Issues with European guidelines for phenylketonuria - Author's reply

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Published in:
Lancet Diabetes & Endocrinology

DOI:
10.1016/S2213-8587(17)30202-4

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2017

honoraria from Nutricia and Vitaflo; investigator payments for clinical trial work with Genzyme, Shire, Biomarin, Ultragenyx, Amicus Pharmaceuticals, and Vitaflo UK; and investigator-led research funding from Nutricia and Sanofi Genzyme. SG declares no competing interests. GFH declares that over the past 3 years in the area of inherited metabolic diseases he has received travel and accommodation support from Danone and Sobi. SK declares that over the past 3 years in the area of inherited metabolic diseases he has received travel and accommodation support and honoraria for lectures and educational activities from Nutricia Metabolics, Vitaflo, and Orphan Europe SARL (Recordati group). His institution has received research funding from Vitaflo, Orphan Europe SARL (Recordati group), and Horizon Pharma International. MLi declares that over the past 3 years he has received accommodation support and honoraria for lectures and educational activities from Nutricia Metabolics and Orphan Europe. JZ declares that over the past 3 years in the area of inherited metabolic diseases he has received travel and accommodation support from Merck Serono and Nutricia Metabolics. His institution has received research funding from Merck Serono and Biomarin as well as funding for educational activities from Nutricia Metabolics and Genzyme.

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Authors' reply

Peter Burgard and colleagues argue that two key statements from our key European guidelines on phenylketonuria[1] are too contentious.

First, referring to the work of Weglage and colleagues,[2] who investigated adolescents and adults with mild hyperphenylalaninaemia, Burgard and colleagues claim that a cutoff value of blood phenylalanine of 360 µmol/L might be too strict to commence treatment in infancy. We opted for the cutoff of 360 µmol/L on the basis of studies with children with mild hyperphenylalaninemia showing worse outcomes when untreated phenylalanine was greater than 360 µmol/L,[3,4] but recognised that other data using advanced statistical methods[5] are essential to fine-tune future statements.

Second, Burgard and colleagues suggest that we wrongly interpreted results for adults with phenylketonuria presented in the meta-analysis by Albrecht and colleagues.[6] However, these data are contradicted by other studies discussed in the European guideline,[1] including the randomised, double-blind, crossover study of reported by ten Hoedt and colleagues.[7] Research data contradicts the opinion of Burgard and colleagues that adult patients with higher blood phenylalanine are happy and unable to adhere to treatment.[8,9]

In the early 1990s, some paediatricians and researchers considered treatment after age 5–6 years unnecessary,[10] and Azen and colleagues reported that in children phenylalanine concentrations of 900 µmol/L were safe.[11] We now know that in childhood the upper target phenylalanine concentrations should be a maximum of 360 µmol/L.[1]

Data are simply not available to be less contentious. Rather than presenting guidelines based on single studies that might be dangerously liberal in interpretation, we opted to use the widely accepted Delphi method to reach consensus.

Burgard and colleagues question the formal commissioning of our group. The European phenylketonuria guidelines group is multidisciplinary, consisting of researchers (who collectively have written 288 scientific publications on phenylketonuria) and experienced clinical professionals; has widely consulted other professionals, parents, and patients; and has been fully transparent at each stage of guideline development.

When developing international guidelines, we would support the possibility to seek commissioning

by international societies like the Society for the Study of Inborn Errors of Metaolism and the European Reference Network rather than seeking commisioning by national societies. Remaining within national frameworks is now outdated practice. European guidelines should not concern (national) politics, but encompass consensus by experts when evidence is unavailable, as stated in the editorial referred to by Burgard and colleagues.[12]

Our condensed European phenylketonuria guidelines[1] do what they should: present key statements based on balanced assessment of available data. They are applicable to daily practice and provide a foundation for new research.[13] The next European phenylketonuria guidelines should be developed in 5 years, giving researchers time to extend current knowledge. This iterative process will enable evidence to slowly replace consensus.

KA has been a member of the European Nutrition Expert Panel (Merck Serono International). AB-Q has received honoraria as a speaker for Nutricia International, Vitaflo International, Merck Serono, and Recordati, and is a member of the European Nutrition Expert Panel (supported by Merck Serono International), the Sapropterin Advisory Board (supported by Merck Serono International and BioMarin), and KAMPER Advisory Board (supported by Merck Serono International, BioMarin). NB has been a member of the Merck Serono and BioMarin and Censa Pharmaceuticals scientific advisory boards for phenylketonuria (PKU), and has received grants and honoraria from Merck Serono and BioMarin. AMB, AB, FF, MG, and ACM have been members of scientific advisory boards for phenylketonuria (supported by Merck Serono, BioMarin, and Nutricia International). AMB has received grants from Nutricia International and honoraria from Merck Serono, BioMarin, and Nutricia International. JC and MG have received honoraria as consultants and speakers from Merck Serono and Nutricia International/Danone. FF has received honoraria from BioMarin, Merck Serono, and Nutricia International/Danone. SCH has participated in strategic advisory boards and received consultant and speaker honoraria from Merck Serono, Biomarin, and Nutricia International. SK has received honoraria from Merck Serono and BioMarin. VL has received honoraria as a consultant from Nutricia International. AM has received research funding and honoraria from Nutricia International, Vitaflo International, and Merck Serono, chairs the European Nutrition Expert Panel (supported by Merck Serono International), has been a member of the Sapropterin advisory board (supported by Merck Serono International), is a member of the Advisory Boards Element (Danone-Nutricia), and is a member of the scientific advisory board of Arla Foods International. FM has received consultant and speaker honoraria from Merck Serono, Nutricia International, Vitaflo International, and Arla Foods International, and research grants from Merck Serono. ACM has received research funding from Nutricia International, Vitaflo International, and Merck Serono, and has received honoraria as a speaker from Merck Serono and Arla Foods International. MvR was a member of the European Nutritionist Expert Panel in Phenylketonuria (supported by Merck Serono International; until 2015), is a member of the ELEMENT (Leading Education in Metabolic Error Nutritional Therapy) steering committee for Nutricia International, and has received grants and fees for educational and research activities from Nutricia International and Orphan Europe. FJvS is a member of scientific advisory boards for phenylketonuria and aminoacid defects that are supported by Merck Serono (past), BioMarin, Arla Foods International, SoBi, and Nutricia International, has received research grants from Nutricia International, SoBi, Alexion, and Merck Serono, and honoraria as a consultant and speaker from Merck Serono and Nutricia International/Danone, and honoraria as a speaker from Vitaflo International. FKT has received grants from Vitaflo and honoraria as a speaker from Merck Serono. AMJvW declares no competing interests.

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