FALL 2025

PROPIONIC ACIDEMIA FOUNDATION

SEARCHING FOR A CURE HOPE FOR OUR CHILDREN

Propionic Acidemia Conference: Advancing Research and Care

On July 11–12, 2025, the Propionic Acidemia Foundation hosted a conference dedicated to advancing research and expanding care possibilities for individuals living with Propionic Acidemia.

The conference welcomed 121 attendees from 12 states and 2 countries, creating a unique space where researchers, healthcare professionals, and families affected by this rare metabolic disorder could connect. The meeting fostered collaboration, shared groundbreaking research, and explored innovative treatments that may transform lives.

The weekend began on Friday evening with a casual dinner from a local food truck, offering families a chance to meet and connect.

Saturday offered a dynamic program of educational presentations, sponsor exhibits, and opportunities for families to contribute to important research initiatives.

Dr. Chowdhury's team generously provided 23 echocardiograms and EKGs, and 17 genetic tests free of charge, ensuring families had access to critical screenings.

The Plain Community invited families to participate in a survey conducted by MPHI, while Rare Patient Voice provided an opportunity to register for future research participation. Videos are available on our YouTube channel.

We are deeply grateful to our Sponsors whose generous support made this event possible.

Finally, we are very thankful to everyone who participated, contributed, and supported this meaningful gathering. Together, we remain committed to advancing research, improving care, and fostering hope for the PA community.

Gold Sponsors

alltrna moderna

Bronze Sponsors

NUTRICIA

RARE PATIENT Voice Also Non-Rare!

PA REGISTRY

Help move research forward for propionic acidemia.

Participate in the Propionic Acidemia International Patient Registry.

For more information on joining the registry, or to update your information, go to paregistry.com

INSIDE

PAF AWARDS $20,250 CONTINUATION GRANT

PROJECT: Reducing the toxicity of propionyl-CoA in propionic acidemia: a case for revising dietary supplementation guidelines
PRINCIPAL INVESTIGATOR: Pawel Swietach, DPhil, University of Oxford, UK

SUMMARY: Studying the epigenetic actions of propionyl-CoA and finding dietary ways of controlling its impact have been highlighted as priority areas by the PA research community. Our latest findings highlight two trajectories for the next project. The first relates to the potential benefit of increasing cardiac beta-alanine levels by dietary supplementation. We propose that higher beta-alanine availability raises carnosine levels, an important anti-oxidant in the heart. Since there is no 'ceiling effect' to levels of beta-alanine attained in the heart, it is plausible that even better outcomes can be attained safely with more dietary beta-alanine. Better anti-oxidant protection reduces PA severity, which we inferred from observations on PA mice where the disease was less severe among males. Sexually mature male mice accumulate higher beta-alanine stores through an effect of testosterone. As a pediatric condition, PA patients will not benefit from this exact mechanism, but there are alternative ways of raising beta-alanine levels. The most plausible intervention is dietary. Indeed, carnosine supplements are routinely used by athletes, and similar formulations could be re-purposed for PA patients. The second direction is to investigate histone methylation, and potential for correcting this by restricting methionine in the diet. The striking increase in liver histone methylation may indicate excessive levels of SAMe, caused by the lack of checks and controls on methionine assimilation, a feature of essential amino acids. Here, the challenge is to titrate a level of methionine that can safely control methylation without causing malnutrition. Our goal is to develop up-to-date dietary guidelines for PA, incorporating new scientific insights into disease mechanisms to deliver immediate benefits to patients.

PAF AWARDS $50,000 NEW GRANT

PROJECT: Systemic Lentiviral Gene Therapy for Propionic Acidaemia
PRINCIPAL INVESTIGATORS: Ala'a Siam, RPh PhDc MRes*, University College London, UK
John Counsell, PhD, University College London, UK

SUMMARY: This pilot research project is expected to result in the necessary proof-of-concept data for the examination of novel disease-modifying gene therapies for PA. Such hepatotropic gene therapies would provide a substitute to liver transplantation. Unlike the latter, this modality bypasses the need for matched liver grafts, risks of surgical complications and requirement for lifelong immunosuppression. It would also enable treatment shortly after diagnosis, thereby arresting the development of complications early on. The permanent nature of gene therapy would ensure continuous expression of PCCA. This aspect bypasses the shortcomings of mRNA nanoparticles, which include the need for repeated dosing at specialised centers and association with high risks of infusion-related reactions. In summary, the gene therapies developed as part of this project are expected to result in clinical outcomes that are similar to those of paediatric liver transplantation, but with a significantly enhanced quality of life and simplified patient access.

Photos: Ala'a Siam (top photo), John Counsell (bottom photo)

OFFICIAL CHARITY PARTNER
tcs NEW YORK CITY MARATHON

NOVEMBER 2ND, 2025
The 2025 TCS NEW YORK CITY MARATHON
TEAM #TCSNYCMARATHON

Meet our 6 amazing 2025 NYC Marathon PA runners.
Show your love; support our runners!

SANDER HOUTEN, New York.
Dr. Houten has been researching rare diseases for more than 25 years. He received a grant from PAF in 2021 to explore alternative metabolic pathways that could improve energy usage in PA. In the year that he turns 50, Dr Houten is running the 2025 NYC Marathon to further support the Propionic Acidemia community. This will be Dr. Houten's 2nd NYC marathon, and he is aiming for a sub-4-hour race. GO DR. SANDER!
https://fundraisers.nyrr.org/sander-houten

NICOLAS KAPOOR, New York.
Nicolas decided to run this year's race for his sister, Emily, who lives with Propionic Acidemia. He wants to raise awareness about PA and funds for research. Every step he takes, he takes it for Emily. Nicolas has run a marathon once before, but this will be his first NYC Marathon. GOOD LUCK, NICK!
https://fundraisers.nyrr.org/nicolas-kapoor

CRAIG THEROS, Michigan.
Craig has been a generous supporter of PAF for many years. Craig is running this year's race in memory of his good friend Angelica, who lost her battle with PA in 2015. Craig is an experienced marathoner, but this will be his first NYC Marathon. WISHING YOU A GREAT RACE, CRAIG!
https://fundraisers.nyrr.org/craig-theros

ALEJANDRO LOPEZ, New York. This year's team welcomes another PA brother, Alex. In his words: "I have a fantastic record of 0 races, but I am running this year's NYC Marathon to support research on the genetic disease that my brother was born with. For the past 20 years of my life, I have been a first-hand witness of the hardships that individuals with PA must live with and thus hope you could donate any amount to be a part of the positive force that people like my brother needs". YOU GOT THIS, ALEX!
https://fundraisers.nyrr.org/alexlopezruns

JOHN MOSS, Missouri. John is our most tenacious NYC Marathon runner, as this will be his 4th marathon in The Big Apple, running with the PARUNNERS team. He is looking forward to raising even more money this year to support PA research and better treatments for his son, Grant. He is also running in memory of Grant's twin, Sebastian, who lost his battle with PA in 2023. HAVE A GREAT RACE, JOHN!
https://fundraisers.nyrr.org/john-moss-2

KRISTIE GUARD, South Carolina. Kristie is an avid runner and loves the Walt Disney marathon. She joined the PARUNNERS team at the last minute, when one of our initial runners had a medical emergency. Kristie is also a good friend of long-time PAF supporter Maria Belen Sánchez and is excited to join this year's fundraising campaign for PA. This will be Kristie's first New York City Marathon. ENJOY THE RACE, KRISTIE!
https://fundraisers.nyrr.org/kristie-guard-2

2024-2025 ANNUAL REPORT

PROPIONIC ACIDEMIA FOUNDATION

Our focus this past fiscal year has been on increasing outreach to families impacted by Propionic Acidemia, funding promising research projects, creating and distributing educational materials to families, collaborating with other rare disease organizations, presenting at conferences, and advising on panels for the development of new treatment options.

- Conducted a virtual Spanish Chat in August 2024, led by Dr. Carolina Galaretta and Jennifer Miles, RD, from the NIH.
- Co-organized the "PA Hope in the Heartland" hybrid conference in Shipshewana, Indiana, USA, in October 2024, in partnership with the Community Health Clinic.
- Organized the "Advancing Research and Care" conference in Kidron, Ohio, USA, in July 2025.

MISSION: The Propionic Acidemia Foundation is dedicated to finding improved treatments and a cure for Propionic Acidemia by funding research and providing information and support to families and medical professionals.

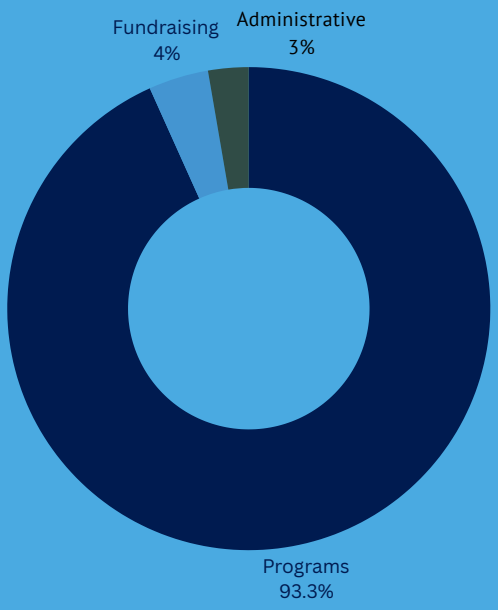
VISION: To create a future where Propionic Acidemia can be prevented, and any affected individual can be cured and live a productive life.

- Shared presentations from both PAF conferences on YouTube, accumulating tens of thousands of views.
- Participated in the ASGTC 2025 Annual Meeting at the Annual Meeting of the Accelerating Medicines Partnership® Bespoke Gene Therapy Consortium (AMP® BGTC) on May 16, 2025, in New Orleans, Louisiana, USA as part of the "Patient Voice Spotlight Panel."
- In June, 2025 Jill Chertow presented at Bio2025 International Convention in Boston, MA, USA with the panel "Next-Gen Advocates: Patients & Families Driving Breakthroughs in Rare Disease Drug Development."
- Awarded a $50,000 grant to Ala'a Siam & Dr. John Counsell at the University College London for the research project "Systemic Lentiviral Gene Therapy for Propionic Acidaemia."
- Awarded a $20,250 grant to Pawel Swietach, University of Oxford, UK, for the research project "Reducing the toxicity of propionyl-CoA in propionic acidemia: a case for revising dietary supplementation guidelines".
- Attended & exhibited at the Illinois PKU and Allied Disorders Annual Meeting in November 2024 in Rosemont, Illinois, USA.
- Met with six families with PA at an Illinois PKU & Allied Disorders "New Parent Cafe" meet up in Naperville, IL, USA.
- Abby Kapoor, a talented volunteer, created a PA Transition Guide utilizing the one created by HCU Network America.

FINANCIAL STATEMENT

Expenses

Programs: Research & Outreach	$91,233
Fundraising	$4,134
Administrative	$2,632
Total Expenses	$97,999



Income

Cash Assets 8/1/2024	$460,486
Cash Assets 7/31/2025	$505,073

Donations	$124,180
Interest Income	$18,406
Total Income	$142,586

Board of Directors

Jill Chertow, President
Brittany Smith, Treasurer
Angela Waits, Secretary
Maria L. Cotrina
Susan M. Weaver
Jennifer Simmons

847-497-0977
www.pafoundation.com
paf@pafoundation.com
@propionic_acidemia
PO Box 151, Deerfield, IL 60015

PROPIONIC ACIDEMIA INDUCES ELECTROPHYSIOLOGICAL ALTERATIONS IN THE HEART: A PIONEERING STUDY IN HUMAN IPSC-DERIVED CARDIOMYOCYTES REVEALS NEW ARRHYTHMIA RISK MECHANISMS

Eva Richard[1], Mar Álvarez[1], Lourdes Ruiz[1], Eva Delpón[2], Ricardo Caballero[2]

1. Centro de Biología Molecular Severo Ochoa UAM-CSIC, CIBERER, IdiPaz, IUBM, Universidad Autónoma de Madrid, Madrid, Spain
2. Department of Pharmacology and Toxicology, School of Medicine, Instituto de Investigación Gregorio Marañón, CIBERCV, Universidad Complutense de Madrid, Madrid, Spain.

Research teams from the Severo Ochoa Centre for Molecular Biology (CBMSO, UAM-CSIC) and the Complutense University of Madrid (Department of Pharmacology and Toxicology, School of Medicine, UCM) have discovered that propionic acidemia (PA) causes electrophysiological alterations in the heart. The study, recently accepted for publication in the Journal of Inherited Metabolic Disease, demonstrates for the first time that deficiency of the enzyme propionyl-CoA carboxylase (PCC) leads to changes in specific ionic currents in human cardiomyocytes derived from induced pluripotent stem cells (iPSC-CMs), thereby increasing the risk of arrhythmias.

Propionic acidemia is a hereditary metabolic disease caused by mutations in the PCCA or PCCB genes, which encode the subunits of the mitochondrial enzyme PCC. The deficiency of this enzyme prevents the proper metabolism of certain amino acids and lipids, leading to the accumulation of toxic compounds such as propionyl-CoA. These metabolites affect multiple organs, with a particularly strong impact on the heart.

Although it is known that PA patients may develop cardiac complications such as dilated cardiomyopathy, prolonged QT interval, and ventricular arrhythmias that can trigger sudden cardiac death, the mechanisms behind these alterations remain poorly understood. The main goal was to understand how PCC deficiency affects the electrical properties of the heart at the cellular level.

The results were conclusive: patient-derived iPSC-CMs exhibited reduced excitability, prolonged action potential duration, and the emergence of delayed afterdepolarizations. In addition, alterations were observed in several key ionic currents: a decrease in sodium current (I_{Na}) and L-type calcium current (I_{CaL}), along with an increase in late sodium current (I_{NaL}) and sodium/calcium exchanger current (I_{NCX}). Together, these findings reflect a disturbance in intracellular calcium handling and an elevated risk of arrhythmias in PA patients.

The novelty of this study lies in the demonstration that these changes can occur independently of the late progression of disease-induced cardiomyopathy. In other words, the enzyme deficiency itself creates a proarrhythmic environment at the cellular level.

This human cell–based model enables a more precise study of the disease's specific pathophysiological mechanisms and opens the door to the development of new therapies. The study also explores the potential therapeutic implications of these findings, concluding that beta-blockers, due to their mechanism of action, are currently the only appropriate class of antiarrhythmic drugs for treating arrhythmias associated with PA.

Further research will be needed to investigate whether other antiarrhythmic agents or novel cardioactive drugs, such as empagliflozin and dapagliflozin (SGLT2 inhibitors), could counteract the electrophysiological alterations induced by PCC deficiency.

(cont. PAGE 7)

RESEARCH CONTINUED FROM PAGE 6

Thanks to the combination of cutting-edge technologies such as iPSCs and cellular electrophysiology, we are able to better understand the molecular basis of rare diseases like PA, with the ultimate goal of improving treatment and the quality of life for patients.

We sincerely thank the Propionic Acidemia Foundation for their financial support, attention, and ongoing assistance throughout this study. Their commitment to advancing scientific research and improving the lives of those affected by propionic acidemia has been a constant source of motivation for our team. We are also grateful to the families of the patients for their trust and collaboration, which have been essential to the success of this research.

Link to the article: https://onlinelibrary.wiley.com/doi/10.1002/jimd.70030

Richard group left
Delpon group right

ALTERED ENERGY FUEL UTILIZATION IN IPSC-DERIVED CARDIOMYOCYTES FROM PATIENTS WITH PROPIONIC ACIDEMIA

Eva Richard[1], Lourdes R. Desviat[1], Guo-Fang Zhang[2]

1. Centro de Biología Molecular Severo Ochoa UAM-CSIC, CIBERER, IdiPaz, IUBM, Universidad Autónoma de Madrid, Madrid, Spain

2. Duke Molecular Physiology Institute and Sarah W. Stedman Nutrition and Metabolism Center, Duke University Medical Center, Durham, NC 27701, USA

Cardiac complications are a major and life-threatening concern in patients with propionic acidemia (PA). Understanding the underlying mechanisms driving cardiac pathology in PA is essential, particularly given the chronic nature of these complications.

We aimed to investigate how energy metabolism in the heart is altered in the context of propionyl-CoA accumulation, as seen in PA. In perfused rat hearts exposed to 3 mM propionate, we observed a metabolic shift from fatty acid oxidation toward increased glucose utilization. This shift is considered energetically inefficient, as long-chain fatty acids yield substantially more ATP per molecule than glucose. Such a change in fuel preference may contribute to the gradual onset of cardiac dysfunction. Additionally, impaired fatty acid oxidation may explain the lipid droplet accumulation observed in myocardial tissue from PA patients, which could be another contributing factor to cardiac pathology in PA. However, these findings were derived from otherwise healthy rats subjected to high levels of propionate, and it remains to be determined whether similar metabolic disturbances occur in the hearts of human PA patients.

In collaboration with Drs. Eva Richard Rodríguez and Lourdes R. Desviat at the Universidad Autónoma de Madrid and with support from the Propionic Acidemia Foundation, we examined induced (cont. PAGE 8)

RESEARCH CONT. PAGE 7

pluripotent stem cell-derived cardiomyocytes (iPSC-CMs) from PA patients. Consistent with the rat heart model, PA iPSC-CMs demonstrated increased glucose metabolism and reduced fatty acid oxidation, confirming that the metabolic shift is also present in iPSC-CMs derived from patients with PA (1).

Importantly, both the rat heart model exposed to high levels of propionate and the PA iPSC-CM model suggest that the observed shift in fuel utilization is not primarily driven by changes in gene or protein expression. Instead, it appears to result from reduced availability of key metabolic cofactors—Coenzyme A and carnitine—due to the accumulation of propionyl-CoA and propionylcarnitine. This conclusion is further supported by studies in carnitine acetyltransferase knockout mouse hearts, where increased carnitine availability enhances CPT1-mediated transport of long-chain fatty acids, thereby promoting fatty acid oxidation and suppressing glucose metabolism (2).

Our results suggest that carnitine depletion limits fatty acid oxidation, and that chronic suppression of this pathway may contribute to cardiac dysfunction in PA. This raises the important question of whether targeted carnitine supplementation could benefit PA patients with cardiac involvement. Notably, one report documented significantly reduced carnitine levels in the heart of a PA patient, despite normal levels in circulation. This finding highlights the need to better understand how to effectively increase cardiac carnitine levels—either through improved delivery or by enhancing endogenous synthesis (3).

Lastly, our collaborative work also revealed that intracellular propionyl-CoA can be rapidly hydrolyzed to propionate. This hydrolysis may serve as an alternative mechanism for regulating intracellular propionyl-CoA levels, though the regulation and biological significance of this process warrant further investigation.

1. Richard E, Marchuk H, Álvarez M, He W, Chen X, Desviat LR, Zhang GF. Metabolic flux analysis in hiPSC-CMs reveals insights into cardiac dysfunction in propionic acidemia. Cell Mol Life Sci. 2025 Apr 2;82(1):137.

2. Muoio DM, Noland RC, Kovalik JP, Seiler SE, Davies MN, DeBalsi KL, Ilkayeva OR, Stevens RD, Kheterpal I, Zhang J, Covington JD, Bajpeyi S, Ravussin E, Kraus W, Koves TR, Mynatt RL. Muscle-specific deletion of carnitine acetyltransferase compromises glucose tolerance and metabolic flexibility. Cell Metab. 2012 May 2;15(5):764-77.

3. Mardach R, Verity MA, Cederbaum SD. Clinical, pathological, and biochemical studies in a patient with propionic acidemia and fatal cardiomyopathy. Mol Genet Metab. 2005 Aug;85(4):286-90.

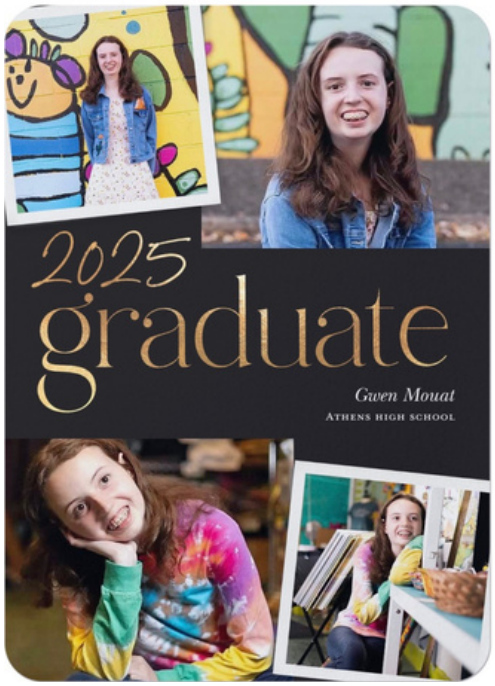
Richard group Zhang group

GWEN'S UPDATE

Gwen graduated from Athens High School in May, 2025. She just started a 1-year internship at O'Bleness Hospital through Project Search - a one-year transition program for seniors with disabilities offering training and internships that lead to competitive employment.

Students are supported by site managers, instructors, and job coaches, receiving feedback and ending each day with reflection and skill-building activities! Project SEARCH has over 750 active sites globally. projectsearch.us

Congratulations, Gwen!



LOW PROTEIN ANNUAL MEETING

BIRTHDAY CLUB

This year, the Warrior Birthday Club cards will be made by students at Oak Lawn Hometown Middle School.

We are thankful they have volunteered. Please sign up at http://www.pafoundation.com/warriors-birthday-club/.

If you signed up last year, you will need to sign up again, so we have current information

ISABEL'S STORY

Soy mamá de Isabel Plascencia. Mi hija fue diagnosticada con Acidemia Propiónica a sus 10 días de nacida. Yo desde el día 1 sentía que algo no estaba bien, no sé cómo explicarlo. Solo les diré: "no ignores ese presentimiento o instinto de mamá".

Los primeros 2 años fueron muy difíciles con entradas y salidas al hospital y aprender a detectar esas banderas rojas que anticipaban una recaída. Aceptar los retos es importante, valorar cuando estamos juntas.

La vida con AP es difícil pues aparecen esos obstáculos económicos, de cansancio e incertidumbre pero finalmente creo que la vida se acomoda y la AP nos enseña que somos capaces por nuestros hijos de cosas impensables. Creo que debemos de dar un paso a la vez y jamás perder la fe y esperar a que la ciencia nos alcance.

Hoy Isabel ya tiene 6 años, es una niña intrépida, le gusta mucho bailar, es muy alegre y disfruta mucho de tener amigos. Continuamos sin quitar el dedo del renglón con terapias y escuelita especial pero, hoy por hoy, lo veo como una bendición.

Me gustaría agregar la bienvenida a las mamitas y familias nuevas en esto. Hoy por hoy salimos adelante gracias al apoyo de los grupos de AP y el apoyo de Rady Children's Hospital.

Atentamente,
Vany

I'm Isabel's mother. My daughter was diagnosed with Propionic Acidemia when she was 10 days old. From day one, I felt something wasn't right. I don't know how to explain it. All I'll say is: "Don't ignore that feeling, that mommy instinct."

The first two years were very difficult, being in and out of the hospital and learning to spot those red flags that signaled a possible relapse. This taught us that accepting challenges is important, and also, appreciating the me when the two of us are together.

Life with PA is difficult because of the financial obstacles, fatigue, and uncertainty, but ultimately, I believe life settles, and PA teaches us that we are capable of unthinkable things for our children. I believe we must take one step at a time and never lose faith, waiting for science to catch up with us.

Today Isabel is 6 years old, she is a fearless girl, she loves to dance, she is very cheerful and she really enjoys having friends. We continue to work tirelessly on therapies and special school, but today, I see it as a blessing.

I'd like to add a welcome to new moms and families. Today we're moving forward thanks to the support of the PA groups and Rady Children's Hospital.

Sincerely,
Vany

MISSION: The Propionic Acidemia Foundation is dedicated to finding improved treatments and a cure for Propionic Acidemia by funding research and providing information and support to families and medical professionals.

VISION: To create a future where Propionic Acidemia can be prevented, and any affected individual can be cured and live a productive life.

PAF OUTREACH AND FUNDRAISING SPOTLIGHT

UPCOMING EVENTS

- OH Families Fall Fest, Athens, OH-11/1
- The TCS New York City Marathon 2025-11/2 (page 3)
- Low Protein Annual Meeting, Rosemont, IL-11/15 (page 10)

PAST EVENTS

- Low Protein Community Virtual New Parent Cafe-4/27
- Presented at ASGCT Meeting-New Orleans, LA-5/16
- Presented at BIO 2025 International Convention-Boston, MA 6/17
- Propionic Acidemia Conference, Advancing Research and Care Dalton, OH-7/11-7/12 (PAGE 1)

MATCHING DONATIONS & VOLUNTEER HOURS

This may enable you to double your donation. Check with Human Resources to see if your employer matches. Some companies have a volunteer program and will donate based on your volunteer hours. PAF is always looking for volunteers.

DEDICATED GIFTS FROM INDIVIDUALS

- IN HONOR OF: Gabriel Lopez, Kate Lowry,Trent McKinley, Jordan Simmons,
- IN MEMORY OF: Megan Manderfield, Jordan Franks, Talii Smith

FACEBOOK

Thank you to all of our Facebook Fundraisers and people that donated to their fundraising pages for birthdays, #GivingTuesday or just because: Tammy Toler Brown, Danny Denice Harris, Andrea Metcalf, Brian Kane, Vivian Sanders, and Jenn Simmons.

INTERNET

Thank you for using iGive, Goodsearch, and Bing and selling on eBay. Every dollar helps.

STOCK DONATIONS

PAF accepts stock donations. Please email paf@pafoundation.com with any questions.

BIO INTERNATIONAL CONVENTION

AMP®BGTC at ASGCT ANNUAL MEETING

Propionic Acidemia Foundation
P.O. Box 151
Deerfield, IL. 60015

SEARCHING FOR A CURE
HOPE FOR OUR CHILDREN

PROPIONIC ACIDEMIA FOUNDATION

Connect with us:

pafoundation.com
paf@pafoundation.com
Patient Registry: paregistry.org
847-497-0977
/propionicacidemia
/company/propionic-acidemia-foundation
/propionic_acidemia/

Publication Note: The PAF Newsletter is published twice a year. Readers may subscribe by writing to PAF, registering online or calling 847-497-0977. Letters and article submissions are welcome for consideration and may be sent to paf@pafoundation.com or mailed to Propionic Acidemia Foundation, P.O. Box 151, Deerfield, IL 60015-4421. If you would like to be removed from our mailing list or receive the newsletter via email, please contact us.