

OXFORD MONOGRAPHS ON MEDICAL GENETICS

INBORN ERRORS OF METABOLISM

**FROM NEONATAL SCREENING
TO METABOLIC PATHWAYS**

EDITED BY
**BRENDAN LEE
FERNANDO SCAGLIA**

OXFORD

Inborn Errors of Metabolism

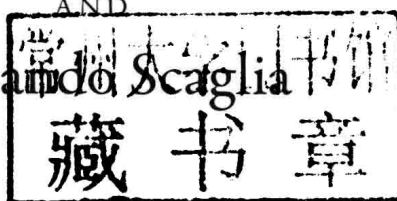
From Neonatal Screening to Metabolic Pathways

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Brendan Lee

AND

Fernando Scaglia



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Published in the United States of America by
Oxford University Press
198 Madison Avenue, New York, NY 10016

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Library of Congress Cataloging-in-Publication Data

Inborn errors of metabolism (Lee)
Inborn errors of metabolism : from neonatal screening to metabolic pathways / edited by
Brendan Lee and Fernando Scaglia.

p. ; cm.

Includes bibliographical references.

ISBN 978-0-19-979758-5 (alk. paper)

I. Lee, Brendan, editor. II. Scaglia, Fernando, editor. III. Title.

[DNLM: 1. Metabolism, Inborn Errors. WD 205]

RC627.8

616.3'9042—dc23

2014010620

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1 3 5 7 9 8 6 4 2

Printed in the United States of America
on acid-free paper

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Introduction

Typically, textbooks on inborn errors of metabolism have focused on presenting the classical biochemical defects, correlating them with different clinical presentations and describing the current therapeutic approaches. However, with the advent of comprehensive newborn screening and improvement in diagnostic methodologies, we are beginning to appreciate the complex natural histories of these disorders. They together underscore that the increasingly diverse disease phenotypes that arise from Mendelian disorders reflect not only the primary effect of the metabolic disturbance, that is, accumulation of toxic metabolites upstream of a biochemical block and deficiency of the product downstream. We and others now appreciate secondary effects of the block as well as new “moonlighting” functions of components of the pathway. Hence, the aim of this textbook focuses on a pathways approach to presenting the phenotypes of inborn errors of metabolism. This textbook covers a myriad of topics from the principles of newborn screening, to presenting the basic underlying biochemical and molecular alterations, to explaining how these basic alterations in pathways may in fact lead to complex secondary and tertiary effects in metabolism that contribute to the complex natural histories of these disorders. The boundaries between Mendelian and complex disorders have become increasingly blurred as we recognize that Mendelian inborn errors of metabolism are indeed complex disorders. An evolving paradigm shift now supported by robust evidence points to complex signaling pathways and networks in inborn errors of metabolism. Thus a new focus on understanding these diseases should be based on studying how their natural histories can inform us about the secondary and tertiary consequences of the primary metabolic defects. The focus on the broad pathway effects of specific metabolic derangements will lead us to a deeper understanding of the mechanisms of pathogenesis. Hence, we hope to extend beyond basic descriptions of the classical biochemistry to prepare future generations of students, clinicians, and scientists in the study of these disorders. We hope that this approach will stimulate new ideas for therapeutic strategies and management.

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SECTION 1

Newborn Screening

