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Undiagnosed Phenylketonuria Can Exist Everywhere: Results From an International Survey

Annemiek M. J. van Wegberg, MSc[1], Friedrich Trefz, MD[2], Maria Gizewska, MD, PhD[3], Sibtain Ahmed, MBBS, FCPS[4], Layachi Chabraoui, MD, PhD[5,6], Maha S. Zaki, MD, PhD[7], François Maillot, MD, PhD[8], and Francjan J. van Spronsen, MD, PhD[1], on behalf of the Study Group on Missed PKU and Missed to Follow-Up*

Many countries do not have a newborn screening (NBS) program, and immigrants from such countries are at risk for late diagnosis of phenylketonuria (PKU). In this international survey, 52 of 259 patients (20%) with late diagnosed PKU were immigrants, and 145 of the 259 (55%) were born before NBS or in a location without NBS. *(J Pediatr 2021;239:231-4).*

Newborn screening (NBS) programs for phenylketonuria (PKU; OMIM 261600) have been successfully implemented in many countries for more than 50 years; however, globally there are still countries without NBS or with an ineffective NBS program.[1,2] Consequently, late diagnosis of PKU still occurs in countries with no NBS programs or without national coverage.[3,4]

Immigrants or refugees from countries without NBS or with recently implemented NBS programs are at risk for missed diagnoses.[4-6] In addition to the lack of national NBS programs, technical issues, such as false-negative results,[5,7,8] failures in follow-up procedures,[8-10] and cultural circumstances,[11] are reported reasons for late diagnosis or delayed treatment of PKU.

The aim of this study was to explore the occurrence of and reasons for late PKU diagnosis through an international survey that includes metabolic centers that diagnose and treat patients with PKU, with the hypothesis that organizational issues were of more importance than technical failures.

Methods

Questionnaire Development

A short Web-based survey was developed in 2020 using Qualtrics software (**Appendix 2**; available at www.jpeds.com). Using adaptive questioning, participants answered 6-12 questions. The technical functionality was tested before the survey was distributed.

Distribution

An anonymous survey link was distributed in June and July 2020 using the mailing lists of Metab-L and Metab-ERN, with reminders distributed in July-August. The Society for Inherited Metabolic Disorders posted a message on their Web site in August 2020. In addition, individual professionals were emailed in June 2020 and asked to distribute the survey within their countries. The Society for the Study of Inborn Errors of Metabolism referred to the Metab-ERN as a more suitable distribution channel.

Data Analysis

Data were collected from June 25 to September 7, 2020. Respondents' general information (name, city, and name of center) were checked to control for multiple entries from the same center. When applicable, participants were individually contacted to detect duplicate cases and for clarification.

Data were analyzed in SPSS version 23 (IBM) and are presented as descriptive data. Multiple responses per center were allowed because different healthcare professionals working in different departments of the same center may have different experiences (**Appendix 3**; available at www.jpeds.com).

Ethics

Ethical consent was not sought, given that the primary purpose of the survey was to explore the occurrence of late diagnosis of PKU without collecting personal data. The purpose was clarified in the email invitation and at the beginning of the questionnaire. It was also stated that the data would be saved in an anonymized form and no personal data was

NBS	Newborn screening
Phe	Phenylalanine
PKU	Phenylketonuria

From the [1]Division of Metabolic Diseases, Beatrix Children's Hospital, University Medical Center Groningen, Groningen, The Netherlands; [2]Dietmar Hopp Metabolic Center, University Children's Hospital, Heidelberg, Germany; [3]Department of Pediatrics, Endocrinology, Diabetology, Metabolic Diseases, and Cardiology of the Developmental Age, Pomeranian Medical University, Szczecin, Poland; [4]Section of Chemical Pathology, Department of Pathology and Laboratory Medicine, Aga Khan University, Karachi, Pakistan; [5]Central Laboratory of Biochemistry, University Hospital Ibn Sina of Rabat, Rabat, Morocco; [6]Faculty of Pharmacy, University Euromed of Fez, Fez, Morocco; [7]Human Genetics and Genome Research Division, Clinical Genetics Department, National Research Center, Cairo, Egypt; and [8]Internal Medicine Department, University Hospital of Tours, UMR INSERM 1253 "iBrain", Tours, France

*A list of additional members of the Study Group on Missed PKU and Missed to Follow-Up is available at www.jpeds.com (**Appendix 1**).

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collected. Participants gave their consent by their voluntary completion and submission of the online questionnaire.

Results

A total of 414 responses were registered, 290 of which answered the first question. In total, 259 cases were reported by 77 different centers from 36 countries (**Figures 1** and **2**; both available at www.jpeds.com). Details of the cases are reported in **Appendix 4**.

Age at Diagnosis

The age at diagnosis ranged from <1 year to >18 years (**Table**). Approximately one-half (n = 140 of 259) of the patients were diagnosed at age <5 years, 25% (64 of 259) were diagnosed at age 5-18 years, and 21% (n = 55 of 259) were diagnosed at age ≥18 years.

Symptomatic or Not

Ninety percent of the patients (n = 233 of 259) were symptomatic at the time of diagnosis. Eighteen patients did not have symptoms, in 5 patients it was unclear, and these data were missing for 3 patients (**Table**). Reported symptoms in the comments section of the survey included mild or severe (neuro)developmental delay, autism, and epilepsy (**Appendix 4**). Eleven of the asymptomatic patients were children, and 6 were adults; in 1 case, age was not clear.

Reason for Missed Diagnosis

Most cases (n = 84) were reported to be missed because of no or partial coverage of the NBS program for PKU, and in 61 cases, the patients were born before the implementation of an NBS program (**Table** and **Figure 3**). Fifty-two of these patients were immigrants or refugees. These cases were reported in Europe (n = 31), North America (n = 18), and Oceania (n = 3). Syria was the most common country of origin.

Twenty-seven cases were missed because of technical failures of the NBS, including false-negative results, followed by no follow-up of the positive result, incorrect interpretation of the result, and no analysis of the blood spot card. In 19 cases, the reason for the missed diagnosis was unclear, and 15 cases were missed for other reasons. The corresponding comments are presented in **Appendix 5** (available at www.jpeds.com).

Reason for Referral

Ninety percent (n = 232 of 259) of the cases were referred through selective screening, such as clinical symptoms, family screening, or maternal PKU syndrome. Only 3 cases were referred by a general policy to screen immigrants. This was the case in Turkey and Sweden. Fifteen cases were referred otherwise (**Appendix 5**; available at www.jpeds.com).

Discussion

The present survey describes cases of PKU missed by NBS programs between 2015 and 2020. The high number of cases was unexpected and supports the hypothesis that organizational issues rather than technical failures are the cause of this high number of late diagnosed patients. The number of undiagnosed PKU cases is most likely larger than this survey suggests, owing to cases not known to survey respondents, such as those in group homes (with or without a diagnosis), those not receiving medical attention, and those with milder than expected symptoms, as shown in recent studies.[12,13] Limitations of the study include an inability to align survey answers with cases when multiple cases were reported; ambiguity with reported cases, such as reporting a patient in the comments section; and potential underreporting by survey participants.

A total of 259 cases were detected. The patient age at diagnosis ranged widely, from <1 to >18 years, but most were aged <5 years, and 21% were aged >18 years. In general, IQ can be improved when PKU is treated before approximately age 7 years, which emphasizes the importance of early diagnosis, and diagnosis at a later age likely affects behavioral issues rather than directly affecting neurocognitive outcomes.[14,15] Even though the potential effect of treatment is somewhat less than in young children, detection of PKU in adults is still relevant, both to prevent maternal PKU syndrome and to prevent such issues as neuropsychiatric symptoms.[12,13] In addition, for at least some severely affected adults with PKU, treatment can decrease challenging behaviors, improve quality of life, and reduce health care costs and thus have significant long-term socioeconomic implications for society.[16,17]

Table. Answer specifications

1. What was the age at diagnosis of the patient? (n = 259)					
<1 year	1-2 years	2-3 years	3-5 years	5-18 years	>18 years
49	29	30	32	64	55
2. Was the patient symptomatic when diagnosed? (n = 256)					
Yes	No	Don't know			
233	18	5			
3. What was the reason for the missed diagnosis through NBS? (n = 258)					
No full NBS coverage	born before NBS	Technical failure	Immigrant/ refugee	Unclear	Other*
84	61	27	52	19	15
4. How was the patient referred to you or your center? (n = 250)					
Selective screening	General policy	Other			
232	3	15			

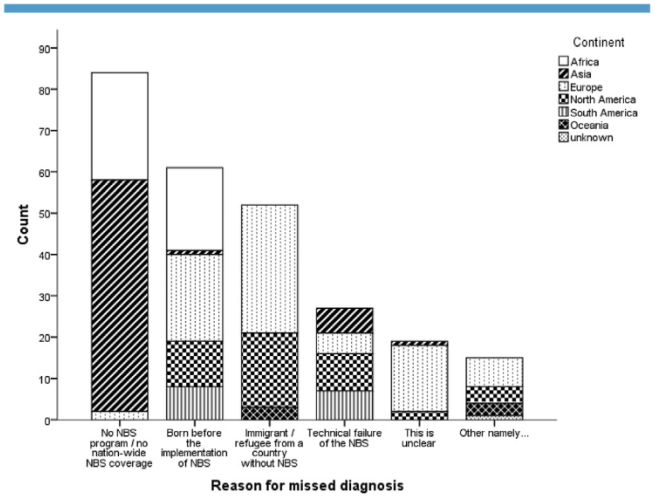

Figure 3. Reasons for missed/late diagnosis per continent (total n = 258). 1) No NBS program/no nationwide coverage: Africa (n = 26; Morocco), Asia (n = 56; Hong Kong, India, Indonesia, Malaysia, Oman, Pakistan, Saudi Arabia), and Europe (n = 2; United Kingdom). 2) Born before NBS implementation: Europe (n = 21; Croatia, Finland, France, Italy, Poland, Turkey, United Kingdom), Africa (n = 20; Egypt), North America (n = 11; Canada, Mexico, United States), South America (n = 8; Brazil, Peru, Uruguay), and Asia (n = 1; Hong Kong). 3) Immigrant/refugee: Europe (n = 31; Belgium, Denmark, France, Germany, Italy, The Netherlands, Spain, Sweden, Switzerland, Turkey, United Kingdom), North America (n = 18; Canada, United States), and Oceania (n = 3; Australia). Countries of origin of the immigrants or refugees were Afghanistan, Armenia, China, Columbia, Egypt, Iran, Iraq, Kosovo, Kuwait, Morocco, Pakistan, North Africa, Sudan, Syria, and Vietnam. 4) Technical failure: North America (n = 9; Mexico, United States), Europe (n = 5; Belgium, Spain, Turkey, United Kingdom), South America (n = 7; Argentina, Brazil), and Asia (n = 6; Georgia, Saudi Arabia).

In this survey, most cases were missed because of organizational issues, including a lack of nationwide coverage of NBS, resulting in a large number of undiagnosed cases as in many countries in northern Africa and the Middle East (**Figure 3**), where PKU is rather frequent.[1,18] Technical failures, such as false-negative NBS results, are becoming rarer owing to the introduction of tandem mass spectrometry.[19] In countries such as Saudi Arabia and Egypt, NBS was introduced only recently (in 2005 and 2015, respectively), leading to family investigations that resulted in a large number of diagnoses from individuals born before NBS implementation.[20,21] In North America and Europe, most missed cases involved immigrants coming from counties without national coverage of NBS.

Given that many countries do not have or only recently have a fully implemented NBS program, immigrants from such countries are at risk of having a missed PKU diagnosis, particularly if the receiving country has not implemented a PKU screening program for immigrants. Common symptoms of untreated PKU are developmental delay, neurocognitive deficits (IQ/executive functioning), and behavioral issues (depression/anxiety/autism), and epilepsy may occur. In refugees, the etiology of mild symptoms such as speech delay in young children can be mistakenly assigned to other factors, such as trauma or unfamiliar language.[22,23] In adult refugees, such symptoms as mild neuropsychological deficits or depression/anxiety symptoms can easily be mistaken as trauma or separation from family or original region.[24,25] In our survey, 6 adults were asymptomatic at diagnosis, in line with previous studies.[12,13] As a result of missed NBS, families often miss the opportunity for genetic counseling and counseling regarding maternal PKU, a condition in which the fetus is affected by a mother with PKU.[26] Because every person deserves an equal chance in treatment and life, existing neonatal screening programs (including, but not restricted, to PKU) in receiving countries should be integrated into a systematic screening policy for all immigrants and refugees of all ages as part of the routine immigration process.

To summarize, many countries do not have or only recently have implemented nationwide NBS. In Western countries, most reported late-diagnosed patients are immigrants from countries without a long history of national coverage of NBS. Accepting that as a fact, it is crucial that receiving countries implement systematic screening programs for immigrants of all ages to detect PKU (and other diseases as included in neonatal screening programs) to improve the prognosis and prevent maternal PKU syndrome. ■

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Reprint requests: Francjan J. van Spronsen, MD, PhD, Division of Metabolic Diseases, Beatrix Children's Hospital, University Medical Center Groningen, Hanzeplein 1, 9700 RB Groningen, The Netherlands. E-mail: f.j.van.spronsen@umcg.nl

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Appendix 1

Additional members of the Study Group on Missed PKU and Missed to Follow-Up

K. Ahring (Copenhagen, Denmark), F. Al Mutairi (Riyadh, Saudi Arabia), J. B. Arnoux (Paris, France), D. Ballhausen (Lausanne, Switzerland), J. Baruteau (London, UK), L. Bernstein (Denver, Colorado), S. Bijarnia-Mahay (New Delhi, India), F. Boemer (Liege, Belgium), A. Bordugo (Verona, Italy), L. Brodosi (Bologna, Italy), S. Brooks (New Brunswick, New Jersey), H. B. Chew (Kuala Lumpur, Malaysia), K. Chyz (Warsaw, Poland), M. Coker (Izmir, Turkey), C. Collingwood (Liverpool, UK), V. Cornejo (Santiago, Chile), M. L. Couce (Santiago de Compostela, Spain), A. Cozens (Edinburgh, UK), S. Dahri (Rabat, Morocco), A. M. Das (Hannover, Germany), C. de Laet (Brussels, Belgium), J. de las Heras Montero (Barakaldo, Spain), A. de Vreugd (Rotterdam, The Netherlands), F.G. Debray (Liege, Belgium), M. Dercksen (Potchefstroom, South Africa), M. Descartes (Birmingham, Alabama), L. Diogo (Coimbra, Portugal), E. Drogari (Athens, Greece), H. Eiroa (Buenos Aires, Argentina), F. T. Eminoglu (Ankara, Turkey), G. M. Enns (Stanford, California), F. Eyskens (Antwerp, Belgium), F. Feillet (Nancy, France), S. Ford (Bristol, UK), L. Franzson (Reykjavik, Iceland), P. Freisinger (Reutlingen, Germany), P. Garcia (Coimbra, Portugal), O. Grafakou (Heraklion, Greece), G. Gramer (Heidelberg, Germany), S. Gray (Farmington, Connecticut), U. Groselj (Ljubljana, Slovenia), S.C. Grünert (Freiburg, Germany), D. Haas (Heidelberg, Germany), B. Handoom (Riyadh, Saudi Arabia), T. B. Harte (Rochester, Minnesota), C. Hendriksz (Pretoria, South Africa), R. S. Heredia (Brasilia, Brazil), J. Hertecant (Al Ain, United Arab Emirates), T. Hoi-Yee Wu (Manchester, UK), A. Inwood (Brisbane, Australia), S. S. Jamuar (Singapore), P. Jesina (Prague, Czech Republic), J. J. Jonsson (Reykjavik, Iceland), A. Jovanovic (Salford, UK), I. Kern (Geneva, Switzerland), S. Kilavuz (Van, Turkey), I. Knerr (Dublin, Ireland), D. Kor (Adana, Turkey), D. Korycinska-Chaaban (Warsaw, Poland), M. Kreile (Riga, Latvia), B. Kumru (Gaziantep, Turkey), B. Lanpher (Rochester, Minnesota), R. Lapatto (Helsinki, Finland), C. Lavigne (Angers, France), E. Leao-Teles (Porto, Portugal), V. Leuzzi (Rome, Italy), N. Longo (Salt Lake City, Utah), A. Lopez-Uriarte (Monterrey, Mexico), C.M.A. Lubout (Groningen, The Netherlands), A. MacDonald (Birmingham, UK), E. M. Megdad (Riyadh, Saudi Arabia), J. Mitchell (Montreal, Canada), F. Mochel (Paris, France), P. J. Moreno-Lozano (Barcelona, Spain), A. Morris (Manchester, UK), C. F. Moura de Souza (Porto Alegre, Brazil), T. Munoz (Santiago, Chile), P. I. Nevalainen (Tampere, Finland), M. Oscarson (Stockholm, Sweden), K. Õunap (Tartu, Estonia), S. Paci (Milan, Italy), G. M. Pastores (Dublin, Ireland), P. L. Pearl (Boston, Massachusetts), F. B. Piazzon (Sao Paulo, Brazil), J. Pitt (Melbourne, Australia), G. Poon (Hong Kong), F. Porta (Torino, Italy), N. Presner (Buenos Aires), A. A. Rabaty (Erbil, Iraq), K. Reinson (Tallinn, Estonia), P. Reismann (Budapest, Hungary), T. Rink (Minneapolis, Minnesota), J. C. Rocha (Lisbon, Portugal), E. Rodrigues (Porto, Portugal), A. G. Saini (Chandigarh, India), A. Sanchez-Valle (Tampa, Florida), J. Sander (Ronnenberg, Germany), P. Sarkhail (Tehran, Iran), I. V. D. Schwartz (Porto Alegre, Brazil), R. Sharma (Salford, UK), B. Sheng (Hong Kong), K. Siriwardena (Edmonton, Canada), S. Sirrs (Vancouver, Canada), D. R. Sjarif (Jakarta, Indonesia), N. Sondheimer (Toronto, Canada), R. Sparkes (Calgary, Canada), N. Specola (La Plata, Argentina), K. M. Stepien (Salford, UK), I. Szatmari (Budapest, Hungary), M. Tchan (Sydney, Australia), T. Tkemaladze (Tbilisi, Georgia), C. Tran (Lausanne, Switzerland), M. G. Valle (Buenos Aires, Argentina), M. Vela-Amieva, Ciudad de Mexico, Mexico), M. L. Verdaguer (Mendoza, Argentina), S. A. Vergano (Norfolk, Virginia), P. Vermeersch (Leuven, Belgium), R. Vulturar (Cluj-Napoca, Romania), M. A. E. M. Wagenmakers (Rotterdam, The Netherlands), N. Weinhold (Berlin, Germany), A. B. Williams (Salt Lake City, Utah), W. G. Wilson (Charlottesville, Virginia), D. Zafeiriou (Thessaloniki, Greece), H. Zhang (Shanghai, China), A. Ziagaki (Berlin, Germany), J. Zolkowska (Warsaw, Poland).

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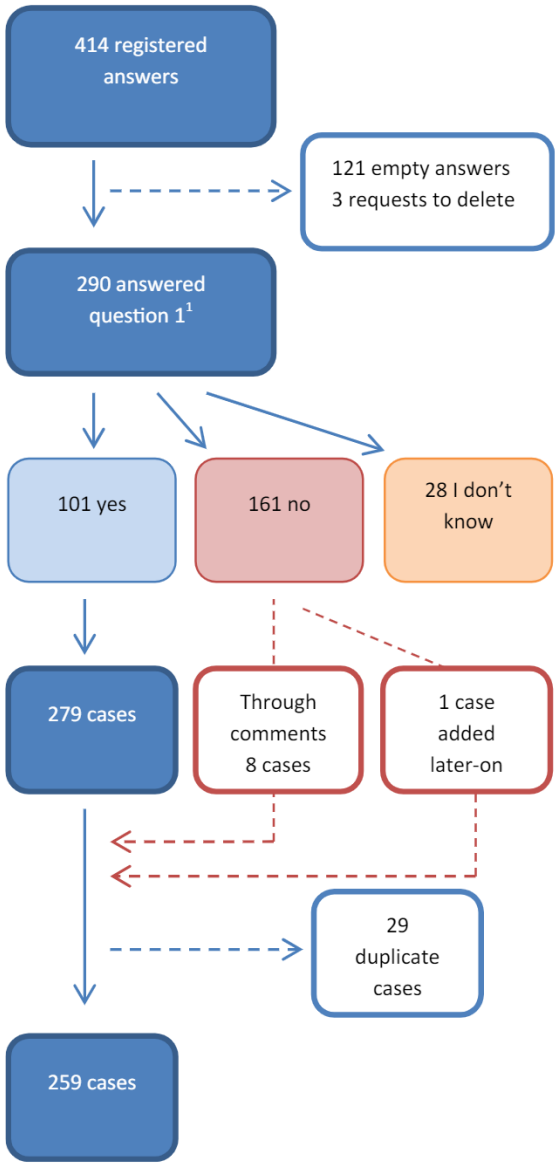

Figure 1. Flowcharts of received responses and collected cases. A total of 414 responses were registered. Of these, 108 were empty, 13 only reported their affiliations, and 3 requested that their answers be deleted. Thus, the first question was answered by 290 respondents. These 290 respondents originated from 56 different countries in Europe (n = 28), Asia (n = 14), South America (n = 6), North America (n = 3), Africa (n = 3), and Oceania (n = 2) (**Appendix 3**). Of the 290 participants who answered the first question, 101 (35%) had diagnosed patients with PKU who were missed by the NBS in the last 5 years. Of the 101 participants who answered "yes," 29 (late-diagnosed PKU) cases were double entries coming from 13 centers. In addition, 16 participants did not complete the rest of the survey, 3 participants were both duplicate and not completed, and 1 participant incorrectly answered "yes." In total, 71 centers reported 250 original cases. In addition, 8 cases were extracted from 5 comments, and 1 case was later added from participants who initially answered that they had not diagnosed any patients. As a result, the survey included a total of 259 reported cases by 77 different centers from 36 countries. [1]Question 1: Did you or your center, in the last 5 years, diagnose patients with PKU who were missed by the newborn screening program?

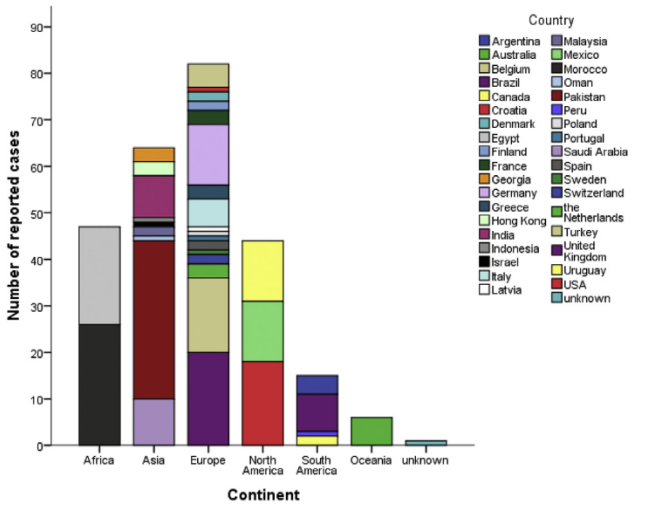

Figure 2. Reported number of cases per continent (total n = 259). Each color represents the number of cases reported for that country. The colors per continent are organized alphabetically.