CASSIDY AND ALLANSON'S

MANAGEMENT OF GENETIC SYNDROMES

FOURTH EDITION

EDITED BY

JOHN C. CAREY | AGATINO BATTAGLIA

DAVID VISKOCHIL | SUZANNE B. CASSIDY

WILEY Blackwell

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Fourth Edition

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We dedicate this book
To our families
Leslie, Patrick, and Andrew Carey
Emi and Chiara Battaglia
Barbara, Richard, Joseph, and Kayla Viskochil
Joshua Cassidy and Christopher, Adam and Alexandra Visher

For all they taught us, for their tolerance, and for their love and encouragement

AND

To our patients
Who have inspired us with their resilience and their living with the unique challenges of rare conditions

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FOREWORD TO THE FOURTH EDITION

Almost a generation has gone by since *Management of Genetic Syndromes* was conceived and the first edition published. That volume provided up-to-date, expert-authored, practical information on clinical features, natural history, medical concerns, and management of 30 conditions, each with an incidence between 1/600 and 1/60,000. Thus, most were considered rare conditions, and unlikely to be on the radar of primary care practitioners or non-genetics specialists unless/until that physician had an affected individual in their practice. Most, if not all, chapter authors had worked closely for many years with a family support group, accumulating a wealth of knowledge on the myriad associated medical consequences and natural history. While diagnostic testing was available for about two-thirds, the remaining conditions could only be diagnosed by recognition of a pattern that might include congenital anomalies, differences in stature, appearance and/or development, and specific health problems.

Over the course of the last 20 years, enormous changes have occurred in the technologies available for testing and interpretation of results, the way we approach pattern recognition as it applies to differences in appearance, the options for management and, occasionally, treatment of associated health concerns, and, perhaps most importantly, the way the medical profession and society view rare diseases. In short, nothing is the same!

Technology has moved away from analysis of chromosomes and individual genes to testing of the genome using microarrays and whole exome and whole genome sequencing. When a diagnosis is suspected, focused testing remains the gold standard. However, ordering a test that evaluates multiple genes that cause conditions with overlapping features, or screening the patient's entire genome if a testable diagnosis is not suspected, is now not only possible but increasingly cost effective. Clinical diagnosis relies on painstaking assessment and recognition of specific physical differences, the phenotype. It is just as important to describe that phenotype in an accurate and consistent manner. The development of a human phenotype ontology with more than 10,000 terms, each of which describes a phenotypic variation seen in human disease, is of great importance for the classification and comparison of affected individuals. Recognition of differences in facial appearance, some quite subtle, has moved from an "art" to a "science". Initially grounded in the experience and observation skills of the clinician, pattern recognition was enhanced by simple linear measurements and then revolutionized by 3D photography, computer modeling, machine learning, and artificial intelligence. Syndrome recognition aided by the use of images taken by a point-and-shoot camera or even a mobile phone now has an established place in clinical practice.

Over the last 20 years, there has been increasing recognition that rare diseases, in aggregate, are common, and estimated to affect 200 million people worldwide. A substantive proportion of the approximately 7000 known rare diseases are due to the altered function of single genes. For an individual with a rare genetic disease, timely provision of a molecularly confirmed diagnosis is critical for many reasons. It shortens the diagnostic odyssey, improves disease management by identifying specific health risks and preventing unnecessary or harmful diagnostic interventions and treatments, and it enables recurrence risk counseling and reproductive choice. This is the cornerstone of precision medicine. Understanding how genes function and interact and concomitant insight into biological mechanisms will not only enhance diagnosis and medical care for individuals with rare diseases, but will transform our understanding of health and disease. Documentation of pathogenic variations

in the same gene in at least two unrelated individuals with the same rare disease is necessary to confirm the identity of a novel disease gene. As we study diseases of increasing rarity, a single academic centre or program is unlikely to achieve this standard. Thus diagnosis (and treatment) of individually rare disorders is best addressed by broad international collaboration. To this end, the International Rare Diseases Research Consortium (IRDiRC) was established in 2011, just a year after publication of the third edition of *Management of Genetic Syndromes*. It now brings together nearly 50 organizations in 18 countries invested in rare disease research. In addition to enabling the formation of scientific groups focused on diagnostics and therapies, close association with private-sector pharmaceutical and biotechnology companies has increased funding, data discovery and data sharing. International databases for genotype-driven and phenotype-driven matching of individuals with unsolved rare diseases have been developed, with an overarching platform that connects the data silos. Critically, partnership with national and continental patient advocacy organizations from Africa, Asia, Australia, Europe, and North America ensures the gene discovery research remains grounded in patient/family experience and relevance.

This fourth edition of *Management of Genetic Syndromes* includes five new conditions, bringing the total to 63 and more than doubling the original cohort of disorders. The thoughtful and consistent layout is unchanged, as it has proved to be a popular, effective, easy to use format. Since individuals with syndromes will be found in all medical practices and will benefit most when their provider is comfortable with the issues that need to be addressed to assure the best medical and quality of life outcomes, the information herein is no longer the purview of the genetics specialist, but is relevant to many other specialists and primary care providers. We know that barriers to the integration of genomic services into these practices include lack of time, knowledge, and confidence in the skills required. Easy access to current, reliable, practical, evidence-based information facilitates the effective transition of genomic medicine into primary care and non-genetics specialty practice. Increasingly, families play a role in the management of what is commonly a lifelong chronic condition and, in many cases, they become more knowledgeable than their doctor. Although *Management of Genetic Syndromes* is not written for the public, its clear and practical presentation style, with management sections that have a system by system, checklist-like format, allows families and providers to follow together the issues to be addressed, in the right way and at the right time. Links to consumer health information are also provided for each condition. Hopefully, as *Management of Genetic Syndromes* evolves to include an alternative electronic format, individual chapters will be available to families and patient advocacy groups.

Management of Genetic Syndromes remains a model for how to organize information in a meaningful format and context for physicians and families. The hype about gene discovery and effective treatment of genetic disorders persists, albeit moving closer to reality in a few circumstances. In the meantime, *Management of Genetic Syndromes* delivers the goods on what is really known about management and treatment of these 63 disorders. I have had the good fortune and honour to be involved in the previous three editions as both an editor and an author. The new editorial team has delivered another great edition of this must-have book.

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FOREWORD TO THE THIRD EDITION

Cassidy and Allanson have done it again: produced a new edition of the one must-have book on management of genetic disorders for health care providers of all specialties. To incorporate advances in medical genetics into their practices, clinicians need an expert-authored resource that provides up-to-date information on available diagnostic approaches and practical day-to-day, age-oriented management. *Management of Genetic Syndromes* does not require that clinicians become genetics experts or fluent in genetics lingo. It is written with the knowledge that persons with inherited disorders are found in all medical practices and, similar to people with other medical conditions, these individuals will benefit most when their health care providers are comfortable with the issues that need to be addressed to assure the best medical and quality-of-life outcomes. This book presents to clinicians in primary care and specialty practice the information necessary to allow the clinician to decide for their patients with rare inherited disorders which care is within the scope of his or her practice and which specific needs should be referred out to other specialists.

Management of Genetic Syndromes is a boon to busy primary care practitioners who, I am told, have 90 seconds in which to answer a question brought up during a patient visit. If clinicians do not have a reliable, easy-to-use resource, those questions will go unanswered. The logical division of chapters by disorder and the thoughtful and consistent layout of each chapter into sections on diagnosis first (how can you provide disorder-specific care if you can't be sure that you have the correct diagnosis?) followed by detailed management issues by organ system for all ages allows the busy clinician to hone in on an authoritative answer in a predictable "place." Eliminating the guess work about specific care issues is tremendously valuable to busy clinicians who want to assure the best care for their patients, but cannot take the time to second guess the exact needs for an individual with a one-of-a-kind disorder in their practice. Similar to all quality information resources, *Management of Genetic Syndromes* provides citations to more detailed documentation of diagnostic and management recommendations for those clinicians with the time or inclination to learn more.

In these days of hype on pending cutting-edge treatment for genetic disorders and "personalized" medicine, clinicians need a filter that can separate what is really known about treatment and what is hypothesis-driven wishful thinking for which no prescription can be written. *Management of Genetic Syndromes* provides this filter, thus assuring clinicians and families that clinicians have at their fingertips information that will be most useful.

Although the promise of the Human Genome Project to provide gene-based therapy for inherited disorders is still a long way from reality, other aspects of the discoveries of the molecular basis of inherited disorders have benefited those with and at risk for inherited disorders. One example is surveillance of those at risk for a potential complication of an inherited disorder, which enables early diagnosis and, hence treatment to improve outcome. For example, in families with an inherited cancer predisposition, such as a hereditary colon cancer syndrome, at-risk relatives benefit from knowing who has inherited the family-specific mutation and who has not, so that those at greatest risk are screened using disease-specific protocols starting at the appropriate age and those who are not at increased risk are advised to follow population-based screening protocols. *Management of Genetic Syndromes* emphasizes the practical approach to the risk-defining use of molecular genetic testing with outcome-oriented surveillance. The reader does not need to be familiar with the jargon or principles of molecular genetics to understand how to use this approach for the benefit of patients in his or her practice.

Those with genetic disorders and their families often appreciate transparency in the care that they receive and they want access to the same information as their health care providers. The workman-like, practical approach to management in this book provides a "checklist-like" view that enables clinician and patient to follow together the issues to be addressed and their timelines. The chapters in *Management of Genetic Syndromes* are excellent "handouts" at clinic visits. In my academic clinical practice of medical genetics, my colleagues and I have on hand a ready supply of copies of the chapters of *Management of Genetic Syndromes*, which we read before the clinic visit and then provide to families at the time of their clinic appointment and to the referring clinicians with the clinic note. We know that, although the primary audience for this book is not affected individuals and their families, and, therefore, it was not written at the appropriate level for this audience, the clear, no-nonsense presentation style makes the content accessible to those families seeking to partner with their physician in their care.

Increasingly, families play a key role in the management of their inherited disorder, which most commonly is a chronic lifelong condition that may affect other family members of all generations. Consumer-oriented health information sources have grown exponentially with the discovery of the molecular genetic basis of inherited disorders, the growing use of the Internet, and the development of hundreds of disease-oriented patient advocate groups. Consumer health information resources, which often provide the most practical day-to-day information available for patients and their families, are a valuable adjunct to clinic visits. The essential role of consumer health information is acknowledged by *Management of Genetic Syndromes* by providing information on these resources in an easy-to-find location at the end of each chapter.

Management of Genetic Syndromes is an unparalleled medical genetics information resource for students, be they medical students, residents in primary care fields or specialty fields, or participants in continuing medical education. It is the one book I tell them to buy.

When I see the *Management of Genetic Syndromes* in a clinician's office, I respect that clinician for taking the initiative to anticipate the needs of his or her patients with rare inherited disorders and know that the clinician, his or her patient, and the patient's family will be grateful for the practical approach of this trusted colleague on the bookshelf.

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FOREWORD TO THE SECOND EDITION

It was not very many years ago that the coupling of the terms "management" and "genetic syndromes" would have been regarded as an oxymoron. With the exception of the inborn errors of metabolism, the notion of managing genetic disorders would have been considered quite foreign and of managing genetic *syndromes*, by which we mean conditions in which several organ systems and/or parts of the body are affected, even more so. The principal role of the medical geneticist was to diagnose these conditions as best as he or she could. Management, such as it was, was essentially symptomatic and was usually left to primary care physicians and medical specialists with little direct knowledge of the syndromes themselves. The literature on genetic syndromes reflected this situation. It was, for the most part, descriptive, and the emphasis was on diagnosis. Although many admirable reference books on diagnosis were written, most notable of which was (and still is), *Smith's Recognizable Patterns of Human Malformations*, it was frequently difficult to find definitive information about how to manage these conditions once the diagnoses had been made.

However, much has changed recently with regard to genetic syndromes, with perhaps the most important change being societal, not medical or scientific. It is now generally accepted that persons with genetic syndromes, whether associated with mental retardation or not, *should*, if possible, be treated. This was not always so, and a graphic example of how thinking has altered is provided by Down syndrome, certainly one of the quintessential genetic syndromes. Within my professional lifetime, there has been a shift from exclusion from society, generally by institutionalization, to rearing at home, educational inclusion, and participation in all aspects of daily life. Similarly, a policy of nonintervention, often with certain death, when major heart or gastrointestinal abnormalities were present has been replaced by aggressive surgical correction. Guidelines for the prevention of known complications have been developed, and their implementation is now commonplace. As a result, these changes have led, even without any specific therapy for Down syndrome, to an increase in lifespan, better cognitive development, and an overall improvement in the quality of life, both physically and socially.

In addition to the attitudinal shift, there have been many medical and scientific advances that have altered our approach to genetic syndromes. The mutations that cause many of the monogenic or contiguous gene syndromes are now known, and more are being discovered almost daily. The functions of the genes that these mutations affect are gradually being elucidated. For the aneuploidies, the mapping of the human genome is providing information about how many and which genes are at dosage imbalance. All of this has changed genetic syndromes from being curiosities that could not be understood to disorders that can be rationally approached in terms of cause and potential therapy, another and quite major change in attitude. This information has also led to the development of molecularly based tests that are greatly improving disease diagnosis and are permitting discrimination among conditions that had hitherto been confused with one another. In the future, this genetic information promises to lead to therapies that are tailored to individual diseases. In addition, medical diagnostic procedures and therapeutic approaches have become much more powerful. These include, for example, the various forms of imaging, surgical techniques such as for complex congenital heart defects or ambiguous genitalia, and highly specific and potent pharmacological agents. And, finally, more is continually being learned about the long-term consequences of genetic syndromes—about their natural histories—which is essential if comprehensive approaches to management are to be developed.

So, if societal attitudes have changed and genetic and medical information and capabilities are rapidly expanding, who should be undertaking the management of persons with genetic syndromes? Who should be reading this book? There is no simple answer to this question because in a sense each syndrome must be dealt with on its own merits. Given the multitude of systems that these syndromes may affect and the different combinations of abnormalities that may occur in one compared with another, the approach to management needs to be quite flexible. Nevertheless, someone must be responsible for the overall coordination of care. Who this will be will depend on local circumstances, but the important thing is that it be someone who is knowledgeable and willing to act in the interests of the affected individual.

In most instances, persons with genetic syndromes are usually managed by a mix of genetic professionals, primary care physicians, and medical and other specialists. By "genetic professional" I mean medical geneticists, genetic counselors and genetic nurses, and laboratory geneticists who have special knowledge about and experience in dealing with a large number of genetic syndromes that are individually quite uncommon or rare. For the most part, genetic professionals have traditionally been engaged in the diagnosis and counseling of these conditions. Unlike the situation with inherited metabolic disorders, in which geneticists do participate directly in therapy, their involvement in the therapeutic aspects of the management of genetic syndromes has generally involved referrals to appropriate specialists for specific forms of medical or surgical therapy. Primary care physicians, in addition to providing day-to-day care of individuals with genetic syndromes, often act as intermediaries in the referral process. And, beyond this list of medical personnel, a variety of other professionals and social and educational organizations, both governmental and voluntary, also provide many services to affected individuals and their families.

In some instances, the medical specialists, genetic professionals, and allied health professionals work together in multidisciplinary clinics devoted to individual disorders (e. g., Marfan or Down syndrome) or groups of related disorders (craniofacial anomalies or skeletal dysplasias) or perhaps even to birth defects more generally. These clinics provide a coordinated approach to management that is usually more efficient from the point of view of providers and of affected individuals and their families than is possible when many independent providers are involved in the care of the patient and may be a model for the provision of services in the future.

Regardless of how the services are organized and of who is actually coordinating management, many providers with different degrees of knowledge about any particular condition are likely to be involved. It is, therefore, essential that each understand what he or she is dealing with and what will be required to properly care for the affected individual and his or her family, and it is here that this volume, *Management of Genetic Syndromes,* uniquely fills a void that has long existed in the literature on genetic syndromes. Gathered together within a reasonably compact volume are authoritative descriptions written for a diverse readership of the management of over 50 of the most common conditions that fall within the rubric of genetic syndromes (including two that are primarily teratogenic, but are usually grouped with the others). The concept of what is entailed in management is broadly interpreted. Therefore, each chapter begins with considerations of etiology, pathogenesis, genetics, and diagnosis (including diagnostic criteria, testing, and differential diagnosis), all of which are necessary if the patient and his or her condition are to be fully understood. These are then followed by detailed discussions of what might be considered to be at the heart of management—the evaluation of each of the relevant systems and the treatment of the abnormalities that are likely to be present. The chapter concludes with selected references and a listing of available support groups and other resources. The evaluation and treatment sections are greatly enhanced by the use of an outline form of presentation, with bullets to highlight individual points.

When it appeared in 2001, the first edition of this book was eagerly seized upon by the medical genetics community. The need was there, and there was nothing else like it. From my own personal experience and observation in a genetics service that handles a large number of persons with genetic syndromes, I can testify that the book rapidly proved to be of great value to all of the clinic personnel—geneticists and counselors, physicians and nonphysicians, students, residents, and fellows. The rapid appearance of this second edition indicates that my own experience has been more generally shared, and the near doubling of the number of conditions covered will make the book even more valuable than before. Given the rapid progress that is being made in genetics and medicine and in the ability to diagnose and treat genetic syndromes, it is likely that frequent revisions will be required.

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FOREWORD TO THE FIRST EDITION

This is a book whose time has come. Genetic disorders and syndromes are usually thought of as being rare, and yet for affected individuals, their families, and their primary and specialty care physicians, it is essential to have reliable information about the natural history and management of the specific disorders.

The thirty conditions described in this book may seem rare (with incidences between 1 in 600 and 1 in 60,000). However, when you put together all the individuals cases or a particular condition in North America, in Europe, and in the world, a very large number of affected individual will benefit from the information in this book. In the past it has been difficult to bring together information of this type about specific disorders, and that is why this book fills a very important niche. It becomes a model for how to organize information that is needed for the families and primary care providers to manage the many, many other genetic disorders, congenital anomalies, and syndromes that are known to occur. The book is written in understandable language appropriate for families and for primary care and specialty physicians. It is major contribution.

Over the last two decades, remarkable progress has been made with regard to developing diagnostic tests and unraveling the human genome. Within the next few years all of the human genes will have been defined. The next major goal in genetics will be to understand how genes interact and function, both in the course of development and over a lifetime. In addition to the remarkable progress in basic and clinical genetics, there has been increasing communication and access to information. Through the Internet, the public has access to research reports and data that were usually not readily available in the past. However, it is essential to put that information into a meaningful form and context. That is exactly what this book does. The communication explosion has allowed the networking of researchers and families. The development of parent/lay support groups has led to a cooperation between researchers and families that has helped to define the natural history and the variation that can be seen in a specific disorder.

What every family and physician wants is to provide the best care possible for the affected individual. Nobody wants to miss the opportunity for that individual to reach his or her full potential, to benefit from a useful therapy, or to avoid a complication. Parents need an understanding of what will happen over time so that they can plan. They don't want to waste money and effort going from expert to expert or doing test after test. They need a realistic approach to what they should expect both in childhood and adulthood. They also usually want to know whether there is some risk of recurrence of the condition in their other children, in other family members, and in the affected individual's offspring. They want to know whether prenatal diagnosis is available, and they want to know the spectrum of variation that can occur. The beauty of this new book is that it provides that kind of information for each specific disorder in a logical and understandable form. Most families and physicians will focus in on the chapter relevant to a specific individual. However, they can't help but glance at other chapters and see the remarkable spectrum of complications that are not present in the disorder of interest to them. They are likely to benefit from this broader perspective.

Most pediatricians will have heard of all thirty disorders; however, some primary care and specialty physicians may not have heard of a specific disorder until they have the affected individual in their practice. The book should help to alert health care professionals to consider these conditions and should lead to appropriate testing to make a correct diagnosis, reducing the time it takes to make a specific diagnosis. Two-thirds of the conditions in this book have a specific diagnostic test, but the other one-third require "pattern recognition" and an alert, trained health care professional to consider the diagnosis.

It can be expected that additional advances will be made over the next few decades leading to better understanding and better management. So this book is already dated! There is still a lot to be learned! In fact, every family and every affected individual will contribute to that increased knowledge by giving feedback to the authors. Disorder-specific parent/lay support groups will continue to play in important role in improving our understanding. The authors of each chapter have worked together with the support groups and are very aware that it is the process of working together with these groups and the members' willingness to provide information that has led to present-day understanding. We are all very grateful to each of the parents and affected individuals who have taken part in studies that have advanced our knowledge.

To write a book about management, it is necessary to know the natural history of the disorder. The authors of each of these chapters have a wealth of experience and knowledge that has been collected over the least couple of decades. Understanding the natural history not only tells us what to expect at various ages but also how to recognize various complications. It is important to understand the natural history of the condition to determine whether various therapies actually improve the outcome. It is important to understand the natural history to recognize subgroups representing the variability and heterogeneity within the disorder. It is important to understand the natural history to learn the mechanisms that lead to the disorder, e.g., what sort of gene is likely to be involved? Where is the mutation in the gene? How does that mutation relate to severity of complications? How big is the deletion? Does that size relate to severity of complications? How does this gene act against the background of other genes or pathways? Is it possible to recognize a cellular mechanism leading to this disorder? Are there parent-of-origin effects on the expression of the gene or the mutation rate? Are there hot spots that have markedly increased mutation rates? Does the place on the chromosome where the gene lies put it at increased risk for mutation? These are only a few of the questions we hope to answer over the next few decades.

No one is more motivated than the family or the affected individual to learn about these disorders. It is important for them to be as knowledgeable as possible. The families of an affected person usually know more about the condition than most of the physicians they visit. It is important for families to continue to ask questions and to gain as much knowledge as possible to ensure the best outcome for the affected individual. It is important for families and affected individuals to keep their own records about the affected individual, such as a notebook of their visits to health care facilities, copies of the reports, and the results of the tests that have been done. It is also important to keep a photographic record of changes over time.

Once a family or an affected individual becomes involved in collecting information about the disorder, they often develop quite creative ideas that challenge the standard way of thinking about the disorder. Part of the advantage of participating in a support group is that those ideas then can be shared with the medical advisors and researchers and may lead to new knowledge.

Much of our understanding of these disorders is based on the manifestations in childhood, on feeding, on growth and development, and on social skills. However, information on adults is also beginning to accumulate and has been included in this book. In some conditions there is a stable situation, in others there is improvement with aging, and in still others deterioration can be expected. For many of the conditions described in this book, behavioral patterns have been recognized.

How should a family and their primary care physician use the experts? It would be impossible for the authors of these chapters to see every individual with the condition, but it is usually helpful for a family and the affected individual to see a clinical geneticist, to visit a developmental center, or to use the multidisciplinary team that is available in their area. Over the years, specialty clinics to deal with specific conditions have been developed. At some time it is probably appropriate to visit such a clinic at least once to review the affected individual's progress and to consider any special complications or responses. On the other hand, it is very important to have a knowledgeable primary care physician who cares for day-to-day medical needs and is aware of the unique complications of the condition.

The parent/lay support groups form an international network keeping up with new information on the specific disorders, and new information is sure to come. Some new information will come through organized studies of natural history; other data will come through clinical trails of new therapies; and further information will come from basic work on cellular mechanisms and biochemical pathways. For many of these disorders animal models will be developed, such as mice with the specific disorder, so that various therapies can be considered before trails in human beings. We live in a very exciting age and can anticipate major advances over the next few decades for each of the disorders described in this book. The international network of families, affected individuals, and researchers should and will communicate about new ideas, innovative approaches, and better understanding about these conditions.

We have begun to enter an era of evidence-based medicine. Only by having natural history information is it possible to understand the benefits of new interventions and therapies. We will hope that this book is outdated very rapidly because of such new developments, but in the meanwhile this book on management of common genetic syndromes is extremely welcome to families and health care providers alike.

JUDITH G. HALL

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PREFACE

This book is designed to assist primary care physicians, medical specialists, other care providers, and families in assuring optimal care for individuals who have multiple problems that are components of genetic syndromes. It represents the combined experience and knowledge of many experts in medical genetics and related fields, each of whom has spent years participating in the diagnosis and clinical management of a specific genetic syndrome. Most of the chapter authors have conducted major clinical research on "their" respective disorders.

The syndromes selected for inclusion in this book are those that are sufficiently common as to be regularly encountered in clinics specializing in genetics, development, neurology, psychiatry, cancer, or craniofacial disorders. Many of these disorders will not have been seen in the practice of most primary care physicians or non-genetics specialists. When they are encountered, the physician typically has little knowledge of how to confirm the diagnosis, identify the associated problems and clinical manifestations, and optimally care for the affected individual. This lack of knowledge is due only partly to infrequent exposure to the disorder. For many of these conditions, few publications devoted to management have been published, and a search for this knowledge is extremely time-consuming, often provides incomplete information, and is frequently futile. This book was designed to provide that knowledge, based on the medical literature and the cumulative experience of an expert or experts on each condition. As a result, a proportion of the information found in this source will be personal experience or observation. For only a few of these disorders is there an established "standard of care" based on controlled trials or outcome studies, though some disorders have recommendations for management based on consensus. Where available, reference to evidence-based studies and other published sources has been included; where unavailable, reference to the "personal experience" or "personal observation" of the author(s) has been noted, to reflect non-peer-reviewed information.

Deciding on which disorders to include is no mean task, and there are some disorders for which there is little accumulated experience in management. In addition to more than 60 genetic (or probably genetic) conditions, we have included two teratogenic disorders, fetal alcohol syndrome and fetal anticonvulsant syndrome, because of their frequency and because genetic factors influence susceptibility.

The editors hope that this continues to be a useful text to primary care physicians, nurse practitioners, medical geneticists, genetic counselors, and many other medical specialists, educators, and providers of care for the individuals and families affected with these genetic syndromes. Like those with more frequent medical conditions, these individuals deserve the best possible medical, educational and psychological care.

We appreciate the guidance and assistance of our contacts at John Wiley & Sons. Most importantly, we thank the contributing authors and the many individuals who gave permission to have their photographs published in this book and who participated in the clinical research that provided the information for its content.

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INTRODUCTION

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This book primarily focuses on genetic disorders involving syndromes of congenital malformations and neurodevelopmental disabilities. Because of the coverage in other published resources of biochemical conditions, the book does not include the disorders due to established inborn errors of metabolism. Rather, we cover the management of selected conditions labeled by Epstein and colleagues as the "inborn errors of development" (Erickson and Wynshaw-Boris 2016).

The need for a comprehensive and current overview of the practice guidelines for genetic syndromes commonly seen in primary care settings, specialty clinics, and the general medical genetics clinic has never been more evident than in the second decade of the 21st century. Because of the ongoing advances in the molecular underpinnings of classical syndromes and the recently described conditions, current diagnostic testing and understanding of pathogenesis have established a new era in phenotype analysis, knowledge of natural history, management options, and in many cases pharmacotherapeutic treatments.

MANAGEMENT OF SYNDROMES AND THE "CENTRAL DOGMA" OF MEDICAL GENETICS

The management of genetic syndromes comprises two principal components: health supervision guidelines and treatment of the manifestations of the disorder. Comprehensive phenotype analysis, including the understanding of the natural history of the condition, logically informs the development of clinical guidelines and treatment modalities. This progression from phenotype to natural history to management can be considered the "central dogma of medical genetics" (following the theme of the central dogma of biology, DNA→RNA→protein) (see Figure 1).

The modern analysis of phenotype has reached a new level of depth in the genomics era (Carey 2017). Moreover, the study of the natural history of genetic syndromes has been a time-honored endeavor dating back to the 1960s but brought to the center of attention of the genetics field by Hall's seminal paper (1988). Hall defined natural history as "an account of all of the consequences of that disorder" over

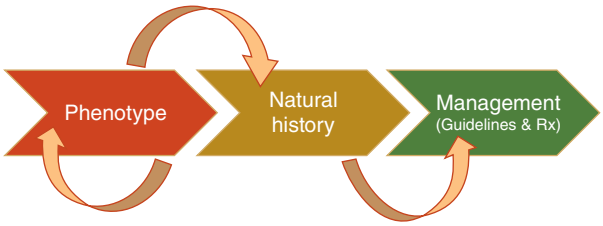

FIGURE 1 Modelled after the central dogma of molecular biology, the "dogma" of medical genetics underlies the process of establishment of the phenotype of a particular condition, including the characterization of its natural history that is so vital to the creation of management guidelines and treatment.

time. Comprehensive and objective review of the clinical manifestations (consequences) of the syndromes covered in this book will be one of the major components of each chapter as outlined in the next section. However, it is important to emphasize that the study of the natural history of these syndromes is daunting: all of the conditions covered herein would be considered "rare diseases". Investigations of the natural history of a rare condition are laden with ascertainment and publication bias, making it difficult to establish the actual frequency of manifestations of the condition. It is challenging to determine the true outcome without multicenter studies and national or international registries because of the small numbers of individuals with the disorder seen clinically by any one investigator. Ensuring accurate diagnosis by all investigators can also complicate collaborative studies for some disorders.

Development of clinical guidelines for health supervision is also difficult because of the lack of randomized clinical trials to determine the efficacy of an intervention or diagnostic modality. While consensus guidelines for a few selected conditions have been published by various academies and societies (e.g., the American Academy of Pediatrics, the American College of Medical Genetics and Genomics), most guidelines for care (as in this book) are based on narrative reviews performed by "experts" combined with the few existing published studies aimed at providing an unbiased approach to management for the condition.

THE ORGANIZATION OF THIS BOOK

Each chapter of this book is dedicated to the diagnosis and management of a specific syndrome (or closely related syndromes) that is encountered with regularity in specialty programs and often in primary care practice. The authors of each chapter are acknowledged "experts" who have considerable personal experience in the management of the disorder. Each chapter thus contains unpublished information based on that experience and on the author's personal approach to management in addition to a comprehensive, unbiased, and current review of published information. Whenever available, evidence-based treatments are included. Each chapter format is similar, providing general information on incidence and inheritance, pathogenesis and etiology, diagnostic criteria and testing, and differential diagnosis. The myriad manifestations of each syndrome are presented system by system, with emphasis on the manifestations, evaluation, management, and prognosis. The first two "systems" in every chapter are "growth and feeding" and "development and behavior." After these, the systems relevant to the specific disorder are discussed, usually in order of importance for that disorder. Every attempt has been made to include whatever is known about the disorder in adulthood. Each chapter concludes with a listing of family support organizations and selected resources available to families and professionals in print and electronic formats. Photographs of physical findings important for diagnosis or management are provided, and in some chapters figures of other aspects, including genetic basis and pathogenesis, are provided. Selected references stressing management issues and citations of the best review articles have been included.

This introductory chapter is designed to inform the reader about genetics-related terms used in this book, inheritance patterns, general methods for genetic testing, measurement methods, and the role of the medical geneticist and genetic counselor in the care of genetic disorders. It also provides some important references to additional resources of information about genetic disorders, differential diagnoses, genetic testing, and support organizations.

While we have sought to place the chapters in alphabetical order by name, for ease of locating, some chapters pose challenges in that regard. In particular, this is true of the disorders that are caused by a chromosomal abnormality and also have an associated name, most of which are deletion syndromes. In this edition, we have clustered the chromosomal syndromes under "deletion" (e.g., Deletion 4p for Wolf–Hirschhorn syndrome, Deletion 22q11.2 for Velo-Cardio-Facial/DiGeorge syndrome). The disorders with more than one causative genetic mechanism remain under the commonly used name (e.g., Smith–Magenis syndrome and Prader–Willi syndrome). While we realize that this organization is not perfect, we hope that this will facilitate finding the reader's chapter of interest.

CATEGORIZATION OF DISORDERS

The descriptive language for patterns of anomalies is somewhat unique to the field of dysmorphology and deserves a brief review. There are a number of different types of patterns of malformation (see Jones et al. 2013). The term **syndrome** is used specifically to describe a broad alteration of morphogenesis in which the simultaneous presence of more than one malformation or functional defect is known or thought to be