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Conference Proceedings

Phenylketonuria Scientific Review Conference: State of the science and future research needs[☆]

Kathryn M. Camp [a,*,1,2], Melissa A. Parisi [b,1], Phyllis B. Acosta [c], Gerard T. Berry [d], Deborah A. Bilder [e], Nenad Blau [f,g], Olaf A. Bodamer [h], Jeffrey P. Brosco [i], Christine S. Brown [j], Alberto B. Burlina [k], Barbara K. Burton [l], Christine S. Chang [m], Paul M. Coates [a], Amy C. Cunningham [n], Steven F. Dobrowolski [o], John H. Ferguson [p], Thomas D. Franklin [j], Dianne M. Frazier [q], Dorothy K. Grange [r], Carol L. Greene [s], Stephen C. Groft [p], Cary O. Harding [t], R. Rodney Howell [h], Kathleen L. Huntington [t], Henrietta D. Hyatt-Knorr [p], Indira P. Jevaji [u], Harvey L. Levy [d], Uta Lichter-Konecki [v], Mary Lou Lindegren [w], Michele A. Lloyd-Puryear [a,2], Kimberlee Matalon [x], Anita MacDonald [y], Melissa L. McPheeters [z], John J. Mitchell [aa], Shideh Mofidi [ab], Kathryn D. Moseley [ac], Christine M. Mueller [ad], Andrew E. Mulberg [ae], Lata S. Nerurkar [p], Beth N. Ogata [af], Anne R. Pariser [ae], Suyash Prasad [ag], Gabriella Pridjian [n], Sonja A. Rasmussen [ah], Uma M. Reddy [b], Frances J. Rohr [ai], Rani H. Singh [c], Sandra M. Sirrs [aj], Stephanie E. Stremer [ak], Danilo A. Tagle [al], Susan M. Thompson [am], Tiina K. Urv [b], Jeanine R. Utz [an], Francjan van Spronsen [ao], Jerry Vockley [o], Susan E. Waisbren [d], Linda S. Weglicki [ap], Desirée A. White [aq], Chester B. Whitley [an], Benjamin S. Wilfond [ar], Steven Yannicelli [as], Justin M. Young [at]

[a] *Office of Dietary Supplements, National Institutes of Health, Bethesda, MD 20982, USA*
[b] *Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD 20892, USA*
[c] *Emory University, Atlanta, GA 30033, USA*
[d] *Boston Children's Hospital, Harvard Medical School, Boston, MA 02115, USA*
[e] *Department of Psychiatry, University of Utah, Salt Lake City, UT 84108, USA*
[f] *University Children's Hospital, Heidelberg, Germany*
[g] *University Children's Hospital, Zürich, Switzerland*
[h] *University of Miami Miller School of Medicine, Miami, FL 33136, USA*

Abbreviations: AAV, adeno-associated virus; ACMG, American College of Medical Genetics and Genomics; AHRQ, Agency for Healthcare Research and Quality; BH_4, tetrahydrobiopterin; BMD, bone mineral density; CDE, Common Data Element; CHD, congenital heart disease; CNS, central nervous system; COA, clinical outcome assessment; DXA, dual-energy X-ray absorptiometry; DHA, docosahexaenoic acid; DHPR, dihydropteridine reductase; DRI, Dietary Reference Intake; EPC, Evidence-based Practice Center; FDA, U.S. Food and Drug Administration; GMDI, Genetic Metabolic Dietitians International; GMP, glycomacropeptide; HPA, hyperphenylalaninemia; IEM, inborn errors of metabolism; IQ, intelligence quotient; LNAA, large neutral amino acids; MPKCUS, Maternal PKU Collaborative Study; MPKUS, maternal PKU syndrome; MRI, magnetic resonance imaging; NBSTRN, Newborn Screening Translational Research Network; NDSI, nutrition and dietary supplement interventions; NICHD, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development; NIH, National Institutes of Health; ODS, Office of Dietary Supplements; ORDR, Office of Rare Diseases Research; PAH, phenylalanine hydroxylase; PAL, phenylalanine ammonia lyase; PEG, polyethylene glycol; Phe, phenylalanine; PKU, phenylketonuria; PKUDOS, Phenylketonuria [PKU] Demographic, Outcomes, and Safety Registry; RUSP, Recommended Uniform Screening Panel; SIMD, Society for Inherited Metabolic Disorders; SOE, strength of evidence; START, Sapropterin Therapy Actual Response Test; Tyr, tyrosine.

☆ The findings and conclusions of this report are those of the authors and do not necessarily represent the views of the National Institutes of Health, the U.S. Food and Drug Administration, the Centers for Disease Control and Prevention, the Centers for Medicare & Medicaid Services, the Agency for Healthcare Research and Quality, or the U.S. Department of Health and Human Services.

* Corresponding author at: 6100 Executive Boulevard, Rockville, MD 20892, USA. Fax: +1 301 480 1845.

E-mail addresses: campkm@od.nih.gov (K.M. Camp), parisima@mail.nih.gov (M.A. Parisi), pja1933@gmail.com (P.B. Acosta), gerard.berry@childrens.harvard.edu (G.T. Berry), deborah.bilder@hsc.utah.edu (D.A. Bilder), nenad.blau@med.uni-heidelberg.de (N. Blau), obodamer@med.miami.edu (O.A. Bodamer), jbrosco@med.miami.edu (J.P. Brosco), christine.brown@npkua.org (C.S. Brown), alberto.burlina@unipd.it (A.B. Burlina), bburton@luriechildrens.org (B.K. Burton), christine.chang@ahrq.hhs.gov (C.S. Chang), coatesp@od.nih.gov (P.M. Coates), acunnin@tulane.edu (A.C. Cunningham), dobrowolskis@upmc.edu (S.F. Dobrowolski), jferg@helix.nih.gov (J.H. Ferguson), tom.franklin@npkua.org (T.D. Franklin), dianne_frazier@med.unc.edu (D.M. Frazier), grange_d@kids.wustl.edu (D.K. Grange), cgreene@peds.umaryland.edu (C.L. Greene), stephen.groft@nih.gov (S.C. Groft), hardingc@ohsu.edu (C.O. Harding), rhowell@miami.edu (R.R. Howell), huntingt@ohsu.edu (K.L. Huntington), henrietta.hyatt-knorr@nih.gov (H.D. Hyatt-Knorr), indira.jevaji@cms.hhs.gov (I.P. Jevaji), harvey.levy@childrens.harvard.edu (H.L. Levy), ulichter@cnmc.org (U. Lichter-Konecki), marylou.lindegren@vanderbilt.edu (M.L. Lindegren), lloydpuryearma@od.nih.gov (M.A. Lloyd-Puryear), kmatalon@uh.edu (K. Matalon), anita.macdonald@bch.nhs.uk (A. MacDonald), melissa.mcpheeters@vanderbilt.edu (M.L. McPheeters), john.mitchell@muhc.mcgill.ca (J.J. Mitchell), shideh_mofidi@nymc.edu (S. Mofidi), kmoseley@usc.edu (K.D. Moseley), christine.mueller@nih.gov (C.M. Mueller), andrew.mulberg@fda.hhs.gov (A.E. Mulberg), lnerurkar@gmail.com (L.S. Nerurkar), bogata@uw.edu (B.N. Ogata), anne.pariser@fda.hhs.gov (A.R. Pariser), sprasad@bmrn.com (S. Prasad), pridjian@tulane.edu (G. Pridjian), skr9@cdc.gov (S.A. Rasmussen), reddyu@mail.nih.gov (U.M. Reddy), frances.rohr@childrens.harvard.edu (F.J. Rohr), rsingh@emory.edu (R.H. Singh), sandra.sirrs@vch.ca (S.M. Sirrs), sstremer@yahoo.com (S.E. Stremer), danilo.tagle@nih.gov (D.A. Tagle), sue.thompson@health.nsw.gov.au (S.M. Thompson), urvtiin@mail.nih.gov (T.K. Urv), jutz1@fairview.org (J.R. Utz), f.j.van.spronsen@umcg.nl (F. van Spronsen), vockleyg@upmc.edu (J. Vockley), susan.waisbren@childrens.harvard.edu (S.E. Waisbren), weglickils@mail.nih.gov (L.S. Weglicki), dawhite@wustl.edu (D.A. White), whitley@umn.edu (C.B. Whitley), benjamin.wilfond@seattlechildrens.org (B.S. Wilfond), steven.yannicelli@nutricia.com (S. Yannicelli), jmichaelyoung@yahoo.com (J.M. Young).

[1] These authors contributed equally to this work.
[2] Consultant.

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[i] University of Miami Mailman Center for Child Development, Miami, FL 33101, USA
[j] National PKU Alliance, USA
[k] University Hospital, 35128 Padova, Italy
[l] Ann and Robert H. Lurie Children's Hospital of Chicago, Chicago, IL 60611, USA
[m] Agency for Healthcare Research and Quality, Rockville, MD 20850, USA
[n] Tulane University Medical School, Hayward Genetics Center, New Orleans, LA 70112, USA
[o] University of Pittsburgh, Pittsburgh, PA 15224, USA
[p] Office of Rare Diseases Research, National Center for Advancing Translational Sciences, National Institutes of Health, Bethesda, MD 20982, USA
[q] University of North Carolina, Chapel Hill, NC 27599, USA
[r] Washington University School of Medicine, St. Louis Children's Hospital, St. Louis, MO 63110, USA
[s] University of Maryland School of Medicine, Baltimore, MD 21201, USA
[t] Oregon Health & Science University, Portland, OR 97239, USA
[u] Office of Research on Women's Health, National Institutes of Health, Bethesda, MD 20817, USA
[v] George Washington University, Children's National Medical Center, Washington, DC 20010, USA
[w] Vanderbilt University School of Medicine, Nashville TN 37203, USA
[x] University of Houston, Houston, TX 77204, USA
[y] Birmingham Children's Hospital, Birmingham B4 6NH, UK
[z] Vanderbilt Evidence-based Practice Center, Institute for Medicine and Public Health, Nashville, TN 37203, USA
[aa] McGill University Health Center, Montreal, Quebec H3H 1P3, Canada
[ab] Maria Fareri Children's Hospital of Westchester Medical Center, Valhalla, NY 10595, USA
[ac] University of Southern California Keck School of Medicine, Los Angeles, CA 90033, USA
[ad] Office of Orphan Products Development, U.S. Food and Drug Administration, Silver Spring, MD 20993, USA
[ae] Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, MD 20993, USA
[af] University of Washington, Seattle, WA 98195, USA
[ag] BioMarin Pharmaceutical Inc., San Rafael, CA 94901, USA
[ah] Centers for Disease Control and Prevention, Atlanta, GA 30333, USA
[ai] Boston Children's Hospital, Boston, MA 02115, USA
[aj] Vancouver General Hospital, University of British Columbia, Vancouver V5Z 1M9, Canada
[ak] PKU & Allied Disorders of Wisconsin, Madison, WI 53705, USA
[al] National Center for Advancing Translational Sciences, National Institutes of Health, Bethesda, MD 20892, USA
[am] The Children's Hospital at Westmead, Sydney, NSW 2145, Australia
[an] University of Minnesota, Minneapolis, MN 55455, USA
[ao] University of Groningen, University Medical Center of Groningen, Beatrix Children's Hospital, Netherlands
[ap] National Institute of Nursing Research, National Institutes of Health, Bethesda, MD 20892, USA
[aq] Department of Psychology, Washington University, St. Louis, MO 63130, USA
[ar] Seattle Children's Research Institute, University of Washington School of Medicine, Seattle, WA 98101, USA
[as] Nutricia North America, Rockville, MD 20850, USA
[at] The Young Face, Facial Plastic and Reconstructive Surgery, Cumming, GA 30041, USA

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ABSTRACT

New developments in the treatment and management of phenylketonuria (PKU) as well as advances in molecular testing have emerged since the National Institutes of Health 2000 PKU Consensus Statement was released. An NIH State-of-the-Science Conference was convened in 2012 to address new findings, particularly the use of the medication sapropterin to treat some individuals with PKU, and to develop a research agenda. Prior to the 2012 conference, five working groups of experts and public members met over a 1-year period. The working groups addressed the following: long-term outcomes and management across the lifespan; PKU and pregnancy; diet control and management; pharmacologic interventions; and molecular testing, new technologies, and epidemiologic considerations. In a parallel and independent activity, an Evidence-based Practice Center supported by the Agency for Healthcare Research and Quality conducted a systematic review of adjuvant treatments for PKU; its conclusions were presented at the conference. The conference included the findings of the working groups, panel discussions from industry and international perspectives, and presentations on topics such as emerging treatments for PKU, transitioning to adult care, and the U.S. Food and Drug Administration regulatory perspective. Over 85 experts participated in the conference through information gathering and/or as presenters during the conference, and they reached several important conclusions. The most serious neurological impairments in PKU are preventable with current dietary treatment approaches. However, a variety of more subtle physical, cognitive, and behavioral consequences of even well-controlled PKU are now recognized. The best outcomes in maternal PKU occur when blood phenylalanine (Phe) concentrations are maintained between 120 and 360 μmol/L before and during pregnancy. The dietary management treatment goal for individuals with PKU is a blood Phe concentration between 120 and 360 μmol/L. The use of genotype information in the newborn period may yield valuable insights about the severity of the condition for infants diagnosed before maximal Phe levels are achieved. While emerging and established genotype–phenotype correlations may transform our understanding of PKU, establishing correlations with intellectual outcomes is more challenging. Regarding the use of sapropterin in PKU, there are significant gaps in predicting response to treatment; at least half of those with PKU will have either minimal or no response. A coordinated approach to PKU treatment improves long-term outcomes for those with PKU and facilitates the conduct of research to improve diagnosis and treatment. New drugs that are safe, efficacious, and impact a larger proportion of individuals with PKU are needed. However, it is imperative that treatment guidelines and the decision processes for determining access to treatments be tied to a solid evidence base with rigorous standards for robust and consistent data collection. The process that preceded the PKU State-of-the-Science Conference, the conference itself, and the identification of a research agenda have facilitated the development of clinical practice guidelines by professional organizations and serve as a model for other inborn errors of metabolism.

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