



The Progeria Handbook

A Guide for Families
& Health Care Providers
of Children with Progeria
2nd Edition

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

Together we *WILL* find the cure!



P.O. Box 3453, Peabody, MA 01961-3453 • 978-535-2594
info@progeriaresearch.org • www.progeriaresearch.org



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The Progeria Handbook and handbook updates are also available in electronic form at <https://www.progeriaresearch.org/patient-care-and-handbook/>

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



My Philosophy for a Happy Life

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

Presented by Sam Berns at
TEDxMidAtlantic
October 26, 2013

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

For Sam

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A Message from the Medical Director

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

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

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

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

This handbook is intended to help 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.

Most importantly, this handbook was created from love – the love that helps us all strive every day to make a difference in the lives of children who deserve every happiness that life can offer.

Together we **WILL** find the cure!



Leslie Gordon, MD, PhD

Co-founder and Medical Director, The Progeria Research Foundation, Inc.



Executive Editor: Leslie B. Gordon, MD, PhD

Co-founder and Medical Director, The Progeria Research Foundation, Inc.

Professor of Pediatrics (Research), Alpert Medical School of Brown University and Department of Pediatrics, Hasbro Children's Hospital, Providence, RI

Research Associate in Anesthesia, Harvard Medical School

Staff Scientist, Department of Anesthesia, Division of Critical Care, Boston Children's Hospital, Boston, MA

Telephone: (978) 535-2594

Email: Lgordon@progeriaresearch.org

Design by Marie Migliaccio Design and Illustration, Topsfield, MA, and Julie Pritchard, JCR Design, Foxboro, MA

Contributors (alphabetical):

In addition to the contributors listed below, we would like to thank the many children with Progeria and their families who contributed to this handbook.

Scott D. Berns, MD, MPH, FAAP; Co-founder and Board Chairman, The Progeria Research Foundation, Peabody, MA; CEO, National Institute for Children's Health Quality, Boston, MA; Departments of Pediatrics and Public Health, Brown University, Providence, RI

Emily Berry, PT, DPT; Department of Physical Therapy and Occupational Therapy, Boston Children's Hospital, Boston, MA

Susan E. Campbell, MA; Brown University Center for Gerontology and Health Care Research, Providence, RI

Isabelle Chase, DDS, FRCD(C); Department of Dentistry, Boston Children's Hospital and Harvard School of Dental Medicine, Boston, MA

Annette Correia, OT; Department of Physical Therapy and Occupational Therapy Services, Boston Children's Hospital, Boston, MA

Brian J. Fligor, Sc.D., PASC; Tobias & Battite, Inc., Hearing Wellness, Boston MA; , Salus University, Elkins Park, PA

Marie D. Gerhard-Herman, MD; Department of Cardiovascular Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA

Audrey S. Gordon, Esq.; Co-founder, President and Executive Director, The Progeria Research Foundation, Inc., Peabody, MA

CONTRIBUTORS

Catherine M. Gordon, MD, MSc; Division of Adolescent Medicine and Endocrinology, Boston Children's Hospital and Harvard Medical School, Boston, MA

Leslie B. Gordon, MD, PhD; Department of Pediatrics, Hasbro Children's Hospital and Alpert Medical School of Brown University, Providence, RI; Department of Anesthesiology, Division of Critical Care Medicine, Boston Children's Hospital and Harvard Medical School, Boston, MA

Maya Mundkur Greer, MSN, FNP-BC; Division of Critical Care Medicine, Boston Children's Hospital, Boston, MA

Sheila M. Hegde, MD; Cardiovascular Medicine, Women's Health, Brigham and Women's Hospital and Harvard Medical School, Boston, MA

Mark W. Kieran, MD, PhD; Dana-Farber Cancer Institute and Harvard Medical School, Boston, MA

Monica E. Kleinman, MD; Division of Critical Care Medicine, Department of Anesthesiology, Critical Care and Pain Medicine, Boston Children's Hospital and Harvard Medical School, Boston, MA

Marilyn G. Liang, MD; Department of Dermatology, Boston Children's Hospital and Harvard Medical School, Boston, MA

Julie Malloy, OT; Department of Physical Therapy and Occupational Therapy Services, Boston Children's Hospital, Boston, MA

Iason S. Mantagos, MD; Department of Ophthalmology, Boston Children's Hospital and Harvard Medical School, Boston, MA

Srinivasan Mukundan, Jr. MD, PhD; Department of Radiology, Brigham & Women's Hospital and Harvard Medical School, Boston, MA

Christine Ploski, PT, MS, PCS, MAc; Department of Physical Therapy and Occupational Therapy Services, Boston Children's Hospital, Boston, MA

Ashwin Prakash, MD; Department of Cardiology, Boston Children's Hospital and Harvard Medical School, Boston, MA

Leslie B. Smoot, MD; Department of Cardiology, Boston Children's Hospital and Harvard Medical School, Boston, MA

Brian Snyder, MD, PhD; Department of Orthopedic Surgery, Boston Children's Hospital and Harvard Medical School, Boston, MA

Andrew L. Sonis, DMD; Department of Dentistry, Boston Children's Hospital and Harvard School of Dental Medicine, Boston, MA

Nicole J. Ullrich, MD, PhD; Department of Neurology, Boston Children's Hospital and Harvard Medical School, Boston, MA

Michele Walters, Department of Radiology, Boston Children's Hospital and Harvard Medical School, Boston, MA

1. Progeria: The Basics

What is Hutchinson-Gilford Progeria Syndrome?

What is PRF's history and mission?

Is there a treatment or a cure for Progeria?



Progeria is a rare genetic disease that is not usually passed down from parents, because it is a chance occurrence (mutation) in the DNA (see Genetics section, Chapter 4). There is a genetic test for Progeria and PRF has a genetic testing program. Progeria affects all races, and both girls and boys equally. Children with Progeria are found all over the world, and PRF's mission is to help every child worldwide.



Dr. Jonathan Hutchinson
Illustration: *Vanity Fair*, Sept. 1890

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 ethnic backgrounds. Although most babies with Progeria are born looking healthy, they begin to display some characteristics of Progeria in the first year of life. Sometimes one of the earliest signs of Progeria is tightness or bulging of the skin in the abdominal and/or thigh area. Other signs of Progeria include growth failure, loss of body fat and hair, skin changes, stiffness of joints, hip dislocation, generalized atherosclerosis, cardiovascular (heart) disease, and stroke. Without Progeria-specific treatment, children with Progeria die of atherosclerosis

1.2 PROGERIA: THE BASICS

(heart disease) or stroke at an average age of 14.5 years (with a range of about 8-21 years). (See *PRF Drug Treatment Trials*, Chapter 3). 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.

What is PRF's history and mission?

The Progeria Research Foundation (PRF) was established in the United States in 1999 by the parents of a child with Progeria, Drs. Leslie Gordon and Scott Berns, and many dedicated friends and family who saw the need for a medical resource for the doctors, patients, and families of those with Progeria, and for funding of Progeria research. Since that time, PRF has become a driving force for promoting advances in the field, including the historic discovery of the Progeria gene and the discovery of the first treatment for Progeria. (See *Diagnosis, Genetics, and Genetic Counseling*, Chapter 4, and *PRF Drug Treatment Trials*, Chapter 3). PRF has developed a comprehensive network of programs to aid those affected by Progeria and researchers who want to conduct Progeria research. (See *PRF Programs and Services*, Chapter 2). PRF is the only nonprofit organization worldwide solely dedicated to finding treatments and the cure for Progeria and its aging-related disorders, including heart disease.

Is there a treatment or a cure for Progeria?

The Progeria Research Foundation funds research to find new treatments and the cure for Progeria. There is currently no cure for Progeria. There is a treatment for Progeria called lonafarnib that helps some, but not all, aspects of disease. (See *PRF Drug Treatment Trials*, Chapter 3). Lonafarnib helps with cardiovascular disease and bone disease in Progeria. It also helps children with Progeria to live longer lives. It does not help with skin, joints, or hair. It is taken orally, as either a capsule or a liquid. Its main side effects are diarrhea, nausea, and loss of appetite, which often lessen or go away after a few weeks to months. To learn more about how to obtain treatment with lonafarnib, contact The Progeria Research Foundation.

In addition to treatment with lonafarnib, The Progeria Research Foundation funds and supports clinical trials that administer drugs that show promise as potential treatments for children with Progeria. To learn more about clinical trials for Progeria, contact The Progeria Research Foundation or go to www.clinicaltrials.gov and search the key word "Progeria."

Update on Lonafarnib: Our First-ever FDA Approved Drug for Children with Progeria.

In November, 2020, the United States Food and Drug Administration (U.S. FDA) approved the use of lonafarnib, branded as 'Zokinvy,' for the treatment of Progeria and processing-deficient Progeroid Laminopathies (PL), in children 12 months of age and older with a body surface area of 0.39 m² and above.

Zokinvy was approved based on its ability to extend the average lifespan of children with Progeria. This is the first-ever approved drug for children with Progeria.

Thanks to PRF's partners at Eiger BioPharmaceuticals, who helped get Zokinvy FDA approved, children and young adults with Progeria in the U.S. may now access Zokinvy by prescription, instead of through a clinical trial. Progeria now joins fewer than 5% of the known rare diseases with an FDA-approved treatment. The team at PRF, as well as the greater Progeria community, are thrilled by this historic milestone.



Zokinvy's clinical development in Progeria spanned 13 years of clinical treatment trials, involving nearly 100 children from 37 countries and six continents, all funded and co-coordinated by The Progeria Research Foundation.

For children and young adults with Progeria who live outside of the USA, pathways for receiving treatment with lonafarnib include a managed access program and the Progeria clinical trials, depending in part on the country where the patient lives. For questions about this and for more information, please contact The Progeria Research Foundation at info@progeriaresearch.org.

2. PRF Programs and Services

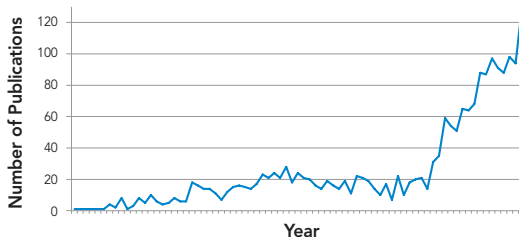
International Patient Registry
 Diagnostic Testing Program
 Medical & Research Database
 Cell & Tissue Bank
 Research funding
 Scientific workshops
 Public awareness
 Volunteers & fundraising



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

Before PRF was created and the Progeria gene mutation was discovered, there was almost no 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 children. The Progeria Research Foundation (www.progeriaresearch.org) provides services for families and children with Progeria, such as patient education and communication with other families affected by Progeria. It serves as a resource for physicians and medical caretakers of these families via clinical care recommendations, a diagnostic testing program, and a medical 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.

Scientific Publications on Progeria 1950-2018



2.2 PRF PROGRAMS AND SERVICES

This section describes the many programs and resources available through The Progeria Research Foundation (PRF). Through these programs, our work is paying off. Research on Progeria has soared! We have increased the rate of scientific publications by over 2,000%, and are still going strong. This is the research that will lead us to new treatments and the cure!

International Patient Registry

Only 1 in 20 million people has Progeria. It is so rare that most physicians have never encountered a child with Progeria. Moreover, the families have few local resources to tap into for help. 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 assures rapid distribution of new information that may benefit patients and their families, such as this handbook, clinical trial opportunities, and new research findings.

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

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

Diagnostic Testing Program

Progeria is caused by a genetic mutation. The PRF Diagnostic Testing Program offers genetic testing for children suspected of having Progeria, provided at no cost to families. 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 evaluate a child's clinical history and photographs. Then we will be in touch with the family and their physicians about having this blood test done. All personal information is kept strictly confidential.

We provide genetic sequence testing by a Clinical Laboratory Improvement Amendments (CLIA)-approved laboratory for either Exon 11 of the *LMNA* gene (the portion of the gene where the HGPS mutation is found) or full *LMNA* gene sequencing (for other types of progeria

called progeroid laminopathies). CLIA is a body of industry regulations ensuring quality laboratory testing.

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

Medical & Research Database

The PRF Medical & Research Database is a collection of medical records and radiological tests such as X-rays, MRIs, and CT scans 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 for children and families. Analysis of these medical records has provided new insights into the nature of Progeria and into the nature of other medical conditions such as heart disease, which in turn will serve to stimulate the advancement of new Progeria research. 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. This care handbook is in part a product 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 PRF Medical & Research Database is approved by the Institutional Review Board at Rhode Island Hospital.

Visit www.progeriaresearch.org/medical_database.html for more 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 the cure. Thanks to the participation of courageous children and their families, PRF provides over 1,000 cell lines and tissues from affected children and their immediate relatives to laboratories and researchers worldwide. This includes cells from blood and skin biopsies; teeth; hair; autopsy tissue and more. This helps ensure not only that research into Progeria is maximized, but also 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.

2.4 PRF PROGRAMS AND SERVICES

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

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 more information.

Research funding

PRF's scientific grants have allowed innovative new research on Progeria and its relationship to heart disease and aging 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 ever-growing field.

Visit www.progeriaresearch.org/research-funding-opportunities.html for more information.

Scientific workshops

PRF organizes cutting-edge international scientific conferences on Progeria every 2-3 years. These meetings bring together scientists and clinicians from all over the world to collaborate, share ideas, and contribute their expertise in our quest for the cure for this currently fatal disease. The workshops are a cornerstone of inspiration for those in the scientific and medical communities, as well as families, who seek to understand Progeria and its relationship to aging and heart disease, and discover new treatments and the cure.

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



*Attendees at The Progeria Research Foundation
9th International Scientific Workshop, held in Boston, MA, USA, in 2018*

Public awareness

Before PRF was formed, Progeria was virtually unknown to the general public and to most health care 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 website, newsletters, educational materials, and the media. PRF’s story has appeared on CNN, BBC, *Primetime*, *Dateline*, *Discovery*, and in *Time* and *People* magazines, *The New York Times*, *The Wall Street Journal*, and dozens of other widely read media outlets. In 2013, the HBO documentary based on children participating in the first-ever treatment trial, *Life According to Sam*, reached millions more. As awareness continues to spread throughout the world, more children come to PRF for help; 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 much-needed support.

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

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

Volunteers & fundraising

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

3. Progeria Research Foundation Drug Treatment Trials

Progeria clinical drug
trials – the basics

The science behind
Progeria clinical trials

Trial medications
at a glance



The Progeria gene discovery opened the floodgates for research into Progeria that has led to clinical drug trials. PRF keeps families informed about upcoming clinical trials through informational phone conferences, newsletters, Facebook posts and other types of outreach. Don't hesitate to check in with PRF periodically about the status of ongoing or planned clinical trials.

Progeria clinical drug trials – the basics

Since 1999 when PRF was created, Progeria has gone from obscurity, to gene finding, and now to the completion of a number of clinical trials. This section will provide information on clinical trials in general, and where the PRF-supported Progeria clinical trials stand as of 2019. Websites where you can find more detailed information are also provided.

› Clinical Trials 101

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

All clinical trials are considered research and are completely voluntary. The basic information for this section is derived from a website located at 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 that examines the natural history of disease, and/or applies an intervention to try to improve disease. For children with Progeria, PRF has 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 define what is happening to the children, and develop treatment strategies for them in our efforts toward 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 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, including the crucial question, “Does this drug help the children?”

> 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 for a period of time after the trial is completed.

For the Progeria trials, each patient's family periodically flies to the trial site for testing and drug supply. Currently, PRF-funded trials are based at Boston Children's Hospital in Boston, MA, USA. There is also some monitoring at home, so that toxicities can be addressed immediately. To date, PRF has provided travel, lodging, clinical trial testing, and medications so that finances do not prevent any child from participating in the clinical trials.

> Reliable measures of disease improvement are essential for the clinical trials

Although studies with cells and mice may be 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 time frame of the trials. Usually the Progeria trials have treated children for about 2 years. 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 trial drugs. To this end, careful analysis of baseline clinical status of children with Progeria is performed, using their medical charts, pretrial weights, 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 trial drugs on the children.

> What is informed consent?

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

To help someone decide whether or not to participate, the investigators involved in the trial explain the details of the study. The information is provided in the primary language of each family to ensure clear communication. Translation assistance is provided. The research team provides an informed consent document that includes details about the study, such as its purpose, duration, required procedures, and key

3.4 PRF DRUG TREATMENT TRIALS

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. In addition, children under age 18 who are able to understand the major issues are usually asked to sign a form after the trial is explained to them in age-appropriate terms. 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 oversight 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 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 while taking the trial drug. Home health care is focused on the general health of the child. In addition, by having the health care provider work with the research team, the participant can ensure that other medications or treatments will not conflict with the trial medications.

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

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

> Where do the ideas for the trials come from?

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

> Who sponsors clinical trials?

Clinical trials can be sponsored or funded by a variety of organizations or individuals. PRF has provided major funding for all Progeria treatment trials in the United States to date. Some of these trials have also been funded in part by the National Institutes of Health (NIH), Boston Children's Hospital, and Dana-Farber Cancer Institute. Children from 37 different countries have participated in these trials.

> 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

3.6 PRF DRUG TREATMENT TRIALS

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 communicate regularly with 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 usually include a large number of people (1,000-3,000) to confirm drug 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 the Progeria trials have been Phase I and Phase II trials, where both toxicity and effect on disease progression are studied. They have also been "open label" trials, in which all the children have received the same drug treatment (none of the participants have received placebo).

The science behind the Progeria clinical drug trials

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

Finding the gene for Progeria was the key element to this 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.” Our goal in every trial is to prevent progerin from damaging cells and thus reduce the severity of the disease in children with Progeria.

Trial medications at a glance

To date, the trial medications have all targeted different places along a common pathway that targets progerin.

There are four drugs that have been studied in treatment trials for Progeria (see **Figure 1**):

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

Clinical Trials – Pathway Based

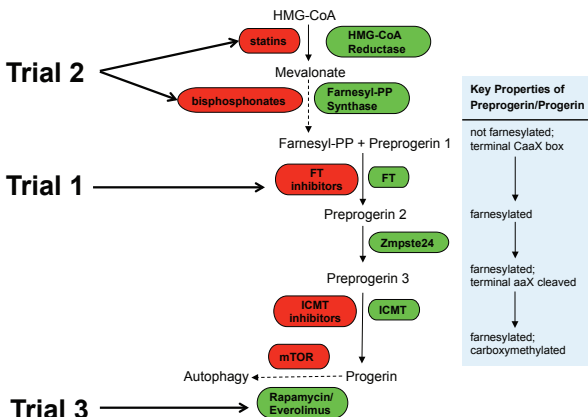


Figure 1

Post-translational processing and medications given in clinical treatment trials for HGPS. Items in green promote the pathways. Items in red inhibit the pathways. *Denotes medications tested in clinical trials. Everolimus is a rapamycin analogue that inhibits mTOR and promotes cellular autophagy. FT=farnesyltransferase.

> **Lonafarnib**

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

Treatment with lonafarnib has yielded a number of positive results. While a very slight increase in weight was observed in children with Progeria taking the drug, the most important effect appeared to be an improvement in some of the function of the cardiovascular system, the part of the disease that causes death in most children. Overall, blood vessels became more flexible with treatment. Lonafarnib also improved bone structure. Most importantly, studies support that lonafarnib may be increasing survival time. When comparing children who were treated with lonafarnib to those who were not, over a 2-year period there was 1 death in the treated group but 9 deaths in the untreated group. In other words, evidence supports lonafarnib treatment may be providing the children with stronger hearts and longer lives.

While the results were positive, it was also clear that lonafarnib alone was not enough to completely reverse the disease. We strive to discover new drugs that will improve upon the benefits provided by lonafarnib.

As of March, 2019, lonafarnib is not approved by the U.S. Food & Drug Administration, and can only be given through approved clinical trials such as the PRF-funded trial in Boston, MA. Outside of the Progeria clinical trials in Boston, MA, there is a study run by Eiger Biopharmaceuticals, the drug manufacturer. This is called an Expanded Access Program, and it allows children in some countries to receive lonafarnib through their local physicians. For more information, contact The Progeria Research Foundation at www.progeriaresearch.org.

> **Pravastatin and zoledronic acid**

The second trial combined pravastatin, zoledronic acid, and lonafarnib in the hopes that the three drugs together would be more effective than lonafarnib on its own. Pravastatin and zoledronic acid act by blocking

(inhibiting) the production of the farnesyl group. However, the trial results showed that the three-drug combination when compared with giving lonafarnib on its own were equally effective. Therefore, the three-drug combination is not recommended as a replacement for lonafarnib on its own as a single therapy.

› Everolimus

Everolimus (marketed under the trade names Afinator, Zortress) is an oral mTOR inhibitor. In children who do not have Progeria this drug has been used to prevent the rejection of transplanted organs such as heart, kidney, and liver. In laboratory experiments, it can increase the breakdown of the abnormal molecule progerin. In this way, it functions differently from the other three drugs above, all of which attempt to reduce the production of the disease-causing progerin. PRF is funding and co-coordinating a clinical trial at Boston Children's Hospital that administers everolimus plus lonafarnib to children with Progeria. Results of this trial are expected in 2023.

Update on Lonafarnib: Our First-ever FDA Approved Drug for Children with Progeria.

In November, 2020, the United States Food and Drug Administration (U.S. FDA) approved the use of lonafarnib, branded as 'Zokinvy,' for the treatment of Progeria and processing-deficient Progeroid Laminopathies (PL), in children 12 months of age and older with a body surface area of 0.39 m² and above.

Zokinvy was approved based on its ability to extend the average lifespan of children with Progeria. This is the first-ever approved drug for children with Progeria.

Thanks to PRF's partners at Eiger BioPharmaceuticals, who helped get Zokinvy FDA approved, children and young adults with Progeria in the U.S. may now access Zokinvy by prescription, instead of through a clinical trial. Progeria now joins fewer than 5% of the known rare diseases with an FDA-approved treatment. The team at PRF, as well as the greater Progeria community, are thrilled by this historic milestone.



Zokinvy's clinical development in Progeria spanned 13 years of clinical treatment trials, involving nearly 100 children from 37 countries and six continents, all funded and co-coordinated by The Progeria Research Foundation.

For children and young adults with Progeria who live outside of the USA, pathways for receiving treatment with lonafarnib include a managed access program and the Progeria clinical trials, depending in part on the country where the patient lives. For questions about this and for more information, please contact The Progeria Research Foundation at info@progeriaresearch.org.

4. Diagnosis, Genetics, and Genetic Counseling



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

FOR FAMILIES

What causes Progeria?

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

In Progeria, the *LMNA* mutation causes the gene to produce an abnormal lamin A protein called progerin. In children with Progeria, many organs in the body – such as the blood vessels, skin, and bones – make the progerin protein. As the children age, progerin builds up in these cells causing progressive disease. The discovery of this new protein called progerin has allowed us to understand why children with Progeria have features of premature aging, and has led us down a pathway to the first-ever

drug treatment trials for Progeria (see *Drug Treatment Trials*, Chapter 3). 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 *Progeria and Aging*, Chapter 22).

How is Progeria diagnosed?

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

Are there different types of Progeria?

In this handbook, we refer to Hutchinson-Gilford Progeria Syndrome as HGPS or Progeria. Classic Progeria is caused by a particular genetic change in a specific location on the *LMNA* gene that results in the production of progerin. Therefore, when we are searching only for classic 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" that do not produce progerin. These diseases can be more or less severe than classic Progeria, and they are typically even rarer than Progeria. When we are searching for progeroid syndromes, we test the entire *LMNA* gene and often other genes as well.

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

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

Is Progeria contagious or inherited?

Progeria is not contagious and is not usually passed down in families. The gene change is almost always a chance occurrence that is extremely rare. Children with other types of progeroid syndromes that 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 his or her cells, but does not have Progeria. Mosaicism occurs a small percentage of the time in many genetic diseases. If some of the parental eggs or sperm have the genetic mutation, then those parents could have another child with Progeria. Prenatal testing is available to look for the *LMNA* genetic change. Each family’s doctor or genetic counselors should be consulted about prenatal testing.

FOR HEALTH CARE PROFESSIONALS

(adapted from “Hutchinson-Gilford Progeria Syndrome” in GeneReviews 2019, Gordon, LB, Brown, WT, Collins, FS; online at <https://www.ncbi.nlm.nih.gov/books/NBK1121/?report=reader>)

Diagnosis/testing

The diagnosis of classic or nonclassic genotype Hutchinson-Gilford Progeria Syndrome (HGPS) is established in a proband with characteristic

4.4 DIAGNOSIS, GENETICS, AND GENETIC COUNSELING

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

Suggestive clinical findings

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

Genetic counseling

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

Incidence and prevalence

The estimated birth incidence for HGPS is 1 in 4 million births with no observed differences based on ethnic background [Hennekam 2006].

The prevalence of children with HGPS per total population is 1 in 20 million [Gordon et al., 2014].

Categories of progeroid diseases

There are 5 major categories that help define *LMNA*-related disorders. The first 2 define HGPS, while the latter 3 are not considered HGPS:

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

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

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

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

Single-gene testing

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

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

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

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

Genotype-phenotype correlations

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

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

HGPS = Hutchinson-Gilford progeria

PRF = Progeria Research Foundation Diagnostic Testing Program

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

Mode of inheritance

Hutchinson-Gilford Progeria Syndrome (HGPS) is typically caused by a *de novo* autosomal dominant pathogenic variant. Penetrance is complete.

Risk to family members

- Almost all individuals with HGPS have the disorder as the result of a *de novo* pathogenic variant.
- Approximately 3% of currently living individuals with the classic HGPS genotype identified through The Progeria Research Foundation Diagnostics Program have HGPS as the result of apparent germline (or somatic and germline) mosaicism in a parent.
- Parents of probands are usually not affected.
- The recurrence risk for subsequent pregnancies after one individual has been genetically diagnosed with HGPS is significantly higher than the 1 in 4 million incidence for the general population, though still low.
- Offspring of a proband: Individuals with classic HGPS are not known to reproduce.

Prenatal testing and preimplantation genetic diagnosis

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

Molecular basis of disease

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

re-association of the nuclear membrane at each cell division.

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

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

Genetically related disorders

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

Non-progerin-producing progeroid laminopathy can be used to describe phenotypes that have overlap with but are obviously different from classic and nonclassic genotype HGPS. Various pathogenic variants in *LMNA* result in a variety of lamin A abnormalities, resulting in various phenotypes.

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

- Autosomal dominant Emery-Dreifuss muscular dystrophy (AD-EDMD)
- Autosomal recessive Emery-Dreifuss muscular dystrophy (AR-EDMD)
- Autosomal dominant familial dilated cardiomyopathy and conduction system defects (see Dilated Cardiomyopathy)

- Autosomal dominant Dunnigan-type familial partial lipodystrophy (FPLD) (OMIM 151660)
- Autosomal dominant limb-girdle muscular dystrophy 1B (LGMD1B) (see Limb-Girdle Muscular Dystrophy)
- Autosomal recessive axonal neuropathy Charcot-Marie-Tooth disease 2B1 (CMT2B1)
- Autosomal recessive mandibuloacral dysplasia (MAD) [Cao & Hegele 2003]
- Single case reports of individuals with *LMNA* variants and unique clinical phenotypes [Caux et al 2003; Kirschner et al., 2005]

Differential diagnosis

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

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

5. Heart Health: Cardiology

Overview of cardiovascular features in Progeria

Monitoring cardiovascular health

Unique issues across the lifespan

Aspirin for heart health



In general, if you sense that there is something serious occurring, get immediate medical attention. You are the best judge of what is new and out of the ordinary for your child.

Overview of cardiovascular features in Progeria

Heart failure is the most frequent cause of death in Progeria. Children with Progeria develop progressive changes of their heart and blood vessels over time; they develop early, progressive atherosclerosis. While they are at risk for heart attacks and strokes at any age, increasing stiffness of the heart and blood vessels initially causes few, if any, symptoms. With age, children with Progeria most commonly develop progressive hardening and calcification of arterial blood vessels and left-sided heart valves. This causes arterial plaques (blockages) in the arteries and abnormal heart valve function.

FOR FAMILIES

Risks and Recommendations

Premature, progressive atherosclerosis leading to cardiovascular failure causes over 80% of deaths in children with Progeria. Your child's cardiologist or other caregiver will recommend annual screenings for blood pressure, cholesterol and heart function tests, including an ECG (electrocardiogram, also known as an EKG) and echocardiogram (cardiac

ultrasound) with additional testing if appropriate. Blood pressure and ECG are often normal in young children with Progeria. Careful, repeated measurements can detect whether there have been significant changes over time.

Regularly monitoring cardiovascular status is extremely important. Here is a list of commonly recommended tests and cardiovascular (CV) considerations for patients with HGPS:

- Annual doctor's visit, ideally with a pediatric cardiologist, including resting heart rate and blood pressure measurement, and attention to pulse quality, murmurs, and vascular bruits
- 12-lead electrocardiogram (ECG) at least annually
- Measurement of fasting blood lipids, including cholesterol and blood sugar, annually
- Education regarding maintaining appropriate fluid intake, treatment of fever, and a heart-healthy diet
- Low-dose aspirin therapy may be prescribed by your child's doctor to help prevent heart attacks and strokes. Aspirin therapy is generally discontinued 1 week prior to any surgery or invasive dental procedure; consult your physician if any surgery is being planned. If your child becomes ill with chicken pox, stop the aspirin therapy.

➤ General guidelines for chest pain

Many families would like guidelines for recognizing urgent versus non-urgent cardiac symptoms. Knowing whether a child with Progeria is having an urgent cardiac event is very difficult. The risk of a serious cardiac event in a younger child without prior evidence of cardiovascular disease would be lower than in an older child or one with pre-existing heart problems. If there is a cardiovascular history of chest pain, recurrent chest pain with breathing difficulty, change in consciousness, sweating, dizziness, or other feelings of being unwell, then urgent medical attention should be sought.

➤ Giving aspirin along with other anti-inflammatory medications

Low-dose aspirin is often prescribed for children with Progeria to help prevent heart attacks and strokes. The decision to start aspirin and/or to

add another type of medication to the aspirin should always be made by speaking to your child's doctors. When taking aspirin routinely, families ask if children can also take other anti-inflammatory medications, such as ibuprofen or naproxen for headaches or body aches. These medications, known as NSAIDS (non-steroidal anti-inflammatory drugs), do have an additive effect to aspirin's effect on blood clotting. In general, short-term use along with aspirin is okay, but longer-term use is not recommended in conjunction with aspirin. If bruising or bleeding occurs, stop the medication and consult your child's physician.

FOR HEALTH CARE PROFESSIONALS

Risks and Recommendations

Monitoring cardiovascular health

Children with HGPS are at high risk for heart attack and stroke at any age. Observations suggest that the atherosclerotic cardiovascular disease in Progeria is characterized by progressive vascular stiffness with variable patterns of vascular occlusion, particularly involving arteries of the head and neck. Frank hypertension appears less common than extreme blood pressure lability. Blood pressure (BP) measurement in both arms and legs, at rest in a calm setting, is particularly important for this population. If an artery is blocked, the blood pressure drops beyond the stenosis. Most children with HGPS have normal or hyperdynamic left ventricular function, though often display echo evidence of diastolic dysfunction (the heart is stiff and does not fill appropriately with blood) starting in early childhood and progressing with age. Mitral and/or aortic valve calcification with obstruction typically occurs later in childhood, and may be accompanied by ventricular hypertrophy, atrial enlargement, or valve insufficiency, with eventual left heart failure.

Annual testing is often the best way to detect any important changes in heart health, particularly for all children with Progeria with or without identified cardiovascular disease. The following testing should be considered for all HGPS patients:

- Cardiology visit with physical examination, including attention to pulses and four extremity manual blood pressure with appropriately sized BP cuff.

5.4 HEART HEALTH: CARDIOLOGY

- Echocardiogram – including anatomic assessment with attention to the left ventricular outflow tract, presence of calcification, valve gradients, tissue Doppler, and biventricular size and function
- 12 lead electrocardiogram – attention to findings including atrial enlargement, ventricular hypertrophy, ischemia, ST-T wave changes, conduction abnormalities
- Carotid duplex ultrasound,* if available
- Pulse wave velocity,* if available

*Note that carotid duplex ultrasound is available in some centers, but is not yet routinely performed on pediatric patients. Please consult the Reference section of this handbook for publications on cardiovascular disease and testing in Progeria to learn about the use of tests that are not routinely performed in children. Carotid-femoral pulse wave velocity is also available in some centers, but is usually an adult special test.

Cardiovascular treatments

Studies in adults and children with risk of arterial occlusions have shown benefits of low-dose aspirin therapy, for both stroke and heart attack prevention. Low-dose aspirin should be considered for all children with HGPS at any age, regardless of whether the child has exhibited overt cardiovascular disease or abnormal lipid profiles. Low-dose aspirin may aid in the prevention of thrombotic events, including transient ischemic attacks (TIAs), stroke, and coronary insufficiency, by inhibiting platelet aggregation. Aspirin dosage is determined by patient weight, and generally dosed in the range of 2-3 mg/kg/day, given once daily or every other day. Dosing is modified in accordance with available dosage forms (i.e., quarter, half, or full tablet [81 mg tab standardly available in the US]) and modified with evidence of bruising, etc. Platelets often become “stickier” (i.e., more likely to form clots) at times of stress with illness, fever, etc. While these recommendations are guidelines, individuals often make adjustments in aspirin dosing based on clinical course.

Once a child develops signs or symptoms of vascular decline, including hypertension, TIA, strokes, seizures, angina, dyspnea on exertion, heart failure, or concerning ECG/echocardiogram findings, a higher level of intervention may be warranted. Any symptom that is worse with activity and goes away with rest is a cause for concern. Antihypertensive or heart failure medications, anticoagulants, and other medications may be prescribed. All medication should be dosed according to weight,

and carefully adjusted according to accompanying toxicity (negative side effects) and efficacy (effectiveness). While surgical interventions are considered with extreme caution in HGPS patients, recently developed catheter-based cardiac interventions for valve disease have been employed. The short- and long-term utility of these types of CV interventions in individuals with HGPS have yet to be determined, and physicians should consider the risks and potential benefits for each patient.

› **Consideration in the use of aspirin**

Aspirin may rarely cause stomach discomfort. If excessive bleeding or bruising is detected, stop aspirin therapy and consult your physician.

› **Reye's syndrome**

There is a weak association between aspirin usage during varicella (chicken pox) 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 benefit of low-dose aspirin treatment in individuals with HGPS, given the increased risk of cardiovascular events in this group.

6. Brain Health / Neurology / Strokes

Strokes and TIAs

Aspirin for stroke prevention

Headaches

Seizures

Imaging recommendations

Sedation

Special circumstances:
travel, hydration



Good hydration is very important in Progeria to avoid low blood flow to the brain and heart. When taking a long trip, especially when on an airplane, encourage your child to drink extra fluids.

Overview of Neurovascular Disease in Progeria

Strokes from cerebrovascular disease are common problems in Progeria. Strokes result when narrowed arteries prevent oxygenated blood from reaching the brain tissue. Although children do not usually die of strokes, strokes can cause serious life-changing medical problems and physical challenges. A TIA, or transient ischemic attack, is like a “mini-stroke” but the symptoms are only temporary.

FOR FAMILIES

Risks and Recommendations

Strokes and transient ischemic attacks (TIAs)

Strokes and transient ischemic attacks (TIAs) are an increased risk for children with Progeria. Signs and symptoms of a stroke or TIA include weakness of an arm or leg or one side of the body, trouble speaking, loss of vision, and/or confusion. If your child has symptoms of stroke or TIA,

call an ambulance or take him or her to an emergency department right away. Your health care provider may recommend a CT (computerized tomography) scan or an MRI (magnetic resonance imaging) of the brain. These tests may show if there has been injury to the brain from lack of blood flow.

Aspirin for stroke prevention

At the recommendation of your child's physician and/or neurologist, low-dose aspirin therapy may be prescribed to help prevent future strokes. 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 consulting with a neurologist to guide appropriate care. Safety of many of these medications and guidelines for use are not well-established in pediatric patients and, therefore, careful evaluation and ongoing monitoring is needed. When taking low-dose aspirin routinely, families wonder if children can also take other anti-inflammatory medications such as ibuprofen and naproxen for headaches or body aches. These medications, known as NSAIDs (non-steroidal anti-inflammatory drugs), do have an additive effect to aspirin's effect on blood clotting. In general, short-term use of NSAIDs along with low-dose aspirin is okay, but longer-term use is not recommended in conjunction with aspirin. If bruising or bleeding occurs, stop the NSAIDs and consult your child's physician. It is fine to take acetaminophen (e.g., Tylenol) for pain while taking low-dose aspirin.

Headaches

Headaches are frequently observed in children with Progeria. Headaches can be a onetime occurrence, or happen repetitively. The headache may be localized (pain in one spot) or your child may complain of pain in multiple areas of the head and face. Some children have headaches associated with 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 monosodium glutamate [MSG]), sugar, caffeine, and alcohol. If a headache does occur, resting in a quiet, dark environment may help, along with drinking fluids and taking acetaminophen (e.g., Tylenol). See a health care provider for a severe headache that doesn't go away.

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.

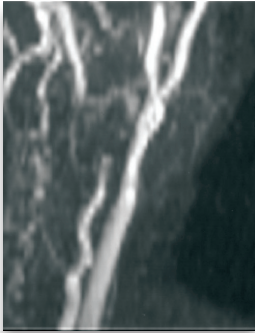
Often, family members who witness a seizure will be asked to record details like the time of day that a seizure occurs, how long it lasts, what parts of the body are affected, and what the mental awareness of the child is immediately before and after. This information can be quite helpful to determine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

Some children experience seizures as a result of a TIA or stroke. 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 which body parts are involved. If your child is sitting or standing, gently ease him or her to the floor and keep the head from falling backward. Place your child on his or her side. It is important to not try to open the mouth or place anything between the teeth. Do not try to stop the movements or "shake" your child out of it. During the seizure, your child may lose control of bowel or bladder function. After the seizure, he or she may be more tired or experience headache or soreness. Call an ambulance or 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 your 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 or she cannot be fully awakened after 10-15 minutes, or if there are any additional concerns.

FOR HEALTH CARE PROFESSIONALS

Risks and Recommendations



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

Strokes and transient ischemic attacks (TIAs)

Strokes and cerebrovascular disease are the leading causes of morbidity in children with Progeria. These are usually thrombotic events. The earliest published incidence of stroke is at the age of 4 years. In some cases, seizures are the presenting symptom of the stroke.

In an effort to provide some clues into the increased susceptibility to developing strokes, a series of children with Progeria have been studied to evaluate the types of changes that occur in the blood vessels of the head and neck with increasing

age. The most frequent finding is narrowing of the internal carotid arteries. Blood flow is slowed by the stenosis, and plaque formation can be a nidus for thrombosis formation. In an attempt to compensate for the decreased blood flow, the cerebral circulation forms collateral vessels 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, and are susceptible to shifts in blood pressure and hydration.

In children with Progeria, the first symptom of cerebrovascular disease is often a stroke or transient ischemic attack. By the time the children present with neurologic symptoms from a stroke, there is often MRI evidence of prior so-called "silent" strokes that have occurred in the past. Silent strokes are those that occur in brain regions that may not produce any clinical symptoms, but over time may accumulate and cause more permanent symptoms. If a stroke with new clinical symptoms occurs, then management of blood pressure is imperative. In the case of a larger stroke, monitoring in an ICU is often indicated until the child's condition is stabilized. Medication treatments such as anticoagulation are often considered at that time.

Aspirin for stroke prevention

Drugs such as antiplatelet agents (like aspirin) are often given to prevent future strokes from occurring, especially in the areas where there is some narrowing of the blood vessels or partial blockage. Low-dose aspirin may aid in the prevention of thrombotic events, including transient ischemic attacks (TIAs), stroke, and coronary insufficiency by inhibiting platelet aggregation. Aspirin dosage is determined by patient weight, and generally dosed in the range of 2-3 mg/kg/day, given once daily or every other day. Dosing is modified in accordance with available dosage forms (i.e., quarter, half, or full tablet [81 mg tab standardly available in the US]) and modified with evidence of bruising or bleeding.

Headaches

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

Seizures

Neurological function in Progeria is normal. Seizures can sometimes occur due to underlying cerebrovascular disease. Seizures should be evaluated and treated according to usual guidelines for pediatric patients.

Imaging recommendations

It is recommended that children with Progeria undergo magnetic resonance imaging (MRI) of the brain, and MR angiography (MRA) of the major arteries in the brain and neck to determine the presence of arterial narrowing and stroke annually. In children with Progeria, strokes are often clinically silent and the identification of infarct is unexpected. MRA of the neck may identify regions of narrowing or occlusion of the four major blood vessels within the neck that supply the brain, and also identify new “collateral” vessels that have formed in order to adequately supply the brain. In addition, MRA of the brain may also identify small, abnormal vessels along the surface of the brain that form in response to the arterial narrowing and provide alternative pathways for blood flow

and brain perfusion. These examinations provide actionable data, as the presence of narrowed or collateral vessels help identify children who may most benefit from daily aspirin and careful attention to proper hydration.

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*, Chapter 8 for additional recommendations.

Special circumstances: travel, hydration

Sudden onset of neurologic symptoms is 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.

7. Emergency Care / Critical Care

Serious Medical
Emergencies
Other considerations



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

Overview of Emergency Care/Critical Care

- Children with Progeria are at an increased risk of having a more “adult” type emergency such as chest pain (angina), a heart attack or a stroke.
- However, children with Progeria can also have common emergencies such as broken bones, head injuries, or lacerations.

FOR FAMILIES

Risks and Recommendations

- Many children with Progeria experience significant bruising for long periods of time even after a minor incident, especially on the head.
- Due to the lack of subcutaneous fat, some children’s veins are difficult when a health care provider tries to draw blood or place an intravenous catheter (IV).
- Learn the signs and symptoms of a heart attack or stroke to help you recognize whether your child is having a true emergency.
- Heart attack symptoms: squeezing pain or pressure in chest, pain radiating down the arm or in the jaw, shortness of breath, lightheadedness
- Stroke symptoms: sudden numbness or weakness in the face, arm or leg, inability to speak or slurred speech, and severe headache with no known cause

FOR HEALTH CARE PROFESSIONALS

Risks and Recommendations

Serious medical emergencies

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

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

Other considerations

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

- **Vascular access:** Although peripheral veins may appear prominent due to the paucity of subcutaneous fat, the vessels are typically less elastic and more difficult to cannulate than they would appear.
- **Trauma:** Children with Progeria may experience significant bruises that are present for long periods of time, even with minor trauma.

Large hematomas of the scalp are not uncommon, especially if the child is taking prophylactic aspirin. Less commonly, but more serious in nature, children with Progeria appear to be at higher risk of subdural hematomas following relatively minor head trauma.

- **Joint symptoms:** Joint pain is a common complaint in children with Progeria, especially in the hips and knees. Most joint symptoms can be treated with over-the-counter analgesics; more significant pain should prompt referral to an orthopedic specialist due to the increased risk of hip subluxation or dislocation. Persistent hip pain should be evaluated due to the risk of avascular necrosis of the femoral head (AVN). For additional guidance on joint dislocations, refer to *Bones/Orthopedics*, Chapter 13.

8. Airway Management / Anesthesia

Challenging airway features
in Progeria

Airway management

Anesthesia and sedation



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

FOR FAMILIES

Risks and Recommendations

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

FOR HEALTH CARE PROFESSIONALS

Risks and Recommendations

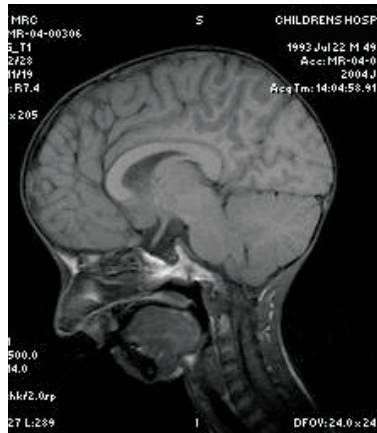
Challenging airway features in Progeria

Improvements in the practice of pediatric anesthesia have enhanced the safety of sedation and general anesthesia for purposes of diagnostic,

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

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

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



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

Airway management

The physical features associated with Progeria may cause difficulty with patient positioning, ventilation mask seal, and visualization of the larynx. As such, the clinician must be prepared to utilize techniques for the difficult airway, including supraglottic airways (SGAs) and fiberoptic intubation techniques. For children who cannot be intubated by direct visualization (laryngoscopy), fiberoptic intubation may be necessary. For most diagnostic tests and minor surgery, if the procedure can be safely accomplished without endotracheal intubation, use of bag-mask ventilation or an SGA should be considered. However, the use

of procedural sedation without a secure airway should be carefully performed by clinicians with expertise in airway management due to the risk of obstruction when using sedating medications.

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

Anesthesia and sedation

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

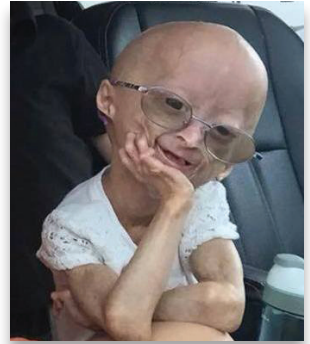
The coronary and cerebral vasculopathy associated with Progeria results in loss of vessel elasticity and increased risk of cardiac or cerebral ischemic events during states of hypovolemia or hypoperfusion. Children should remain well-hydrated prior to and following planned procedures, and medications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

9. Eye Care / Ophthalmology

Overview of ocular features
in Progeria

Risks and recommendations
for the family

Recommendations for the
eye care professional



Sleeping with eyes slightly open can cause “dry eye.” Keeping eyes moist decreases the chances of exposure keratitis.

Overview of ocular features in Progeria

Most children with Progeria have the following eye problems:

- Eyes slightly open when sleeping, likely due to tight skin and a lack of subcutaneous fat
- Eyes tear frequently, which 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, which can decrease protection from dust and other irritants
- Photophobia, which is excessive sensitivity to light and the aversion to sunlight or well-lit places

FOR FAMILIES

Risks and Recommendations

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

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

9.2 EYE CARE / OPHTHALMOLOGY

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

> Dry eye

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

Here are some strategies that the ophthalmologist may recommend:

- Administer artificial tears multiple times per day. Artificial tears are available over the counter in any drug store. However, if you are using them more than 4 times per day, you should use artificial tears that are preservative-free. Preservative-free artificial tears come in individual vials that have to be used within 1 day once they are opened.
- At night, lubricating ointment can be placed into the eye to moisten and protect the opening.
- Skin tape can be used to close the eyelids gently at night.

> Photophobia

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

FOR HEALTH CARE PROFESSIONALS

Risks and Recommendations

> Typical Ophthalmic Findings

- | | | |
|---|---------------------|------------------------|
| • Mild to moderate hyperopia | • Lack of brow hair | • Exposure keratopathy |
| • Accommodative insufficiency | • Madarosis | • Corneal scarring |
| • Decreased orbital fat leading to "shallow orbits" | • Lagophthalmos | • Pterygia |

Most patients with Progeria have ocular surface disease secondary to exposure keratopathy. They can present with photophobia, discomfort, and decreased vision. Aggressive management of the ocular surface disease is recommended with the use of sunglasses, artificial tears, tape tarsorrhaphy at night, and the use of punctual plugs. Ocular surface lubrication with artificial tears is recommended. Patients with Progeria have also reported significant relief using umbilical cord serum eyedrops; however, these are not commercially available in many countries, including the United States. In severe cases one could consider temporal tarsorrhaphy and the use of scleral lenses. The potential benefits of surgical management of the ocular surface disease should be carefully weighed against the risks of anesthesia.

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

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

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



Figure 1. Note the lack of eyebrow hair.

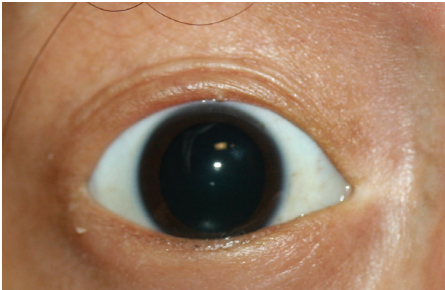


Figure 2. Madarosis worse for the upper than the lower eyelid

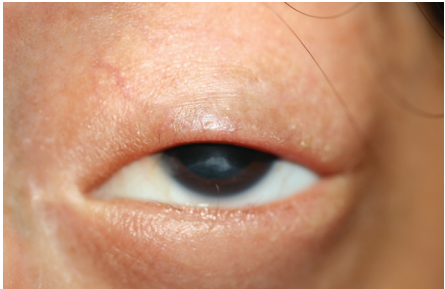


Figure 3. Inferior corneal scarring from exposure keratopathy

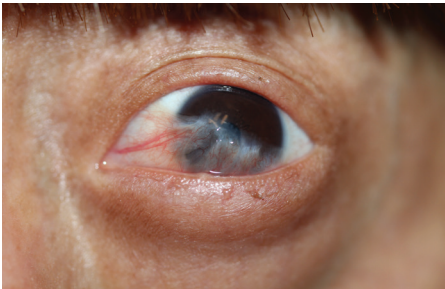


Figure 4. Aggressive pterygium involving the visual axis

10. Hearing / Audiology

The external ear of the child with Progeria

Behavioral testing for assessing hearing thresholds

Objective electrophysiologic tests of auditory function

Summary



Children with Progeria often develop low frequency conductive hearing loss. In general, this does not lead to functional impairment, but sitting toward the front of the classroom is recommended.

Overview of the Ear and Audiology in a Child with Progeria

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

FOR FAMILIES

Risks and Recommendations

- Due to the shape of the ear and the loss of skin flexibility, the outer ear can be very sensitive to pressure.
- Families report that children with Progeria often have wax build-up in their ears. Talk to your child's health care provider about using products to soften the wax.
- Children with Progeria frequently have mild to moderate low-frequency hearing loss. Your child's health care provider should routinely test your child's hearing and refer you to a specialist should it be needed.

FOR HEALTH CARE PROFESSIONALS

Risks and Recommendations

> The external ear of the child with Progeria

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

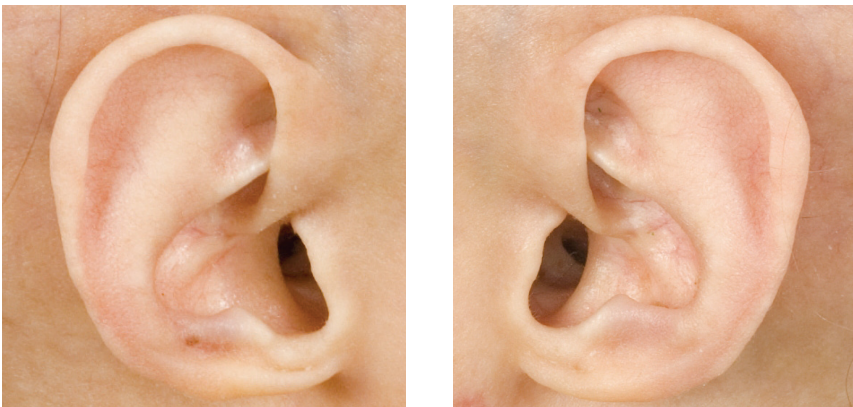


Figure 1. The right and left ears of children with Progeria. Note the large size of the entrance of the external auditory canal relative to the pinna.

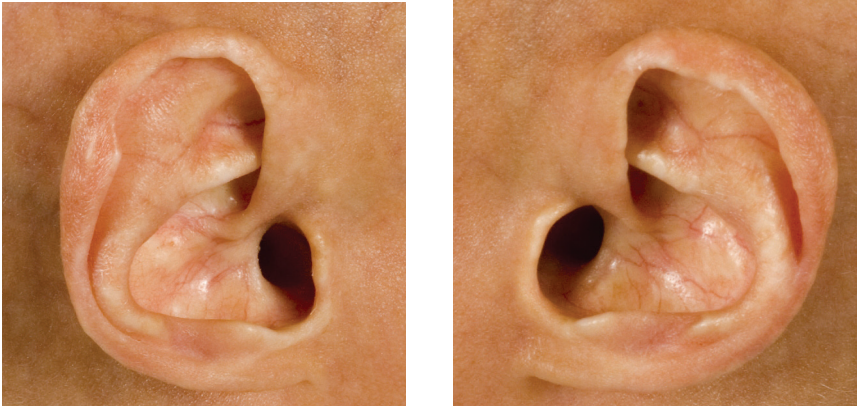


Figure 2. The right and left ears of a child with Progeria. Note the obviously smaller diameter of the ear canal in the deep (bony) portion of the ear canal, compared to the more shallow (cartilaginous) portion of the ear canal.

The cartilaginous portion of the ear canal often has an appearance of a general loss of cartilage, resulting in a diameter significantly larger than the bony portion that comprises the medial 2/3 of the ear canal. This difference in the size of the soft tissue vs. the bony portion of the ear canal can be confusing to the clinician who is attempting to place an earphone in the canal. Usually, an earphone or tympanometry probe tip is coupled manually to the cartilaginous portion of the ear canal. The significant size discrepancy can make it difficult to obtain an airtight seal when attempting tympanometry and middle-ear muscle reflex testing. While potentially easier to obtain an airtight seal by coupling the eartip to the bony portion of the canal (rather than the cartilaginous portion), that bony part of the canal is very sensitive in everyone, 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 him or her to the next test and explaining that the eartips are made with assumptions (that is, the appropriate size and rigidity of the eartips) that don't necessarily apply to a child with Progeria. Children should also be uniformly given full license to suspend any test at any time, which may also increase their trust in the examiners and perhaps their tolerance of mild discomfort.

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

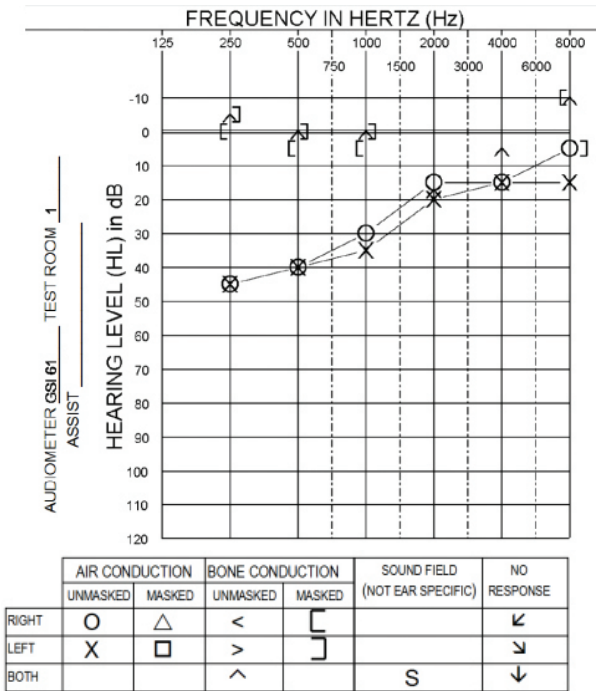
Behavioral testing for assessing hearing thresholds

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 their 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. But, the configuration of the hearing loss has been seen consistently in children with Progeria: low-to-mid frequency upsloping to better (and perhaps normal) hearing in the higher frequencies.

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



Objective electrophysiologic tests of auditory function

> Tympanometry

Tympanometry is a test to assess the gross function of the middle ear. It is performed by manually applying or inserting a rubber-tipped probe that is intended to hermetically seal the ear canal. A low frequency tone (226 Hz) is presented in the ear canal while air pressure is changed from +200 daPa to -400 daPa. This change in air pressure is quite gentle and usually is completed in seconds. The change in the sound pressure level of the low frequency tone in the ear canal is a result of sound being transmitted more or less efficiently through the middle-ear system as a function of the air pressure in the ear canal. There are normative data for equivalent ear canal physical volume, peak pressure, static compliance, and tympanic width. Findings on tympanometry are essentially normal in many children with Progeria (regardless of hearing test results). When

abnormal, static compliance is usually reduced and tympanic width is consequently wider than normal. This would suggest a “stiffening” of the eardrum and/or the ligaments connecting the 3 bones of the middle ear. Physical ear canal volume and peak pressure is typically normal. Otologic examination in a few patients by a pediatric otolaryngologist did not reveal middle-ear effusion in any of these patients with reduced static compliance. Definitive reasons for abnormally reduced compliance on tympanometry remain unknown at this time.

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

Middle-ear muscle reflex threshold is a gross measure of middle-ear function that incorporates a reflex arc ascending from the 8th cranial nerve to the level of the superior olivary complex and descending the 7th cranial nerve both ipsilateral and contralateral to the stimulus. The test is conducted much the same way as tympanometry, making use of the same probe tip used in tympanometry. A hermetic seal is necessary to complete this testing, which can usually be completed within a few minutes. A low-frequency probe tone (226 Hz) is presented in the ear canal and the ear canal air pressure is kept stable. A stimulating tone of varying frequencies (typically 500 Hz, 1,000 Hz, and/or 2,000 Hz) is presented in the ear canal at relatively high intensity (normal reflex thresholds are 85-90 dB HL). A stimulating tone sufficient to engage the middle-ear muscle reflex causes the stapedius muscle to contract, stiffening the middle-ear system. This stiffening can be detected in much the same way as it is with tympanometry. When there is middle-ear dysfunction, middle-ear muscle reflexes are typically elevated (> 90 dB HL) or absent (no reflex elicited using a maximum stimulus intensity level of 110 dB HL). Children with Progeria almost uniformly have elevated or absent middle-ear muscle reflexes, regardless of findings on tympanometry.

> **Otoacoustic emissions**

Otoacoustic emissions are a measure of the functional integrity of the cochlea, up to the level of the outer hair cell. These “ear sound” emissions are thought to arise from the electromotility of healthy outer hair cells, and so are a by-product of the normal hearing mechanism. People with sensorineural hearing loss, such as that caused by age (“presbycusis”) or noise (“noise-induced hearing loss”), have absent

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

➤ **Auditory brainstem response (also known as brainstem auditory evoked response)**

Auditory brainstem response measures the far field electrical potentials evoked by a sound stimulus from the auditory brainstem nuclei through the level of the lateral lemniscus. Testing is typically used to estimate hearing thresholds in children too young or too developmentally impaired to participate in behavioral audiometry, or in cases where there is suspicion for a lesion of the ascending auditory neural pathway (such as a tumor on the 8th cranial nerve). As this test requires the passive participation of the patient, sleep is often desired during this testing (either natural or through the use of sedation). Similar concerns regarding placement of a transducer in the ear canal continue here, as the transducers used for auditory brain stem response are the same as

those used in behavioral audiometry. An additional concern is that the evoked response is recorded far field, using three or four scalp electrodes which must have low ($< 5k$ ohm) and well-balanced skin impedance (all within $5k$ ohm). Usually, a mild abrasive is used to exfoliate the skin and remove dead skin cells. Given the extremely thin skin of the patient with Progeria, care must be taken to not compromise skin integrity should this testing be conducted.

Interventions

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

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

Summary

Children with Progeria have low-to-mid frequency conductive hearing loss that is usually mild, but can be moderate (or greater) in degree. The pathophysiology of this hearing loss is not clear at this time. Some children have grossly abnormal tympanometry with hearing thresholds that are relatively normal, while other patients with normal tympanometry have significantly impaired hearing. This conductive hearing loss exists even in the absence of cerumen and middle-ear effusion. Middle-ear muscle reflexes are almost uniformly elevated or absent. Otoacoustic emissions are almost uniformly normal at frequencies where the conductive hearing mechanism is normal to near normal (in the mid-to-high frequencies). The site of lesion then would appear to be some dysfunction in the middle-ear system that is not related to an ear infection/middle-ear effusion. This dysfunction results in a stiffening of the system and thus loss of sound transmission properties of the middle ear.

When needed, audiological interventions are successful at helping the child with Progeria hear well. These interventions include assistive listening devices (such as FM systems) and hearing aids.

11. Mouth Care / Dentistry



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

Overview

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

FOR FAMILIES

Risks and Recommendations

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

- Crowding of the teeth
- 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

It is important to 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, he or she should see a dentist – preferably a pediatric dentist. Due to your child's increased risk for dental disease, it is recommended that he or she visit the dentist at least twice per year, for routine checkups, cleanings, and fluoride treatment, and more frequently if the dentist finds dental issues that need attention. This will not only enable frequent oral assessments, but will also help your child feel comfortable in the dental setting.

FOR HEALTH CARE PROFESSIONALS

Risks and Recommendations

> Typical dental findings in Progeria

- Severe crowding
- Malocclusion
- Ectopic tooth eruption
- Delayed and/or 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
- Short lingual frenum (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
- If possible, establish a relationship with the patient by age 1 year or within 6 months of the first tooth eruption.

› Importance of educating parents

- High cavity 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.
- Between meals and at night, drink water only, and avoid juice or other types of drinks that can promote dental problems.

- Begin brushing the teeth as soon as they erupt using a small smear of fluoride toothpaste.
- Early implementation of fluoride toothpastes, rinses, and in-office application of fluoride
- Obstructive sleep apnea may be increased due to micrognathia/retrognathia.

> Orthodontic consideration

- Severe crowding and eruption disturbances may necessitate dental extractions. When secondary teeth have erupted ectopically behind primary teeth, extraction of primary teeth may facilitate secondary teeth mobilizing into the appropriate position. (See **Figures demonstrating typical dental findings**, page 11.5.)
- Susceptibility to periodontal disease and limited opening may contraindicate conventional orthodontic therapy.

> Tooth extractions

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

> Figures demonstrating typical dental findings



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



Cavities



Crowding with malposition of permanent teeth



Attrition (wear) of primary teeth



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



Palatal pseudocleft



Ankyloglossia

12. Skin / Dermatology

Common skin findings in Progeria Hair and nails



Small, soft skin bulges on the abdomen or legs can sometimes be one of the first signs of Progeria.

FOR FAMILIES

Risks and Recommendations

- Changes in the skin can be the first symptom parents notice that indicates that their child may have a medical problem. This could be in the form of restrictive, tight skin; dark spots; or a soft bulging on the stomach and/or legs.
- Skin can get dry and itchy. Gentle cleansers and creams are recommended.
- All children with Progeria lose their hair.
- Nails can become dry and cracked or split. Be vigilant for ingrown nails as they can become infected.
- Skin calcifications are sometimes found, and can be itchy and sometimes become infected. While dietary calcium intake is important, calcium supplements are not recommended long term.
- See a dermatologist for any concerns regarding your child's skin or hair loss.

FOR HEALTH CARE PROFESSIONALS

Risks and Recommendations

Common skin findings in Progeria

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

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

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

Calcinosis cutis has been observed in about 5%-10% of children with Progeria, at the distal digits, heel, trunk, upper and lower leg, chest, and abdomen. X-ray diffraction has shown that they are composed of bone-like hydroxyapatite. Thus, a calcium dysfunction likely exists in children with Progeria. Because of this finding, along with the presence of extraskelatal calcifications on X-ray (see *Bones/Orthopedics*, Chapter 13), calcium intake via dietary means is likely the safest intake strategy for these young patients, while long-term calcium supplementation is not recommended.

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 but can be scant.

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.

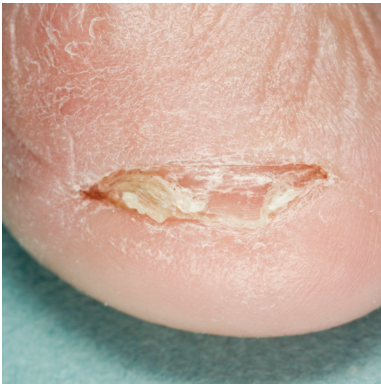
There is no specific treatment that prevents these dermatologic changes.



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 in this photo, and can also occur in the legs.



Nail dystrophy



Calcinosis cutis: Skin calcifications can erupt, and become irritated and/or infected.

13. Bones / Orthopedics

Bone structure

Radiographic findings in children with Progeria

Osteoarthritis of the hip



To minimize the chance of hip dislocation, children with Progeria should not play on trampolines, “bouncy houses,” or other uneven surfaces that could facilitate hip instability.

Overview

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

FOR FAMILIES

Risks and Recommendations

Bone structure

- Children with Progeria have smaller (narrower) bones than their age-matched peers, but the overall bone dimensions are relatively proportionate to their small body size (i.e., low height and weight for age). While compared to healthy children of the same age, the bones are weaker, they are nearly equivalent in strength to healthy children of similar body size, and the rate of bone fracture is the same as other children of similar age.
- Reasonable caution should be exercised when children with Progeria are playing with their larger peers to avoid inadvertent injury.
- Weight-bearing activities such as walking, running, and jumping are encouraged to maintain bone health.

13.2 BONES / ORTHOPEDICS

- Certain bones (fingertips, clavicles) can undergo bone resorption. Fingertips may take on a bulbous look.
- Children with Progeria have very small jaws. (See *Mouth Care / Dentistry*, Chapter 11.)

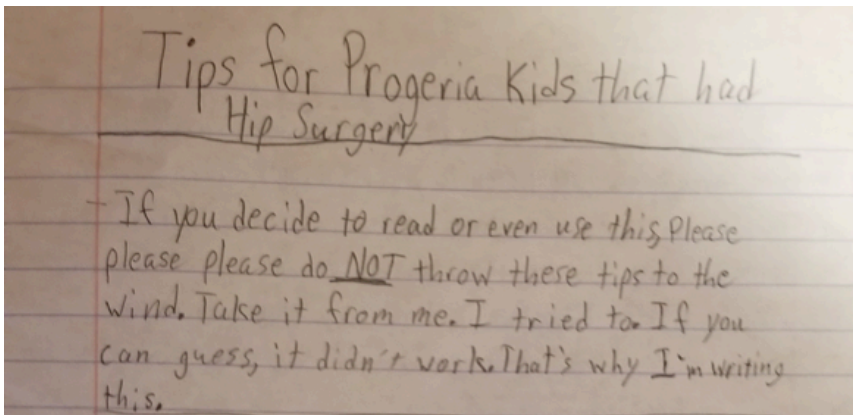
Bone Health as Your Child Grows

- Although the bones of children with Progeria are smaller in size compared to their peers, the density (calcium mineral mass) of the bone tissue is essentially normal. This is why bones break at a rate similar to their healthy peers.
- To maintain good bone health, it is important that children receive adequate vitamin D and calcium in their diet. Children with Progeria do not usually have abnormal calcium blood levels. However, children with Progeria can have extra calcium deposits in the soft tissues outside of the skeleton (extraskkeletal calcifications). Therefore, it is recommended that calcium intake be obtained through the diet (food and drink). Daily intake should be about 1,300 mg of elemental calcium. Short-term calcium supplementation when medically indicated is appropriate. Long-term calcium supplements are not recommended.
- Vitamin D helps the body absorb calcium from the diet. It can be obtained from some foods such as fish and eggs. However, vitamin D is more difficult to consume in the diet than calcium. Children with Progeria can take a multivitamin daily that contains 400-600 IU of vitamin D. If a child's level is found to be low, higher doses will be prescribed by a doctor for 6-8 weeks (2,000 IU/day). Vitamin D levels should be checked routinely, especially in northern climates where there is less sun exposure. An annual measurement is recommended to make sure that a child or adolescent is not vitamin D deficient.
- Periodic bone screening by low radiation imaging (dual-energy X-ray analysis) is used to measure the bone mineral mass. However, because children with Progeria are smaller than their peers, it is important that these studies be compared to children of similar size rather than similar age.
- Osteoarthritis (OA) of the hip: Many children with Progeria develop osteoarthritis of the hip. Although most children with Progeria eventually have radiographic evidence of osteoarthritis, only a minority develop

persistent, significant pain. Your child's health care team will be able to determine the best course of treatment and pain management.

- **Shoulder dislocation:** A minority of children with Progeria experience shoulder dislocation, mainly due to their shortened collar bones. This can be painful. The shoulder sometimes goes back into place on its own, or can be placed back into the socket by a physician. Once shoulder dislocation has occurred, it is more likely to occur again. To date, no surgery has been needed for this problem.
- **Hip dislocation:** Some children with Progeria experience hip dislocation as they get older. This is due to changes in the shape of the leg bones in the hip socket and changes to the shape of the hip socket itself. This can be painful and usually requires a trip to the hospital to put the hip back into place. Once hip dislocation has occurred, it tends to recur and sometimes leads to permanent dislocation. This may affect activities such as running, walking, and other activities of daily living. Several children have undergone hip surgery to correct the hip condition. Early results have been positive, with walking activity resumed after appropriate physical therapy, and no post-operative dislocations. *To minimize the chance of hip dislocation, children with Progeria should not play on trampolines, "bouncy houses," or other uneven surfaces that could facilitate hip instability.*

Here are some tips from Lindsay, who underwent hip reconstruction surgery:



13.4 BONES / ORTHOPEDICS

- Do not cross your surgery leg over the other. Moreso for your thighs than anything.
- If you have the resources, I recommend getting a shoe lift. It will help balance out your walking.
- The previous tip brings me to shoes, If you do decide to get a lift. Shoes are very difficult to find that works for as it is. I recommend getting a wider soled shoe. Such as Converse, Nike have more curved ∂ soles. If the Converse do not work, stick to a more straight ∂ soled shoe.

• **PHYSICAL THERAPY!!!** I could not emphasize this more. You will want to give up. ^①

- If you are a lady, I would stay away from the heels that are sticks. Because the lift would be in two pieces. Making it much easier to mis-place your foot and fall.

^① You might cry even. Just DO NOT GIVE UP. You'll get through it. Just listen to your therapist and do exactly as they say. It will take a while to start walking again. For me it was roughly 6 and a half months, give or take. But it could vary depending on how often and how hard you work. Just keep at it. Things will get easier.

- Ok, I don't intend this as awkward, but it might be. There are feelings you can get in your hip. I like to describe it as pinching, but it's in the muscles of your hip. If you get this I recommend just rubbing the muscle or putting ice on it for 15-20 minutes. It usually helps.

FOR HEALTH CARE PROFESSIONALS

Risks and Recommendations

Bone structure

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

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

In order to maintain the best possible bone health, it is important that children receive adequate calcium and vitamin D in their diet. The goal for calcium intake is 1,000-1,200 mg per day (3-4 cups of milk or other calcium-rich foods or beverages). To facilitate the absorption of dietary calcium for proper bone growth, it is recommended that children ingest

at least 400 IU of vitamin D per day. Since it can be difficult to get adequate vitamin D in food alone, supplementary vitamin D (e.g., children's multivitamin tablet or vitamin D supplement) is recommended by the American Academy of Pediatrics. Please note that we do not recommend calcium supplementation, due to the concern that, unlike when getting calcium through the diet, calcium supplements can promote vascular and/or extraskeletal calcification.



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

> Dual-energy X-ray absorptiometry

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

> Quantitative computed tomography

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

Radiographic findings in children with Progeria

> Abnormal findings

- **Acroosteolysis:** resorption of bone at the distal phalanges. Externally, the fingertips become bulbous. This is seen as early as infancy, but it is not observed in all children until later years. It becomes progressively more severe with increasing age. There is typically no pain associated with acroosteolysis. This is the earliest radiographic manifestation of Progeria.
- **Maldevelopment of the mandible:** The mandible exhibits micrognathia and retrognathia. It is small, and the angle of the mandible is abnormally obtuse.

- **Clavicular resorption:** There is osteolysis at the distal ends of the clavicles. This is often an early finding.
- **Thinning and tapering of ribs:** The ribs are thin in caliber and tapered at their ends.
- **Bell-shaped Thorax:** The ribs have a “drooped” appearance and the thoracic apex is tapered. This gives the chest a bell-shaped or pyramidal configuration.
- **Coxa valga deformity:** The femoral neck-shaft angle is abnormally increased (>125 degrees). This leads to a “horse riding” stance with a wide-based gait and, together with hip dysplasia, predisposes to hip joint instability and subluxation.
- **Coxa breva deformity:** The femoral neck is short and broad.
- **Coxa magna deformity:** The femoral head has a large, broad, aspherical configuration.
- **Acetabular dysplasia:** The acetabulum is abnormally shallow. This may lead to pain with weight bearing, hip subluxation, loss of range of motion, and osteoarthritis.
- **Avascular necrosis of the femoral heads:** The femoral heads may lose proper blood supply, leading to flattening, fragmentation, and subchondral collapse.
- **Long-bone abnormalities:** The diaphyses have a gracile appearance, the metaphyses are flared (proximal humerus, distal femur, proximal tibia), and the epiphyses are large and broad. Mineralization of the diaphyses may appear normal, while the metaphyses and epiphyses appear relatively demineralized.
- **Enlarged capitellum of the distal humerus:** The growth center at the lateral aspect of the distal humerus is atypically large.
- **Cardiovascular and soft tissue calcifications:** Extraskelatal calcifications may be seen in a cardiovascular distribution or in the soft tissues overlying the abdomen or extremities, commonly surrounding the tufts of the digits of the hands. The pathophysiology of this calcium dysfunction is not well defined. However, there is evidence that calcium supplements aggravate this condition, and should be avoided in lieu of dietary calcium for bone health. Calcium supplementation in short-term or emergent situations is warranted.

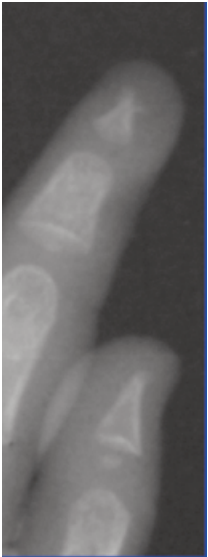
13.8 BONES / ORTHOPEDICS

Many X-ray findings develop later in life, so most are not used for diagnosis. The earliest findings are usually acroosteolysis and clavicular resorption.

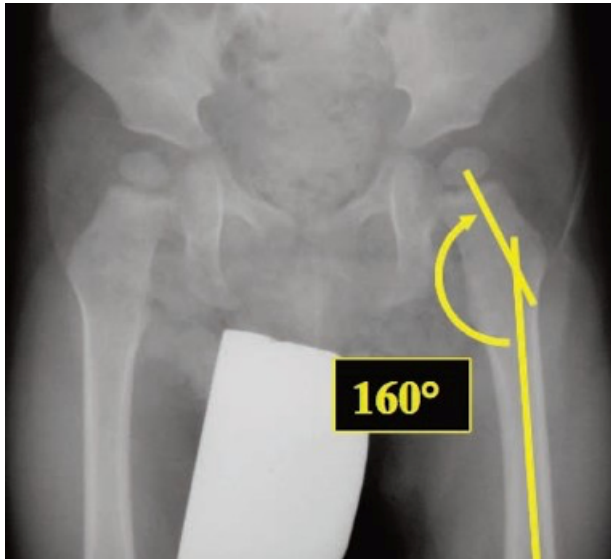
> Normal findings

- Bone age is variable; it can be normal, slightly advanced, or slightly delayed for chronological age.
- Physes are normal; the growth plates at the ends of long bones are normal.
- Elbow, wrist, knee, and ankle joints are normal, though their range of motion is often abnormal. (See *Physical Therapy*, Chapter 14.)
- Cranial sutures are normal; the spaces between the bones of the skull are normal.

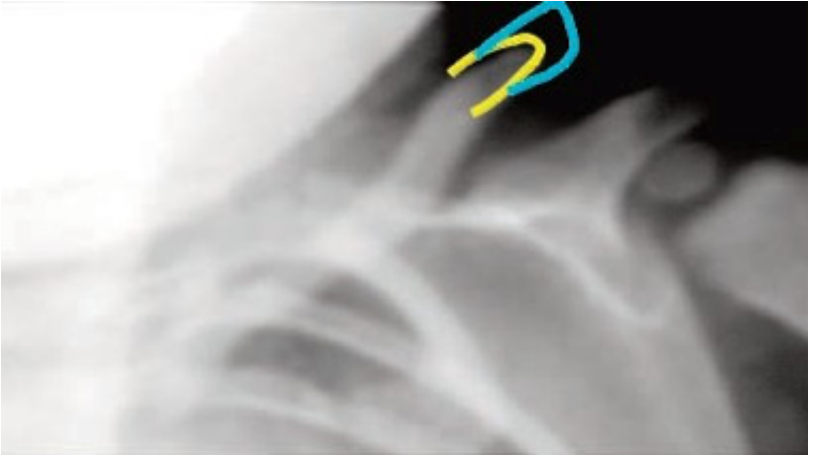
> Radiographic findings



Acroosteolysis



Coxa valga



Clavicular resorption



Soft-tissue calcification of the distal phalanges

Osteoarthritis of the hip

Osteoarthritis (OA) is a painful, chronic, incurable, noninflammatory 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. The broad, aspherical femoral head does not articulate properly with the shallow bony acetabulum, leading to mechanical instability, hip subluxation/dislocation, and early degenerative change with cartilage loss. Thus, 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 can be used to diagnose the earliest changes of osteoarthritis before irreversible changes are evident radiographically.

Treatment for osteoarthritis can help relieve pain and stiffness, but cartilage degradation may continue to progress. Initial treatment includes physical therapy to restore range of motion, muscle strength, and anti-inflammatory medications to relieve pain. To facilitate ambulation, children with advanced hip OA may require augmentative supports such as walkers. Preventative care recommendations include sleeping with a pillow between the knees, bending with knees instead of at the waist whenever possible, and not crossing the legs above the knees. When children are unable to ambulate independently, they often require a wheelchair. Although most children with Progeria eventually have radiographic evidence of OA, only a minority develop persistent, significant pain or permanent subluxation within their life span.

As arthritic changes progress, surgical alternatives to reconstruct the involved hip, to create a stability and congruency in the joint, may be considered. There have been at least 3 surgical reconstructive surgeries performed in children with Progeria. It is important to consider

associated risks (e.g., complicated intubation, anesthesia) and medical conditions (e.g., cardiovascular disease) when considering these or any procedures in this high-risk population. To surgically treat the unstable hip, a varus derotational femoral osteotomy (VDRO) is performed to correct the coxa valgus. Open hip reduction and a redirection periacetabular osteotomy may need to be done if the hip is still unstable after the VDRO. Allograft bone should be used to stabilize the osteotomy gap in the redirected orientation. Low-profile proximal femoral hip plates should be used to avoid prominence and irritation of the overlying muscle and skin.

14. Physical Therapy (PT)

Clinical presentation

Interventions

Precautions

Activity guidelines

Swimming



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

Overview of Physical Therapy for Children with Progeria

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

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

(Please also refer to *Going to School*, Chapter 21, for additional advice on physical adaptations from parents and children with Progeria.)

FOR FAMILIES

Risks and Recommendations

Children with Progeria have limited movement of some of their joints, including hips, knees, ankles, and fingers. The joint limitations are likely due to disease in the tendons and ligaments, as well as bone and skin changes in Progeria that can limit movement. These impairments are sometimes progressive and impact their ability to perform activities of daily living and to fully participate in the typical activities of similarly aged peers. Rate and degree of progression is highly variable. Children with Progeria are also at risk for stroke. Clinical signs of stroke may include weakness, changes in sensation, and changes in speech or mentation.

14.2 PHYSICAL THERAPY (PT)

Some strokes may be subclinical, meaning no obvious signs are present. The effects of these strokes on development and function have not yet been determined.

There have been no studies to determine the effectiveness of physical therapy interventions on physical activity in children with Progeria. The recommendations in this handbook are based on clinical observations and discussion with patients and their health care providers. Depending on the issues at hand, and the availability of specialists to families, the health care provider may be a physical therapist, physiologist, orthopedic surgeon, chiropractor, or other health professional.

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 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.

The frequency of PT services is determined by the PT and may differ for each child and vary over time. A home exercise program may be a component of the overall plan.

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.

What to watch out for

- Any sudden change in functional status, such as the loss of ability to walk, pain, or significant change in range of motion, should be evaluated by a physician, even if there is no traumatic event.
- Cardiovascular disease can affect ability to perform physical activity and physical therapy. Watch for increased fatigue, shortness of breath with exercise, and inability to perform physical activities. These may be tip-offs to changes in your child's heart condition, and should be evaluated by a physician.

> Global joint contractures



Activity guidelines

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

Children can engage in a wide variety of physical activities, such as walking, dancing, hiking, and swimming. They may not be able to participate in some team sports as they have shorter stature and have

14.4 PHYSICAL THERAPY (PT)

less body mass than their peers; therefore safety may be an issue. Bony deformities may also be a limiting factor for some physical activities. High-impact activities and trampolines should be avoided due to the possibility of hip dislocation.

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

Children and families may need assistance from a therapist in order to find appropriate physical activities or programs. They may also need assistance finding appropriate-sized toys or adapted toys (e.g., 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 wet suit, fitted to the child if possible. Standard children's wet suits 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.

FOR HEALTH CARE PROFESSIONALS

Risks and Recommendations

Clinical presentation

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

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

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

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

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

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 that cause the child to move through the full excursion of joint range of motion are more functional and more enjoyable for the child 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

14.6 PHYSICAL THERAPY (PT)

maximus, quadriceps, and gastrocsoleus 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 are needed to allow the children to function similarly to their age-matched peers. Home modifications may also be necessary. (Refer to *Occupational Therapy (OT)*, Chapter 15.)

> 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 environment is often necessary as the disease progresses.

Mobility devices allow children with Progeria independence, 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 (i.e., electric wheelchair) is preferable to a manual wheelchair due to the limitations in the upper extremities.

Physical therapists can help determine the most appropriate wheelchair, taking into account the child's age and functional status. Walkers may also be of some use, particularly in children who have had strokes or who have more severe contractures.

Precautions

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

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

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

15. Occupational Therapy (OT)

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



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

Overview of occupational therapy for the child with Progeria

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

(Please also refer to *Living with Progeria*, Chapter 20, for additional advice on physical adaptations from parents of children with Progeria.)

FOR FAMILIES

Risks and Recommendations

Evaluation

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

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

15.2 OCCUPATIONAL THERAPY (OT)

- Functional skills
- Visual perceptual skills
- Visual motor integration skills

There have been no studies on the effectiveness of occupational therapy interventions with this population and the recommendations in this 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 an OT, and if one is not available, a physician, even if there is no traumatic event.

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

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

Self-care

› Dressing

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

extremity dressing. They often develop adaptive dressing strategies, such as positional changes or the use of adaptive equipment such as reachers that can help them to be independent with donning lower extremity clothing. A sock aid can be used to put on socks, while a long-handled shoe horn may assist with putting on their shoes independently.

> Hygiene

Most children with Progeria are independent with age-appropriate hygiene by the age of 4 or 5; however, they require some environmental adaptations to assist with height obstacles and with what appears to be postural instability (e.g. hesitation on step stool). In the bathroom, stools should be placed at the toilet and sink. Parents may assist or supervise when they are getting in and out of the tub or shower due to safety concerns. Rarely do the children require adaptive equipment to assist with hygiene tasks such as bathing. However, equipment such as long-handle sponges may be used to assist with lower extremity washing. Some children have trouble opening and pouring from squeeze-bottle containers due to wrist limitations; pump-style dispensers are easier to manipulate. Some children are not able to wipe themselves after toileting due to range-of-motion limitations and difficulty with balance. Aides such as long-handled tongs (tongs with toilet paper wrapped around them) or wet wipes to decrease the amount of wiping can be helpful. Toilet-seat inserts may increase the child's comfort due to the child's size and balance difficulty. Padded toilet seats may also be used to address discomfort with prolonged sitting due to increased bony prominences. With grooming or oral hygiene, an electric or battery-operated toothbrush may be used as the children may fatigue with brushing due to decreased strength and range-of-motion limitations. Flossing sticks and automated hands-free toothpaste dispensers may also be helpful. (Please refer to *Dental Recommendations*, Chapter 11, for further information on tooth hygiene.) Although it is important for the children to participate in brushing their own teeth, in some instances parents may need to 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

15.4 OCCUPATIONAL THERAPY (OT)

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 are 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. Stools placed in the kitchen also allow for access to counter tops and the sink. If the child is starting to cook and there are difficulties, seek out an OT assessment for further assistance with bowl and pan holders, electric peelers, and other cooking aides. Adapted seats such as tripp-trapp or right-height chairs with additional foot plates allow the children to sit at the dinner table with their families.

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

> House management

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

Education

› Positioning

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

Chairs within the classroom setting should allow them to be at standard seat height, with their feet supported. The use of chairs such as a tripp-trapp or right-height chairs, 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 the child to be an active participant and to 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 appear to be related to joint limitations, reduced fatty pads, and the functional position of the carpometacarpal thumb joint (which remains fixed in mid-abduction or extension) and their limited wrist positioning (neutral to slight palmar flexion). Some parents report reduced motor control during handwriting. Others report difficulty with mastering writing. In most of the children, this appears to be a result of abnormal wrist and hand positioning and decreased strength rather than visual perceptual, visual motor integrative, and/or fine motor incoordination. OT intervention often helps children with Progeria master handwriting, with improved motor control. Children can benefit from an individualized strengthening program, including stretching exercises and activities to enhance in-hand manipulation skills along with dexterity skills. Some children also benefit from using unique crayons and pencils that are shorter and narrower, to assist with the structure of their hands and their decreased strength. Padded pencil grips or padded pens may be used to decrease the amount of finger pain that is often experienced from the pressure of the writing utensil, due to the lack of fat deposits in fingertips. The use of a vertical surface is recommended to improve wrist dorsiflexion

15.6 OCCUPATIONAL THERAPY (OT)

(the ability to bend upward) and strength. Slant boards should only be used at the recommendation of a therapist after full evaluation, due to possible contraindications. Many children report fatigue and hand pain with lengthy writing assignments. Early education and exposure to keyboarding may increase the amount of written output the child can produce. Older children may benefit from voice-activated software if they experience motor problems with keyboarding and writing.

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

> Scissors

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

> Carrying objects

Many children with Progeria are not able to carry their own school bag or books to and from school or during the school day. Those with difficulty in this area require accommodations such as a second set of books (one set at home and the second set in the appropriate classroom). Bags can then be lightweight, as all they need to carry are their notebooks or paperwork. If the child does wear a backpack, the bag should be no more than 15% of his or her 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 his or her peers (for example, ways to access the table tops or carry lunch trays). The children also often have difficulty walking and carrying moderately weighted objects. Most frequently they are unable to carry objects up or down stairs and thus require help from a peer, teacher, or parent.

Social participation

Most children report participation in sports, playing on the playground, and other leisure activities. There is no evidence suggesting that these children should not participate in these activities unless it impacts their health. Activities such as contact sports, team sports, or leisure activities

with their peers may require some adaptation to accommodate for their abilities and medical conditions. At times the activity demands may be too great or the child may need specialized equipment. (Please refer to *Physical Therapy (PT)*, Chapter 14, 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 type of chair allows the child to get in and out of the chair safely and to reach items at different heights, as well as navigate within the classroom, home, and community.

FOR HEALTH CARE PROFESSIONALS

Risks and Recommendations

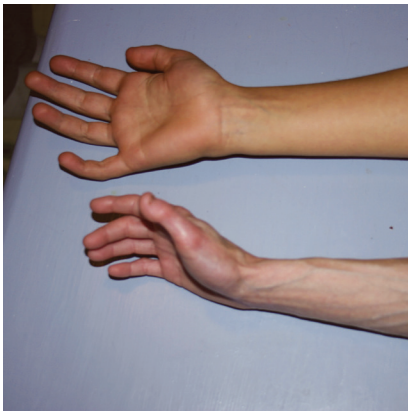
Physical findings

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

- Joint contractures of all upper extremity joints
- Upper extremity asymmetries
- Reduced upper extremity strength
- Prone to shoulder dislocations (which should be taken into consideration with weight-bearing and strengthening activities such as gymnastics)
- Wrists typically have limited dorsiflexion (bending upward)
- Some children's thumbs do not go into carpometacarpal (CMC) extension plane

15.8 OCCUPATIONAL THERAPY (OT)

- 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 (joints closest to the hand) most often have limited flexion.
- Distal and proximal interphalangeal joints (the middle joint and the joint closest to the tip of the finger) tend to have flexion contractures.
- Resorption of the distal phalangeals
- Distal phalangeals are often painful with pressure.
- Decreased fat deposits within the hand (most notably at the thumb and finger tips)



Maximum finger extension in a child with Progeria

- Short in stature
- Increased bony prominences
- Difficulty tolerating extreme hot or cold temperatures (e.g., weather, water)
- Some have decreased fine motor coordination
- Some have visual perceptual and visual motor integration deficits

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. 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 preadolescent.

Summary of environmental changes to help children with Progeria

> House

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

> Mobility

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

> Allow for functional mobility

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

> Recreation

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

> School

- (See *Going to School*, Chapter 21.)

> Hand held devices

- Tablets
Due to the hand span, the smaller tablets are easier to manipulate and hold.
- Keyboards
Mini keyboards are ideal.

> Dressing

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

16. Foot Care / Podiatry

Podiatric problems in children with Progeria Shoe inserts



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

FOR FAMILIES

Risks and Recommendations

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

FOR HEALTH CARE PROFESSIONALS

Podiatric problems in children with Progeria

Several factors contribute to the challenging foot care issues for children with Progeria. These include a lack of 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 is 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.

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.

17. Nutrition

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



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

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

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

> Blood lipids

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

> Dietary supplements

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

Increasing calories

Try these simple additions to increase calorie count:

- Add healthy oils (canola or olive) to rice, pasta, vegetables, soups and 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, granola and/or nuts into yogurt; add peanut butter to vanilla yogurt
- Add cooked meats, ham, poultry, tuna, and/or shrimp to casseroles, cooked noodles, sauces, or scrambled eggs

Healthy high-calorie snacks

- Peanut butter or cheese on whole-grain crackers
- Whole-wheat toast with peanut butter and banana cut up; add some honey for sweetness

- Peanut butter on fruit
- Trail mix with nuts, dark chocolate, dried fruit, and whole-grain, high-fiber cereals
- Make a fun smoothie with your child using whole milk, frozen fruits, and yogurt or ice cream (see shake recipes below)

Making healthy food choices

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

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

Shakes & smoothies

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

Chocolate Peanut Butter Milkshake	Oreo Milkshake
½ cup whole milk 3 Tablespoons peanut butter 3 Tablespoons chocolate syrup 1 ½ cups chocolate ice cream <i>1,330 calories, 31 grams protein</i>	½ cup crumbled Oreos 2 Tablespoons chocolate syrup 1 ½ cups vanilla ice cream ¾ cup whole milk <i>940 calories, 16 grams protein</i>
Double Chocolate Milkshake	Chocolate Peanut Butter Banana Milkshake
1 cup chocolate milk 2 Tablespoons chocolate syrup 1 packet chocolate Carnation Instant Breakfast 1 cup chocolate ice cream <i>940 calories, 25 grams protein</i>	½ cup whole milk 3 Tablespoons peanut butter 1 Tablespoon chocolate syrup ½ cup vanilla ice cream ½ banana <i>600 calories, 19 grams protein</i>

17.4 NUTRITION

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

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

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

- **Serve cold and covered:** Due to the fact that supplements contain a lot of added vitamins and minerals, they taste better than they smell. If you are serving the supplement to your child as a beverage, be sure it is cold. Serve it from the can with a straw or put it in a bottle or a cup with a cover.
- **Be creative!**
 - > Use vanilla-flavored products as a substitute for milk in baked products
 - > Add fruit and crushed ice and place in the blender to make a "smoothie"
- **Powdered products:** When mixing the powdered supplements with liquid to make a beverage, be sure to let keep it 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.

18. Pubertal Changes in Adolescent Females with Progeria

Growth and body fat
Tanner staging
Menstruation



Young women with Progeria often experience periods. If bleeding is heavy, consult your adolescent's local doctor for treatment.

FOR FAMILIES

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

FOR HEALTH CARE PROFESSIONALS

In healthy girls without Progeria, menarche is typically a late pubertal event, following the gradual development of breasts and pubic hair, the pubertal growth spurt, and changes in body composition that are characterized by increasing body fat. Some previous studies have suggested menarche and regular menstrual function in healthy adolescents and women to be dependent on the maintenance of a

18.2 PUBERTAL CHANGES IN ADOLESCENT FEMALES

minimal weight for height and a critical percentage of body fat. Study of adolescents with HGPS demonstrates that these typical events are not required for menarche to occur.

Growth and body fat

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

Tanner staging

Around 40% remain Tanner stage 1, and the remainder develop Tanner stage 2 characterized by sparse pubic hair and/or breast buds. Adolescent females with HGPS do not achieve Tanner stage 3.

Menstruation

An estimated 60% of females with HGPS experience menarche. Mean age of menarche is not significantly different from established mean age of menarche in healthy females without HGPS (around 14.5 years of age). Cyclicity is highly variable, with some experiencing irregular, light bleeding and others experiencing heavy bleeding with increased flow (menorrhagia) causing anemia. When menorrhagia occurs, with risk of anemia, consider treatment with low-dose oral contraceptive agents with $\leq 20 \mu$ ethinyl estradiol to arrest the menstrual bleeding. (Studies in the general population have shown that doses $> 20 \mu$ ethinyl estradiol can increase clotting risk.)

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

Ovulation and the ability to conceive have not been studied in Progeria. To date, pregnancy has not been documented in any young adult with Progeria.

19. 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 in the body, 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 – Though they look different from others, children with Progeria have age-appropriate intellect and personalities. Because of this, interaction with peers is very important. They do not experience Alzheimer's disease. However, the blood vessels in the brain become diseased and this can cause strokes.
- Liver
- Kidney
- Gastrointestinal system
- Immune function is normal; the healing of cuts and broken bones occurs at the usual rate. Immunizations, including flu vaccines, are recommended for children with Progeria in the same way they are recommended for the general pediatric population. In addition, although the children are not immunocompromised or elderly, vaccines that are indicated for people

Normal liver, kidney, gastrointestinal, and immune function are often important for clinical drug trial inclusion, because some drugs need one or more of these systems to function normally in order to be administered safely.

19.2 SYSTEMS THAT FUNCTION NORMALLY

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.

- 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 generally functions normally, though pubertal changes such as growth spurts, and genital and adult hair development do not generally occur. Menstruation can occur. (See *Pubertal Changes in Adolescent Females*, Chapter 18).
- Some children are treated with growth hormone, which may increase their overall size. However, 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.

20. Living with Progeria: Advice from Parents of Children 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



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

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

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."

"Parents tend to focus only on their children's needs. It's important to recognize that parents need to take care of themselves and their adult relationships too."

Talking to your child with Progeria: what to tell her/him, 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."

"This is the hardest part for a parent, deciding when it is the right time to talk about Progeria, before someone approaches your child and asks why they look so different! My son is 7 and he doesn't see any difference between himself and his peers, except for his hair. He knows he has to be more careful when playing, and needs special cushions and stools to be independent, but he is not worried that something is wrong with him. We talk about Progeria in front of him, so I am sure he is more aware of it than I think he is, but he is not asking about it. We decided to wait for him to ask questions but so far he has not asked us anything, so I guess growing up in a safe environment, where the school is supportive, and his friends accept him the way he is, has made him grow up very happy,

without any worries. As he is getting older, we plan to talk to him, so that he knows the name Progeria if someone asks him, but our plan is to assure him that his life won't change because of Progeria. He can enjoy life and be happy. We will sort out the problems as they come."

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."

"Helping the kids with handling other people's stares and questions would of course be very different for each kid. My teenager prefers not to interact after people are staring or rude because she gets so uncomfortable. When she was younger we had business cards made that included our names, a picture and the address to her website. We hoped that people would educate themselves without too much pressure in public. Now that she is older she is having to come up with ways to handle this if we are not with her. She said that now she mostly waves or smiles and people stop looking."

"Incorporate cousins and neighboring children in your child's circle to build long-term friendships."

20.4 LIVING WITH PROGERIA: ADVICE FROM PARENTS

"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."

"If you are able to talk to the community, try to do it. It is hard, but it will help to your child. We are trying to educate and create awareness in our town, so people know what my son has and stop staring at him; but even in a small town, you will always find someone who stares. When I have the opportunity, I express myself in public and tell people it is better to approach us and ask than to stare at our child."

Siblings

"Give all your children special attention; don't neglect siblings for being normal. Sibling jealousy 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."

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

"If my son did not have Progeria I am sure he would be doing sports all day. We have read that kids with Progeria have to give up contact sports at around 9 to 11 years old and our child is 7 now. So, our plan has been to try to find physical activities that he can keep doing as long as he

wants to. He is doing swimming lessons with a wetsuit. Even though the water is warm, it is not warm enough for him, so the wetsuit helps him complete a 30-minute class. He is allowed to take breaks or rest during swim class so he can complete the class. He is also doing dance class. Going to the floor is very challenging, so he normally does not do this as part of his choreography. It is amazing how much he feels he is part of the group. He also loves running and participates in a 6km walk every year. Between his wheelchair and walking, he is able to cross the finish line, which is what he loves!!!"

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 waistbands 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."

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

"This is always a challenge, but waistbands help a lot with keeping our son's pants up. Orthotics have helped with his footwear, and he has also started using a sneaker with gel support. This combination has stopped his limping."

Religious and community-based affiliations

"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 or she will find it empowering."

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

“Being in a small Catholic school has helped us to go through life with Progeria.”

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.”

“It is very positive for the kids to be around pets. If they are able to get a companion dog it is very beneficial for them.”

Practical accommodations that parents say they have found helpful 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 light switches, and for getting on and off of the toilet.
- Arrange for furniture on which the child will be comfortable. Arrange for chairs that allow for feet to touch the floor, and table heights that work with those lower chairs. Some chairs and tables are adjustable. This avoids cramps.
- In the bathroom, attach a cushioned seat to the toilet, and place a stool next to the toilet.
- Place foam on the floor wherever your child might need it for comfortable play on the floor.
- One family highly recommends the Tripp Trapp chair for both home and school use. They are made to provide a comfortable ergonomic seat at any age. This family's child has had one at home since she was about three. The school system provided one in each of her classrooms

since middle school. These chairs have allowed her to sit at any height tables and desks with her peers while supporting her feet and sitting in an ergonomically correct position. They also have pads made to fit and stay on the chairs for comfort.

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!"

"Take a tram where possible to get around the airport. Talk to the airline so they will leave a tram at the door of the plane for when you arrive."

"Take pediasure during travel in case your child doesn't like the food on the plane."

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 chiropodist or podiatrist to help with nail cutting and removal of hard skin areas. Watch for ingrown nails/toenails, since their fingers and toes are so narrow."

21. 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. There is a significant overlap between this chapter and the recommendations in the Occupational Therapy chapter, so please read both to learn about suggestions for accommodations in school.

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

Utilize the laws that require accommodations:

Depending on the country and school setting, certain laws may govern the requirements for schools to accommodate special needs. These can be crucial when working with schools to make sure your child has a positive school experience. In the United States, there are two such laws:

- > **Section 504 of the Rehabilitation Act** is a blueprint for how the school will provide supports and remove barriers for a student with a disability, so the student has equal access to the general education curriculum. This is a federal civil rights law to prevent discrimination against people with disabilities.
- > **The Individuals with Disabilities Education Act** (IDEA) is a federal special education law for children with disabilities.

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.

Important topics may also include emergency preparedness training, demeanor of a particular teacher, and classroom proximity to the nurse's office or building entrance. Bring copies of this handbook to meetings; these are available from PRF. Everyone will be appreciative of the shared communication to help ensure optimal preparedness.

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, teachers' assistants, and other helpers can enter observations that 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.

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's 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.
- A rolling book bag is advised.
- Monitor writing fatigue in the classroom.
- Create a space in the classroom for resting at will, or in between assignments. This avoids the need to leave class in order to obtain a needed break.

Writing suggestions:

- > A scribe or keyboarding can be used as needed for longer writing assignments.
- > A sloped drawing board to place on the desk can be far more comfortable than writing on a flat surface.
- > Large pencils or pencil grips similar to ones supplied to arthritis sufferers may be more comfortable for writing.
- > A laptop computer can reduce fatigue or “writer’s cramp.”

Locker suggestions:

Lockers can be particularly challenging. They sometimes have high internal shelves, heavy doors, and rotating combination locks; handles must be lifted to open, and there is often student crowding in the hallways.

There have been various accommodations for locker use.

- > The school can move the locker shelves and hooks lower.
- > To assist with opening, the school can install a locker with a key instead of a rotating combination lock, or a punch code to open the locker, or install a key fob system on the locker. The student would touch the fob to a plate on the front of the locker and it would open.
- > To reduce crowding, assign a lower locker on the end of a row so there is no student on at least one side of his or her locker.
- Allow the child to wear a hat in school. Most schools do not allow children to wear hats, but it's important to allow children with Progeria to wear caps or hats if this makes them more comfortable.
- Accommodations for standardized and state testing:
 - > Arrange for the test to be administered in short periods with frequent breaks.
 - > The child can use a word processor and/or answers to open-response questions as needed.
 - > Another option is Scribe ELA (English Language Arts) 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 or she wants to try, but also lets the child rest whenever needed. Making sure the child is always involved (not feeling left out) with the activity is also 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 or she can stay in with a buddy.

- Children with Progeria should not to 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 to 30 minutes per session, and for occupational therapy 1 to 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 or 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 or 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 should escort your child from classroom to classroom and dining areas, carry heavy items such as back packs and books, and reach items on high shelves as needed depending on the child’s age, health status, and school regulations. As the children get older, their peers can assist with these types of tasks, thus avoiding the need for an assigned adult assistant in school.
- The child should leave class 2 to 3 minutes earlier than the regular dismissal time 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 him or her on all field trips.

21.6 GOING TO SCHOOL

- Arrange for a minibus 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 most of 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 he or she feels tired. Rest periods at the nurse’s office may be needed as the child gets older.
- Nursing staff should be directed to call parents whenever the child is seen at the 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 predetermined 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.

22. Progeria and Aging

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



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

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.

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 people (see figure on next page), while young people have less or no detectable progerin. In addition, progerin is found in cells of the artery wall, and increases by 3% per year as we age. 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.

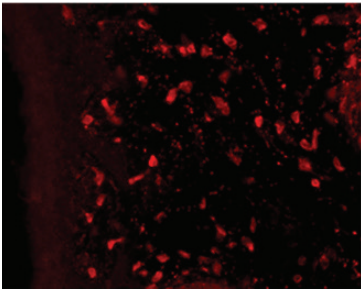
22.2 PROGERIA AND AGING

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 globally.¹

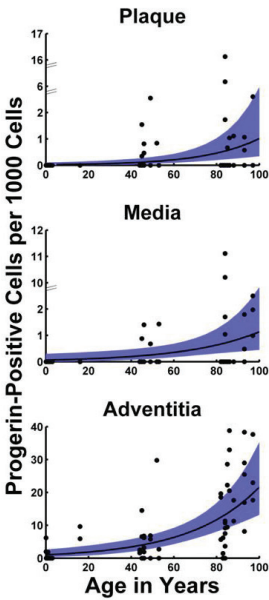
As with any person with heart disease, children and young adults with Progeria are at high risk for strokes, high blood pressure, angina, enlarged heart, and heart failure—all conditions associated with aging. Thus, there is clearly a tremendous need for research in Progeria. Finding a cure for Progeria 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.

Conversely, learning from the thousands of studies that occur each year in the aging population can help us to understand and possibly treat and cure children with Progeria. Learning from each other is the best way to help everyone!



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



Vascular progerin increases by 3% per year in arteries in the general population
(Olive et al, 2011)

¹World Health Organization

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-and-handbook/

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/dispmomim.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/

PRF Medical & Research Database

www.progeriaresearch.org/cell-and-tissue-bank/

PRF Cell & Tissue Bank

Review Articles and Book Chapters

Worman HJ, Michaelis S. *Permanently Farnesylated Prelamin A, Progeria, and Atherosclerosis*. *Circulation* (New York, NY). 2018;138(3):283.

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

> Subspecialty Studies on Progeria:

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Cardiac: Prakash, A, Gordon, LB, Kleinman, ME, Gurary, EB, Massaro, J, D'Agostino, R, Kieran, MW, Gerhard-Herman, M, Smoot, L. *Cardiac Abnormalities in Patients with Hutchinson-Gilford Progeria Syndrome*. *JAMA Cardiology*. 2018 Apr. doi: 10.1001/jamacardio.2017.5235.

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

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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.

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Running on the Wind by Meghan Waldron and Dallas Graham (Red Fred Project, 2017)

Young at Heart: The Likes and Life of a Teenager with Progeria by Hayley Okines and Alison Stokes (Accent Press, Ltd, 2015)

Old Before My Time by Hayley Okines and Kerry Okines (Accent Press, Ltd, 2011)

Old at Age 3, The Story of Zachary Moore by Keith Moore (Boss Pulishing, 2007)

This is My Life: With Ashley, a Girl Living Up with Progeria by Lori Hegi (Hawking Books and Fusosha, 2004)