PRF By The Numbers

Progeria Research Foundation
FOR THE CHILDREN ♥ FOR THE CURE

Produced by Leslie B. Gordon, MD, PhD; Medical Director

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June 30, 2024
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PRF By The Numbers is a data sharing tool originating from The Progeria Research Foundation’s programs and services.

We translate information collected within our programs and services, and develop charts and graphs which track our progress from year to year.

This allows you to assess where we’ve been, and the improvements we’ve made for children with Progeria.
Why Sharing Data Is Essential

➢ According to the National Institutes of Health:
   “data sharing is essential for expedited translation of research results into knowledge, products, and procedures to improve human health.”


➢ In other words, everyone benefits by knowing and learning as much as possible about Progeria - the scientific and medical communities, the public, and the children.
We take raw data collected through our programs and services, remove any personal information to protect the participant, and present it to you in a format that is engaging and informative.

PRF programs and services include:

- The PRF International Registry
- The PRF Diagnostics Program
- The PRF Cell & Tissue Bank
- The PRF Medical & Research Database
- PRF Research Grants
- Scientific Workshops
- Clinical Trial Funding and Participation
- Progeria Connect
Our Target Audience

➢ PRF By The Numbers is intended for a broad array of users
   - Families and children with Progeria
   - The general public and nonscientists of all ages
   - Scientists
   - Physicians
   - The media

➢ This means that different types of slides will be of interest depending on who is looking at the information. We have designed this slide set so that you can pull out what is most important to you.

➢ We love suggestions - if you don’t see some facts and figures here that you think would be informative, please let us know at

   info@progeriaresearch.org
Our participants come from all over the world. They find us through our outreach - the PRF website, our publications, television documentaries, their doctors, neighbors, friends and family.
Program Collaborations For Success

Hasbro Children's Hospital
The Pediatric Division of Rhode Island Hospital
A Lifespan Partner

PRF Cell & Tissue Bank Core Laboratory

PRF Diagnostics Program Sequencing Laboratory

PRF Cell Bank Submission: Immortalized Fibroblast Cell Lines

Harvard University

Non-HGPS Progeroid Patient Diagnosis

UK

PRF Cell & Tissue Bank: Lymphoblast Cell Line Generation

PRF Clinical Trials

Boston Children's Hospital
BRIGHAM AND WOMEN'S HOSPITAL
A Teaching Affiliate of Harvard Medical School

BOSTON UNIVERSITY

PRF Cell & Tissue Bank: iPSC Cell Line Generation

Ottawa Hospital Research Institute
L'Hôpital d'Ottawa
Institut de recherche

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June 30, 2024
Our Program Collaborators

Our collaborating institutions are crucial to our ability to help children with Progeria. We are extremely grateful for these ongoing partnerships:

**Hasbro Children’s Hospital**
- Location of The PRF Cell & Tissue Bank
- Program IRB approval

**PreventionGenetics**
- CLIA*-approved genetic sequence testing

**Ottawa Hospital Research Institute**
- Induced Pluripotent Stem Cell (iPSC)
- CLIA*-approved generation and distribution
Our Clinical Trial Collaborators

Our collaborating institutions are crucial to our ability to help children with Progeria

- Harvard University - Associated Hospitals:
  - Boston Children’s Hospital
  - Brigham and Women’s Hospital
  - Dana Farber Cancer Institute

- NIH - funded Clinical and Translational Study Unit at Boston Children’s Hospital

- Sentynl Therapeutics, Inc.
June 30, 2024

Total Number of Children with HGPS* and PLs** Worldwide: 210

HGPS* Worldwide: 154

HGPS* in the United States: 18

Progeroid Laminopathies** Worldwide: 56

Progeroid Laminopathies** in the United States: 12

*Children in the HGPS category have a progerin-producing mutation in the LMNA gene

**Those in the Progeroid Laminopathy category have a mutation in the lamin pathway but don’t produce progerin

**Cases of PL do not include those identified solely from published scientific journal articles

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PRF-Identified People Living with HGPS & PLs Reside In 52 Countries

154 Known Children and Young Adults with HGPS and 56 Known People with PLs Living Around the World as of June 30, 2024

Note that previous versions of PRF By the Numbers have also reported on cases of PL solely from the literature. These cases are no longer included in this report.
<table>
<thead>
<tr>
<th>Language</th>
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<td>Hindi</td>
<td>Malayalam</td>
<td>Serbian</td>
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</table>

...and Speak 37 Languages

прогерии исследовательский фонд

조로증 연구 재단

Progeria Araştırma Vakfı

早衰症研究基金會

Progeria रिसीच फाउंडेशन

早老症研究財団
Living Children and Adults PRF has identified with Progeria and the countries they reside in from 2000 - 2011

- Total number of known cases include both HGPS & PL
- When a child passes away, numbers are decreased

Year | Number of Progeria Cases* | Number of Countries
--- | --- | ---
2000 | 16 | 16
2001 | 17 | 17
2002 | 34 | 34
2003 | 35 | 35
2004 | 37 | 37
2005 | 19 | 19
2006 | 41 | 41
2007 | 44 | 44
2008 | 45 | 45
2009 | 26 | 26
2010 | 52 | 52
2011 | 54 | 54

* Total number of known cases include both HGPS & PL
* When a child passes away, numbers are decreased
Living Children and Adults PRF has identified with Progeria and PLs and the countries they reside in from 2012 – June 2024*

- Cases of PL do not include those identified solely from published scientific journal articles
- When a child passes away, numbers are decreased
Tracking Children with Progeria Through Prevalence

➢ How does PRF estimate how many children we are searching for, and in what countries? We use *population prevalence*.

➢ Prevalence is the proportion of children with Progeria per total population.
How Prevalence Is Estimated

➢ At PRF, we use a formula based on the number of children we’ve identified in the US. We then expand that out to the world population.

➢ We do this because we have the most complete reporting for the US and since Progeria has no gender, ethnic, or other biases, we assume that the prevalence in the US is the same prevalence in other countries.

➢ PRF calculates prevalence for the US based on Worldometer population estimates.
USA Prevalence of Progeria

June 30, 2024 population statistics:

The US population is:

341,766,367 people

Number of PRF-identified children with HGPS in the US (3 year average):

18

Average prevalence of HGPS in the US: 18 in 342 million is about

1 in 19 million people

*estimates routinely fall between 1 in 18 - 1 in 20 million people.
Prevalence and World Population of Progeria

Given the world population on June 30, 2024

There are between 350 and 450 children living with Progeria worldwide

PRF strives to find every child with Progeria because in order to help every child, we must find every child.
Using Prevalence To Find Children In A Certain Country

We can now use the total population estimates for any given country, in order to understand whether we have found most or all children in a particular country.

➢ For example, as of June 30, 2024:

Brazil’s population was estimated as

\[
217,605,199 \text{ people}
\]

Using Prevalence, the number of children living with Progeria in Brazil is \(217,605,199/19,000,000 = 11\)

PRF has identified 9 of these 11 children, and is searching for the 2 others

* Data based on the latest Worldometers estimates
Program Goals:

➢ Patient identification
➢ Outreach to patient families and their physicians
➢ A springboard for program enrollment

Registry forms available at
https://www.progeriaresearch.org/international-registry-2/

*PRF International Registry includes those with genetically confirmed or clinically suspected Progeria, as well as those with ZMPSTE24 and other possible progeroid syndromes
407 Children and Adults Have Been Registered With PRF
From 72 Countries and 1 Territory

Algeria
Argentina
Australia
Bangladesh
Belgium, Bolivia
Brazil, Bulgaria
Canada, Chile
China, Colombia
Czech Republic
Denmark
Dominican Republic
Ecuador, Egypt
England, Ethiopia, Finland
France, Germany
Guatemala, Guyana
Honduras
Hong Kong
India, Indonesia
Iran, Iraq
Ireland, Israel
Italy, Japan,
Kazakhstan,
Kyrgyzstan
Libya, Luxembourg
Malaysia, Mexico
Morocco, Nepal
Netherlands
Oman, Pakistan
Palestine
Papua New Guinea
Panama
Peru, Philippines
Poland, Portugal
Puerto Rico
Romania, Russia
Saudi Arabia
Serbia, South Africa
South Korea
Spain, Sri Lanka
Suriname, Sweden
Switzerland,
Tanzania
Thailand, Togo
Turkey, Ukraine
USA, Uzbekistan,
Venezuela
Vietnam

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June 30, 2024
...And All Continents

Participation (%) By Continent

- **Africa**: 7.4% (N=30)
- **Asia**: 38.1% (N=155)
- **Europe**: 16.2% (N=86)
- **North America**: 21.8% (N=89)
- **South America**: 15% (N=61)
- **Australia**: 1.5% (N=6)

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Program Goal:
➢ Genetic Sequence Testing for Progeria-causing mutations

Pre-requisites for Testing:
➢ Registration with PRF International Registry
➢ One or more of the following
  Family history - proband, prenatal
  Phenotypic presentation - proband, postnatal
  Relative of positive proband
Testing information available at:
https://www.progeriaresearch.org/the-prf-diagnostic-testing-program/
Diagnostics Testing Summary

June 30, 2024

Total Number of Proband Tests Performed: 171

Exon 11 (HGPS) Mutations: 118

Other Progeroid Laminopathies (Exons 1 - 12): 13

ZMPSTE24 Mutations: 2

Average Number of Patients Tested Per Year: 6

All tests are performed in a Clinical Laboratory Improvement Amendments (CLIA) certified facility.
## Mutations Identified Through PRF Diagnostics Program

<table>
<thead>
<tr>
<th>DNA Mutation</th>
<th>Amino Acid Effect</th>
<th>Zygosity</th>
<th>Progerin Producing?</th>
<th>Number Diagnosed</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Classic HGPS - LMNA Mutation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1824 C&gt;T, exon 11</td>
<td>G608G</td>
<td>heterozygous</td>
<td>Yes</td>
<td>104</td>
</tr>
<tr>
<td><strong>Non Classic HGPS- LMNA Mutation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1822 G&gt;A, exon 11</td>
<td>G608S</td>
<td>heterozygous</td>
<td>Yes</td>
<td>4</td>
</tr>
<tr>
<td>1821 G&gt;A, exon 11</td>
<td>V607V</td>
<td>heterozygous</td>
<td>Yes</td>
<td>2</td>
</tr>
<tr>
<td>1868 C&gt;G, exon 11</td>
<td>T623S</td>
<td>heterozygous</td>
<td>Yes</td>
<td>1</td>
</tr>
<tr>
<td>1968+5 G&gt;C, intron 11</td>
<td>None</td>
<td>heterozygous</td>
<td>Yes</td>
<td>2</td>
</tr>
<tr>
<td>1968+1 G&gt;C, intron 11</td>
<td>None</td>
<td>heterozygous</td>
<td>Yes</td>
<td>3</td>
</tr>
<tr>
<td>1968+2 T&gt;A, intron 11</td>
<td>None</td>
<td>heterozygous</td>
<td>Yes</td>
<td>1</td>
</tr>
<tr>
<td>1968+1 G&gt;A, intron 11</td>
<td>None</td>
<td>heterozygous</td>
<td>Yes</td>
<td>1</td>
</tr>
<tr>
<td><strong>Progeroid Laminopathy- LMNA Mutation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1579 C&gt;T, exon 9</td>
<td>R527C</td>
<td>heterozygous</td>
<td>No</td>
<td>1</td>
</tr>
<tr>
<td>1579 C&gt;T, exon 9</td>
<td>R527C</td>
<td>homozygous</td>
<td>No</td>
<td>6</td>
</tr>
<tr>
<td>1580G&gt;T, exon9</td>
<td>R527L</td>
<td>Homozygous</td>
<td>No</td>
<td>2</td>
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<tr>
<td>1619 T&gt;C, exon 10</td>
<td>M540T</td>
<td>homozygous</td>
<td>No</td>
<td>3</td>
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<tr>
<td>331 G&gt;A, exon 1</td>
<td>E111K</td>
<td>heterozygous</td>
<td>No</td>
<td>1</td>
</tr>
<tr>
<td><strong>Progeroid Laminopathy- ZMPSTE2424 Mutation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1274T&gt;C, exon 10</td>
<td>L425P</td>
<td>homozygous</td>
<td>No</td>
<td>2</td>
</tr>
</tbody>
</table>
Number of Affected Children/Adults Tested and the Number Testing Positive for *LMNA* Gene Mutation*

*Graph does not include Parents/Siblings tested*

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June 30, 2024
PRF Cell & Tissue Bank

Program Goals:

➢ Provide a resource for researchers worldwide

➢ Ensure the sufficient availability of genetic and biological materials essential for research aimed at understanding the pathophysiology of disease and the links between Progeria, aging and heart disease

➢ Obtain long-term clinical data

Resource information available at: https://www.progeriaresearch.org/cell-and-tissue-bank/
As of June 30, 2024

Total Number of Participants: 404*

- 71 Dermal Fibroblast Lines from 47 affected and 24 parents
- 6 Immortalized Fibroblast Cell Lines from 1 affected and 5 parents
- 125 Lymphoblast Lines from 71 affected, 46 parents and 8 siblings
- 9 Induced Pluripotent Stem Cell Lines from 5 affected and 4 parents

* Participants may have donated multiple times
* Additional sample types are available for special projects upon request
## Mutations Available in PRF Cell & Tissue Bank

<table>
<thead>
<tr>
<th>DNA Mutation</th>
<th>Amino Acid Effect</th>
<th>Zygosity</th>
<th>Progerin Producing</th>
<th>Cell Type</th>
</tr>
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<tbody>
<tr>
<td><strong>Classic HGPS - LMNA Mutation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>c.1824 C&gt;T, exon 11</td>
<td>p.G608G</td>
<td>heterozygous</td>
<td>Yes</td>
<td>DFN, LBV, iPSC</td>
</tr>
<tr>
<td><strong>Non Classic HGPS - LMNA Mutation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>c.1822 G&gt;A, exon 11</td>
<td>p.G608S</td>
<td>heterozygous</td>
<td>Yes</td>
<td>DFN, LBV</td>
</tr>
<tr>
<td>c.1821 G&gt;A, exon 11</td>
<td>p.V607V</td>
<td>heterozygous</td>
<td>Yes</td>
<td>LBV</td>
</tr>
<tr>
<td>c.1868 C&gt;G, exon 11</td>
<td>p.T623S</td>
<td>heterozygous</td>
<td>Yes</td>
<td>LBV</td>
</tr>
<tr>
<td>c.1968+5 G&gt;C, intron 11</td>
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<td>heterozygous</td>
<td>Yes</td>
<td>DFN</td>
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<tr>
<td>c.1968+5 G&gt;A, intron 11</td>
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<td>heterozygous</td>
<td>Yes</td>
<td>DFN</td>
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<tr>
<td>c.1968+1 G&gt;A, intron 11</td>
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<td>heterozygous</td>
<td>Yes</td>
<td>DFN</td>
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<tr>
<td>c.1968+2 T&gt;C, exon 11</td>
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<td>heterozygous</td>
<td>Yes</td>
<td>DFN</td>
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<tr>
<td><strong>Progeroid Laminopathy - LMNA Mutation</strong></td>
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<tr>
<td>c.1579 C&gt;T, exon 9</td>
<td>p.R527C</td>
<td>heterozygous</td>
<td>No</td>
<td>LBV</td>
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<td>c.1579 C&gt;T, exon 9</td>
<td>p.R527C</td>
<td>homozygous</td>
<td>No</td>
<td>LBV</td>
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<tr>
<td>c.1580 G&gt;T, exon 9</td>
<td>p.R527L</td>
<td>homozygous</td>
<td>No</td>
<td>LBV</td>
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<td>c.1619 T&gt;C, exon 10</td>
<td>p.M540T</td>
<td>homozygous</td>
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<td>DFN</td>
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<td>c.1762 T&gt;C, exon 11</td>
<td>p.C588R</td>
<td>heterozygous</td>
<td>No</td>
<td>DFN</td>
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<td>c.1930 C&gt;T, exon 11</td>
<td>p.R644C</td>
<td>heterozygous</td>
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<td>DFN</td>
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<td>c.331 G&gt;A, exon 1 &amp; c.1158-44 C&gt;T, intron 6</td>
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<td>c.412 G&gt;A</td>
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<td>c.973 G&gt;A, exon 6</td>
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<td><strong>Progeroid Laminopathy - ZMPSTE24 Mutation</strong></td>
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<td>c.1274 T&gt;C, exon 10</td>
<td>p.L425P</td>
<td>homozygous</td>
<td>No</td>
<td>DFN, LBV</td>
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</tbody>
</table>
PRF Cell & Tissue Bank Distribution

As of June 20, 2024:

240 Research Teams From 29 Countries Have Received

1574 Cell Lines
204 DNA Samples
457 Tissue, plasma, serum and other biological samples
33 Lonafarnib Samples
Cells and biological material have been distributed to 240 laboratories in 29 countries

Complete list of researchers available at:
https://www.progeriaresearch.org/cell-and-tissue-bank-recipient
Program Goals:

➢ Collect the patient health records for living and deceased children with Progeria

➢ Obtain long-term clinical data

➢ Abstract data for longitudinal and cross-sectional analyses

➢ Better understand the clinical disease process in Progeria and aging related diseases

➢ Develop treatment strategies and recommendations for health care professionals and families
How The PRF Medical & Research Database Works

➢ Project staff obtain the patient’s medical records and film studies from birth throughout the participant’s lifespan.

➢ Medical records include visits to: primary care physicians, specialty physicians, hospital emergency rooms, hospital admissions, dentists, physical therapy, occupational therapy and school health records.

➢ Retrospective data abstraction protocol allows for specifically targeted or broad spectrum of data.

Enrollment information available at: https://www.progeriaresearch.org/medical-database/
222 Participants are enrolled from 55 countries and 1 US territory

Algeria
Argentina
Australia
Bangladesh
Belgium
Brazil
Canada, Chile
China, Columbia
Denmark
Dominica Republic
Egypt, England
France, Germany
Guatemala,
Guyana
Honduras, India
Indonesia, Ireland
Israel, Italy
Japan, Kazakhstan
Libya, Mexico
Morocco, Nepal
Netherlands
Oman, Pakistan
Papua New Guinea
Peru, Philippines
Poland, Portugal
Puerto Rico
Romania, Russia
Senegal, Serbia
South Africa
South Korea
Spain, Sri Lanka
Suriname, Sweden
Tanzania, Togo
Turkey, Ukraine
USA, Venezuela
Vietnam
Medical & Research Database Longitudinal Enrollment

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<th>Participants</th>
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</tr>
<tr>
<td>2023</td>
<td>207</td>
<td>55</td>
</tr>
<tr>
<td>2024</td>
<td>221</td>
<td>55</td>
</tr>
<tr>
<td>Jun, 2024</td>
<td>222</td>
<td>55</td>
</tr>
</tbody>
</table>
Types Of Data Collected

- Participants with Medical Records Reports: 166
- Participants with Radiology Studies: 65
PRF Weighing-In Program

➢ A sub-program of The PRF Medical & Research Database
➢ Collects weight-for-age data prospectively:

‡ Home scale provided by PRF
‡ Parents weigh child weekly or monthly
‡ Report weights electronically
Weighing-In Program Participation

Participants are enrolled from 42 countries and 1 US territory

Argentina
Australia
Bangladesh
Belgium
Brazil
Canada
China
Colombia
Denmark
Dominion Republic
England
Germany
Guatemala
Honduras
India
Indonesia
Ireland
Israel
Italy
Japan
Mexico
Morocco
Nepal
Pakistan
Peru
Philippines
Poland
Portugal
Puerto Rico
Romania
Russia
Senegal
South Africa
South Korea
Spain
Sri Lanka
Togo
Tanzania
Turkey
Ukraine
USA
Venezuela
Vietnam

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Participants Enrolled In The PRF Weighing-In Program and Countries of Residence

<table>
<thead>
<tr>
<th>Year</th>
<th>Number Enrolled</th>
<th>Number of Countries</th>
</tr>
</thead>
<tbody>
<tr>
<td>2008</td>
<td>44</td>
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<tr>
<td>2009</td>
<td>49</td>
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<td>2010</td>
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<td>2011</td>
<td>74</td>
<td>29</td>
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<td>2012</td>
<td>77</td>
<td>30</td>
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<tr>
<td>2013</td>
<td>80</td>
<td>31</td>
</tr>
<tr>
<td>2014</td>
<td>88</td>
<td>34</td>
</tr>
<tr>
<td>2015</td>
<td>99</td>
<td>37</td>
</tr>
<tr>
<td>2016</td>
<td>106</td>
<td>39</td>
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<tr>
<td>2017</td>
<td>118</td>
<td>42</td>
</tr>
<tr>
<td>2018</td>
<td>122</td>
<td>43</td>
</tr>
</tbody>
</table>
Clinical Trials And The Weighing-In Program

➢ Data from this program were key in the development of primary outcome measure for the first drug treatment trial for Progeria.

➢ As of December 1, 2018, 90 children from The PRF Weighing-In Program have entered clinical treatment trials using this data.

Failure to Thrive Starts Towards End of Year One
Clinical Drug Treatment Trials

Goals:

➢ To define the natural history of HGPS in quantifiable terms that will expand our ability to measure treatment outcome

➢ To assess the safety of new treatments for HGPS

➢ To measure effects of treatments for children with HGPS on disease status, changes in health, and survival
Current Therapeutic Intervention Strategies

Post-translational processing and medications currently under investigation in clinical treatment trials for Progeria. Items in green = enzymes. Items in red = clinical trial medications that inhibit corresponding enzymes. Lonafarnib is a farnesyltransferase inhibitor. Everolimus is a rapamycin analogue that inhibits mTOR and promotes cellular autophagy. FT=farnesyltransferase.
<table>
<thead>
<tr>
<th>Year</th>
<th>Drug(s)</th>
<th>Phase</th>
<th>Location</th>
<th># Enrolled</th>
<th>Countries Represented</th>
</tr>
</thead>
<tbody>
<tr>
<td>2007-2010</td>
<td>Lonafarnib</td>
<td>2</td>
<td>Boston</td>
<td>29</td>
<td>16</td>
</tr>
<tr>
<td>2009</td>
<td>Lonafarnib Pravastatin Zoledronate</td>
<td>Feasibility</td>
<td>Boston</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>2009-2013</td>
<td>Lonafarnib Pravastatin Zoledronate</td>
<td>2</td>
<td>Boston</td>
<td>45</td>
<td>24</td>
</tr>
<tr>
<td>2014-2021</td>
<td>Lonafarnib</td>
<td>2 (Extension)</td>
<td>Boston</td>
<td>71</td>
<td>32</td>
</tr>
<tr>
<td>2016-2023</td>
<td>Lonafarnib Everolimus</td>
<td>1/2</td>
<td>Boston</td>
<td>60</td>
<td>27</td>
</tr>
<tr>
<td>2018-present</td>
<td>Lonafarnib</td>
<td>2 (Extension)</td>
<td>Boston</td>
<td>62 from 30 countries enrolled as of June 30, 2024</td>
<td></td>
</tr>
</tbody>
</table>
Children have participated in PRF Clinical Trials from **42** countries:

- Argentina
- Australia
- Belgium
- Brazil
- Canada
- China
- Colombia
- Denmark
- Dominican Republic
- Egypt
- England
- Germany
- Guyana
- Honduras
- India
- Israel
- Italy
- Japan
- Kazakhstan
- Libya
- Mexico
- Morocco
- Pakistan
- Peru
- Philippines
- Poland
- Portugal
- Romania
- Russia
- Serbia
- South Africa
- South Korea
- Spain
- Sri Lanka
- Suriname
- Sweden
- Tanzania
- Togo
- Turkey
- Ukraine
- USA
- Venezuela
Lonafarnib, a type of farnesyltransferase inhibitor (FTI) is our first treatment for Progeria.

- Results showed improvement in:
  - Rate of weight gain
  - Increased vascular distensibility
  - Improved bone structure
  - Better neurosensory hearing
  - Increased Lifespan

Gordon et al, PNAS, 2011
Positive Effects of Lonafarnib (Zokinvy) on Progeria: Results of PRF’s Clinical Treatment Trials

- Average increased lifespan of 4.3 years
- Increased vascular distensibility
- Improved bone structure
- Better neurosensory hearing
- Modest increase in rate of weight gain

Gordon et al., PNAS, 2011 and Gordon et al., JAMA, 2018
Gordon et al., Circulation 2023
Zokinvy (lonafarnib) is an FDA approved drug in the US. It is the current standard of care for those with Progeria. It is available through

1. Prescription in the US and in select non-US countries
2. PRF’s clinical treatment trials
3. The manufacturer’s (Eiger) Managed Access Program in select non-US countries

We are far from finished!
We must forge ahead with increased intensity and collaborative efforts to find additional treatments, and the cure!

Please contact PRF at info@progeriaresearch.org for more information on how to access Zokinvy (lonafarnib) for your child or patient with Progeria.
Treatment Trial Collaborations For Success

➢ The children are seen by physicians from:
  - Boston Children’s Hospital
  - Dana-Farber Cancer Institute
  - Brigham and Women’s Hospital

➢ Data were also generated by scientists from:
  - Alpert Medical School at Brown University
  - Brown University School of Public Health
  - University of California Los Angeles
  - National Human Genome Research Institute
  - Schering-Plough Research Institute

➢ Lonafarnib generously provided by Sentynl
➢ Everolimus generously provided by Novartis
Drug Effect:


FDA approval summary for lonafarnib (Zokinvy) for the treatment of Hutchinson-Gilford progeria syndrome and processing-deficient progeroid laminopathies. Suzuki et al., *Genetics in medicine*, 2023;25(2):100335


**Survey of Plasma Proteins in Children with Progeria Pre-therapy and On-Therapy with Lonafarnib.** Gordon et al., *Pediatric Research*, 2018;83(5):982-992

**Clinical Trial of the Protein Farnesylation Inhibitors Lonafarnib, Pravastatin, and Zoledronic Acid in Children With Hutchinson-Gilford Progeria Syndrome.** Gordon et al., *Circulation*, 2016 Jul 12;134(2):114-25.


**Neurologic Features of Hutchinson-Gilford Progeria Syndrome after Lonafarnib Treatment.** Ullrich et al., *Neurology*, 2013, 81:427-430.


**General:**


**Pubertal Progression in Adolescent Females with Progeria.** Greer et al., *Journal of Pediatric and Adolescent Gynecology*, 2018;31(3):238-241


**Dermatology:**

Clinical Trial Publications Continued

Dental:


Cerebrovascular:

Cardiology:

Skeletal:

Ophthalmology:

Audiology:
Progerin as a Biomarker for Progeria

Progerin is the toxic protein produced by cells with progeria in place of the normal lamin A protein.

Normal lamin A plays a role in cell division, but the toxic progerin gets stuck to the nuclear membrane of cells, and its accumulation causes progeria.

A biomarker is “a biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process, or of a condition or disease” (National Cancer Institute).

Treatments for progeria aim to decrease the amount of progerin produced by the body.
Dr. Gordon et al. 2023 developed an assay to measure progerin in blood plasma
Further Findings of the Progerin Biomarker Study

Plasma progerin levels were 95x higher in those with progeria than in the average healthy human.

Treatment with lonafarnib decreased progerin levels by 35-62% on average.

Lifespan increase was shown to be linked to decreased progerin levels and longer time on treatment.

Long-term treatment with lonafarnib (10+ years) resulted in a lifespan increase of about 35%.

Gordon et al. 2023, Circulation
PRF’s research focus is highly translational. Topics must fall within the following research priorities:

- Projects that are likely to lead to clinical treatment trials within 5 years. This includes the discovery and/or testing of candidate treatment compounds in cell-based or animal models of HGPS. Only proposals that test compounds in a progerin-producing animal or cell model will normally be considered. Analyses in non progerin-producing models are acceptable, but only as a comparison to progerin-producing models and with strong justification.

- Development of gene-and cell-based therapies to treat Progeria

- Assessment of natural history of disease that may be important to developing outcome measures in treatment trials (preclinical or clinical)

Phase I Proposals: Awards are typically for 1-2 years in the range of $75,000/year. PRF will conduct a thorough cost analysis for each project during evaluations of submissions.

Required Qualifications. Principal investigators must hold a faculty appointment or equivalent. Awards will be granted only to applicants affiliated with institutions with 501(c)3 tax-exempt status, or the equivalent for foreign institutions.

Letter of Intent (LOI). A letter of intent is required and must be approved before a full application will be considered. Instructions to submit a Letter of Intent and grant application information, can be found at https://www.progeriaresearch.org/grant-application/.
PRF Medical Research Committee

Volunteer MRC Reviews Grant Applications Semi-annually

In person left to right: Bob Bishop, Thomas Glover, Vicente Andres, Leslie Gordon, Christine Harling-Berg, Bryan Toole, Maria Eriksson, Ted Brown

Virtually: Judith Campisi, Tom Mistelli

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June 30, 2024
PRF Granting Structure

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Grant Funding Topics

As of June 30, 2024:

➢ Since inception 281 grant application received and 85 funded
➢ PRF has funded 69 principal investigators from 55 institutions in 14 countries

- Lamina A, progerin, Lamin B in HGPS and aging
- Genetics and nuclear function
- Preclinical Drug Therapy
- Molecular Abnormalities and Therapies
- Vascular Pathology
- Mouse Models
- Stem Cell Investigations and Therapy
- Clinical Trials

* Submissions include Letters of Intent and Full Grants
PRF has funded **69** principal investigators from **55** institutions in **14** countries

Complete list of Grantees available at:

[https://www.progeriaresearch.org/grants-funded/](https://www.progeriaresearch.org/grants-funded/)
Meeting Goals:

➢ To promote collaboration between basic and clinical scientists toward progress in Progeria, cardiovascular, and aging research PRF has held international scientific meetings.
These are large multi-day workshops open to all scientists. Clinical and basic researchers spend intense days sharing data and planning new collaborations for progress towards treatments and cure.

Various NIH Institutes have funded all international workshops through R13 and other granting mechanisms.

Other organizations have also generously sponsored workshops.
Growth of Global Interest In PRF Workshops

Number of Posters
Registrant Countries
Registrant Number

<table>
<thead>
<tr>
<th>PRF Workshop Year</th>
<th>Number of Posters</th>
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<td>2018</td>
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<tr>
<td>2020</td>
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</tr>
<tr>
<td>2022</td>
<td>124</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

* 2020 was a webinar. Posters N/A
Small, focused meetings designed to promote and support work in areas of high interest for Progeria

First Genetics Consortium Meeting - “Searching for the Progeria Gene”, August 23, 2002, Brown University, Providence, RI

Second Genetics Consortium Meeting - “Post- gene Discovery”, July 30, 2003, Bethesda, MD

Bone Marrow Transplant Meeting - “Forging Ahead by Exploring Potential Treatments”, April 25-26, 2004, National Institutes of Health, Bethesda, MD

New Frontiers in Progeria Research (2012), Boston, MA

The first “Progeria Aortic Stenosis Intervention Summit”, May 2, 2023, Virtual by Zoom
As of June 21, 2024:

189 Scientific articles have been published citing The Progeria Research Foundation Grants Funding Program

133 Scientific articles have been published citing PRF Cell & Tissue Bank resources:
   Publication list at www.progeriaresearch.org/prf-cell-and-tissue-bank-publications/

35 Scientific articles have been published citing The PRF Medical & Research Database:
   Publication list at www.progeriaresearch.org/medical-database/

29 Scientific articles have been published from clinical trial data
   See slide #54 and #55

4 Scientific articles have been published concerning PRF Scientific Workshops
Today over 100 publications on Progeria a year are published in well-known, respected scientific journals read by researchers worldwide.

Provided in Chinese, English, Italian, Japanese, Portuguese and Spanish

Expert contributors from Boston Children’s Hospital

Number of Progeria Care Handbooks distributed to families of those with Progeria and their care givers: 932
The Progeria Research Foundation

Finding...
Diagnosing...
Studying...
Treating...
CURING

Together We *WILL* Find The Cure!

www.progeriaresearch.org

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June 30, 2024