PEDIATRIC ENDOCRINOLOGY AND INBORN ERRORS OF METABOLISM

SECOND EDITION

KYRIAKIE SARAFOGLOU
GEORG F. HOFFMANN KARL S. ROTH

Mc Graw Hill Education

PEDIATRIC ENDOCRINOLOGY AND INBORN ERRORS OF METABOLISM

NOTICE

Medicine is an ever-changing science. As new research and clinical experience broaden our knowledge, changes in treatment and drug therapy are required. The authors and the publisher of this work have checked with sources believed to be reliable in their efforts to provide information that is complete and generally in accord with the standards accepted at the time of publication. However, in view of the possibility of human error changes in medical sciences, neither the editors nor the publisher nor any other party who has been involved in the preparation or publication of this work warrants that the information contained herein is in every respect accurate or complete, and they disclaim all responsibility for any errors or omissions or for the results obtained from use of the information contained in this work. Readers are encouraged to confirm the information contained herein with other sources. For example and in particular, readers are advised to check the product information sheet included in the package of each drug they plan to administer to be certain that the information contained in this work is accurate and that changes have not been made in the recommended dose or in the contraindications for administration. This recommendation is of particular importance in connection with new or infrequently used drugs.

PEDIATRIC ENDOCRINOLOGY AND INBORN ERRORS OF METABOLISM

Second Edition

Editors

Kyriakie Sarafoglou, MD

Director, Leo Fung Center for Congenital Adrenal Hyperplasia & Disorders of Sex Development
Division of Pediatric Endocrinology
Division of Genetics & Metabolism
University of Minnesota Medical School
Minneapolis, Minnesota, USA

Georg F. Hoffmann, MD

Professor & Chair
University Children's Hospital
Ruprecht-Karls-University Heidelberg
Heidelberg, Baden-Württemberg, Germany

Karl S. Roth, MD

Professor & Chair (Retired)
Department of Pediatrics
Creighton University School of Medicine
Omaha, Nebraska, USA

Consulting Editors

Howard Courtney, M.Phil.

Maria Teresa Gonzalez-Bolaños, MD

New York Chicago San Francisco Athens London Madrid Mexico City
Milan New Delhi Singapore Sydney Toronto

ISBN: 978-0-07-177313-3

MHID: 0-07-177313-4.

The material in this eBook also appears in the print version of this title: ISBN: 978-0-07-177314-0,
MHID: 0-07-177314-2.

eBook conversion by codeMantra
Version 1.0

DEDICATION

Medicine is art, science, and method. Its subspecialities have been shaped by distinguished colleagues and friends who paved the way. This history can and should be fundamental for us.
The pioneering work of our predecessors gives us knowledge, guidance, and perseverance.
Illustrious examples of such pioneering clinical scientists we commemorate are
Horst Bickel (Heidelberg), Ivar Asbjørn Følling (Oslo), Robert Guthrie (Buffalo),
James M. Tanner (London), and Richard Koch (Los Angeles).

This page intentionally left blank

CONTENTS

This page intentionally left blank

CONTRIBUTORS

S. Faisal Ahmed, MD, FRCPCH
Samson Gemmell Chair of Child Health
Consultant in Paediatric Endocrinology
Royal Hospital for Children
Glasgow School of Medicine
University of Glasgow
Glasgow, United Kingdom

Brage Storstein Andresen, PhD, FRCPath
Professor of Human Molecular Genetics
Department of Biochemistry and Molecular Biology
University of Southern Denmark
Odense, Denmark

Sudha Anupindi, MD
Department of Radiology
Children's Hospital of Philadelphia
Associate Professor of Radiology
Perelman School of Medicine at the University of Pennsylvania
Philadelphia, Pennsylvania, USA

Jesús Argente, MD, PhD
Full Professor and Chairman, Department of Pediatrics
Universidad Autónoma de Madrid
Head, Department of Pediatrics & Pediatric Endocrinology
Hospital Infantil Universitario Niño Jesús
Instituto de Investigación La Princesa
Director, National Program of Childhood Obesity
Instituto de Salud Carlos III
Madrid, Spain

Philippe F. Backeljauw, MD
Professor of Pediatrics
Director, Pediatric Endocrinology Fellowship Program
Cincinnati Children's Hospital Medical Center
Cincinnati, Ohio, USA

Bruce A. Barshop, MD, PhD
Professor of Pediatrics
Biochemical Genetics Program
University of California, San Diego
San Diego, California, USA

Andrew J. Bauer, MD
Director, The Thyroid Center
Division of Endocrinology and Diabetes
Children's Hospital of Philadelphia
Associate Professor of Pediatrics
Perelman School of Medicine at the University of Pennsylvania
Philadelphia, Pennsylvania, USA

Michael Beck, MD
Professor Emeritus
Institute of Human Genetics
University of Mainz
Mainz, Germany

Jirair K. Bedoyan, MD, PhD, FACMG
Clinical and Biochemical Geneticist
Assistant Professor, Departments of Genetics and Genome Sciences and Pediatrics
Associate Director, Center for Inherited Disorders of Energy Metabolism (CIDEM)
University Hospitals Cleveland Medical Center
Case Western Reserve University
Cleveland, Ohio, USA

Melena Bellin, MD
University of Minnesota Medical Center
Schulze Diabetes Institute
Associate Professor Pediatric Endocrinology
Director of Research, Islet Autotransplant Program
Minneapolis, Minnesota, USA

Michael J. Bennett, PhD, FRCPath, FACB, DABCC
Professor of Pathology and Laboratory Medicine
Perelman School of Medicine at the University of Pennsylvania
Evelyn Willing Bromley Endowed Chair in Clinical Laboratories and Pathology
Chief, Division of Laboratory Medicine
Director, Clinical Chemistry and Metabolic Disease Laboratories
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania, USA

Ignacio Bergadá, MD
Chief, División de Endocrinología
Assistant Director, Centro de Investigaciones Endocrinológicas "Dr. César Bergadá"
CONICET-FEI-División de Endocrinología
Hospital de Niños Ricardo Gutiérrez
Buenos Aires, Argentina

Gerard T. Berry, MD
Director, Metabolism Program
Boston Children's Hospital
Professor of Pediatrics
Harvard Medical School
Boston, Massachusetts, USA

Bala Bhagavath, MD
Associate Professor of Obstetrics and Gynecology
Division of Reproductive Endocrinology and Infertility
Director, Scibetta Fellowship in Minimally Invasive Gynecologic Surgery
Director, Third Party Reproduction
Co-Director, URMC Fibroid Center
University of Rochester Medical Center
Rochester, New York, USA

Ingemar Björkhem, MD, PhD
Professor of Clinical Chemistry
Division of Clinical Chemistry
Department of Laboratory Medicine
Karolinska Institutet
Karolinska University Hospital Huddinge
Stockholm, Sweden

Nenad Blau, PhD
Senior Consultant in Biochemical Genetics
Professor of Clinical Biochemistry
Dietmar-Hopp Metabolic Center
University Children's Hospital
Heidelberg, Germany

Henk J. Blom, PhD
Professor Biochemistry of Inherited Metabolic Diseases
Head of Laboratory/Clinical Biochemical Geneticist
Laboratory of Clinical Biochemistry and Metabolism
Department of General Pediatrics, Adolescent Medicine and Neonatology
University Medical Centre Freiburg
Freiburg, Germany

Rubén Bonilla-Guerrero, MD, FACMG, FACB, CGMBS
Medical Director, Medical Affairs, Genetics
Associate Medical Director, Genetics
Quest Diagnostics, Inc.
Nichols Institute
San Juan Capistrano, California, USA

Olivier Braissant, PhD
Service of Biomedicine
Department of Laboratories
University Hospital of Lausanne
Lausanne, Switzerland

Peter Burgard, PhD
Consultant of Pediatric Psychology
Department of General Pediatrics
Heidelberg University Hospital
Heidelberg, Germany

Alberto Burlina, MD
Division of Inherited Metabolic Diseases Reference Centre
Expanded Newborn Screening Department of Women's and Child's Health
University Hospital
Padova, Italy

Amy R.U.L. Calhoun, MD
Clinical Assistant Professor
Stead Family Department of Pediatrics
Division of Medical Genetics
Medical Consultant to the Iowa Newborn Screening Program
University of Iowa Hospitals and Clinics
Iowa City, Iowa, USA

Audrey Campbell, MD, MHSc, FRCPC (Public Health & Preventive Medicine)
Clinical Assistant Professor
Department of Family Practice
Faculty of Medicine
University of British Columbia
Vancouver, British Columbia, Canada

Bruce R. Carr, MD
Holder, Paul C. MacDonald Distinguished Chair in Obstetrics and Gynecology
Professor of Obstetrics and Gynecology
Director, Division of Reproductive Endocrinology and Infertility
University of Texas Southwestern Medical Center
Dallas, Texas, USA

Anupam Chakrapani, MD, FRCPCH
Consultant in Metabolic Medicine
Great Ormond Street Hospital NHS Foundation Trust
London, United Kingdom

Jean-Pierre Chanoine, MD, Agrégé de l'Enseignement Supérieur, FRCPC (Academic)
Clinical Professor
Endocrinology and Diabetes Unit
British Columbia Children's Hospital and University of British Columbia
Vancouver, British Columbia, Canada

Evangelia Charmandari, MD, MSc, PhD, MRCP(UK), CCST(UK)
Professor of Pediatric and Adolescent Endocrinology
Division of Endocrinology, Metabolism and Diabetes
First Department of Pediatrics, University of Athens Medical School
Aghia Sophia Children's Hospital
Division of Endocrinology and Metabolism
Clinical Research Center
Biomedical Research Foundation of the Academy of Athens
Athens, Greece

Timothy Cheetham, BSc, MB ChB, MRCP, MRCPCH, MD
Senior Lecturer in Pediatric Endocrinology
School of Clinical Medical Sciences (Child Health)
Sir James Spence Institute of Child Health
Royal Victoria Infirmary
Newcastle Upon Tyne, United Kingdom

George P. Chrousos, MD, MACP, MACE, FRCP(London)
Professor and Chairman
First Department of Pediatrics
University of Athens Medical School
Aghia Sofia Children's Hospital
Athens, Greece

Bruce H. Cohen, MD
Professor of Pediatrics, Northeast Ohio Medical University
Department of Pediatrics
Director, NeuroDevelopmental Science Center
Children's Hospital Medical Center of Akron
Akron, Ohio, USA

Gerard S. Conway, MD, FRCP
Professor of Reproductive Endocrinology
Institute for Women's Health
University College London
London, United Kingdom

Martine Cools, MD, PhD
Professor Consultant in Paediatric Endocrinology
Senior Clinical Investigator
Flanders Research Foundation
Queen Elisabeth Children's Hospital
Ghent University Hospital
University of Ghent
Ghent, Belgium

Tina M. Cowan, PhD, FACMG
Associate Professor of Pathology and Pediatrics
Director, Stanford Biochemical Genetics Laboratory
Stanford University Medical Center
Stanford, California, USA

Melanie Cree-Green, MD, PhD
Assistant Professor, Pediatric Endocrinology
Center for Women's Health Research
University of Colorado
Aurora, Colorado, USA

Mehul Dattani, MD, FRCP, FRCPCH
Professor of Paediatric Endocrinology
Head of Section of Genetics and Epigenetics in Health and Disease
Genetics and Genomic Medicine Programme
UCL Great Ormond Street Institute of Child Health
Consultant and Head of Clinical Service in Paediatric Endocrinology
Great Ormond Street Hospital for Children
Consultant in Adolescent Endocrinology
UCL Hospitals
London, United Kingdom

Leo Dunkel, MD, PhD
Professor of Paediatric Endocrinology and Metabolism
Honorary Consultant in Paediatric Endocrinology
Centre for Endocrinology
William Harvey Research Institute
Barts and The London School of Medicine and Dentistry
London, United Kingdom

Gösta Eggertsen, MD, PhD
Professor of Clinical Chemistry
Division of Clinical Chemistry
Department of Laboratory Medicine
Karolinska Institutet
Karolinska University Hospital Huddinge
Stockholm, Sweden

Bjorn Fischler, MD, PhD
Associate Professor of Pediatrics
Department of Pediatrics
Karolinska University Hospital and CLINTEC Karolinska Institutet
Stockholm, Sweden

Gregory Forlenza, MD
Assistant Professor of Pediatrics
Barbara Davis Center for Childhood Diabetes
Pediatric Endocrinology
University of Colorado Denver
Aurora, Colorado, USA

Brian Fowler, PhD
Former Head of Labs
Paediatrics
University Children's Hospital Basel
Basel, Switzerland

Aaron Friedman, MD
Professor of Pediatrics, Emeritus
University of Minnesota Medical School
Minneapolis, Minnesota, USA

Brigitte I. Frohnert, MD, PhD, FAAP
Assistant Professor of Pediatrics
Department of Pediatric Endocrinology
Barbara Davis Center for Diabetes
University of Colorado
Aurora, Colorado, USA

Toshiyuki Fukao, MD, PhD
Professor of Pediatrics
Graduate School of Medicine
Gifu University
Gifu, Japan

K. Michael Gibson, PhD, FACMG
Allen I. White Professor and Chair
Experimental and Systems Pharmacology (ESP)
WSU College of Pharmacy
Spokane, Washington, USA

William T. Gibson, MD, PhD (Cantab), FRCPC, FCCMG
Associate Professor, Department of Medical Genetics
University of British Columbia
Senior Clinician Scientist
British Columbia Children's Hospital
Vancouver, British Columbia, Canada

Roberto Giugliani, MD, PhD
Professor, Department of Genetics
Universidade Federal do Rio Grande do Sul
Chief, Medical Genetics Service
Hospital de Clínicas de Porto Alegre
Porto Alegre, Brazil

Gregory A. Grabowski, MD
Professor Emeritus
University of Cincinnati College of Medicine and Division of Human Genetics
Cincinnati Children's Hospital Medical Center
Cincinnati, Ohio, USA

Stefan Grebe, MD, PhD
Professor of Laboratory Medicine and Pathology
Mayo College of Medicine
Consultant, Department of Laboratory Medicine and Pathology
Mayo Clinic
Rochester, Minnesota, USA

Dorothea Haas, MD
Adjunct Associate Professor
Department of General Pediatrics
Division of Neuropediatrics and Metabolic Medicine
University Children's Hospital
Heidelberg, Germany

Johannes Häberle, MD
Assistant Professor, Senior Lecturer
Division of Metabolism
University Children's Hospital
Zürich Eleonore Foundation
Zürich, Switzerland

Cary O. Harding, MD
Professor of Molecular and Medical Genetics
Professor of Pediatrics
Oregon Health & Science University
Portland, Oregon, USA

Gail E. Herman MD, PhD
Professor, Institute for Genomic Medicine
The Research Institute at Nationwide Children's Hospital
Department of Pediatrics
The Ohio State University
Columbus, Ohio, USA

Nastassja Himmelreich, PhD
Department of Paediatrics
Center for Child and Adolescent Medicine
University of Heidelberg
Heidelberg, Germany

Peter C. Hindmarsh, BSc, MD, FRCP, FRCPCH
Professor of Paediatric Endocrinology
Divisional Clinical Director for Paediatrics, Adolescents and Young People at UCLH
Developmental Endocrinology Research Group
University College London
Institute of Child Health
London, United Kingdom

Victor Ho-Fung, MD
Pediatric Radiologist
Children's Hospital of Philadelphia
Assistant Professor of Radiology
Perelman School of Medicine at the University of Pennsylvania
Philadelphia, Pennsylvania, USA

Georg F. Hoffmann, MD
Professor and Chair
University Children's Hospital
Ruprecht-Karls-University
Heidelberg, Germany

Stephen G. Kaler, MD
Senior Investigator and Head, Section on Translational Neuroscience
Molecular Medicine Program, NICHD
Porter Neuroscience Research Center II
National Institutes of Health
Bethesda, Maryland, USA

Andrea Kelly, MD, MSCE
Attending Physician
Children's Hospital of Philadelphia
Associate Professor of Pediatrics
Perelman School of Medicine at the University of Pennsylvania
Philadelphia, Pennsylvania, USA

Stephen F. Kemp, MD, PhD
Professor of Pediatrics and Medical Humanities
Division of Pediatric Endocrinology
University of Arkansas for Medical Sciences
Arkansas Children's Hospital
Little Rock, Arkansas, USA

Douglas S. Kerr, MD, PhD
Emeritus Professor of Pediatrics, Biochemistry, Nutrition, and Pathology
Case Western Reserve University School of Medicine
Former Director
Center of Inherited Disorders of Energy Metabolism
University Hospitals Case Medical Center
Cleveland, Ohio, USA

Karen M. Kloke, MS, MT (ASCP)
Department of Laboratory Medicine and Pathology
Mayo Clinic and Foundation
Rochester, Minnesota, USA

David M. Koeller, MD
Professor of Molecular and Medical Genetics
Professor of Pediatrics
Oregon Health & Science University
Portland, Oregon, USA

Victor N. Konji, PhD
Pediatric Bone Health Research Associate
Pediatric Bone Health Clinical and Research Programs
Children's Hospital of Eastern Ontario Research Institute
Ottawa, Ontario, Canada

Christian Körner, PhD
Professor of Biochemical Genetics
University Children's Hospital
Ruprecht-Karls-University
Heidelberg, Germany

Eleni Magdalini Kyritsi, MD, PhD Candidate
National and Kapodestrian University of Athens
Clinical Resident in Endocrinology
Division of Endocrinology, Metabolism and Diabetes
First Department of Pediatrics
University of Athens Medical School
Aghia Sophia Children's Hospital
Athens, Greece

Peter A. Lee, MD, PhD
Professor of Pediatrics
Penn State College of Medicine
The Milton S. Hershey Medical Center
Hershey, Pennsylvania, USA

Michael A. Levine, MD
Professor of Pediatrics
Chief, Division of Endocrinology and Diabetes Medical Director of the Center for Bone Health
Children's Hospital of Philadelphia
Perelman School of Medicine at the University of Pennsylvania
Philadelphia, Pennsylvania, USA

Harvey L. Levy, MD
Professor of Pediatrics
Harvard Medical School
Boston, Massachusetts, USA

Nicola Longo, MD, PhD
Professor and Chief of Medical Genetics/Pediatrics
University of Utah
Salt Lake City, Utah, USA

Pascal de Lonlay, MD, PhD
Centre de Reference des Maladies Hereditaries du Metabolisme de l'Enfant et l'Adulte
Hopital Necker-Enfants Malades, AP-HP
University Paris Descartes
Paris, France

Xiaoping Luo, MD, PhD
Professor of Pediatrics
Tongji Medical College
Huazhong University of Science and Technology
Wuhan, P.R. China

Jinhui Ma, PhD
Assistant Professor
School of Epidemiology, Public Health and Preventive Medicine
University of Ottawa
Scientist
Children's Hospital of Eastern Ontario Research Institute
Ottawa, Ontario, Canada

Dietrich Matern, MD, PhD, FACMG
Professor of Laboratory Medicine, Medical Genetics, and Pediatrics
Chair, Division of Laboratory Genetics
Co-Director, Biochemical Genetics Laboratory
Mayo Clinic College of Medicine
Rochester, Minnesota, USA

Ertan Mayatepek, MD
Professor and Chair
Department of General Pediatrics, Neonatology and Pediatric Cardiology
University Children's Hospital
Dusseldorf, Germany

Lillian R. Meacham, MD
Professor of Pediatrics
Division of Pediatric Endocrinology
Medical Director, Cancer Survivor Program
Kathelen V. Amos Children's Chair for Cancer Survivorship
Aflac Cancer and Blood Disorders Center of Children's Healthcare of Atlanta
Emory University School of Medicine
Atlanta, Georgia, USA

Bradley S. Miller, MD, PhD
Associate Professor
Department of Pediatric Endocrinology
University of Minnesota Masonic Children's Hospital
Minneapolis, Minnesota, USA

Chantal F. Morel, MD, FRCPC, FCCMG
Clinical and Metabolic Geneticist
Assistant Professor, Department of Medicine
University of Toronto
University Health Network and Mount Sinai Hospital
Toronto, Ontario, Canada

Andrew A.M. Morris, BM, BCh, PhD, FRCPCH
Consultant in Paediatric Metabolic Medicine
Central Manchester University Hospitals and Institute of Human Development
University of Manchester
Manchester, United Kingdom

Craig F. Munns, MD
Associate Professor
Department of Endocrinology and Diabetes
University of Sydney
Children's Hospital at Westmead
Sydney, Australia

Alessandro Mussa, MD, PhD
Department of Public Health and Pediatrics
University of Torino
Neonatal Intensive Care Unit and Neonatology
Department of Obstetrics and Gynecology
S. Anna Hospital
Città della Scienza e della Salute
Torino, Italy

William L. Nyhan, MD, PhD
Distinguished Professor of Pediatrics
Department of Pediatrics
University of California San Diego
La Jolla, California, USA

Karel Pacak, MD, PhD, DSc, FACE
Senior Investigator
Chief, Section on Medical Neuroendocrinology
Head, Developmental Endocrine Oncology and Genetics Affinity Group
Eunice Kennedy Shriver National Institute of Child Health and Human Development
National Institutes of Health
Bethesda, Maryland, USA

Darius A. Paduch, MD, PhD
Associate Professor of Urology and Reproductive Medicine
Associate Research Director, Male Infertility Fellowship
Assistant Laboratory Director, Male Infertility Genetics Laboratory
Director of Sexual Health & Medicine
Department of Urology
Weill Cornell Medical College
New York, New York, USA

Marzia Pasquali, PhD, FACMG
Professor of Pathology
University of Utah School of Medicine
Medical Director, Biochemical Genetics and Supplemental Newborn Screening
ARUP Laboratories
Salt Lake City, Utah, USA

Briana C. Patterson, MD, MS
Assistant Professor of Pediatrics
Division of Pediatric Endocrinology
Aflac Cancer and Blood Disorders Center of Children's Healthcare of Atlanta
Emory University School of Medicine
Atlanta, Georgia, USA

Anna Petryk, MD
Professor
Division of Pediatric Endocrinology
Department of Pediatrics
University of Minnesota Masonic Children's Hospital
Minneapolis, Minnesota, USA

Michel Polak, MD, PhD
Pediatric Endocrinology Gynecology and Diabetology
Université Paris Descartes, INSERM U1016, IMAGINE Institute
Centre de référence des Maladies Endocriniennes Rares de la Croissance
Hôpital Universitaire Necker Enfants Malades
Paris, France

Lynda E. Polgreen, MD, MS
Assistant Professor of Pediatrics
David Geffen School of Medicine—UCLA
Division of Pediatric Endocrinology
Los Angeles Biomedical Research Institute at
Harbor-UCLA Medical Center
Torrance, California, USA

Constantin Polychronakos, MD, FRCPC, FRSC
Paediatric Endocrinologist
Professor, Paediatrics and Human Genetics
Leader, Child Health and Human Development Programme
McGill University Health Centre Research Institute
Editor, Journal of Medical Genetics
Montréal, Québec, Canada

Francesco Porta, MD, PhD
Department of Pediatrics
University of Torino
Torino, Italy

Charmian A. Quigley, MBBS, FRACP
Pediatric Endocrinologist
Sydney, Australia

Sandeep Raha, PhD
Associate Professor
Department of Pediatrics
McMaster University Medical Center
Hamilton, Ontario, Canada

Shamima Rahman, FRCP, FRCPCH, PhD
Professor of Paediatric Metabolic Medicine
UCL Great Ormond Street Institute of Child Health
London, United Kingdom

Michael B. Ranke, MD, PhD
Professor Emeritus
Division of Pediatric Endocrinology
University Children's Hospital
Tübingen, Germany

Samuel Refetoff, MD
Professor Emeritus of Medicine and Pediatrics
University of Chicago Medicine
Chicago, Illinois, USA

William G. Reiner, MD
Professor of Pediatric Urology and Child and Adolescent
Psychiatry (Retired)
University of Oklahoma Health Sciences Center
Oklahoma City, Oklahoma, USA

Rodolfo A. Rey, MD, PhD
Director, Centro de Investigaciones Endocrinológicas
"Dr. César Bergadá"
CONICET-FEI—División de Endocrinología
Hospital de Niños R. Gutiérrez
Associate Professor, Departamento de Histología, Biología Celular,
Embriología y Genética
Facultad de Medicina
Universidad de Buenos Aires
Buenos Aires, Argentina

William B. Rizzo, MD
Professor
Division of Inherited Metabolic Diseases
Department of Pediatrics
University of Nebraska College of Medicine
Omaha, Nebraska, USA

Gary L. Robertson, MD
Emeritus Professor of Medicine
Northwestern University School of Medicine
Chicago, Illinois, USA

David S. Rosenblatt, MD
Holder, Dodd Q. Chu and Family Chair in Medical Genetics
Professor, Departments of Human Genetics, Medicine,
Pediatrics, and Biology
McGill University
Montreal, Quebec, Canada

Arlan L. Rosenbloom, MD
Adjunct Distinguished Service Prof. Emeritus
Division of Endocrinology
Department of Pediatrics
University of Florida College of Medicine
Gainesville, Florida, USA

Christopher G. Roth, MD, MS-HQS
Associate Professor
Director, Abdominal Imaging Division
Vice Chair, Quality and Performance
Vice Chair, Methodist Hospital Division
Department of Radiology
Sidney Kimmel Medical College
Thomas Jefferson University
Philadelphia, Pennsylvania, USA

Karl S. Roth, MD
Professor & Chair (Retired)
Department of Pediatrics
Creighton University School of Medicine
Consulting Staff
University of Nebraska School of Medicine
Omaha, Nebraska, USA

Amy K. Saenger, PhD, DABCC
Associate Professor
Department of Laboratory Medicine and Pathology
University of Minnesota
Minneapolis, Minnesota, USA

Denise Salazar, PhD
Quest Diagnostics, Inc.
Nichols Institute
San Juan Capistrano, California, USA

Kyriakie Sarafoglou, MD
Director, Leo Fung Center for Congenital Adrenal Hyperplasia and Disorders of Sex Development
Division of Pediatric Endocrinology
Division of Genetics & Metabolism
University of Minnesota Medical School
Minneapolis, Minnesota, USA

Juergen R. Schaefer, MD
Department of Internal Medicine
Cardiology, Angiology and CAD Prevention
Center for Undiagnosed and Rare Diseases
University Clinic Marburg
Philipps University
Marburg, Germany

Rajesh Sharma, PhD
Quest Diagnostics, Inc.
Nichols Institute
San Juan Capistrano, California, USA

Peter N. Schlegel, MD, FACS
James J. Colt Professor and Chairman, Department of Urology
Weill Cornell Medical College
Urologist-in-Chief
New York Presbyterian Hospital
New York, New York, USA

Andrea Schlune, MD
Department of General Pediatrics, Neonatology and Pediatric Cardiology
University Children's Hospital
Heinrich-Heine-University Dusseldorf
Dusseldorf, Germany

Benedikt Schoser, MD
Professor of Neurology
Friedrich-Baur-Institute
Clinic of Neurology
University of Munich
Munich, Germany

Andreas Schulze, MD, PhD, FRCPC
Associate Professor
Department of Paediatrics
Department of Biochemistry
University of Toronto
Head, Section of Metabolic Genetics
Medical Director, Newborn Screening Program
Associate Scientist, Research Institute
The Hospital for Sick Children
Toronto, Ontario, Canada

Janet Silverstein, MD
Professor of Pediatrics
Chief, Division of Pediatric Endocrinology
University of Florida College of Medicine
Gainesville, Florida, USA

G. Peter A. Smit, MD, PhD
Department of Paediatrics
University of Groningen
The Netherlands

Leandro Soriano-Guillén, MD, PhD
Associate Professor of Pediatrics
Universidad Autónoma de Madrid
Head, Department of Pediatrics
Hospital Universitario Fundación Jiménez Díaz
Instituto de Investigación Fundación Jiménez Díaz
Madrid, Spain

Muhidien Soufi, PhD
Department of Internal Medicine
Cardiology, Angiology and CAD Prevention
University Hospital Giessen and Philipps University Marburg
Center for Undiagnosed and Rare Diseases
University Clinic Marburg Philipps
Marburg, Germany

Charles A. Stanley, MD
Senior Physician, Division of Endocrinology & Diabetes
Children's Hospital of Philadelphia
Emeritus Professor of Pediatrics
Perelman School of Medicine at the University of Pennsylvania
Philadelphia, Pennsylvania, USA

Constantine A. Stratakis, MD, DMSci
Senior Investigator and Scientific Director
Eunice Kennedy Shriver National Institute of Child Health and Human Development
National Institutes of Health
Bethesda, Maryland, USA

Marshall L. Summar, MD
Chief, Genetics and Metabolism
Professor of Pediatrics
George Washington University
Children's National Medical Center
Washington D.C., USA

Gabor Szinnai, MD, PhD
Senior Lecturer
Division of Pediatric Endocrinology and Diabetology
University Children's Hospital Basel
University Basel
Basel, Switzerland

Mark A. Tarnopolsky, MD, PhD, FRCP(C)
Professor of Pediatrics and Medicine,
Hamilton Hospitals Assessment Centre Endowed Chair in Neuromuscular Disorders
Director of Neuromuscular and Neurometabolic Clinic
McMaster University Medical Center
Hamilton, Ontario, Canada

Carrie Ann Terrell, MD
Assistant Professor
Department of Obstetrics, Gynecology and Women's Health
Director, Division of Obstetrics & Gynecology
Medical Director, Women's Health Specialists Clinic
University of Minnesota
Minneapolis, Minnesota, USA

Christian Thiel, PhD
Department of Paediatrics
Center for Child and Adolescent Medicine
University of Heidelberg
Heidelberg, Germany

Beat Thöny, PhD
Professor of Clinical Biochemistry
Division of Metabolism
University Children's Hospital Zürich
Eleonore Foundation
Zürich, Switzerland

Paul Thornton, MD
Medical Director, Division of Endocrinology
Cook Children's Medical Center
Fort Worth, Texas, USA

Filippo Vairo, MD, PhD
Medical Genetics Service
Hospital de Clínicas de Porto Alegre
Porto Alegre, Brazil

Johan L.K. Van Hove, PhD, MBA
Professor of Pediatrics
Section of Clinical Genetics and Metabolism
Department of Pediatrics
University of Colorado Denver
Aurora, Colorado, USA

Guy Van Vliet, MD
Professeur de Pédiatrie
Université de Montréal,
Service d'Endocrinologie, Hôpital Sainte-Justine
Montreal, Quebec, Canada

Jerry Vockley, MD, PhD
Cleveland Family Professor of Pediatric Research
University of Pittsburgh
Professor of Human Genetics
Chief of Medical Genetics
Director of the Center for Rare Disease Therapy
Children's Hospital of Pittsburgh
Pittsburgh, Pennsylvania, USA

Ronald J.A. Wanders, PhD
Professor Clinical Enzymology of Metabolic Diseases
Departments of Clinical Chemistry & Pediatrics
Emma Children's Hospital
Laboratory Genetic Metabolic Diseases
Academic Medical Center
University of Amsterdam
Amsterdam, The Netherlands

Leanne M. Ward, MD
Division of Endocrinology and Metabolism
Children's Hospital of Eastern Ontario
Department of Pediatrics
University of Ottawa
Ottawa, Ontario, Canada

Garry Warne, AM, MBBS, FRACP
Professorial Fellow, Department of Paediatrics
University of Melbourne
Honorary Emeritus Visiting Medical Officer, Department of Endocrinology
Royal Children's Hospital Melbourne
Esteemed Honorary Fellow, Murdoch Children's Research Institute
Parkville, Victoria, Australia

David Watkins, PhD
Department of Human Genetics
McGill University
Montreal, Quebec, Canada

David A. Weinstein, MD, MMSc
Professor of Pediatrics
Director, Glycogen Storage Disease Program
Division of Pediatric Endocrinology
University of Florida College of Medicine
Gainesville, Florida, USA

Perrin C. White, MD
Professor of Pediatrics
University of Texas Southwestern Medical Center
Chief of Endocrinology
Children's Medical Center Dallas
Dallas, Texas, USA

Michèl A.A.P. Willemsen, MD
Professor of Pediatric Neurology
Radboud University Medical Centre
Nijmegen, The Netherlands

Joseph I. Wolfsdorf, MB, Bch
Professor of Pediatrics
Harvard Medical School
Boston Children's Hospital Chair in Endocrinology
Director, Diabetes Program
Division of Endocrinology
Boston Children's Hospital
Boston, Massachusetts, USA

Jamie R. Wood, MD
Associate Professor of Clinical Pediatrics
The Keck School of Medicine of USC
Medical Director, Comprehensive Childhood Diabetes Center
Center for Diabetes, Endocrinology, and Metabolism
Children's Hospital Los Angeles
Los Angeles, California, USA

J. Ed. Wraith, MB ChB, FRCPCH
Honorary Professor of Paediatric Inherited Metabolic Medicine
Manchester Academic Health Sciences Centre
Genetic Medicine
St Mary's Hospital
Manchester, United Kingdom

Marc Yudkoff, MD
WT Grant Professor of Pediatrics
Perelman School of Medicine at the University of Pennsylvania
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania, USA

PREFACE

This book is designed as a source of practical information for the diagnosis and management of pediatric patients with endocrine diseases and inborn errors of metabolism. From its conception, Pediatric Endocrinology and Inborn Errors of Metabolism (PEIEM) was created with this dual purpose: to be both a comprehensive, clinically-focused medical reference for a broad audience from specialist nurses and general physicians to specialists in each discipline, and to be an information bridge providing inroads into the fundamental concepts of the two interrelated disciplines. The contributors and editorial team strove to make the chapters on inborn errors approachable by endocrinologists and the endocrine chapters approachable by metabolic specialists through what became the underlying precept of the textbook—explanation, not simplification. Following this paradigm, chapters first elucidate the mechanisms underlying a disorder and how they relate to the corresponding phenotypes through clinically relevant discussions of genetics and pathophysiology, thus framing the basis of disease; and second, provide complete and detailed discussions of clinical features, laboratory evaluations, treatment modalities, and follow-up management. Rather than simply listing signs and symptoms under the assumption that their occurrence within a disorder is always self-explanatory, PEIEM explains through the pathophysiology why and how these manifestations occur and how they can be approached, modified, or prevented. As a result of this step-wise approach, we hope that medical professionals at any level involved in caring for endocrine and metabolic patients will find this textbook a useful and comprehensive resource.

We are very grateful for the wide acceptance the first edition of PEIEM quickly achieved and are proud of recognition such as the Medical Book Award of the British Medical Association in 2010. In 2009, the New England Journal of Medicine review stated "it is a unique book that is pleasing to the eye, nurturing for the mind, and instructive for a broad readership." It has quickly become an in-depth clinical reference resource for inborn errors of metabolism and pediatric endocrinology.

Since PEIEM's release in 2009, huge advances of knowledge and important improvements in diagnostics as well as therapeutic approaches necessitated a second edition. This allowed the corrections of some errors of the first edition that maybe only authors and editors spotted, as well as the inclusion of additional disorders not covered previously and those that were recently identified. Following a stringent concept, it was still possible to provide even more detailed and clinically relevant information concerning presentation, diagnosis, and treatment of more than 700 disorders within a single volume. To achieve this goal, we had to address the question "What is the most pertinent information needed for the practicing physician to fully understand the etiology and pathophysiology of a disease in order to make informed decisions concerning the diagnosis and management of a patient?" To remain a single volume, we focused on describing disease pathogenesis, clinical presentation, and therapy, and where relevant, the most frequently recurring mutations in relation to phenotype, rather than lengthy discussions of a disorder's historical background and itemized accounts of the discovery of each mutation, both of which can be found in many textbooks and established internet databases.

What is unique to this book and not easily found in other textbooks or on the internet is a single organized source that provides detailed information for the practicing physician concerning the pathophysiology, diagnosis, and management of both inborn errors of metabolism and endocrine disorders. By combining the two disciplines, a physician contemplating the differential diagnosis of a patient with hypoglycemia, for example, will need only one textbook to find full coverage of the potential underlying disorders (ie, hyperinsulinism, glycogen storage diseases, fatty acid oxidation disorders, adrenal insufficiency, and disorders of growth). As there can be many subtypes of a disorder, to assist in identifying the information you need quickly, disease-oriented chapters begin with the At-A-Glance page, a quick reference summary for easy access to the biochemical profile, presentation, occurrence rate, locus, etc., of the disorders covered in the chapter. Another important feature of this textbook that aids in the differential diagnosis is that many subtypes of disorders—even rare ones—covered within a chapter are individually discussed following a specific format. In most cases, each subtype of a disorder is structured in the following format: Etiology/Pathophysiology, Presentation, Diagnosis, and Treatment. Full descriptions of the etiology/pathophysiology of the overall disorder are aided by multiple graphics to show how the different enzymatic defects affect a pathway, rather than a single graphic with a multitude of defect markers. Thus, with PEIEM, the reader can readily and consistently find the information (s)he seeks. The structured format also has the added benefit of addressing the heterogeneity of contributors and writing styles created by any multi-author textbook.

Kyriakie Sarafoglou, MD
Georg F. Hoffmann, MD
Karl S. Roth, MD

This page intentionally left blank

PART I

Newborn Screening, Emergency Treatment, and Molecular Testing

PART I CONTENTS

CHAPTER 1

Newborn Screening

Andreas Schulze, MD, PhD, FRCPC; Dietrich Matern, MD, PhD, FACMG; and Georg F. Hoffmann, MD

Protecting children from the burden of inherited diseases is the aim of newborn screening. Selection of candidate disorders depends upon the following prerequisites: 1) feasible means of disease detection in a presymptomatic/early stage of the disease; 2) treatability of the disease; 3) ability to start of treatment in the presymptomatic/early stage.

Screening of neonates for signs of disease or distress has several components, with the perinatal clinical evaluation being of first and foremost importance. The clinical approach to screening is limited to the detection of symptoms, which in many disorders have been proven to be irreversible if not treated. For example, classic phenylketonuria (PKU) due to phenylalanine (Phe) hydroxylase deficiency is characterized by the insidious development of irreversible neurological damage unless treatment is initiated within the first few weeks of life. Newborn screening was first developed for the identification of this inborn error of amino acid metabolism, which was typically not diagnosed before 6 months of life and mostly even much later when developmental delay or other nonspecific neurologic symptoms become apparent. Treatment based on a Phe-restricted diet was developed by Horst Bickel in the 1950s, but it was quickly realized that therapy only improved the patient's symptoms but was inadequate to reverse neurologic damage.[1] Furthermore, it was recognized that a limited intake of the essential amino acid Phe requires the regular monitoring of its concentration in blood. A simple method for Phe determination was developed by Robert Guthrie, a scientist initially working in cancer research and the father of a child with mental retardation.[2] This test was a bacterial inhibition assay (BIA) performed on serum dried on filter paper. Guthrie then began to apply his BIA to the analysis of Phe in small blood samples also dried on filter paper with the aim of allowing the presymptomatic identification of PKU in patients and facilitating the timely initiation of dietary intervention.[3] Once the efficacy of this assay was established, newborn screening began 50 years ago in several regions of the United States and Germany and rapidly spread around the world using the Guthrie test.[4,5] Over the ensuing 30 years, a few additional disorders such as congenital hypothyroidism, galactosemia, and sickle cell disease were gradually added to many newborn screening programs, usually one new assay for each additional disorder.

The BIA was initially modified to detect other disease markers and eventually more sophisticated technologies were applied, such as fluorometric, colorimetric, and immunoassays to determine either disease-related metabolites or specific enzyme activities. Over the last two decades, the introduction of tandem mass spectrometry (MS/MS) into newborn screening laboratories has dramatically expanded the number of disorders that can be detected in a single blood spot. More than 30 additional conditions can be detected by simultaneous acylcarnitine and amino acid analyses, including inborn errors of amino acid, organic acid, and fatty acid metabolism.

DISORDERS INCLUDED IN NEWBORN SCREENING PROGRAMS

To aid in the selection of diseases to be included into screening programs, screening principles were developed by Wilson and Jungner on behalf of the World Health Organization in 1968.[6] Although these principles were not developed specifically for newborn screening, with some adaptation they remain the most commonly used selection criteria for newborn screening in almost all countries. However, despite seemingly agreed-upon criteria, diseases included vary widely between countries—for example, in Europe from 1 to 30 conditions.[7] In general there is an increase in the number of conditions screened for in many countries over the last years. Screening raises concerns about privacy and autonomy, highlighting the importance of the evaluation of ethical, legal, and societal aspects. As most screened conditions are inherited disorders, consequences for family members often exist. Furthermore, healthcare expenses need to be balanced: if screening programs are funded, other activities may not be possible. When deciding which diseases to include in any newborn screening program, careful consideration must be given to weighing the impact for affected individuals against the burden for unaffected individuals. Detailed recommendations for screening policy will vary from country to country and region to region, depending on local economic, political, and medical factors and public health organizations.

In 2002, the American College of Medical Genetics (ACMG) was commissioned by the Maternal and Child Health Bureau of the Health Resources and Services Administration of the United States Department of Health and Human Services to review the scientific basis of newborn screening and develop recommendations for which disorders should be included in newborn screening programs. The impetus for a comprehensive review of the status of newborn screening was the scattered implementation of MS/MS in screening laboratories in the United States, which led to marked discrepancies in the number of conditions included in the various screening programs. Several states provided newborn screening for only three diseases, whereas those that implemented amino acid and acylcarnitine profiling by MS/MS were screening for more than 30 conditions. (A regularly updated list of conditions screened for in each state is available at: http://genes-r-us.uthscsa.edu/.) In 2006, the ACMG reported their conclusions,[8,9] recommending screening for 29 diseases by all programs, and three additional conditions have been added since then (core conditions; Table 1-1). These conditions were considered to fulfill three basic principles that were developed to update and replace the original Wilson and Jungner criteria: 1) each condition is identifiable in a period of time

AT-A-GLANCE

Newborn Screening

Newborn screening is an important and widely established program of preventive medicine. It typically is a public health program and represents a population-based method to identify newborns with inherited or congenital, metabolic, endocrine, and other disorders. Detection of affected children in the pre-symptomatic state of the disease is the prerequisite for early initiation of treatment, to prevent most if not all disease manifestations and complications.

Newborn screening was implemented for phenylketonuria (PKU) more than half a century ago and today more than 50 different conditions can be tested for. However, agreement on and interpretation of criteria such as those outlined by Wilson and Jungner[6] (Table 1-1) for inclusion of a condition into a screening program is not universal. Although there is consensus that a careful balance between benefit and harm is important, the number of conditions included in newborn screening programs is variable between and also within countries.

Blood from newborns is taken during the first 1 to 4 days of life by a heel prick, spotted onto filter paper, and sent to a screening laboratory. The laboratory investigates the dried blood spots for the diseases of the respective screening panel. In addition to testing of dried blood spots, bedside testing for hearing loss and critical congenital heart disease are increasingly added to newborn screening programs. In the majority of newborns, the presence of disease can be ruled out as result of the first investigation. In the case of a positive result in the screening test, most screening programs request a repeated blood spot sample (recall); some refer positive-tested newborns to treatment and follow-up centers for recall testing and counseling. Of those newborns who underwent a recall investigation, up to 90% are not affected. Distinct abnormalities in the primary test or confirmation of abnormal primary results in the recall investigation raise strong suspicion for a disease and necessitate the initiation of confirmatory testing. Because the conditions screened for are rare and confirmation and treatment are complex, care of the presumptively affected newborns should occur in close consultation and collaboration with a pediatric specialist.

DISORDER	PREVALENCE[a]	KEY METABOLITE	COMMENTS/CONFIRMATION ANALYSIS
Phenylketonuria (PKU)	1:~10,000 (1:16,500)[b]	↑ Phe ↓ Tyr ↑ Phe/Tyr ratio	Confirmation: Plasma Phe, Tyr; pterins in urine, dihydropteridine reductase activity in DBS, molecular genetic analysis.[d]
Galactosemia	1:~70,000 (1:53,500)[b]	↑ Total galactose ↓ Galactose-1-phosphate uridyltransferase (GALT)	Galactokinase def. and UDP-gal-epimerase def. are also detected by total galactose screening. Total galactose screening gives false negatives when baby has not yet received lactose-containing milk. Confirmation: Enzyme in erythrocytes, molecular genetic analysis.[d] Galactokinase def. and UDP-gal-epimerase def. are not detected by GALT screening. GALT screening is independent from feeding.
Biotinidase deficiency	1:~60,000 (1:68,000)[b]	↓ Biotinidase activity	Confirmation: Enzyme in serum, molecular genetic analysis.[d]
Congenital hypothyroidism (CH)	1:~3500	↑ Thyroid-stimulating hormone (TSH)	T_4 may also be measured as part of newborn screening. Hypothalamo-hypophyseal forms of hypothyroidism are not detected by TSH screening. Citrate and EDTA blood causes false positives. Confirmation: Plasma thyroid hormones.
Congenital adrenal hyperplasia (CAH)	1:~13,000	↑ 17-OH-Progesterone (17-OHP)	Screening does not reliably detect 11- and 17-hydroxylase/17,20-lyase, and 3β-OH-steroid dehydrogenase deficiency. For preterm newborns cut-offs adjusted for gestational age, birth weight, and/or age at sample collection are necessary. Confirmation: Plasma steroids, molecular genetic analysis.[d]
Glucose-6-phosphate dehydrogenase (G6PD) deficiency	1:~3000	↓ G6PD activity	Enzyme in EDTA blood, molecular genetic analysis.
Maple syrup urine disease (MSUD)	1:160,000 (1:198,000)[b]	↑ Leucine + Isoleucine + Allo-Isoleucine ↑ Valine ↑ (Leu+Ile+Allo-Ile)/Phe -ratio	Screening during the first 24 hours might miss cases. Confirmation: Plasma amino acids and urine organic acids, molecular genetic analysis.[d]
Hepatorenal tyrosinemia type 1 (TYR-1)	1:100,000 (1:781,000)[b]	(↑) Tyr ↑ Succinylacetone	Confirmation: Plasma amino acids, α-fetoprotein, succinylacetone, enzyme in fibroblasts, molecular genetic analysis.[d]
Homocystinuria (HCY)	< 1:200,000 (1:457,000)[b]	↑ Methionine ↑ Homocysteine	Confirmation: Total homocysteine in plasma, molecular genetic analysis,[d] enzyme in fibroblasts.

(Continued)

(CONTINUED)

DISORDER	PREVALENCE[a]	KEY METABOLITE	COMMENTS/CONFIRMATION ANALYSIS
Citrullinemia (ASS)	1:~250,000 (1:156,000)[b]	↑ Citrulline ↓ Arginine	Confirmation: Plasma amino acids, orotic acid in urine, molecular genetic analysis.[d]
Argininosuccinate lyase deficiency (ASL)	1:220,000 (1:305,000)[b]	↑ Arginino-succinate ↑ Citrulline ↓ Arginine	Confirmation: Plasma and urine amino acids, orotic acid in urine, enzyme in erythrocytes/fibroblasts, molecular genetic analysis.[d]
Medium-chain acyl-CoA dehydrogenase deficiency (MCAD)	1:~15,000 (1:18,000)[b]	↑ C8 carnitine ↑ C8/C2 ratio ↑ C8/C10 ratio ↑ C8/C12 ratio	CDmay cause a non-informative acylcarnitine profile; C_8 may be also elevated in glutaric type II (along with other acylcarnitines). Confirmation: Acylcarnitines in DBS/blood, urine organic acids, molecular genetic analysis[d], enzyme in lymphocytes/fibroblasts.
(Very) long-chain acyl-CoA dehydrogenase deficiency (VLCAD)	1:85,000 (1:63,500)[b]	↑ C14:1 carnitine ↑ C14 carnitine	CDor glucose infusion may cause a non-informative acylcarnitine profile. Blood for acylcarnitine profiling has to be taken prior to (not after) regular meal. Confirmation: Acylcarnitines in DBS/blood, urine organic acids, molecular genetic analysis[d], enzyme in lymphocytes/fibroblasts.
Long-chain 3-OH-acyl-CoA dehydrogenase deficiency (LCHAD) and trifunctional protein deficiency (TFP)	1:250,000 (1:300,000)[b]	↑ C16OH carnitine ↑ C18OH carnitine	CDmay cause a non-informative acylcarnitine profile. Fat infusion may cause false positives. C16OH may be the only abnormal finding in LCHAD/TFP deficiency even with normal C2. Confirmation: Acylcarnitines in DBS/blood, molecular genetic analysis,[d] enzyme in lymphocytes/fibroblasts.
Carnitine-palmitoyl transferase I deficiency (CPTI)	< 1:750,000	↑ C0 (free) carnitine ↓ C16 carnitine ↓ C18 carnitine ↑ C0/(C16+C18) ratio	Carnitine supplementation (prematures) may cause false positives. Confirmation: Acylcarnitines in DBS/blood, free carnitine in blood, enzyme in lymphocytes/fibroblasts, molecular genetic analysis.[d]
Carnitine-palmitoyl transferase I deficiency (CPTII) and carnitine-acylcarnitine-translocase deficiency (CAT)	< 1:750,000	↑ C14 carnitine ↑ C16 carnitine ↑ C18 carnitine ↑ C18:1 carnitine	CDmay cause a non-informative acylcarnitine profile. Special premature formula gives false positives. Confirmation: Acylcarnitines in DBS/blood, enzyme in lymphocytes/fibroblasts, molecular genetic analysis.[d]
Carnitine uptake deficiency (CUD)	1:77,000 (1:142,000)[b]	↓ ↓ C0 (free) carnitine	Organic acid disorders, prematurity, and maternal carnitine deficiency may also cause low free carnitine. Maternal carnitine supplementation can cause false negatives. Confirmation: Determine free carnitine in plasma and urine, determine fractional tubular reabsorption of free carnitine (normal > 98%) in child and mother; carnitine uptake studies in fibroblasts and/or molecular genetic analysis.[d]
Isovaleric aciduria (IVA)	1: 100,000 (1:159,000)[b]	↑ C5 carnitine	CDmay cause a non-informative acylcarnitine profile. Treatment with pivalic acid containing antibiotics may cause false positive results. C5 carnitine is also elevated in SBCAD deficiency. Confirmation: Urine organic acids and acylglycines, acylcarnitines in DBS/blood, molecular genetic analysis.[d]
Glutaric aciduria type 1 (GA-1)	1:100,000 (1:92,000)[b]	↑ C5DC ↑ C_5DC/C_8 ↑ C_5DC/C_{16}	CDmay cause a non-informative acylcarnitine profile. Confirmation: Urine organic acids (glutaric and 3-hydroxyglutaric acid by a sensitive stable isotope dilution method), acylcarnitines in DBS/blood, enzyme in lymphocytes/fibroblasts, molecular genetic analysis.[d]
Propionic aciduria (PA)	1:200,000 (1:238,000)[b]	↑ C3 carnitine ↑ C3/C0 ratio ↑ Methylcitrate	CDmay cause a non-informative acylcarnitine profile. Confirmation: Urine organic acids, acylcarnitines in DBS/blood, ammonia, enzyme in fibroblasts, molecular genetic analysis.[d]
Methylmalonic aciduria (MMA)	1:150,000 (1:160,000)[b]	↑ C3 carnitine ↑ C3/C0 ratio ↑ Methylmalonic acid ↑ Methylcitrate	CDmay cause a non-informative acylcarnitine profile. Confirmation: Urine organic acids, plasma methylmalonic acid, plasma amino acids (methionine) and total homocysteine, ammonia, enzyme in fibroblasts, molecular genetic analysis.[d]

(Continued)

(CONTINUED)

DISORDER	PREVALENCE[a]	KEY METABOLITE	COMMENTS/CONFIRMATION ANALYSIS
Cobalamin deficiency (CBLA, B, C, D, F, J, X, TC-II) and succinyl-CoA synthetase (SUCLA2) deficiency	1:100,000	↑ C3 carnitine ↑ C3/C0 ratio ↑ Methylmalonic acid ↑ Methylcitrate	CD may cause a non-informative acylcarnitine profile. Confirmation: Urine organic acids, plasma methylmalonic acid and acylcarnitines, plasma amino acids (methionine) and total homocysteine, ammonia, molecular genetic analysis[d] complementation analysis in fibroblasts; vitamin B_{12} levels in the mother.
3-Methylcrotonyl-CoA carboxylase deficiency (3-MCC)	1:60,000 (1:39,000)[b]	↑ C5OH carnitine	CD may cause a non-informative acylcarnitine profile. C5OH carnitine can also be elevated in 3-methylglutaconic aciduria type I, multiple carboxylase deficiency including biotinidase and holocarboxylase deficiency, biotin deficiency, β-ketothiolase deficiency, 2-methyl 3-hydroxy butyryl-CoA dehydrogenase deficiency and 3-hydroxy-methylglutaryl (HMG)-CoA lyase deficiency. Confirmation: Urine organic acids, blood ammonia, enzyme in fibroblasts, molecular genetic analysis;[d] acylcarnitines and urine organic acids in the mother.
3-Hydroxy-methylgutaryl-CoA lysase deficiency (HMG)	< 1:200,000 (1:1,528,000)[b]		
Cystic fibrosis (CF)	1:5000	↑ Immune reactive trypsinogen (IRT) ↑ Pancreatitis associated protein (PAP) Presence of common CFTR mutations	Confirmation: Comprehensive molecular genetic analysis (if not part of newborn screening); sweat chloride.
Severe combined immuno-deficiency syndrome (SCID) Severe B cell deficiency	1:~ 70,000 1:100,000	↑ T-cell receptor excision circles (TREC) ↓ Kappa-deleting recombination excision circles (KREC)	In addition to SCID, 22q11.2 deletion syndrome is detected by TREC screening but not B cell defects. X-linked agammaglobulinemia, Ataxia Teleangiectasia and Njimegen-Breakage Syndrome are detected in a Duplex PCR assay (TREC/KREC). Confirmation: CBC with differential and lymphocyte enumeration, antibody levels, lymphocyte proliferation to mitogens, and molecular genetic testing.[d]
Sickle cell disease	< 1:200,000 – 1:300[c]	Hemoglobin analysis by electrophoresis, HPLC or MS/MS	Confirmation: Hemoglobin electrophoresis with other than screening method.

[a]Prevalence as estimated from newborn screening in a Caucasian population, it may vary among screening populations of different ethnic background.
[b]Newborn screening data US 2001–2010.[106]
[c]In black population.
[d]Molecular genetic analysis is typically not required to establish a diagnosis and its value should be evaluated on a case-by-case basis.
CD, carnitine deficiency; DBS, dried blood specimen; Phe, phenylalanine; Tyr, tyrosine.
Note: Information and suggestions for follow up of abnormal newborn screening results is also available at: http://www.ncbi.nlm.nih.gov/books/NBK55832/.

(24 to 48 hours after birth) at which it would not ordinarily be clinically detected; 2) a test with appropriate sensitivity and specificity is available; and, 3) benefits of early detection, timely intervention, and efficacious treatment have been demonstrated. Because screening tests do not primarily determine disease status, but measure analytes that in most cases are not specific for a particular disease, the ACMG report also included 25 conditions (secondary targets) that did not meet all three selection criteria but are identified nevertheless because most of them are included in the differential diagnosis of screening results observed in core conditions (Table 1-1). Most of these secondary conditions are identified through metabolite profiling by MS/MS, which enables the determination of more than 50 analytes and analyte ratios in a small newborn screening blood spot punch. This also increases the responsibility of newborn screening laboratories to provide testing with the highest sensitivity and specificity to allow identification of affected patients while minimizing the false-positive rate.

The current state of newborn screening programs in Europe was evaluated through a comprehensive survey in the European Union (EU) program of Community Action in Public Health 2010/2011 among 27 EU member states, four candidate countries, three potential candidates, and two European Free Trade Association (EFTA) countries. The comprehensive overview addressed all aspects of screening, spanning from the supporting legislation to confirmation diagnostics and start of treatment. For each step it evaluated existing guidelines, actual practices, quality assurance, and training schemes and resulted in an agreed-upon Expert Opinion document with recommendations to the EU Commission for improvement. Ethical aspects and the systematic evaluation of the screening programs were investigated. The survey documented large discrepancies concerning 1) education of parents, including informed consent; 2) which conditions are screened for, ranging from 2 to more than 30; 3) age at sample collection; 4) screening methodology; 5) storage of residual specimens, varying from 1 to 1000 years. Confirmatory diagnostics, treatment, and follow-up displayed similar differences.[7,10,11] All reports are available at: http://www.iss.it/cnmr/prog/cont.php?id=1621&lang=1&tipo=64.

PERFORMANCE OF A NEWBORN SCREENING PROGRAM

An ideal screening test would detect all newborns in a population affected with the disease with 100% sensitivity and the unaffected newborns would have normal results (100% specificity). In practice, every screening test fails under certain circumstances and to a different extent. Metabolites or hormones are used as marker(s) for most of the screening conditions (eg, Phe in screening for PKU, thyroid stimulating hormone [TSH] in congenital hypothyroidism [CH]). These metabolites reveal usually a bimodal distribution, where the "disease range" is ideally separated from the "normal range" (Figure 1-1). However, based on the (patho)physiologic distribution of the metabolite(s) and the characteristics of the screening test the ranges often overlap. Diagnostic sensitivity and specificity then depends on how the decision limit ("cutoff" point) for the marker is set. In the example given in Figure 1-1, the cutoff set at point A yields 100% sensitivity but many false positives; the cutoff set at point B yields 100% specificity but many false negatives, and at point C yields some false positives and false negatives. Note that sensitivity and specificity vary reciprocally to the setting of the cutoff.

Setting the cutoff at the 99.5th percentile of healthy newborns often results in 100% sensitivity while keeping the specificity in an acceptable range. A higher cutoff is feasible when missing of disease variants (mildly affected subjects not needing treatment) is acceptable or when there is a gap between "normal" and "disease."

Applying a screening test to a population will produce four categories of results (true positives, false positives, false negatives, and true negatives; Table 1-2). If the number of cases for each category is known, the false-positive rate and positive predictive value (PPV) can be calculated. The false-positive rate should be low and the PPV, which is a measure of the proportion of persons with positive test results who are truly affected, should be high. These measures provide insight into the performance of a screening program and physicians receiving newborn screening results should be able to obtain this information from their respective screening programs. Physicians must be aware, however, that screening programs have different definitions of what constitutes a positive result. Some programs count any abnormal result as positive, whereas others consider only a confirmed abnormal result on a repeated blood spot test as positive.[12,13]

To illustrate how indices help in the assessment of a screening test, consider the situation

TABLE 1-1 Recommended Uniform Screening Panel (US) and Key Analytes

Analyte	Core Condition	Secondary Targets	Other Identifiable Conditions
Phe	PKU	BS HPA RFLG	
Leu/Ile/AlloIle, Val	MSUD		BCKDK (if branched-chain amino acids below reference range)
Met	HCY	MET	RMD (if Met is below reference range)
Cit, Arg, Asa	ASA CIT	ARG CTLN2	
Tyr	TYR-I	TYR-II TYR-III	TIN
C0	CUD	CPT-I (when elevated)	Maternal CUD or conditions associated with secondary C0 deficiency
C3	CBLA, CBLB MUT PA	CBLC, CBLD	CBLF CBLJ CBLX TG-II SUCLA2
C4		IBDH SCAD	RCHLU
C5	IVA	SBCAD	Medication artifact Ethylmalonic encephalopathy
C5-OH	BKT HMG MCC MCD	MGA-I MHBD	Maternal MCC
C8	MCAD	GA-II MCKAT M/SCHAD	
C3-DC		MAL	
C10:2		DR	
C5-DC	GA-I		
C14:1, C16, C18:1	VLCAD	CACT CPT-II CPT-I (when below reference range)	
C16-OH	LCHAD TFP		
Biotinidase	BIOT		
17-OHP	CAH		
TSH and/or fT_4	CH		
Total galactose and/or GALT	GALT	GALE GALK	
IRT+/- PAP+/-CFTR mutation panel	CF		
TREC	SCID	Secondary immunodeficiencies (eg, DiGeorge syndrome, trisomy 21, CHARGE syndrome)	

(Continued)

TABLE 1-1 Recommended Uniform Screening Panel (US) and Key Analytes (Continued)

Analyte	Core Condition	Secondary Targets	Other Identifiable Conditions
Hemoglobin electrophoresis	Sickle cell anemia; S, β-thalassemia; S,C disease	Other hemoglobinopathies	
Audiometry	Hearing loss		
Pulse oximetry	Critical congenital heart disease		

Phe, phenylalanine; PKU, phenylketonuria; BS, defects of biopterin cofactor biosynthesis; HPA, benign hyperphenylalaninemia; REG, defects of biopterin cofactor regeneration; Leu, leucine; Ile, isoleucine; Alloile, Allo-isoleucine; Val, valine; MSUD, maple syrup urine disease; BCKDK, branched-chain ketoacid dehydrogenase kinase deficiency; Met, methionine; HCY, homocystinuria (due to cystathionine β synthase deficiency); MET, hypermethioninemia; RMD, remethylation disorders; TIN, transient tyrosinemia of the neonate; Cit, citrulline; Arg, arginine; Asa, argininosuccinate; ASA, argininosuccinic acidemia; CIT, citrullinemia; ARG, argininemia; CIT-II, citrullinemia type II (citrin deficiency); Tyr, tyrosine; TYR-I, tyrosinemia type I; TYR-II, tyrosinemia type II; TYR-III, tyrosinemia type III; TIN, transient hypertyrosinemia of the newborn; CUD, carnitine uptake defect; CBL, methylmalonic acidemia due to a cobalamin deficiency; MUT, methylmalonic acidemia (mutase deficiency); PA, propionic acidemia; TC-II, transcobalamin II deficiency, SUCLA2, succinyl-CoA synthetase deficiency, IBDH, isobutyryl-CoA dehydrogenase deficiency, SCAD, short-chain acyl-CoA dehydrogenase deficiency, FIGLU, glutamate formiminotransferase deficiency, IVA, isovaleric acidemia; SBCAD, short branched-chain acyl-CoA dehydrogenase deficiency, BKT, β-ketothiolase deficiency, HMG, 3-hydroxy 3-methyl glutaric aciduria (HMG-CoA lyase deficiency); MCC, 3-methylcrotonyl-CoA carboxylase deficiency, MCD, multiple carboxylase deficiency, MGA-I, methylglutaconic aciduria type I; MHBD, 2-methyl 3-hydroxybutyryl-CoA dehydrogenase deficiency, MCAD, medium-chain acyl-CoA dehydrogenase deficiency, GA-II, glutaric aciduria type II (multiple acyl-CoA dehydrogenase deficiency); MCKAT, medium-chain ketoacyl-CoA thiolase deficiency, M/SCHAD, medium/short-chain 3-hydroxy acyl-CoA dehydrogenase deficiency, MAL, malonic aciduria; DR, dienoyl-CoA reductase deficiency, GA-I, glutaric acidemia type I; VLCAD, very long-chain acyl-CoA dehydrogenase deficiency, CACT, carnitine:acylcarnitine translocase deficiency, CPT-I, carnitine palmitoyltransferase I deficiency, CPT-II, carnitine palmitoyltransferase II deficiency, LCHAD, long-chain 3-hydroxy acyl-CoA dehydrogenase deficiency, TFP, trifunctional protein deficiency, BIOT, biotinidase deficiency, 17-OHP, 17-OH-Progesterone; CAH, congenital adrenal hyperplasia (21-hydroxylase deficiency); TSH, thyroid-stimulating hormone; CH, congenital hypothyroidism; GALT, classical galactosemia; GALE, galactose epimerase deficiency, GALK, galactokinase deficiency, IRT, immune reactive trypsinogen; PAP, pancreatitis associated protein; CF, cystic fibrosis; TREC, T-cell receptor excision circles; SCID, severe combined immune deficiency syndrome. (http://www.hrsa.gov/advisorycommittees/mchbadvisory/heritabledisorders/recommendedpanel/index.html).

of screening for tyrosinemia type I (TYR-I). Traditionally, the primary marker used to identify patients (with TYR-I is tyrosine Tyr); however, Tyr levels in newborns with TYR-I can be in the normal range. Furthermore, Tyr elevation is most often associated with other disorders or benign transient hypertyrosinemia of the newborn. Assuming two patients with TYR-I were born among a screened population of 200,000 newborns and Tyr was 160 and 240 μmol/L in the patients' respective screening samples, a cutoff for Tyr chosen at the 99.5th percentile corresponding to a Tyr concentration of 180 μmol/L would yield an insufficient sensitivity of only 50%, a false-positive rate of 0.5%, and a PPV of 0.1% (Table 1-3). Lowering the cutoff to the 97th percentile (150 μmol/L) raises the sensitivity to 100% but has its drawback in an increased false-positive rate (3%), and further reduction of the PPV (0.03%) (Table 1-3). To overcome this untenable situation, some screening programs have stopped screening for TYR-I and others have implemented testing for succinylacetone, a specific marker for TYR-I[14-16] The latter can be performed as a primary screening[16] test or in a second-tier approach in which any sample yielding an elevated Tyr value will be analyzed for succinylacetone.[14,15] Using the two-tier approach, which is not 100% sensitive, only samples containing both elevated analytes would be reported as abnormal.[17]

A second-tier approach has also been introduced for several other conditions associated with high false-positive rates and poor PPV in which biochemical or molecular genetic approaches are used.[18-22] For example, screening for cystic fibrosis (CF) is performed by determining immunoreactive trypsinogen. If trypsinogen is abnormally elevated, DNA is extracted from the existing blood spot to determine the presence of at least the most common CFTR mutations. A screening report is not issued until both tests have been completed.[21,22] Despite this approach, however, the false-positive rate for CF screening remains high because any elevated immunoreactive trypsinogen (IRT) concentration associated with at least carrier status for one of the evaluated CFTR mutations requires follow-up, thereby identifying mostly CF carriers. As an alternative, IRT/PAP (pancreatitis-associated protein) protocols have been shown to have similar sensitivity with respect to detection of CF patients when compared to an IRT/DNA–based protocol.[23-25] One advantage of using PAP as second tier test is that in contrast to genetic CF newborn screening the majority of carriers are not detected. This strategy can be combined with DNA testing as third tier.

In addition to second-tier tests, an increasing number of screening programs have improved their performance at least for the conditions identified through amino acid and acylcarnitine analysis by departing from the use of strict and arbitrary cutoffs to determine whether a result can be considered normal or abnormal.[26] The Region 4 Collaborative's Laboratory Performance Database (freely available by registering at: https://www.nbstrn.org/research-tools/lab-performance-database) has established a web-based system that allows laboratories to determine within seconds the relevance of amino acid and acylcarnitine results obtained by MS/MS analysis. This system establishes risk factors for a result being presumptive positive for relevant conditions by determining and weighing the degree of penetration into the disease range of multiple analytes and ratios of analytes. The disease ranges are based on a minimum of 50 true positive result sets obtained from a continuously growing number of collaborating newborn screening programs worldwide.[27] Application of these tools in routine newborn screening leads to significant performance improvements over the static use of cutoffs

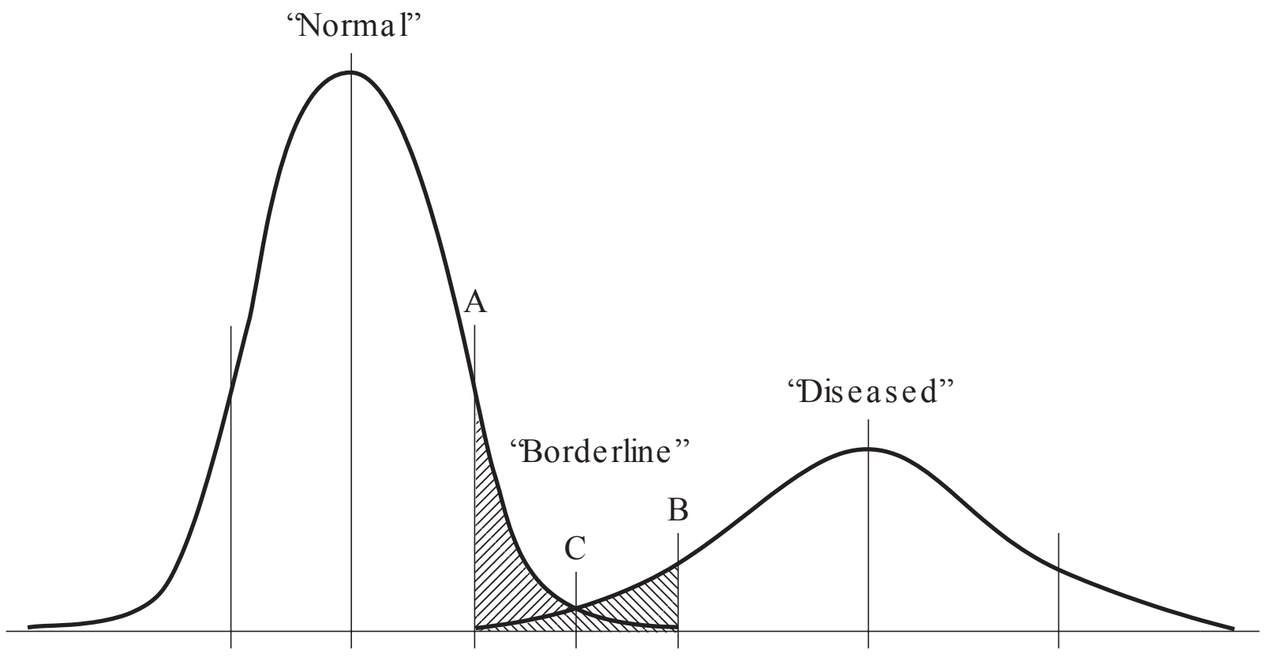

FIGURE 1-1. Bimodal distribution of a variable (eg, the marker metabolite for a screening disease) in a population.

TABLE 1-2 The Performance of a Screening Test

	No. of Newborns w/ Positive Screening Result	No. of Newborns w/ Negative Screening Result	Total
No. of newborns w/ disease	True positives (TP)	False negatives (FN)	TP + FN
No. of newborns w/o disease	False positives (FP)	True negatives (TN)	FP + TN
Total	TP + FP	FN + TN	All newborns screened

$$\text{Sensitivity} = \frac{\text{Affected newborns with positive test (TP)}}{\text{All affected newborns in tested population (TP + FN)}}$$

= Proportion of affected patients that have a positive test result

$$\text{Specificity} = \frac{\text{Healthy newborns with negative test (TN)}}{\text{All healthy newborns in tested population (FP + TN)}}$$

= Proportion of unaffected newborns having a negative test result

$$\text{False-positive rate} = \frac{\text{Healthy newborns with positive test (FP)}}{\text{All newborns with positive test (TP + FP)}}$$

$$\text{PPV}^{a} = \frac{\text{Affected newborns with positive test (TP)}}{\text{All positive tests (TP + FP)}}$$

= Proportion of newborns with positive test results who are truly affected

[a]Positive predictive value.

for single analytes while avoiding unnecessary costs for repeat analyses and follow-up investigations.[28]

Additional performance improvements in the interpretation of metabolite profiles such as those obtained for amino acids and acylcarnitines can be achieved when any available information provided on the newborn screening card is considered. Such result interpretation requires knowledge of and experience with not only detectable diseases but also with typical clinical situations encountered in neonates. For example, C5 acylcarnitine is a marker for isovaleric aciduria (IVA), a classic organic aciduria that can result in a devastating outcome unless metabolic decompensation is prevented. IVA is therefore included in most screening panels; however, C5 acylcarnitine is also elevated in 2-methylbutyrylglycinuria and in a milder variant of IVA, both of which are of uncertain clinical significance.[29-31] To further complicate the differential diagnosis of C5 acylcarnitine elevations, this analyte is also present at abnormal levels in patients treated with pivalic acid–containing medications.[32] Simple notification of the referring birthplace about any C5 acylcarnitine elevation will therefore increase the number of false-positive results, in particular when it is encountered in premature neonates exposed to particular medications.[32,33]

A screening program's performance is also determined through ongoing assessment of the outcome or consequences of abnormal results. The impact of false-positive results was documented through an objective and quantitative assessment by Waisbren et al.[34,35]

TABLE 1-3 Effect on Screening Performance of Variable Cut-off Levels of Tyrosine in Detecting Two Cases of Tyr-I in a Population of 200,000 Newborns

Case #1

Tyr Cut-off Set at 99.5% (180 μmol/L)	No. of Newborns w/ Positive Screening Result	No. of Newborns w/ Negative Screening Result	Total
No. of newborns w/ disease	1 (Tyr 240 μM)	1 (Tyr 160 μM)	2
No. of newborns w/o disease	999	198,999	199,998
Total	1000	199,000	200,000

Sensitivity, 50%; specificity, 99.5%; false-positive rate, 0.5%; PPV, 0.1%

Case #2

Tyr Cut-off Set at 95% (150 μmol/L)	No. of Newborns w/ Positive Screening Result	No. of Newborns w/ Negative Screening Result	Total
No. of newborns w/ disease	2 (Tyr 160 and 240 μM respectively)	0	2
No. of newborns w/o disease	5998	194,000	199,998
Total	6000	194,000	200,000

Sensitivity, 100%; specificity, 97%; false-positive rate, 3%; PPV, 0.03%

Although it was found that expanded screening provides better long-term outcome for those patients subjected to early initiation of treatment because of early identification of their condition, infants with false-positive screening results were more often hospitalized than healthy children with normal screening results. Families who received false-positive newborn screening results were at higher risk of developing dysfunctional parent–child relationships.[35] Furthermore, with the ability to identify newborns with conditions of either uncertain clinical significance (ie, short chain acyl-CoA dehydrogenase [SCAD] deficiency) or for which there is no effective long-term treatment (ie, carnitine-acylcarnitine translocase deficiency), the impact of these conditions on the newborns, their families, and the healthcare system must be continuously evaluated to obtain evidence that can be used to determine whether to continue screening for specific conditions. Despite the major advantages of newborn screening for physical and cognitive outcome, living with a metabolic disorder causes considerable stress on patients and their families. Although in a German study more than 90% of families expected that their child's future development will be normal and that their child will lead an independent adult life, the majority of families also reported a significant strain posed on the family (child) by the disorder.[36] For some disorders the perceived burden was highly variable between families, and disorders grouped as potentially very burdensome according to expert rating were not necessarily perceived as such by parents. This emphasizes the need for comprehensive