Participant Involvement: USA

International Rare Disease Research Consortium
08 November 2014

Sharon F. Terry
President & CEO, Genetic Alliance
Founding CEO, PXE International
President, EspeRare
Principal Investigator, CENA
An ecosystem is a community of living organisms (plants, animals and microbes) in conjunction with the nonliving components of their environment (things like air, water and mineral soil), interacting as a system. These components are regarded as linked together through nutrient cycles and energy flows.
Why are we here?

A drug development **ecosystem** is a community of stakeholders (universities, companies, patient organizations, patients, government organizations) in conjunction with the nonliving components of their environment (things like regulations, economic factors, reimbursement potential), interacting as a system. These components are regarded as linked together through clinical research cycles and funding flows.
Challenges in Rare Genetic Disease Research

• Limited participants
• Variable disease phenotyping
• Limited bio-sample & data repositories
• Fragmentation / lack of scale
• Limited privacy & data security
• Limited funding → limited research
• Poor feedback to participants
There is no deli number...
Our Approach

Create a Commodity to:

- Organize a Community
- Leverage & Offer Funding
- Coordinate Research & Studies
- Coordinate Communications
- Focus on Clinical Significance
Elizabeth and Ian diagnosed with pseudoxanthoma elasticum (PXE) 1994

2014

Elizabeth: Teach for America
Ian: Organic Farmer
20 Years Into Project Plan

- PXE Gene
  - Sequence Analysis
  - Genomic SNP/rSNPs
  - Associated Protein Expression
    - Regulomics
    - Proteomics

- Code Sequence
- Protein Structure/Function
- Molecular Pathway
- Model Organisms
- Cellular Modeling
- In vivo Studies

- Cause Mutations
- Epidemiological Research
- Genotype / Phenotype Associations
- Protein Production
- Experimental Assays
- Delivery Vectors
- Rational Intervention Design

- Diagnostics
  - Accurate Correlative Linkage
  - Phenotype Severity Prediction

- Therapeutic Intervention

- Rational Intervention Design
• 1995 Incorporation
• Nonprofit Advocacy Foundation
• Raised/Invested ~$2,800,000
• Leveraged ~$19,000,000 Federal Funds
• Gene & Diagnostic Patents
• Animal Model
• Clinical Genetic Testing
• Human Clinical Intervention Trials
• Drug Discovery Screening Program
Figure 1 | **The PXE International strategy.** PXE International uses a variety of approaches to bring the PXE community together with research scientists to accelerate translational research. IRB, institutional review board.

*Terry SF, Terry PF, Rauen K, Uitto J, Bercovitch L. Advocacy Organizations as Research Organizations: the PXE International example. Nature Reviews Genetics. 2007 Feb; Vol. 8, No. 2*
PXE: Taming the disease through industrialized translational research - scale, focus and collaboration.

**PXE International Consortium:**
- Research Management
- Secure Informatics Infrastructure
- Genomic Sample & Data Bank
- Collaborative Research Projects
  - Correlative Science
  - FDA Diagnostic Kit
- Scientific & Commercial Partnerships
Pediatric Symposium: Focus on Pediatric Rare Diseases
November 6, 2014

Audrey Gordon, Esq.
President, Executive Director - The Progeria Research Foundation
<table>
<thead>
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Children Living Around the World with Progeria
As of October 1, 2014
...and Speak 28 Languages

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<tr>
<th>Arabic</th>
<th>English</th>
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<th>Marathi</th>
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<td>Dutch</td>
<td>Hindi</td>
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مؤسسة أبحاث الشياخ
早衰症研究基金會
Progeria रिसर्च फाउंडेशन
早老症研究財団
조로증 연구 재단
Progeria Araştırma Vakfı
 прогерии исследовательский фонд
Our History, Our Future…

1999: No research, No awareness, No knowledge

2003: Gene Discovery – The doors of science are flung open

2007: First Trial – A drug is identified as a potential treatment

2012: First Treatment – Trial results show the drug benefits children’s cardiovascular status

2014: Longer Life - Time reveals the first treatment shows increased estimated lifespan

ONGOING: Discovering better treatments and a cure
PRF Programs: Collaborations For Success

Brown Alpert Medical School
Brown School of Public Health
Rutgers
Prevention Genetics
National Institutes of Health
Hasbro Children's Hospital
The Pediatric Division of Rhode Island Hospital
A Lifespan Partner
Boston Children's Hospital
Until every child is well
Brigham and Women's Hospital
A Teaching Affiliate of Harvard Medical School
uOttawa
Our participants come from all over the world. They find us through our outreach - the PRF website, social media, publications, television documentaries, their doctors, neighbors, friends and family.
Growth of Global Interest in Progeria Research

Research Grants:
- 54 projects ($6 million) to
- 51 researchers in 10 countries

Scientific Workshops:
- 11 International conferences
  (30-40% participation increase)
Progeria Publications Trend

- Year
- Number of Publications

2013 → 2,000 % increase since 2003 HGPS gene discovery

Progeria Research Foundation
## PRF -Funded Clinical Treatment Trials

<table>
<thead>
<tr>
<th>Year</th>
<th>Drug</th>
<th>Phase</th>
<th>Location</th>
<th>#</th>
<th>Countries</th>
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<td>2007-2010</td>
<td>Lonafarnib</td>
<td>2</td>
<td>Boston</td>
<td>28</td>
<td>17</td>
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<tr>
<td>2009</td>
<td>Lonafarnib, Pravastatin, Zoledronate</td>
<td>1/2</td>
<td>Boston</td>
<td>5</td>
<td>1</td>
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<tr>
<td>2009-2013</td>
<td>Lonafarnib, Pravastatin, Zoledronate</td>
<td>2</td>
<td>Boston</td>
<td>45</td>
<td>24</td>
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<tr>
<td>2014</td>
<td>Lonafarnib</td>
<td>2</td>
<td>Boston</td>
<td>Enrolling up to 80/35</td>
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</table>
Clinical Treatment Trial Publications

As of October 1, 2014:


Collectively, the Coalition of Patient Advocacy Groups (CPAG) represents the perspective and interests of all patient advocacy organizations associated with the clinical research consortia. Through collaboration, patient advocacy groups and researchers can make faster progress toward new treatment options and cures, which can improve the lives of all persons and families affected by a rare disease. Learn More > CPAG Committee Roster

Rare Diseases Advocacy Groups
Click on a Rare Diseases Network Consortium to see corresponding advocacy groups:

- Angelman, Ret, and Prader-Willi Syndromes Consortium
- Genetic Disorders of Mucociliary Clearance Consortium
- Inherited Neuropathies Consortium
- Lysosomal Disease Network
- NEPTUNE: Neuropathic Syndrome Rare Disease Clinical Research Network
- North American Mitochondrial Diseases Consortium
- Porphyrias Consortium
- Primary Immune Deficiency Treatment Consortium (PIDTC)
- Rare Kidney Stone Consortium
- Salivary Gland Carcinomas Consortium
- STAIR: Sterol and Isoprenoid Diseases Consortium
- Urea Cycle Disorders Consortium
- Vasculitis Clinical Research Consortium

News
<table>
<thead>
<tr>
<th>Organization</th>
<th>PI</th>
<th>Condition</th>
<th>Proposed PPRN Population Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Accelerated Cure Project for Multiple Sclerosis</td>
<td>Robert McBurney</td>
<td>Multiple Sclerosis</td>
<td>20,000</td>
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<tr>
<td>American Sleep Apnea Association</td>
<td>Susan Redline</td>
<td>Sleep Apnea</td>
<td>50,000</td>
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<tr>
<td>Cincinnati Children’s Hospital Medical Center</td>
<td>Peter Margolis</td>
<td>Pediatric Crohn's Disease and Ulcerative Colitis</td>
<td>15,000</td>
</tr>
<tr>
<td>COPD Foundation</td>
<td>Richard Mularski</td>
<td>Chronic Obstructive Pulmonary Disease</td>
<td>50,000</td>
</tr>
<tr>
<td>Crohn’s and Colitis Foundation of America</td>
<td>R. Balfour Sartor</td>
<td>Inflammatory Bowel Disease (Crohn’s disease and ulcerative colitis)</td>
<td>30,000</td>
</tr>
<tr>
<td>Global Healthy Living Foundation</td>
<td>Seth Ginsberg</td>
<td>Arthritis (rheumatoid arthritis, spondyloarthritis), musculoskeletal disorders (osteoarthritis), and inflammatory conditions (psoriasis)</td>
<td>50,000</td>
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<tr>
<td>Massachusetts General Hospital</td>
<td>Andrew Nierenberg</td>
<td>Major Depressive Disorder (MDD) and Bipolar Disorder (BP)</td>
<td>50,000</td>
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<tr>
<td>Univ of California, San Francisco</td>
<td>Mark Pletcher</td>
<td>Cardiovascular health</td>
<td>100,000</td>
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<tr>
<td>University of South Florida</td>
<td>Rebecca Sutphen</td>
<td>Hereditary Breast and Ovarian Cancer (HBOC)</td>
<td>17,000</td>
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</table>
...in both rare and common disorders

<table>
<thead>
<tr>
<th>Organization</th>
<th>PI</th>
<th>Condition</th>
<th>Proposed PPRN Population Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALD Connect, Inc</td>
<td>Florian Eichler</td>
<td>Adrenoleukodystrophy</td>
<td>3,000</td>
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<td>Arbor Research Collaborative for Health</td>
<td>Bruce Robinson</td>
<td>Primary Nephrotic Syndrome (Focal Segmental Glomerulosclerosis [FSGS], Minimal Change Disease [MCD], and Membranous Nephropathy [MN] Multiple Sclerosis</td>
<td>1,250</td>
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<tr>
<td>Duke University</td>
<td>Laura Schanberg</td>
<td>Juvenile Rheumatic Disease</td>
<td>9,000</td>
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<tr>
<td>Epilepsy Foundation</td>
<td>Janice Beulow</td>
<td>Aicardi Syndrome, Lennox-Gastaut Syndrome, Phelan-McDermid Syndrome, Hypothalamic Hamartoma, Dravet Syndrome, and Tuberous Sclerosis</td>
<td>1,500</td>
</tr>
<tr>
<td>Genetic Alliance, Inc</td>
<td>Sharon Terry</td>
<td>Alström syndrome, Dyskeratosis congenital, Gaucher disease, Hepatitis, Inflammatory breast cancer, Joubert syndrome, Klinefelter syndrome and associated conditions, Metachromatic leukodystrophy, Pseudoxanthoma elasticum (PXE)</td>
<td>50-50,000</td>
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<td>Immune Deficiency Foundation</td>
<td>Kathleen Sullivan</td>
<td>Primary Immunodeficiency Diseases</td>
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<tr>
<td>Parent Project Muscular Dystrophy</td>
<td>Holly Peay</td>
<td>Duchenne and Becker muscular dystrophy</td>
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<td>Phelan-McDermid Syndrome Foundation</td>
<td>Megan O’Boyle</td>
<td>Phelan-McDermid Syndrome</td>
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<tr>
<td>University of Pennsylvania</td>
<td>Peter Merkel</td>
<td>Vasculitis</td>
<td>500</td>
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</table>
Our Mission:

To improve the treatment, quality of life and long-term outlook for all individuals affected by Duchenne muscular dystrophy through research, education, advocacy and compassion.
A Drug Development Pipeline in Duchenne Full of Potential
DMD caregiver study

- To promote patient-centered drug development in the area of DMD, PPMD conducted a national survey caregivers of a child with DMD.

- To quantify treatment preferences of caregivers of a child with DMD for the potential benefits and risk of potential treatments we utilize a cutting edge stated-preference method: Best-Worst Scaling (BWS)

- In our BWS experiment, we presented caregivers with potential treatments (profiles) and asked them to select the best and worst features.

- Features included benefits, risk and other characteristics of potential treatments
Community-centered research

• PPMD led the study, guided by an advocacy oversight team comprising PPMD staff members who collaborated with the research team to design and implement the study.

• The broader DMD community was engaged to develop the survey (clinicians, sponsors, families).

• The oversight team made study-related decisions through a consensus process.

• Contributing authors included PPMD staff and academic collaborators from Johns Hopkins.
Treatment preferences

• A pool of treatment features (attributes) identified and refined in consultation with parents, clinicians, and industry

• Six attributes were chosen to cover the potential benefits, risks and other features, each varying across three levels each.

• A main-effects orthogonal array was used as the basis of the experimental design - identifying 18 potential treatments that systematically varied across the six chosen attributes.
Attributes and levels

• **Effect on muscle function** (none, slows, stops)

• **Gain in expected lifespan** (none, 2, 5 years)

• **Post-approval information** (none, 1, 2 years)

• **Nausea** (none, loss of appetite, loss of appetite and occasional vomiting)

• **Risk of bleeds** (none, risk of bleeding gums and increased bruising, risk of hemorrhagic stroke)

• **Risk of heart arrhythmia** (none, risk of harmless heart arrhythmia, risk of dangerous heart arrhythmia and sudden death)
Conclusions – Treatment priorities

• Within the context of our preference experiment:

  – Stopping/slowing the **progression of muscle weakness** accounted for the largest proportion of the variation.

  – The presence of a serious **risk** could be compensated for by a treatment that stops/slow progression to muscle function.

  – **Nausea** was viewed negatively, but not nearly as negatively as a risk for a serious health event.

  – Caregivers **marginally valued post-market data**
Advocacy owned and managed data repository and samples

Clinical Information       Medical Records
DNA/RNA                   Self-reported Data
Cell Lines                Tissue / Organs

30,000 samples + 20,000 clinical records

BioBank.org
# Genetic Alliance Registry and BioBank Toolbox

<table>
<thead>
<tr>
<th>Question</th>
<th>Resource</th>
</tr>
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<tbody>
<tr>
<td>Where do I begin?</td>
<td>What is a biobank?</td>
</tr>
<tr>
<td>How do I make this a reality?</td>
<td>Registry/repository start-up guide</td>
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<tr>
<td>Is my organization ready?</td>
<td>Organizational readiness checklist</td>
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<tr>
<td>How do I select a vendor?</td>
<td>Vendor assessment summary</td>
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<td>Considering Genetic Alliance?</td>
<td>Genetic Alliance BioBank</td>
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<tr>
<td>What else do I need to know?</td>
<td>Biobank governance</td>
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<tr>
<td>How do I stay current?</td>
<td>Registry and Biorepository Bulletin</td>
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<td>Advocates are leaders in biobanking</td>
<td>Making your organization's biobank a reality</td>
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<td>Genetic Alliance registry/repository boot</td>
<td>Biobank question &amp; answer session</td>
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**Categories:**
- Publication
- Training/mentoring
- Videos
- Webinar
- Webpage
- Worksheet
White label registry – branded according to the advocacy organizations wishes

The portal fits directly onto any web page and retains the host site’s top and bottom navigation.
White label registry – branded according to the advocacy organizations wishes

The portal fits directly onto any web page and retains the host site’s top and bottom navigation.

The headline, colors, theme, video and other content can be tailored to fit seamlessly into the host site and support each group’s message.

Everything is ready and because it is patient-centric. It supports both new users as well as individuals who may have started on a different organization’s Private Access-enabled site. Everyone benefits!
Public Policy

- Genetic Information Nondiscrimination Act – led the Coalition that charged the Bill to passage
- Genetic Testing – Eyes On the Prize: Truth-telling about Genetic Testing
- Patenting – filed an amicus to support innovation and support responsible patenting (Supreme Court)
- Health Information Technology – serve on the HIT Standards committee, filed amicus supporting the responsible use of pharmacy data (Supreme Court)
- Regulation – Filed citizen’s petition to create reasonable oversight of genetic tests
- Standards – Work to harmonize ontologies and nomenclature for clinical trials, integrate HL7, LOINC
- Reimbursement – Convene payers to determine reasonable evidence levels for diagnostics and therapies in stratified medicine
- Newborn screening translational network – collaborate with our Newborn Screening Clearinghouse
Contact Information

For more information:

Sharon Terry  
President and CEO, Genetic Alliance, Inc.  
(202) 966-5557, Ext. 201  
sterry@geneticalliance.org

General Information: http://www.geneticalliance.org