecan, Coffee Latte
- Plus (350 calories and 13g of protein), High Protein (230 calories and 12g of protein), and High Calcium (220 calories, 10g of protein and 50% of daily calcium needs) versions available; powder and flavored puddings
- 250 calories and 9g of protein in an 8oz bottle of regular Ensure

BOOST KIDS ESSENTIAL®

Manufactured by Nestlé Nutrition
www.boost.com / www.nestle-nutrition.com

Order on-line or call: 1 (800) 422-2752

Recommended age for use 1-13 years

Product specific information:

- Lactose-free, Gluten-free
- Flavors: Vanilla, Chocolate, Strawberry
- Use as an oral supplement
- 240 calories and 7g of protein in a 8.25oz

**BOOST®**

Manufactured by Nestlé Nutrition
www.boost.com / www.nestle-nutrition.com

Order on-line or call: 1 (800) 422-2752

Check with pediatrician for >2 years

Product specific information:

- Nutritionally complete and can be used to supplement diet
- Lactose-free, Gluten-free, Kosher
- Flavors: Vanilla, Chocolate, Strawberry, Butter Pecan
- Boost High Protein, Boost Plus, and Boost Nutritional Pudding



NUTREN JR®

Manufactured by Nestlé Nutrition
www.nestle-nutrition.com

Order on-line or call: 1 (800) 422-2752

Recommended age for use 1-10 years

Product specific information:

- Lactose-free, Gluten-free, Kosher
- Nutritionally complete and can be used to supplement diet
- 1 calorie/ml
- Vanilla flavored



ENLIVE®

Manufactured by Abbott Nutrition
www.abbott.com

Order on-line or call: 1 (800) 258-7677

Adult formula, under the guidance of pediatrician can be used as an occasional supplement for children > 4

Product specific information:

- Lactose-free, Gluten-free, Kosher
- Used to supplement diet
- 9g of protein per 8.1oz
- Flavors: Apple, Mixed Berry



RESOURCE BENEALORIE®

Manufactured by Nestlé Nutrition
www.nestle-nutrition.com

Order on-line or call: 1 (800) 422-2752

Adult supplement, check with pediatrician or dietitian for use in children >2 years

Product specific information:

- Lactose-free, Gluten-free, Kosher
- 1.5oz liquid provides 330 kcals and 7g of protein
- Neutral flavor
- Mixes easily into a wide variety of foods and liquids without changing the taste



RESOURCE BENEPROTEIN®

Manufactured by Nestlé Nutrition
www.nestle-nutrition.com

Order on-line or call: 1 (800) 422-2752

Adult supplement, check with pediatrician
 or dietitian for use in children >2 years

Product specific information:

- Lactose-free, Gluten-free, Kosher
- Mixes easily into a wide variety of foods and liquids without changing the taste
- 6g of protein per serving

**RESOURCE BREEZE®**

Manufactured by Nestlé Nutrition
www.nestle-nutrition.com

Order on-line or call: 1 (800) 422-2752

Adult supplement, check with pediatrician
 or dietitian for use in children >2 years

Product specific information:

- Lactose-free, Gluten-free, Kosher
- Used to supplement diet
- Flavors: Orange, Peach, Wild Berry
- 250 calories and 9g of protein in 8oz

**CARNATION INSTANT BREAKFAST ESSENTIALS®**

Manufactured by Nestlé Nutrition
www.carnationinstantbreakfastessentials.com
www.nestle-nutrition.com

Order on-line or call: 1 (800) 422-2752

Adult supplement, for children:

- 1-3 years – maximum of two 4oz servings/day
- 4-8 years – maximum of four 4oz servings/day

Product specific information:

- Kosher
- Used to supplement diet
- Sugar-free available, Lactose-free available in ready to drink cans
- Mix with milk or ready to drink in a 325ml bottle
- Flavors: Rich Milk Chocolate, Strawberry Sensation, Classic Chocolate Malt, Dark Chocolate, Classic French Vanilla



7. Eye Care

Ocular features in Progeria Risks and recommendations



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

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.

Dry eye increases the risk of exposure keratitis. 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; this is available as over the counter drops in any drug store
- 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.

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.

8. Audiological Evaluation

The external ear of the child with Progeria

Behavioral testing for assessing hearing thresholds

Objective electrophysiologic tests of auditory function

Summary



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

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 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 they 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 earphones often used for air-conduction testing) and to the ear canal (such as tympanometry probes for performing acoustic immittance or insert earphones used for air-conduction testing or otoacoustic emissions). See Figures 1 and 2 (next page) 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 patient if that pressure causes discomfort before placing TDH supra-aural earphones.

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

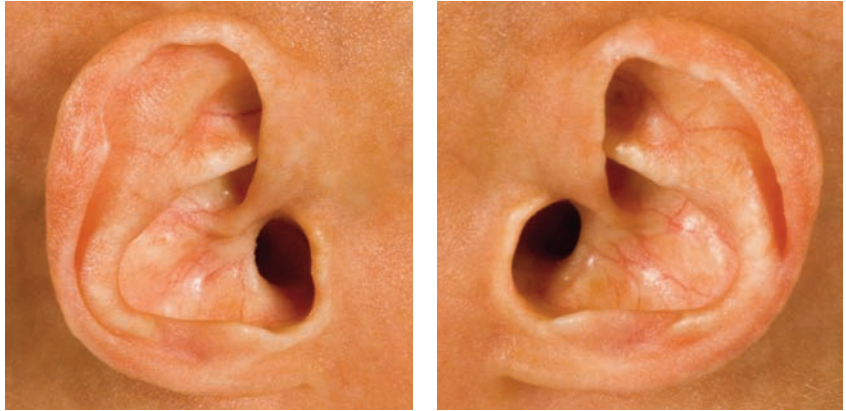


Figure 1. The right and left ears of children with Progeria. Note the large size of the entrance of the external auditory canal relative to the pinna.

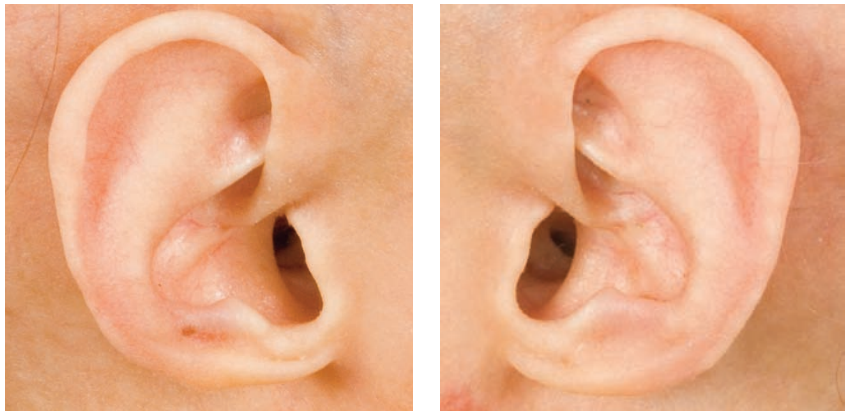


Figure 2. The right and left ears of a child with Progeria. Note the obvious stenosis at the cartilaginous-bony juncture of the ear canal, most easily seen in the left ear.

The cartilaginous portion of the ear canal often has an appearance of a general loss of cartilage, resulting in a caliber significantly larger than the bony portion that comprises the medial 2/3 of the ear canal. This difference in the size of the cartilaginous and bony portion of the ear canal can be confusing when 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 a hermetic seal when attempting tympanometry and middle-ear muscle reflex testing. While potentially easier than obtaining a seal by coupling the eartip to the bony portion of the canal, that part of the canal is very sensitive in anyone, 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 manufactured 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 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.

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. The configuration is the same, however, when hearing loss existed: low-to-mid frequency upsloping to better (and perhaps normal) hearing in the higher frequencies.

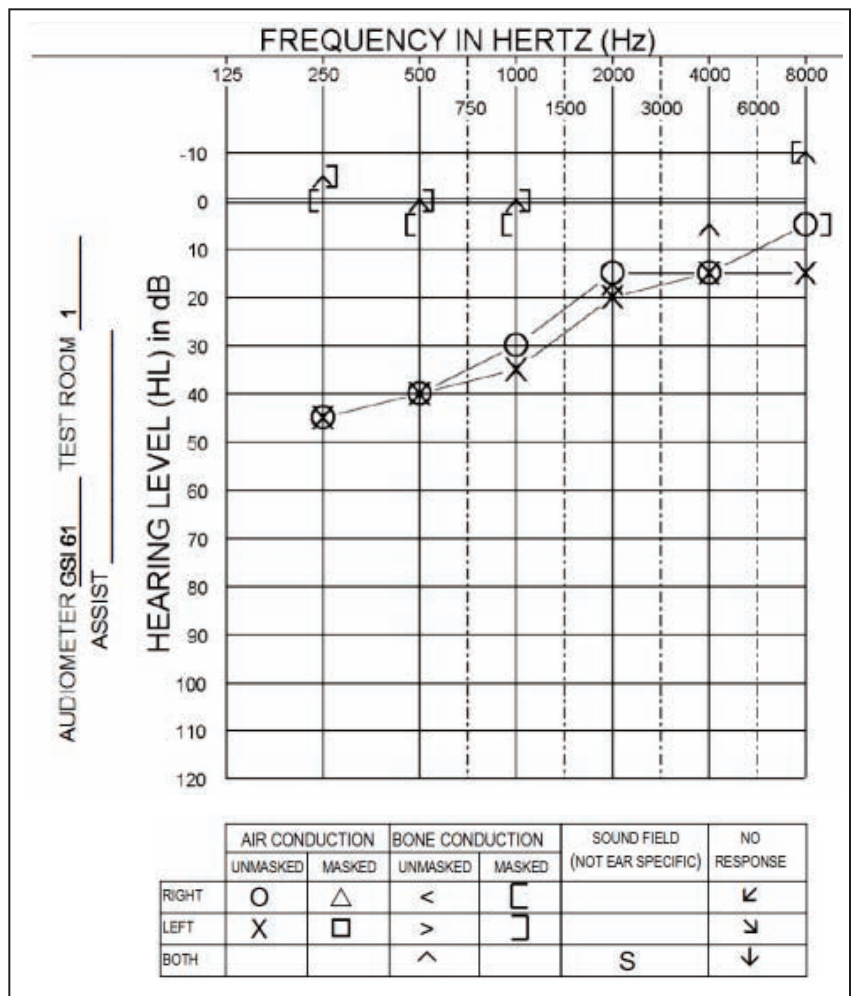


Figure 3. Typical audiogram of a child with Progeria.

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 (regardless of hearing test results). When abnormal, static compliance is usually reduced and tympanic width is consequently wider than 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. The reason for the abnormal tympanometry findings remains unclear 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 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. They 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 a hermetic seal, but a reasonably good coupling to the walls of the ear canal are necessary 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 age prematurely.

> 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 developmentally impaired who cannot 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 truly thin skin of the patient with Progeria, care must be taken to not compromise skin integrity should this testing be conducted.

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 in other patients with normal tympanometry their hearing thresholds could be significantly elevated (hearing significantly impaired). Cerumen and middle ear effusion are not usually factors contributing to the hearing losses recorded. Middle-ear muscle reflexes were 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 unrelated 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.

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 were 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. Given the anatomical changes of the external ear described earlier in this document, coupling a hearing aid to the ear via personal custom earmold could be challenging. 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.

9. Dental Recommendations

For the families

For the medical and dental professional



For the families

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 twice per year, for routine check ups, 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

> 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
- 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
 - Early implementation of fluoride toothpastes, rinses, and in-office application of fluoride
- Orthodontic consideration:
 - Severe crowding and eruption disturbances may necessitate extraction therapy
 - Susceptibility to periodontal disease and limited opening often contraindicates conventional orthodontic therapy

> 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



Ankyloglossia



Palatal pseudocleft

10. Skin / Dermatology

Common skin findings in Progeria

Hair and nails



Common skin findings in Progeria

Skin changes can be the very first indication that there is a problem in a child 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 are variable 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.

Tight skin 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 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.

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.

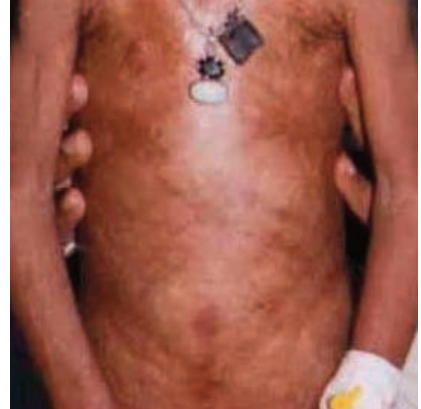
*Hair is lost gradually
(not in large clumps) over
several months to years.*

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



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.

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 the bones are smaller, they are relatively weaker than age-matched children without Progeria. Spontaneous bone fractures are unusual and children with Progeria 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 Progeria can 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

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



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

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 (eg., children's multi-vitamin tablet) is recommended by the American Academy of Pediatrics.

> Dual energy x-ray absorptiometer

Yearly bone density measurements by dual energy x-ray absorptiometer (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. 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 status.

Radiographic findings in children with Progeria

> Abnormal findings

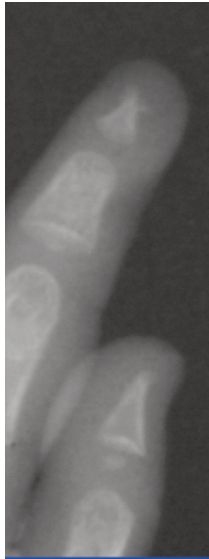
- Acroosteolysis (resorption of bone at distal pharynx) is found as early as infancy, but it is observed in all children in later years; it becomes progressively severe with increasing age; it is not usually found in every finger; externally, the fingertips become bulbous; there are no painful sequences associated with acroscleriosis
- Maldevelopment of the mandible; the mandible is small with an increased obtuse angle to its shape
- Clavicular resorption
- Thinning and tapering of ribs
- The thorax develops a pyramidal configuration with the ribs having a “drooped” appearance resulting in narrowing at the apex
- Coxa valga (femoral head-neck axis in excess of 125 degrees) leads to a “horseriding” stance and a wide based gait; it predisposes to hip joint instability and subluxation
- Coxa breva (shortened femoral neck)
- Coxa magna (broadened femoral head)
- Acetabular dysplasia (relatively shallow acetabulum) progressing to hip subluxation resulting in loss of hip joint motion, osteoarthritis, and pain with weight-bearing
- Avascular necrosis of the femoral head
- Long bones: Slender diaphyses, large, broadened epiphyses with atypical demineralization; cortical bone at the diaphysis has normal thickness and mineralization; cancellous bone at the metatheses and epiphyses has decreased mineralization
- Flared proximal humeral metaphysis
- Enlarged capitellum of the distal humerus
- Flaring of the distal femoral metaphysis/epiphysis and the proximal tibial metaphysis/epiphysis

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

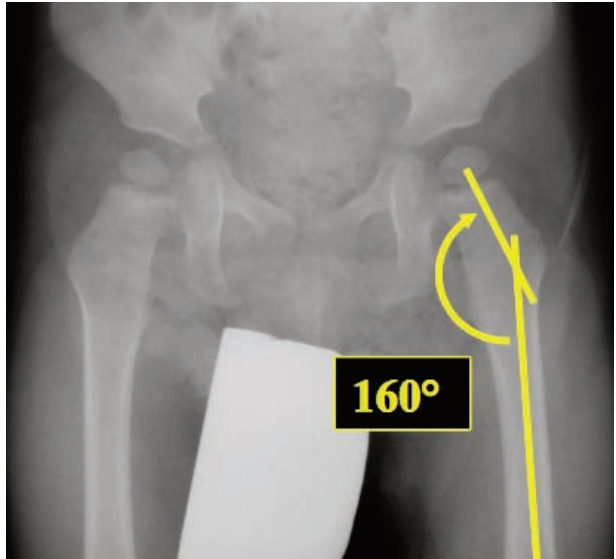
> Normal findings

- Bone age is variable; it can be normal, slightly delayed, or slightly ahead at any chronological age
- Growth plates are normal
- Cranial sutures are usually normal
- Normal configuration of bony pelvis
- Normal joint spaces at the wrists, ankles, knees, and elbows

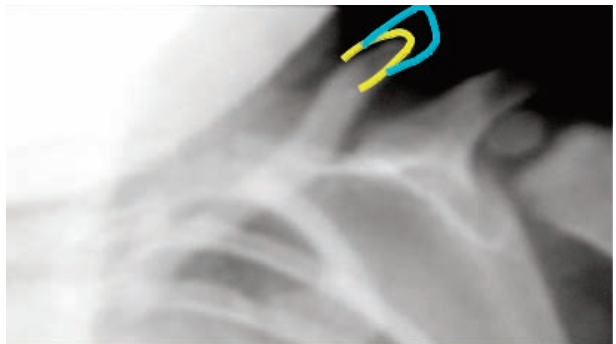
> Radiographic findings



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 radio-graphically.

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. However, there is little experience with these surgical interventions 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.

Though 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



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

Children with Progeria develop contractures of their joints and associated bony 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.

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.

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-

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

> Global joint contractures



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.

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 and acetabular dysplasia are found in virtually all children. Progression to unilateral or bilateral hip dislocation can also occur in later stages.

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 limited to absent.

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 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 may play a role, especially in the more severely affected child.

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*, 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.

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.

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. 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 and rescue.

13. Occupational Therapy (OT)

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



Generally, occupational therapy (OT) promotes health with a focus on 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.

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
- Functional skills
- Visual perceptual
- Visual motor integration skills

There have been no studies on the effectiveness of occupational therapy interventions with this population and the recommendations in this handbook 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 a physician even if there is no traumatic event.

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

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
- 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



Maximum finger extension in a child with Progeria



Small size, difficulty with supination, contracted finers, lack of fat, and prominent veins in a child with Progeria (below) compared with an age-matched child without Progeria (above)

- 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

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.

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 the 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 difficulty with balance. 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.

> 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 high 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

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.

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.

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 backwards) 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.

> 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*, 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.

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
- Adapted switches and knobs
- Lower the placement of items for food preparation

> 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 16

14. Podiatry

Podiatric problems in children with Progeria Shoe inserts



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 Progeria have markedly diminished soft tissues of the foot, walking is unstable for the children.

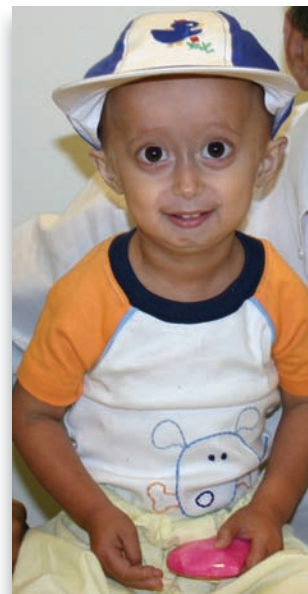
Feet become sensitive to hard surfaces and shoes. Shoe inserts and slippers help prevent pain, blisters, and calluses.

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. Systems that Function Normally in Children with Progeria



It is important to recognize that there are a number of body systems that function normally in children with Progeria. This may be because progerin is not produced by some types of cells, or because certain organs are more resilient to the effects of progerin, or it may be due to other unrecognized reasons.

› Children with Progeria generally have normal function in the following:

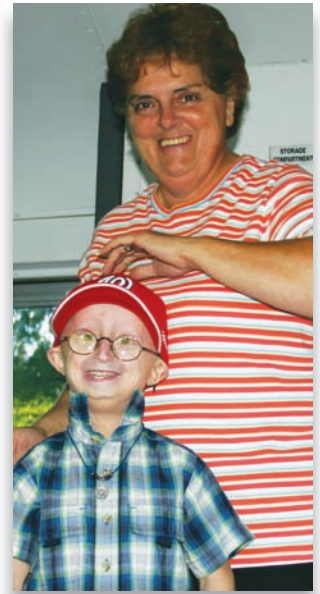
- Brain, except for the blood vessels in the brain, which become diseased and can cause strokes
- Liver
- Kidney
- The gastrointestinal system
- Immune function is normal; the healing of cuts and broken bones occurs at the usual rate. Immunizations are recommended for children with Progeria in the same way they are recommended for the general pediatric population, including flu vaccines. In addition, vaccines that are indicated for children in high risk categories should be given to children with Progeria. When vaccines are in short supply, children with Progeria should be given special consideration, as they may be more frail than their age-matched peers and therefore less capable of handling an illness. Please confer with your child's primary care doctor for more information on specific vaccines.

Immunizations are recommended, including annual flu vaccines.

- The lungs are not known to function abnormally, but a small chest cavity and tight skin over the chest area may cause restrictive lung problems in some children.
- The endocrine system functions normally, though pubertal changes such as growth spurt, genital, and adult hair development do not generally occur. Some children are treated with growth hormone, which may increase their overall size. It is not clear whether growth hormone increases overall health in children with Progeria. Evaluation by a qualified endocrinologist is recommended if considering growth hormone treatment.

16. 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

Give copies of this handbook to your child's school staff; it may help answer many questions.

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 or AlphaSmart 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, Alpha-Smart, or similar electronic keyboard to type long composition 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 backpacks 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.

17. Living with Progeria

- General thoughts about daily life
- Talking to your child with Progeria
- Dealing with the outside world
- Siblings
- Sports
- Clothing and footwear
- Religious affiliation
- Pets
- Practical accommodations around the house
- Travel
- Other thoughts



Parents and siblings of children with Progeria have shared the following insights on how they have dealt with the challenges of living with Progeria.

You are not alone. Families help each other by sharing experiences.

General thoughts about daily life

“In the beginning, prior to and just after our son was diagnosed, daily life was very difficult. We didn’t know how to “deal” with our first-born’s diagnosis because we couldn’t even begin to assimilate it, much less share it with the rest of the family. We dreamed that our son’s pediatrician would call to tell us they’d made a terrible mistake and misdiagnosed our son. Now, having received nothing but support and love from so many, and love from our son, we would do it all over again if we had to. Our son is now 11 years old. He has touched our lives and the lives of others in ways I cannot explain.”

“As the parents of a 3 year-old boy with Progeria, we try very hard to treat him as if he doesn’t have Progeria. At times, this is difficult. He does get to eat whatever he wants and he does get more attention than his big sister. We don’t discourage his waking up at night wanting Pediasure. We do try to make sure he gets the same experiences we provide his older sister.”

Talking to your child with Progeria: what to tell them, when, and how

“There is no right or wrong answer for when and how to discuss Progeria with affected children and siblings. Decisions will be based on each child’s personality, and the different cultures we all live in.”

“Generally, children hear and understand what they are ready to understand. They ask what they are ready to hear about. As a rule, we answer what is asked and assume that our child wants to hear only what he asks. We don’t go any deeper than that, because we believe that in time he will make it clear that he is ready to hear more. Also, things are changing so quickly because of the trial that we don’t actually know if what we are saying is accurate about his future.”

“She knows she’s shorter, no hair, thin skinned, and it’s called Progeria – that’s it. We are not sure how or when the time will come. We believe she already knows, but we just don’t talk about it.”

Dealing with the outside world

“Be prepared for stares and even rude comments; have answers ready but don’t get into arguments. Your child may not be aware of the stares and comments, but you will. Siblings may be upset by strangers’ stares and questions; prepare them for it.”

“You will experience a lot of whispering, stares, and questions. When the child is younger it’s easier – he/she doesn’t understand. Remember, you are the parent, you can say ‘NO’ or say ‘not now’ if someone approaches you. Sometimes it can be annoying, but most times they are just concerned, so just smile and they will smile back.”

“The most difficult thing for us at first was not the medical issues. It was the psychological and emotional challenges we feared that our child would have to face. His happiness was the first thing on our minds. We made sure we made strong friends within our community. Real friends don’t think about how a person looks or what they CAN’T do. Real friends only see their friend in front of them and want to play and have fun. Friends and family are the core to our child’s happiness. The rest of the world with their stares and comments have only a minor effect on ego and self-confidence.”

“Incorporate cousins and neighboring children in your child’s circle to build long-term friendships.”

“Getting the word out in our local community has been very helpful in two ways: It helps with fundraising activities and it will help our son and family better deal with the differences in appearance. With awareness, we have gotten tremendous support from our community. That has helped us as parents and we hope that as our son gets older it will help him to feel comfortable [about] looking different.”

“It would be very helpful to meet other children with Progeria and, at some point, children with other health problems.”

Siblings

“Give all your children special attention; don’t neglect siblings for being normal. Siblings-jealously issues will arise. Try to have a day just for brother or sister, so they feel special.”

“What to tell siblings depends on the child’s place in birth order, but we don’t tell siblings anything we haven’t told our child with Progeria.”

“Our older children know what the diagnosis is, and our child with Progeria does not.”

“Our 11 year-old child with Progeria has a 3 year-old sibling and so far we have tried in the clearest way possible to explain to the 3 year-old that he must be careful and not be too rough with his older brother. We believe the 3 year-old understands his brother is special.”

“Siblings can participate in PRF activities, work at raising funds, and would enjoy meeting other children with Progeria and their siblings. We believe all this is very positive for them.”

“Growing up in a household with a child who has special needs can give rise to challenging issues for siblings. The need for extra attention given to the child affected with Progeria may cause a sibling to feel that he/she is not as special or valued by their family because he/she does not have an illness. When the identity of the family centers around caring for a child with Progeria, siblings may have difficulty developing their own independent roles and sense of self within the family. Make sure to be extra vigilant that siblings do not feel that they are any less special because they do not require a special diet, special accommodations, or special visits to the doctor. This form of logic may seem preposterous to

an adult, but it is not to a young child. A sibling child may feel guilty about his or her own good health and physical abilities. Support for siblings can come in the form of friendship with other children who are living with a 'difference' in their family. There most likely will not be other families with children with Progeria in your vicinity, so you might want to look for this support in the form of families who are dealing with another type of disability. Make sure that all children in the family have the opportunity to explore their own interests and unique talents."

Sports

"We give our child plenty of exercise, up to his/her capacity. We have a lowered basketball hoop at home. Miniature golf and candlepin bowling are sports he can share with friends. Water play is excellent but we make sure adult supervision is constant. Also, we have balls, hoops, etc. for play inside the home."

"Introduce children with Progeria to sports as early as possible. This not only allows them to be an active part of the community early on, but also it is the best time to ensure accommodations are made to enable their participation. Over the years, we have dealt with changes that have affected his participation by introducing our child to other types of sports that do not require extreme amounts of endurance and aggressive competition."

"Swimming: The baby wetsuit never fit his odd-shaped body, and therefore didn't keep him warm. He would turn blue after 5 minutes in the pool. We recently purchased a 3mm full, custom-made wetsuit from Harvey's Dive Suits."

"A regular session at a hydrotherapy pool promotes relaxation, relieves pain, assists movement, and is good exercise. It's also pretty good fun!"

Clothing and footwear

"You may have to make some clothes by hand, or have them custom-made. Favor cottons and materials that don't irritate their sensitive skin."

"Pants with adjustable waist bands are extremely helpful as the waist remains much smaller than the usual pant length needed."

“If sneakers – perhaps with orthotics – are comfortable, don’t worry about fashion or formality.”

“Use soft, padded insoles in shoes – leather, if possible.”

“In winter, your child’s fingers and toes may get very cold easily, so thick gloves or two pairs of gloves can help.”

Religious affiliation

“This can be an excellent source of acceptance and companionship. Discuss with your family’s clergy your understanding of why this is happening to your child. Religious youth groups and/or scouting programs can be good. Involve your child in helping others; he/she will find it empowering.”

“Church youth groups are extremely important and vital to our children because they establish fundamental faith and belief that there is a higher being, and we firmly believe God will take care of our son and guide us to raising him to be all He intends him to be.”

Pets

“Pets can be a wonderful source of companionship and unconditional love, but large and/or strange dogs can be a hazard.”

“Animals are extremely important! Our kids need to feel as though they have the ability to watch over and be responsible for something.”

Practical accommodations around the house

- Install lever type taps (faucets) to baths and basins
- Lower coat hooks, light switches, and door handles, and ease door closers so they are not so stiff – this will make it easier for your child to enter rooms and cupboards
- Fit smaller hand rails below the normal ones on stairs
- Use a memory foam mattress (like Tempur) on the bed; an occupational therapist may be able to help with this
- Keep small step stools or boxes handy for reaching counters, basins, and getting on and off of the toilet
- Arrange for furniture in which the child will be comfortable

Travel

“Use a car seat made from memory foam instead of the normal hard plastic seats.”

“Be aware of how easily your child may tire.”

“When flying, ask for a seat upgrade to make long flights more comfortable. Also, ask if it’s possible to use the airline lounge to avoid waiting in busy departure areas. If you travel with your child regularly – such as to Boston for the clinical trials – try to find a good contact with the airline in a senior position. This can be very helpful when asking for assistance.”

“Make sure your child gets lots of rest the night before a trip, and lots of fluids before and during the trip.”

“When checking in before flights, tell staff that you have a disabled child so that you can avoid long lines.”

“Arrange for a wheelchair to be waiting for you at your destination so that your child doesn’t have to stand in (the immigration) line or walk through the airport.”

“Some airlines will put a ‘disabled’ sticker or tag on your luggage so that it comes off of the plane first with the first class luggage.”

“Pack all necessary medications in your hand baggage in case your checked luggage gets lost.”

“Ensure hospitals are within close distance.”

“Don’t be afraid to embark on new adventures. Although some cultures are a little more alienated and/or accepting of people who appear different, you will be OK!”

Other thoughts

“Make allowances that the child may have to snack at otherwise forbidden times, for energy and to stave off headaches, but otherwise try to treat him as normally as possible.”

“Let them eat what they crave. They need the calories and energy sources and may not be able to handle ‘regular’ food the rest of the family is eating. Be aware that this may cause problems with siblings.”

“The child may act out at times as he becomes aware of his differences.”

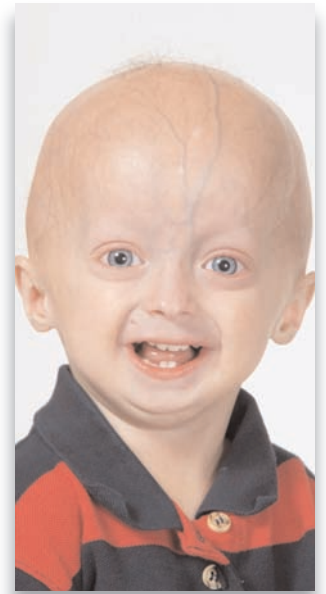
“Provide plenty of stimulation such as sports, art, music, drama, and a variety of social situations.”

“Physical therapy: We were surprised at how quickly his joints started to become less flexible. One day he only had slightly bent knees, the next he had tight arms (at the elbows), wrists, ankles, and hips. This seemed to happen overnight around the age of 3. We also noticed he wasn’t standing up straight about the age of 3. His shoulders were hunching over. To remedy this, we do stretching every day. He sees a physical therapist once a month to check his progress.”

“Have regular visits to a chiroprapist to help with nail cutting and removal of hard skin areas. Watch for in-grown nails/toe nails, since their fingers and toes are so narrow.”

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.

Understanding Progeria promises exciting new avenues for understanding the natural aging process.

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

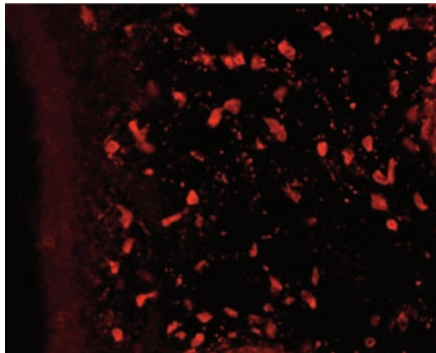
The discovery that Progeria is caused by a newly discovered protein called progerin raised entirely new questions: Is progerin produced by all of us? Does progerin have a role in aging and heart disease? Perhaps our most exciting new clue to the aging process is the discovery that the progerin protein 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.

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. Djabali)

¹World Health Organization; www.who.int/mediacentre/factsheets/fs317/en/index.html

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

There are three drugs currently being studied in treatment trials for Progeria:

- 1) Farnesyltransferase Inhibitor (FTI)
- 2) A statin called Pravastatin
- 3) A bisphosphonate called Zoledronic Acid

All of these drugs work in different places along a common pathway that we hope will improve disease symptoms in Progeria.

› How did we get from gene discovery to drug therapy for children with Progeria?

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. Since 2003, research has focused on systematically examining this possibility, first testing these drugs on Progeria cells and then on Progeria mice.

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

> How will the drugs work in Progeria?

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. Each of the three drugs in this protocol target a different step in that process. Pravastatin, Zoledronic Acid, and Lonafarnib act by blocking (inhibiting) the production or the attachment of the farnesyl group onto progerin (see figure 1). The current clinical trial will evaluate whether the three drugs administered in this trial can effectively block this farnesyl group attachment to progerin with a resulting reduction in disease severity. Since all three drugs work at a different point in the pathway that leads to the production of the protein that is believed to cause the disease, their combination provides the opportunity to amplify the efficacy over the drugs used individually.

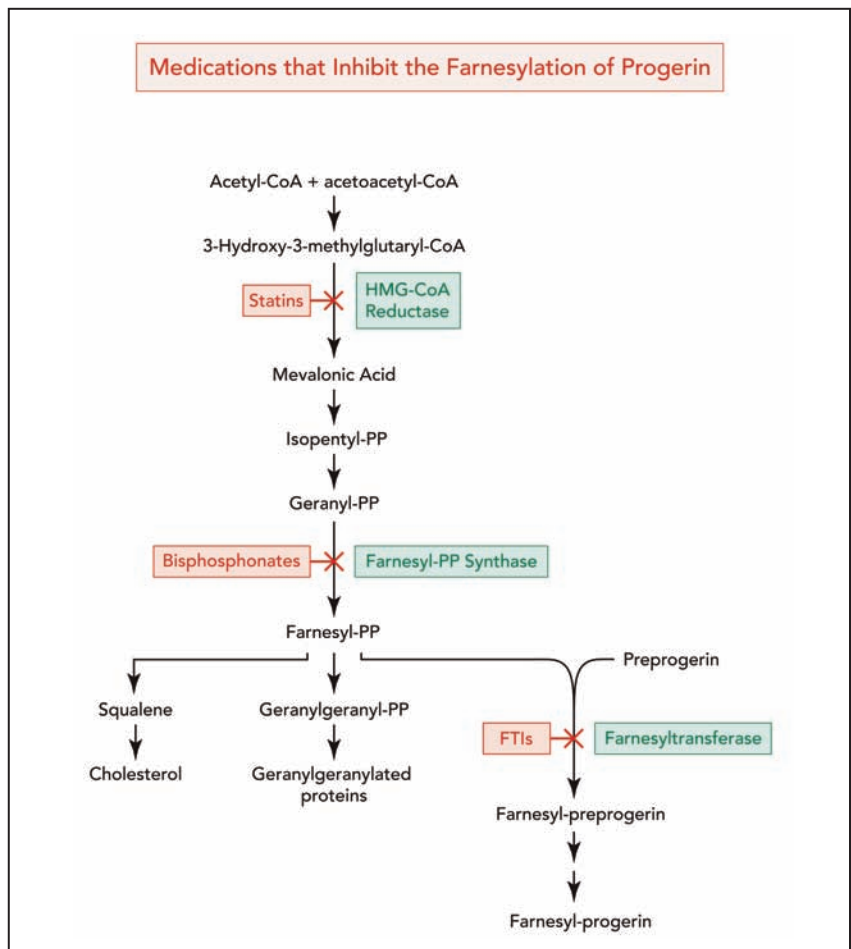


Figure 1

Trial medications at a glance

> What is Lonafarnib?

Lonafarnib is a Farnesyltransferase Inhibitor (FTI). FTIs are a class of drugs that inhibit an enzyme that is required to attach the farnesyl group to proteins. Because many proteins that regulate cancer cell growth require farnesylation, drug companies have been developing and testing these drugs to evaluate their effect on cancer cells. Progeria cells are not cancer cells, but progerin is a protein that shares this need to be farnesylated in order to fully function. The farnesylated form of progerin leads to some of the cellular damage observed in Progeria. FTIs prevent this farnesyl group attachment, and were therefore evaluated as a possible therapy for Progeria. Lonafarnib is not approved by the U.S. Food & Drug Administration, and can only be given through approved clinical trials.

All three drugs affect progerin protein in a similar manner. The hope is that they will make the progerin less toxic to cells.

> What is Pravastatin?

Pravastatin (marketed as Pravachol or Selektine) is a member of the drug class of statins. It is usually used for lowering cholesterol and preventing cardiovascular disease. Children with Progeria do not usually have high cholesterol. Pravastatin is being used for Progeria because it also has an effect on blocking the production of the farnesyl molecule that is needed for progerin to create disease in progeria. The U.S. Food & Drug Administration approved Pravastatin for sale in the United States for the first time on April 2006. It comes as a tablet that can be crushed into food for administration. It is usually given once daily.

> What is Zoledronic Acid?

Zoledronic Acid or Zoledronate (marketed under the trade names Zometa and Reclast) is a bisphosphonate. This agent is used to improve bone density in women with osteoporosis, and to prevent skeletal fractures in people suffering from some forms of cancer. It has been used in children with a bone disease called osteogenesis imperfecta, and for other bone problems. Children with Progeria can have low bone density and Zoledronic Acid may, over time, help with that problem. It also has an effect on blocking the production of the farnesyl molecule that is needed for progerin to create disease in Progeria. The U.S. Food & Drug Administration approved Zoledronic Acid for sale in the United States for the first time on August 2001 for the treatment of hypercalcemia of malignancy. It is administered intravenously several times per year.

> Treating cells in the laboratory: FTL improves Progeria in cell cultures

The nucleus (plural nuclei) is the structure at the center of each cell that contains DNA (the genes). Unlike the round nuclei from normal cells, Progeria cells have abnormally shaped nuclei. These abnormally shaped nuclei with multiple “lobes” can look like a cluster of grapes or bubbles (see figure 2).

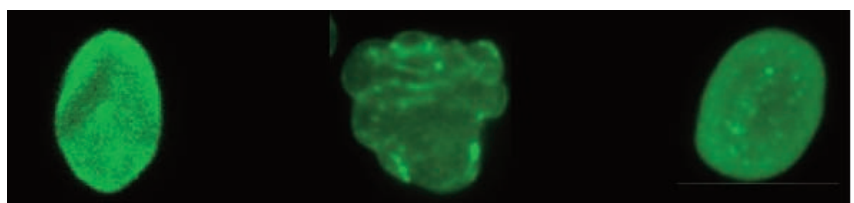
The gene LMNA normally produces a protein called prelamin A. When this gene is mutated, as occurs in Progeria, it causes abnormal cell shape and function that results in the clinical problems that are characteristic of this disease. Prelamin A requires a molecule attached to the end of it called a farnesyl group. It needs this farnesyl molecule to anchor the protein to the nuclear membrane. In normal cells, this farnesyl group is removed, but this step does not take place in Progeria because of the mutation and the progerin protein therefore remains stuck in the membrane, where it does its damage. FTLs function by not allowing the farnesyl molecule to attach onto progerin in the first place. In the laboratory, treating Progeria cells with FTLs restored their nuclei to a normal appearance (see figure 2).

> Training mouse models of Progeria: FTL, statins, and bisphosphonates improve Progeria in mouse models of disease

Whenever possible, new medications are given to mice before they are considered for humans. These mice are observed for side effects and toxicity effects, as well as for changes that may indicate the medicines would improve disease in people.

PRF-funded researchers at the University of California in Los Angeles developed two separate mouse models of Progeria that mimic many aspects of the human disease. They treated these mice with FTLs at a young age

Figure 2



Normal Skin Cell

Progeria Skin Cell

Progeria Skin Cell
Treated with FTL

Capell et al., PNAS, 2005

before the onset of symptoms. Both types of Progeria mice received FTIs in their water and were followed for several months. FTI treatment dramatically prevented the development of disease characteristics. FTI reduced bone fractures, delayed the onset of the disease, helped with weight gain, and increased life spans. There were minimal side effects at the dose of drug that was given. It is not clear whether these two UCLA Progeria mice develop heart (vascular) disease. In a separate study, researchers at the National Institutes of Health created a mouse model of Progeria that does develop cardiovascular disease. They began daily treatments with FTIs at a young age before the onset of symptoms, and found that the heart disease was improved in treated mice when compared to untreated mice. Based on these studies, a first-ever clinical trial was undertaken in which a single FTI was given to children with Progeria.

Subsequently, researchers in Spain also treated a Progeria-like mouse model with Pravastatin and Zoledronic Acid. The mice experienced longer, healthier lives with more body fat and improved hair and bones. This experiment provided the scientific evidence needed for the development of clinical trials using these drugs in children with Progeria, either alone or in combination with an FTI.

› **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.

Progeria clinical drug trials

Over the past 10 years, Progeria has gone from obscurity, to gene finding, to first-ever treatment trials. There are currently two clinical drug trials ongoing for Progeria. 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.

Thanks to the 2003 Progeria gene discovery, studies in the years that followed paved the way for The Progeria Research Foundation to fund and co-coordinate a first-ever clinical trial for children with Progeria at Children's Hospital Boston, USA. Twenty-eight children from 15 different countries, speaking 9 different languages, flew to Boston every 4 months for a period of 2.5 years, from May 2007 through December 2009. The trial drug was an FTL. FTIs have shown great promise in the laboratory and in animal models of Progeria. Results will be announced in 2010.

Since 2007, two additional treatment trials for Progeria have begun. A trial in France was initiated in 2008 and is treating children with the drugs Pravastatin and Zoledronic Acid.

The third trial, which began in 2009 and is taking place at Children's Hospital Boston, is treating children with all three drugs: FTL, Pravastatin, and Zoledronic Acid. Forty-five children from 24 different countries, speaking 17 different languages, fly to Boston every 6 months for testing and treatment, for a period of 2 years.

> 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.

> 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 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. (See *The science behind the Progeria clinical drug trials* on page 19.1 of this section.) 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), Children's Hospital Boston, and Dana-Farber Cancer Institute. There is also a treatment trial ongoing in France for which European resources are used.

> 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 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
 The Weighing-in Program
 Cell & Tissue Bank
 Progeria Family Network
 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.

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 any new information that may benefit patients and/or their families.

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

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

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 atypical 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 Boards at Brown University and Rhode Island Hospital.

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

The Weighing-in Program

Each child with Progeria has a consistent and slow weight gain. We have used this data to track baseline weight gain, and potentially to track improvements with treatment. We are using rate of weight gain as a substitute marker for general health, since we can easily and reliably track weight over time. When families participate in the weighing-in program, we send families a scale, log book, and instructions so that they can report weekly weights directly to PRF. This is part of the PRF Medical & Research Database program and consent is required to participate.

Rate of weight gain has been used to decide whether the treatment trial drugs are having a beneficial effect on the children who participate in the trials. To do this, pre-drug weights should be followed carefully for about 6 to 12 months or longer if the child is very young, since weight gain does not become reliable until about the age of 3 years in Progeria.

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 100 cell lines and tissues from affected children and their immediate relatives. 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, 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.

Progeria Family Network

Because Progeria is so rare, it is unlikely that families will be located close to one another. Yet, it is essential that families share feelings and advice, and give each other emotional support. To help families connect, PRF has created a private message board website. This on-line tool helps the families get to know each other, and develop a support network of people with whom they can share concerns and ideas on how best to care for their children. PRF also provides contact information to families privately, so that they can exchange emails, phone calls, and even meet in person.

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

Research funding

PRF's grants of up to \$100,000 over two years, 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 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

Judith A. Campisi, PhD
Senior Staff Scientist, Lawrence Berkeley National Laboratory

Thomas Glover, PhD
Professor of Human Genetics, University of Michigan

Leslie Gordon, MD, PhD
Medical Director, The Progeria Research Foundation
Associate Professor of Pediatric Research,
Alpert Medical School of Brown University

Christine Harling-Berg, PhD
Assistant Professor of Pediatrics,
Alpert Medical School of Brown University
Memorial Hospital of Rhode Island

Monica Kleinman, MD
Clinical Director, Medical-Surgical ICU, Children's Hospital Boston

Paul Knopf, PhD (Retired 2009)
Professor of Medical Science, Emeritus, Brown University

Frank Rothman, PhD
Professor of Biology and Provost, Emeritus, Brown University

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.

Scientific workshops

PRF organizes successful scientific conferences every two 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. 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.

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/dispmim.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

Reviews and book chapters

Gordon, LB. The Premature Aging Syndrome Hutchinson-Gilford Progeria Syndrome: Insights Into Normal Aging. In H. M. Fillit, K. Rockwood, K. Woodhouse (Eds.) Brocklehurst's Textbook of Geriatric Medicine and Gerontology (7th ed.). W.B. Saunders, Elsevier 2010;66-72.

Rodriguez S, Eriksson M. Evidence for the Involvement of Lamins in Aging. *Curr Aging Sci* 2010.

Capell BC, Tloutan BE, Orlow SJ. From the Rarest to the Most Common: Insights from Progeroid Syndromes into Skin Cancer and Aging. *J Invest Dermatol* 2009.

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Capell BC, Collins FS. Human laminopathies: nuclei gone genetically awry. *Nat Rev Genet* 2006;7(12):940-52.

DeBusk FL. The Hutchinson-Gilford progeria syndrome. Report of 4 cases and review of the literature. *J Pediatr* 1972;80(4):697-724

Primary Research Articles

> Global Clinical Studies on Progeria:

Hennekam RC. Hutchinson-Gilford Progeria syndrome: review of the phenotype. *Am J Med Genet A* 2006;140(23):2603-24.

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.

> Subspecialty Studies on Progeria:

Anesthesia: Liessmann CD. Anaesthesia in a child with Hutchinson-Gilford progeria. *Paediatr Anaesth* 2001;11(5):611-4.

Dental: Domingo DL, Trujillo MI, Council SE, Merideth MA, Gordon LB, Wu T, et al. Hutchinson-Gilford Progeria syndrome: oral and craniofacial phenotypes. *Oral Dis* 2009;15(3):187-95.

Growth and Bones: Gordon LB, McCarten KM, Giobbie-Hurder A, Machan JT, Campbell SE, Berns SD, et al. Disease progression in Hutchinson-Gilford Progeria syndrome: impact on growth and development. *Pediatrics* 2007;120(4):824-33.

Dermatology: Gillar PJ, Kaye CI, McCourt JW. Progressive early dermatologic changes in Hutchinson-Gilford progeria syndrome. *Pediatr Dermatol* 1991;8(3):199-206.

Growth Hormone: Sadeghi-Nejad A, Demmer L. Growth hormone therapy in progeria. *J Pediatr Endocrinol Metab* 2007;20(5):633-7.

> Aging and Progeria:

McClintock D, Ratner D, Lokuge M, Owens DM, Gordon LB, Collins FS, et al. The mutant form of lamin A that causes Hutchinson-Gilford Progeria is a biomarker of cellular aging in human skin. *PLoS One* 2007;2(12):e1269.

Scaffidi P, Gordon L, Misteli T. The cell nucleus and aging: tantalizing clues and hopeful promises. *PLoS Biol* 2005;3(11):e395.

> Genetics - Discovery:

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Eriksson M, Brown WT, Gordon LB, Glynn MW, Singer J, Scott L, et al. Recurrent de novo point mutations in lamin A cause Hutchinson-Gilford Progeria syndrome. *Nature* 2003;423(6937):293-8.

> Cell Shape:

Goldman RD, Shumaker DK, Erdos MR, Eriksson M, Goldman AE, Gordon LB, et al. Accumulation of mutant lamin A causes progressive changes in nuclear architecture in Hutchinson-Gilford progeria syndrome. *Proc Natl Acad Sci USA* 2004;101(24):8963-8.

> Treatments in Cells:

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Capell BC, Erdos MR, Madigan JP, Fiordalisi JJ, Varga R, Conneely KN, et al. Inhibiting farnesylation of progerin prevents the characteristic nuclear blebbing of Hutchinson-Gilford progeria syndrome. *Proc Natl Acad Sci USA* 2005;102(36):12879-84.

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> Treatments in Mice:

Yang SH, Meta M, Qiao X, Frost D, Bauch J, Coffinier C, et al. A farnesyltransferase inhibitor improves disease phenotypes in mice with a Hutchinson-Gilford progeria syndrome mutation. *J Clin Invest* 2006;116(8):2115-21.

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Varela I, Pereira S, Ugalde AP, Navarro CL, Suarez MF, Cau P, et al. Combined treatment with statins and aminobisphosphonates extends longevity in a mouse model of human premature aging. *Nat Med* 2008;14(7):767-72.

Clinical Care-at-a-Glance

Summary of Recommendations and Management in Progeria

Exam	At diagnosis	Regularly	As needed
Complete Physical Exam with Growth	✎	✎	
Genetics Evaluation	✎		✎
Genetic Testing	✎		
Early Intervention Services	✎	✎	
Cardiac Evaluation and ECG	✎	✎	
Echocardiogram	✎	✎	
Carotid Duplex Ultrasound	✎	✎	
Neurologic Evaluation	✎		✎
Brain MRI	✎		✎
Nutrition and Feeding Evaluation	✎	✎	
Endocrine Evaluation			✎
Ophthalmologic Evaluation	✎		✎
Audiologic Evaluation	✎		✎
Dental Evaluation	✎	✎	
Dermatologic Evaluation	✎		✎
Bone and Orthopedics Evaluation			✎
Physical and Occupational Therapy	✎	✎	
Podiatric Evaluation	✎	✎	

Cinical Care-at-a-Glance

Caretaker Phone Numbers

Specialist	Phone Number
Pediatrician	
Geneticist	
Cardiologist	
Neurologist	
Nutritionist	
GI specialist	
Endocrinologist	
Ophthalmologist	
Audiologist	
Dentist	
Dermatologist	
Orthopedist	
Physical Therapist	
Occupational Therapist	
Podiatrist	
Others	