Genetic Disorders
and the Fetus
Dedicated to

Laura and Kiran

For their love, support and understanding

and to

our grandchildren and children,

Julie, Miranda, and Cody,

who endow life with joy and meaning.

“Make assurance double sure.”
Shakespeare, Macbeth
Genetic Disorders and the Fetus
Diagnosis, Prevention, and Treatment

SEVENTH EDITION

EDITED BY

Aubrey Milunsky MB BCh, DSc, FRCP, FACMG, DCH
Adjunct Professor of Obstetrics and Gynecology
Tufts University School of Medicine
Founder and Co-Director, Center for Human Genetics
Cambridge, MA, USA

Jeff M. Milunsky MD, FACMG
Co-Director, Center for Human Genetics
Director, Clinical Genetics
Senior Director, Molecular Genetics
Cambridge, MA, USA

WILEY Blackwell
## Contents

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preface</td>
<td>ix</td>
</tr>
<tr>
<td>Acknowledgements</td>
<td>xi</td>
</tr>
<tr>
<td>List of Contributors</td>
<td>xii</td>
</tr>
<tr>
<td>1 Genetic Counseling: Preconception, Prenatal, and Perinatal</td>
<td>1</td>
</tr>
<tr>
<td>Aubrey Milunsky and Jeff M. Milunsky</td>
<td></td>
</tr>
<tr>
<td>2 Amniocentesis, Chorionic Villus Sampling, and Fetal Blood Sampling</td>
<td>68</td>
</tr>
<tr>
<td>Anthony O. Odibo</td>
<td></td>
</tr>
<tr>
<td>3 Amniotic Fluid Constituents, Cell Culture, and Neural Tube Defects</td>
<td>98</td>
</tr>
<tr>
<td>Daniel L. Van Dyke and Aubrey Milunsky</td>
<td></td>
</tr>
<tr>
<td>4 Prenatal Diagnosis of Chromosomal Abnormalities through Chorionic Villus Sampling and Amniocentesis</td>
<td>178</td>
</tr>
<tr>
<td>Peter A. Benn</td>
<td></td>
</tr>
<tr>
<td>5 Prenatal Diagnosis of Sex Chromosome Abnormalities</td>
<td>267</td>
</tr>
<tr>
<td>Jeff M. Milunsky</td>
<td></td>
</tr>
<tr>
<td>6 Molecular Cytogenetics and Prenatal Diagnosis</td>
<td>313</td>
</tr>
<tr>
<td>Stuart Schwartz</td>
<td></td>
</tr>
<tr>
<td>7 Prenatal Diagnosis and the Spectrum of Involvement from Fragile X Mutations</td>
<td>350</td>
</tr>
<tr>
<td>Randi Hagerman and Paul Hagerman</td>
<td></td>
</tr>
<tr>
<td>8 Prenatal Diagnosis by Microarray Analysis</td>
<td>366</td>
</tr>
<tr>
<td>Joris Robert Vermeesch</td>
<td></td>
</tr>
<tr>
<td>9 Molecular Genetics and Prenatal Diagnosis</td>
<td>380</td>
</tr>
<tr>
<td>Aubrey Milunsky, Clinton Baldwin, and Jeff Milunsky</td>
<td></td>
</tr>
<tr>
<td>10 Preimplantation Genetic Diagnosis</td>
<td>419</td>
</tr>
<tr>
<td>Anver Kuliev and Svetlana Rechitsky</td>
<td></td>
</tr>
<tr>
<td>11 Noninvasive Prenatal Screening and Diagnosis Using Cell-free Fetal DNA</td>
<td>453</td>
</tr>
<tr>
<td>Melissa Hill and Lyn S. Chitty</td>
<td></td>
</tr>
<tr>
<td>12 Maternal Serum Screening for Chromosomal Abnormalities and Neural Tube Defects</td>
<td>483</td>
</tr>
<tr>
<td>Howard Cuckle, Eugene Pergament, and Peter Benn</td>
<td></td>
</tr>
<tr>
<td>13 Prenatal Diagnosis of Fetal Malformations by Ultrasound</td>
<td>541</td>
</tr>
<tr>
<td>Yves G. Ville and Jean-Philippe Bault</td>
<td></td>
</tr>
</tbody>
</table>
14 Prenatal Diagnosis and Management of Abnormal Fetal Development in the Third Trimester of Pregnancy ................................................................. 599
  Roland Axt-Fliedner and Aline Wolter

15 Prenatal Diagnosis by Fetal Magnetic Resonance Imaging .......................... 660
  Nadine Girard and Kathia Chaumoitre

16 Prenatal Diagnosis of Skeletal Dysplasias and Connective Tissue Disorders ................................................................. 681
  Andrea Superti-Furga and Sheila Unger

17 Prenatal Diagnosis of Cystic Fibrosis .................................................... 700
  Wayne W. Grody

18 Prenatal Diagnosis of the Hemoglobinopathies ..................................... 718
  John M. Old

19 Prenatal Diagnosis of Primary Immunodeficiency Diseases ...................... 755
  Jennifer M. Puck

20 Prenatal Diagnosis of Disorders of Lipid Metabolism .............................. 773
  Steven Humphries, Sara Mole, and Bryan Winchester

21 Prenatal Diagnosis of the Peroxisomal and Mitochondrial Fatty Acid Oxidation Deficiencies ................................................................. 838
  Ronald J.A. Wanders

22 Prenatal Diagnosis of the Mucopolysaccharidoses and Postnatal Enzyme Replacement Therapy ................................................................. 857
  John J. Hopwood

23 Disorders of Metabolism of Amino Acids and Related Compounds ............ 877
  Georgianne L. Arnold and Jerry Vockley

24 Prenatal Diagnosis of Disorders of Carbohydrate Metabolism .................. 903
  Deeksha Sarihyan Bali, Stephanie Austin, and Yuan-Tsong Chen

25 Prenatal Diagnosis of Miscellaneous Biochemical Disorders .................... 927
  David S. Rosenblatt and David Watkins

26 Prenatal Diagnosis of Fetal Infection .................................................. 942
  Yves G. Ville and Marianne Leruez-Ville

27 Fetal Medical Therapy ........................................................................ 976
  Phyllis W. Speiser and Aubrey Milunsky

28 Fetal Surgery .................................................................................... 989
  Benjamin A. Keller, Shinjiro Hirose, and Diana L. Farmer

29 Induced Abortion for Genetic Indications: Techniques and Complications .... 1011
  Lee P. Shulman

30 Molecular Aspects of Placental Development ......................................... 1031
  Wendy P. Robinson and Deborah E. McFadden

31 Grief after Perinatal Loss .................................................................... 1048
  Anette Kersting and Michaela Nagl
32 Medicolegal Aspects of Prenatal Diagnosis ............................................. 1063
   Ellen Wright Clayton

33 Prenatal and Preimplantation Diagnosis: International Policy Perspectives ........ 1091
   Minh Thu Minh Nguyen and Bartha Maria Knoppers

34 Ethical Issues in the Diagnosis and Management of Genetic Disorders in the Fetus .......... 1106
   Frank A. Chervenak and Laurence B. McCullough

Index ........................................................................................................... 1131

A color plate section falls between pages 624 and 625.
The seductive nature of novel technologies that introduce new preventive, diagnostic and therapeutic avenues is at once appealing, exciting and inherently risky. A faster, sleeker, cheaper ship may flounder on the hidden rocks of uncertainty. The primary destination may be reached with greater speed and efficiency, only to end accountable for initially unforeseen damage or loss. In the context of prenatal genetic diagnosis, as for all fields of medicine, abiding by the overriding principle of *primum non nocere*, remains paramount. This is especially pertinent given the unique responsibility of simultaneous caring for mother and fetus. In this compact there is the challenge to help and not to harm, given the complexity of genome interpretation.

The new and exciting developments in non-invasive prenatal testing, reflected in this volume, make prenatal detection of certain common chromosomal disorders and less common (or rare) monogenic diseases, available to all pregnant women. The inherent limitations of these innovations need careful explanations and informed consent to avoid a patient thinking that all genetic disorders have been excluded, when a screening negative has been provided. The principles and prerequisites for prenatal and preconception genetic counseling with special reference to potential pitfalls and limitations, open this text with an extensive, heavily referenced discussion.

Rapid progress in the application of molecular genetics methods to prenatal diagnosis, including fetal microarray analysis, whole exome sequencing, next generation sequencing and whole genome sequencing, have outstripped the knowledge base required to provide consistent reliable interpretation for a DNA diagnostic test result. Witness the spawning of terms, such as, 'variations of uncertain significance,' that inevitably create unwanted anxieties, but frequently accompany DNA sequencing reports. Worse still, clear delineation of normal variation or polymorphisms remains far from complete, and is compounded by the difficulty of determining the pathogenicity of variants. Common anticipated complications of these sequencing technologies include depth of coverage, regions of high GC content, mosaicism, DNA contamination, digenic inheritance, locus heterogeneity, and false-positive and false-negative results. Waiting in the wings is the management and counseling challenge following determination of a clinically significant incidental (secondary) finding on fetal DNA analysis of a disorder that predictably would manifest in adulthood. Indeed, increasingly, prenatal diagnosis for serious/fatal adult-onset diseases is being pursued (e.g., breast cancer).

This edition is fully up-to-date and replete with authoritative guidance about the applications of molecular genetics to the vast panoply of genomic disorders in the context of prenatal diagnosis and preimplantation genetic diagnosis (PGD). Detailed consideration is devoted to the prenatal diagnosis of monogenic disorders, now more approachable than previously for the extensively described biochemical genetic diseases that include the lipid and carbohydrate storage disorders, the mucopolysaccharidoses, the aminoacidopathies, peroxisomal and mitochondrial fatty acid oxidation, and folate and cobalamin disorders.

Notwithstanding the remarkable applications to prenatal diagnosis and PGD following discovery of thousands of culprit genes and their mutations, original pillars of prenatal diagnosis remain fundamental and require full comprehension, even when molecular diagnosis is pursued. Hence, very detailed and superbly referenced chapters delineate
the necessary current knowledge-base of prenatal diagnosis procedures (amniocentesis, chorionic villus sampling, periumbilical blood sampling, amniotic fluid constituents and cell culture), chromosomal and FISH analysis, neural tube defect detection, and the very important microarray analysis.

Critical progress and analysis is also reflected in detailed chapters on the prenatal diagnosis of the Fragile-X syndrome, cystic fibrosis, the hemoglobinopathies, the immunodeficiency disorders, and fetal infection. Whereas maternal serum multianalyte screening has for decades dominated the prenatal detection of neural tube defects and chromosomal abnormalities, refinements in fetal imaging for these and other fetal structural defects have assumed key roles. The twin complementary diagnostic roles of fetal ultrasound and magnetic resonance imaging in the first, second and third trimesters of pregnancy are critically assessed by internationally recognized experts. Emphasis is given to the concomitant imaging and molecular diagnostics, especially for the skeletal dysplasias. The role of fetal medical and surgical therapy has expanded and for specific disorders demands great skill and expertise.

For the first time this edition focuses on new molecular advances that inform about placental development and the implications for fetal health. Another new addition is the moving and insightful analysis concerning the psychology of prenatal and perinatal grief. Understanding the development and utility of established approaches and novel technologies to prenatal diagnosis and PGD, invariably antedates ethical and legal applications and implications, and the evolution of public policy. Key authoritative chapters on ethics, law, and public policy reflect new thought and developments in these critical, non-static arenas.

The discerning reader in search of accurate and reliable information would welcome a source that reliably dispenses evidence-based facts embellished by knowledge, experience and wisdom. This precious distillate, tinctured with recommendations and guidance born of long experience, is not attainable by the most avid electronic voyeur. Sifting through mountains of unfiltered, irrelevant, unreliable or misleading information, electronic searches simply spawn reams of paper, mostly lacking critical analysis of the subject in question. At best, authors will describe “limitations” in their studies, while awaiting guidance from their clinical colleges or societies, which often takes years.

Fortunately, this volume, a major repository of facts about prenatal diagnosis, provides a critical analysis and synthesis of established and new knowledge based on the long experience of the contributing authorities in their respective fields. In addition, a broad international perspective is presented with contributions from recognized experts in 10 countries. The guidance provided and the insights and perspectives of these authors make this volume a valuable and indispensable resource for all those whose focus is securing fetal health through prenatal diagnosis.

This text is very heavily referenced, replete with evidence-based guidance, and reflective of the lifetime experience and wisdom of the authors. This edition encompasses 158 tables, 108 figures, including 14 color plates, and about 9,000 references. A valuable index will enrich the reader’s search for specific information. It is our fervent hope that the progress mirrored in this volume will help prospective parents recognize their reproductive risks and options, and reassure many that they can avoid having children with serious or lethal genetic disorders. Indeed, parents initially unaware of their risks may also benefit from the remarkable advances in prenatal and preimplantation genetic diagnosis.

Aubrey Milunsky and Jeff M. Milunsky
Cambridge
Acknowledgements

This seventh edition marks the 36th year of this text and reflects the continuing remarkable advances made in achieving accurate prenatal diagnoses. The first book on this subject (The Prenatal Diagnosis of Hereditary Disease) was published some 42 years ago (by AM). The distillation of accrued biological, technological, ethical and legal knowledge has graced these pages and enriched the reference value of these editions. The wisdom, insight, perspective, expertise and knowledge of contributing authors has made these volumes a valuable and authoritative text. Moreover, these authors have again provided an international perspective, this edition having contributions from 19 countries.

Knowledge in human genetics and maternal–fetal medicine has demanded up to date information, guidance and expertise in each volume. This has been achieved only by the willingness of internationally recognized authoritative authors who have taken the time to share their knowledge, experience, and wisdom. For this we are most appreciative.

We are also grateful and indebted to our friends and colleagues who have died and who were contributing authors to earlier editions. We remember them with pride and sadness: David J. H. Brock, Ph.D., Jacob A. Canick, Ph.D., Louis Dalliaire, M.D., Ph.D., Sherman Elias, M.D., John C. Fletcher Ph.D., Albert B. Gerbie, M.D., Leonard A. Herzenberg, Ph.D., Mary Z. Pelias, Ph.D., J.D., Arthur Robinson, M.D., Margery W. Shaw, M.D., J.D., Irving Umansky, M.D., Yury Verlinsky, Ph.D., and Dorothy C. Wertz, Ph.D.

It is likely that we are unaware of the passing of a few authors, and regret their omission. We remain eternally grateful to all.

Aubrey Milunsky
Jeff Milunsky
List of Contributors

Georgianne L. Arnold, MD
Professor of Pediatrics
University of Pittsburgh School of Medicine
Clinical Director, Division of Medical Genetics
Children's Hospital Pittsburgh
Pittsburgh, PA, USA

Stephanie Austin, MS, MA, CGC
Genetic Counselor
Duke University Medical Center
Durham, NC, USA

Roland M. Axt-Fliedner, MD, PhD
Professor of Obstetrics and Gynecology
Justus-Liebig-University
Head
Division of Prenatal Medicine and Fetal Therapy
University Hospital
Gießen, Germany

Clinton Baldwin, PhD
Director
Molecular Genetics Research
Center for Human Genetics, Inc.
Cambridge, MA, USA

Deeksha S. Bali, PhD, FACMG
Professor of Pediatrics
Laboratory Director
Division of Medical Genetics
Duke University Medical Center
Durham, NC, USA

Jean-Philippe Bault, MD
Consultant in Obstetrics
Obstetrics Department
Hôpital Bicêtre
University Hospital Paris-Sud
Centre Hospitalier Intercommunal de Poissy-St. Germain en Laye
Poissy, France

Peter A. Benn, MSc, PhD, FAMG, DSc
Professor
Departments of Genetics and Genome Sciences
Pediatrics and Laboratory Medicine
Director
Human Genetics Laboratories
University of Connecticut Health Center
Farmington, CT, USA

Kathia Chaumoitre, MD, PhD
Department of Radiology
Timone Hospital
Aix-Marseille University
Marseille, France

Yuan-Tsong Chen, MD, PhD
Professor of Pediatrics and Genetics
Duke University Medical Center
Durham, NC, USA
Institute of Biomedical Sciences
Academia Sinica
Taiwan

Frank A. Chervenak, MD
Given Foundation Professor and Chairman
Department of Obstetrics and Gynecology
Obstetrician and Gynecologist-in-Chief
Weill Cornell Medical Center
New York Presbyterian Hospital
New York, NY, USA

Lyn S. Chitty, PhD, MB, BS, MRCOG
Professor of Genetics and Fetal Medicine
UCL Institute of Child Health
Great Ormond Street Hospital for Children and
University College London Hospital NHS Foundation
Trusts
London, UK

Ellen Wright Clayton, MD, JD
Craig-Weaver Professor of Pediatrics
Professor of Law
Co-Founder
Center for Biomedical Ethics and Society
Howard Cuckle, MSc, DPhil
Adjunct Professor, Obstetrics and Gynecology
Columbia University
New York, NY, USA

Diana L. Farmer, MD, FACS, FRCS
Pearl Stamps Stewart Professor and Chair
Department of Surgery
UC Davis School of Medicine
Surgeon-in-Chief
UC Davis Children's Hospital
UC Davis Health System
Sacramento, CA, USA

Nadine Girard, MD, PhD
Professor of Neuroradiology
Centre de Resonance Magnetique Biologique et Medicale
Centre National de la Recherche Scientifique
Faculte de Medicine la Timone
Universite de La Mediterrane
Head of Neuroradiology
Timone Hospital
Aix-Marseille University
Marseille, France

Wayne Grody, MD, PhD
Professor
Divisions of Medical Genetics and Molecular Diagnostics
Departments of Pathology and Laboratory Medicine
Pediatrics, and Human Genetics
UCLA School of Medicine
UCLA Institute for Society and Genetics
Director
Molecular Diagnostic Laboratories and Clinical Genomics Center
UCLA Medical Center
Los Angeles, CA, USA

Paul J. Hagerman, MD, PhD
Distinguished Professor
Department of Biochemistry and Molecular Medicine
School of Medicine
UC Davis Health System
Sacramento, CA, USA

Randi J. Hagerman, MD
Medical Director
MIND Institute
Distinguished Professor of Pediatrics
Endowed Chair in Fragile X Research
UC Davis Health System
Sacramento, CA, USA

Melissa Hill, BSc, PhD
Senior Researcher
North East Thames Regional Genetics Service
Great Ormond Street Hospital for Children NHS Foundation Trust
London, UK

Shijiro Hirose, MD
Associate Professor and Chief
Division of Pediatric General Thoracic and Fetal Surgery
Department of Surgery
UC Davis School of Medicine
Sacramento, CA, USA

John J. Hopwood, PhD
Professor and Director
Lysoosomal Diseases Research Unit
South Australian Health and Medical Research Institute
Adelaide, Australia

Steven E. Humphries, PhD
Professor of Cardiovascular Genetics
Centre for Cardiovascular Genetics
Institute of Cardiovascular Science
University College London
London, UK

Benjamin A. Keller, MD
Department of Surgery
UC Davis School of Medicine
UC Davis Health System
Sacramento, CA, USA

Anette Kersting, MD
Professor
Department of Psychosomatic Medicine
Director
Clinic for Psychosomatic Medicine
University of Leipzig
Leipzig, Germany

Bartha M. Knoppers, PhD, OC, OQ
Canada Research Chair in Law and Medicine
Director
Centre of Genomics and Policy
Faculty of Medicine
Department of Human Genetics
McGill University
Montreal, Quebec, Canada

Anver Kuliev, MD, PhD
Director of Research
Reproductive Genetics Innovations
Northbrook, IL, USA
Marianne Leruez-Ville, MD, PhD
Consultant in Medical Virology
National Reference Laboratory for Congenital
Cytomegalovirus Infections
Hôpital Necker-Enfants-Malades
Université Paris Descartes
Paris, France

Laurence B. McCullough, PhD
Dalton Tomlin Chair
Medical Ethics and Health Policy
Center for Medical Ethics and Health Policy
Baylor College of Medicine
Houston, TX, USA

Deborah E. McFadden, MD, FRCPC
Head and Medical Director
Department of Pathology and Laboratory Medicine
Children’s & Women’s Hospitals of British Columbia
Clinical Professor
Department of Pathology and Laboratory Medicine
University of British Columbia
Vancouver, BC, Canada

Aubrey Milunsky, MD BCh, DSc, FRCP, FACCME, DCH
Professor of Obstetrics and Gynecology
Tufts University School of Medicine
Founder and Co-Director
Center for Human Genetics
Cambridge, MA, USA

Jeff M. Milunsky, MD, FACMG
Co-Director
Center for Human Genetics
Director
Clinical Genetics
Senior Director
Molecular Genetics
Cambridge, MA, USA

Sara Mole, PhD
Reader in Molecular Cell Biology
UCL Institute of Child Health
MRC Laboratory of Molecular Cell Biology
Genetics and Epigenetics in Health and Disease Section
Genetics and Genomics Medicine Programme
Department of Genetics
Evolution and Environment
University College London
London, UK

Michaela Nagl, PhD
Department of Psychosomatic Medicine
and Psychotherapy
University of Leipzig
Leipzig, Germany

Minh Thu Minh Nguyen, LLM, LLB, BSc
Research Associate
Centre of Genomics and Policy
McGill University
Montreal, Quebec, Canada

Anthony O. Odibo, MD, MSCE
Professor
Maternal Fetal Medicine
Department of Obstetrics and Gynecology
University of South Florida
Tampa, FL, USA

John M. Old, PhD, FRCPath
Consultant Clinical Scientist and Reader
in Haematology
National Haemoglobinopathy
Reference Laboratory Haematology
John Radcliffe Hospital
Oxford University Hospitals NHS Trust
Oxford, UK

Eugene Pergament, MD, PhD
Professor of Clinical Obstetrics and Gynecology
Feinberg School of Medicine of Northwestern University
Northwestern Reproductive Genetics
Chicago, IL, USA

Jennifer M. Puck, MD
Professor of Pediatrics
UCSF Smith Cardiovascular Research Institute
San Francisco, CA, USA

Svetlana Rechitsky, PhD
President
Reproductive Genetic Innovations
Northbrook, IL, USA

Wendy P. Robinson, PhD
Professor, Department of Medical Genetics
University of British Columbia; and Senior Scientist
Child and Family Research Institute
Vancouver, BC, Canada

David S. Rosenblatt, MDCM
Dodd Q. Chu and Family Chair in Medical Genetics
Professor
Departments of Human Genetics
Medicine, Pediatrics, and Biology
Faculties of Medicine and Science
McGill University
Montreal, Quebec, Canada
Stuart Schwartz, PhD
Strategic Director
Cytogenetics
Laboratory Corporation of America® Holdings
Research Triangle Park, NC, USA

Lee P. Shulman, MD
Anna Ross Lapham Professor in Obstetrics and Gynecology
Chief
Division of Clinical Genetics
Director, Northwestern Ovarian Cancer Early Detection
and Prevention Program
Co-Director
Cancer Genetics Program
Robert S. Lurie Comprehensive Cancer Center
Feinberg School of Medicine of Northwestern University
Medical Director
Insight Medical Genetics
Adjunct Professor
Department of Medicinal Chemistry and Pharmacognosy
University of Illinois at Chicago College of Pharmacy
Chicago, IL, USA

Phyllis W. Speiser, MD
Professor
Department of Pediatrics
New York University School of Medicine
Chief
Division of Pediatric Endocrinology
Schneider Children’s Hospital
North Shore–LIJ Health System
New Hyde Park, NY, USA

Andrea Superti-Furga, MD
Professor of Pediatrics
University of Lausanne and Chair
Department of Pediatrics
Lausanne University Hospital
Lausanne, Switzerland

Sheila Unger, MD, FRCPC, Privat-Docent
Medical Genetics Service
Lausanne University Hospital
Lausanne, Switzerland

Daniel L. Van Dyke, PhD
Professor of Laboratory Medicine and Pathology
Mayo Medical School and Mayo Clinic
Cytogenetics Laboratory
Rochester, MN, USA

Joris Robert Vermeesch, PhD
Professor of Molecular Cytogenetics and Genome Research
Head of Constitutional Cytogenetics
Coordinator of Genomics Core
Center for Human Genetics
Katholieke Universiteit Leuven
Leuven, Belgium

Yves G. Ville, MD
Professor of Obstetrics and Gynecology
Hôpital Necker-Enfants-Malades
Université Paris Descartes
Paris, France

Gerard Vockley, MD, PhD
Chief, Division of Medical Genetics
Children’s Hospital of Pittsburgh
Professor of Pediatrics; Professor of Human Genetics
University of Pittsburgh School of Medicine
University of Pittsburgh Graduate School of Public Health
Pittsburgh, PA, USA

Ronald J.A. Wanders
University of Amsterdam, Academic Medical Center
Departments of Clinical Chemistry and Pediatrics
Emma Children’s Hospital
Laboratory of Genetic Metabolic Diseases
Amsterdam, the Netherlands

David Watkins, PhD
Research Associate
Department of Human Genetics
McGill University
Scientist
Department of Medical Genetics
McGill University Health Centre
Montreal, Quebec, Canada

Bryan G. Winchester, MA, PhD
Emeritus Professor of Biochemistry
ULC Institute of Child Health
University College London
London, UK

Aline Wolter, MD
Justus-Liebig-University, Gießen
Department of Obstetrics and Gynecology
Division of Prenatal Medicine and Fetal Therapy
University Hospital
Gießen, Germany
Clinical cognizance of the veritable explosion in the knowledge of the human genome is more vital than ever. Precise identification of genes and their pathogenic mutations has injected an urgency among care providers to become aware of the rapidly escalating opportunities parents have to avoid having offspring with serious or fatal genetic disorders. For any health or life-threatening genetic disorder, prenatal diagnosis (or even preimplantation genetic diagnosis) has become a viable option, and should be offered. Even adult-onset malignant, neurodegenerative, cardiovascular and other serious systemic disorders now feature in the indications, not only for presymptomatic or predictive diagnosis, but for prenatal diagnosis.

Given the wide scope of clinical genetics in all medical specialties, the need for clinicians to confer and refer has never been greater. The coalescence of advances in molecular genetics, fetal imaging and noninvasive prenatal screening, has culminated in the provision of new opportunities for the prevention or avoidance of genetic disorders and congenital malformations.

In context, women at risk for having progeny with abnormalities expect to be informed about their odds and options, optimally during preconception counseling. Their concerns are serious, given the significant contribution of genetic disorders to morbidity and mortality in children and adults.

**Incidence, prevalence and burden of genetic disorders and congenital malformations**

An estimated 7.9 million infants worldwide are born each year with a major congenital malformation. Over 7,000 rare genetic disorders are known, with about 1 in 12 individuals affected, aware or unaware. More than 3,412 genes with phenotype-causing mutations have been identified. Severe intellectual disability is considered to be largely genetic in origin and is estimated to occur in 0.5 percent of newborns. The European Organization for Rare Diseases maintained that about 30 percent of all patients with a rare disease died before the age of 5 years. In the United States in 2010, congenital malformations, deformations and chromosomal abnormalities accounted for the most infant deaths – 5,107 (20.8 percent) out of 24,586 – in any category of causation. Many factors influence efforts to accurately determine the incidence or prevalence of congenital anomalies or genetic disorders. Box 1.1 encompasses the
majority of known etiologic categories, discussed below, which help explain sometimes striking differences among major studies. It is almost impossible to account for all these potentially confounding factors in a study and rarely has any one study come close.

**Incidence and prevalence**

Estimates of aneuploidy in oocytes and sperm reach 25 percent and 3–4 percent, respectively.\textsuperscript{13,14} Not surprisingly, then, about one in 13 conceptions results in a chromosomally abnormal conceptus,\textsuperscript{15} while about 50 percent of first-trimester spontaneous abortions are associated with chromosomal anomalies.\textsuperscript{16} A study of blastocysts have revealed that 56.6 percent were aneuploid. Moreover, these blastocysts produced in vitro from women of advanced maternal age also revealed mosaicism in 69.2 percent.\textsuperscript{17} Similar results have been reported by others.\textsuperscript{18} Clinically significant chromosomal defects occur in 0.65 percent of all births; an additional 0.2 percent of babies are born with balanced structural chromosome rearrangements that have implications for reproduction later in life. Between 5.6 and 11.5 percent of stillbirths and neonatal deaths have chromosomal defects.\textsuperscript{19}

Congenital malformations with obvious structural defects are found in about 2 percent of all births.\textsuperscript{20} This was the figure in Spain among 710,815 livebirths,\textsuperscript{21} with 2.25 percent in Liberia,\textsuperscript{22} 2.03 percent in India,\textsuperscript{23} and 2.53 percent among newborn males in Norway.\textsuperscript{24} The Mainz Birth Defects Registry in Germany in the 1990–1998 period reported a 6.9 percent frequency of major malformations among 30,940 livebirths, stillbirths and abortions.\textsuperscript{25} Pooled data from 12 US population-based birth defects surveillance systems, which included 13.5 million livebirths (1999–2007), revealed that American Indians/Alaska natives had a ≥50 percent greater prevalence for seven congenital malformations (anotia or microtia, cleft lip, trisomy 18, encephalocele, limb-reduction defect).\textsuperscript{26} Factors that had an impact on the incidence/prevalence of congenital malformations are discussed below.

Over 22,700 entries for genetic disorders and traits have been catalogued.\textsuperscript{4} Estimates based on 1 million consecutive livebirths in Canada suggested a monogenic disease in 3.6 in 1,000, consisting of autosomal dominant (1.4 in 1,000), autosomal recessive (1.7 in 1,000) and X-linked-recessive disorders (0.5 in 1,000).\textsuperscript{27} Polygenic disorders occurred at a rate of 46.4 in 1,000 (Table 1.1).

At least 3–4 percent of all births are associated with a major congenital defect, intellectual disability or a genetic disorder, a rate that doubles by 7–8 years of age, given later appearing and/or later diagnosed genetic disorders.\textsuperscript{28,29} If all congenital defects are considered, Baird et al.\textsuperscript{27} estimated that 7.9 percent of liveborn individuals have some type of genetic disorder by about 25 years of age. These estimates are likely to be very low given, for example, the frequency of undetected defects such as bicuspid aortic valves that occur in 1–2 percent of the population.\textsuperscript{30} The bicuspid aortic valve is the most common congenital cardiac malformation and in the final analysis may cause higher mortality and morbidity rates than all other congenital cardiac defects.\textsuperscript{31} Mitral valve prolapse affects 2–3 percent of the general population, involving more than 176 million people worldwide.\textsuperscript{32} A Canadian study of 107,559 patients with congenital heart disease reported a prevalence of 8.21 per 1,000

**Table 1.1 The frequencies of genetic disorders in 1,169,873 births, 1952–1983**\textsuperscript{27}

<table>
<thead>
<tr>
<th>Category</th>
<th>Rate per million livebirths</th>
<th>Total births (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dominant</td>
<td>1,395.4</td>
<td>0.14</td>
</tr>
<tr>
<td>Recessive</td>
<td>1,665.3</td>
<td>0.17</td>
</tr>
<tr>
<td>X-linked</td>
<td>532.4</td>
<td>0.05</td>
</tr>
<tr>
<td>Chromosomal</td>
<td>1,845.4</td>
<td>0.18</td>
</tr>
<tr>
<td>Multifactorial</td>
<td>46,582.6</td>
<td>4.64</td>
</tr>
<tr>
<td>Genetic unknown</td>
<td>1,164.2</td>
<td>0.12</td>
</tr>
<tr>
<td>Total</td>
<td>53,175.3</td>
<td>5.32\textsuperscript{a}</td>
</tr>
<tr>
<td>B</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All congenital anomalies 740–759\textsuperscript{b}</td>
<td>52,808.2</td>
<td>5.28</td>
</tr>
<tr>
<td>Congenital anomalies with genetic etiology (included in section A)</td>
<td>26,584.2</td>
<td>2.66</td>
</tr>
<tr>
<td>C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disorders in section A plus those congenital anomalies not already included</td>
<td>79,399.3</td>
<td>7.94</td>
</tr>
</tbody>
</table>

Notes: \textsuperscript{a}Sum is not exact owing to rounding. \textsuperscript{b}International Classification of Disease numbers.
livebirths, rising to an overall prevalence of 13.11 per 1,000 in adults.\textsuperscript{33} The authors concluded that adults now account for some two-thirds of the prevalence of congenital heart disease. Categorical examples of factors associated with an increased risk of congenital heart disease in the fetus are shown in Box 1.1. A metropolitan Atlanta study (1998–2005) showed an overall prevalence of 81.4 per 10,000 for congenital heart disease among 398,140 livebirths,\textsuperscript{35} similar to a Belgium study of 111,225 live and stillborn infants $\geq$ 26 weeks of gestation with an incidence of 0.83 percent, chromosome abnormalities excluded.\textsuperscript{36} These numbers lead to a significant genetic disease burden and have accounted for 28–40 percent of hospital admissions in North America, Canada and England.\textsuperscript{37,38} Notwithstanding their frequency, the causes of about 60 percent of congenital malformations remain obscure.\textsuperscript{39,40}

The availability of prenatal diagnosis and maternal serum screening for neural tube defects (NTDs) and Down syndrome (DS) has also affected the birth frequency of these two most common congenital defects. One French study of the impact of prenatal diagnosis over a 21-year period (1979–99) in a well defined population showed a drop of 80 percent in the birth prevalence of DS.\textsuperscript{41} A later report from the Paris Registry of Congenital Anomalies (2001–2005) noted a “fairly stable prevalence of DS (7.1 per 10,000 livebirths) over time.”\textsuperscript{42} Multiple studies have recorded a reduction in the birth prevalence of NTDs following folic acid supplementation and/or fortification of cereal grain products with folic acid\textsuperscript{43–47} (see Chapter 3).
However, in Ireland there appears to be an increasing incidence of NTDs, almost certainly due to a lack of adherence to periconceptional folic acid supplementation.\textsuperscript{48} A Scottish study aimed to assess the impact of prenatal diagnosis on the prevalence of DS from 1980 to 1996. Both births and pregnancy terminations were included. Pregnancy terminations for DS rose from 29 percent to about 60 percent.\textsuperscript{49} In contrast, the prevalence of DS noted by the Dutch Paediatric Surveillance Unit in 2003 was 16 per 10,000 livebirths, exceeding earlier reports and thought to reflect an older maternal age cohort.\textsuperscript{50} In the United States, a DS prevalence rate of 13 per 10,000 was found in metropolitan Atlanta (1979–2003).\textsuperscript{51}

Folic acid supplementation, via tablet or food fortification, is now well known to reduce the frequency of NTDs by up to 70 percent.\textsuperscript{52,53} A Canadian study focused on the effect of supplementation on the prevalence of open NTDs among 336,963 women. The authors reported that the prevalence of open NTDs declined from 1.13 in 1,000 pregnancies before fortification to 0.58 in 1,000 pregnancies thereafter.\textsuperscript{54}

In a population-based cohort study by the Metropolitan Atlanta Congenital Defects Program, the risk of congenital malformations was assessed among 264,392 infants with known gestational ages, born between 1989 and 1995. Premature infants (< 37 weeks of gestation) were found to be more than twice as likely to have been born with congenital malformations than infants at term.\textsuperscript{55}

In a prospective study of infants weighing 401–1,500 g between 1998 and 2007, a congenital malformation was noted in 4.8 percent of these very low birth weight infants. The mean gestational age overall was 28 weeks and the mean birth weight was 1,007 g.\textsuperscript{56} Twins have long been known to have an increased rate of congenital anomalies. A UK study of 2,329 twin pregnancies (4,658 twins) and 147,655 singletons revealed an anomaly rate of 405.8 per 10,000 twins versus 238.2 per 10,000 singletons (relative risk (RR) 1.7).\textsuperscript{57} The prevalence rate of anomalies among known monochorionic twins (633.6 per 10,000) was nearly twice that found in dichorionic twins (343.7 per 10,000) (RR 1.8).

A key study of homozygosity in consanguineous patients with an autosomal recessive disease showed that, on average, 11 percent of their genomes were homozygous.\textsuperscript{58} Each affected individual had 20 homozygous segments exceeding 3 cM.

Incidence/prevalence rates of congenital defects are directly influenced by when and how diagnoses are made. Highlighting the importance of how early a diagnosis is made after birth, the use of echocardiography, and the stratification of severity of congenital heart defects, Hoffman and Kaplan\textsuperscript{59} clarified how different studies reported the incidence of congenital heart defects varying from 4 in 1,000 to 50 in 1,000 livebirths. They reported an incidence of moderate and severe forms of congenital heart disease in about 6 in 1,000 livebirths, a figure that would rise to at least 19 in 1,000 livebirths if the potentially serious bicuspid aortic valve is included. They noted that if all forms of congenital heart disease (including tiny muscular ventricular septal defects) are considered, the incidence increases to 75 in 1,000 livebirths.

The frequency of congenital defects is also influenced by the presence or absence of such defects in at least one parent. A Norwegian Medical Birth Registry population-based cohort study of 486,207 males recorded that 12,292 (2.53 percent) had been born with a congenital defect.\textsuperscript{24} Among the offspring of these affected males, 5.1 percent had a congenital defect, compared with 2.1 percent of offspring of males without such defects (RR 2.4). Ethnicity, too, has a bearing on the prevalence of cardiovascular malformations. In a New York State study of 235,230 infants, some 2,303 were born with a cardiovascular malformation. The prevalence among non-Hispanic whites (1.44 percent) was higher than in non-Hispanic blacks (1.28 percent).\textsuperscript{60} However, racial/ethnic disparities clearly exist for different types of congenital defects.\textsuperscript{51}

Maternal obesity is associated with an increased risk of congenital malformations.\textsuperscript{62–71} The greater the maternal body mass index (BMI), the higher the risk, especially for congenital heart defects,\textsuperscript{67,68,70} with significant odds ratios between 2.06–3.5. In a population-based case-control study, excluding women with pre-existing diabetes, Watkins et al.\textsuperscript{72} compared the risks of selected congenital defects among obese women with those of average-weight women. They noted significant odds ratios for spina bifida (3.5), omphalocele (3.3), heart defects (2.0), and multiple anomalies (2.0). Our own\textsuperscript{73,74} and other studies,\textsuperscript{75} have pointed in the direction of a prediabetic state or gestational diabetes as the
biologic mechanism accounting for the increased rate of congenital anomalies in the offspring of obese women. In this context, preconception bariatric surgery seems not to reduce the risks of congenital anomalies.\textsuperscript{69} It appears that folic acid supplementation attenuates but does not eliminate the risk of spina bifida when associated with diabetes mellitus\textsuperscript{76} or obesity.\textsuperscript{77} In contrast, markedly underweight women reportedly have a 3.2-fold increased risk of having offspring with gastroschisis,\textsuperscript{77} in all likelihood due to smoking.\textsuperscript{78} Indeed, a study of 173,687 malformed infants and 11.7 million unaffected controls, when focused on maternal smoking, yielded significant odds ratios up to 1.5, for a wide range of major congenital malformations in the offspring of smoking mothers.\textsuperscript{78} Young nulliparous women have an increased risk of bearing a child with gastroschisis, those between 12 and 15 years of age having a more than fourfold increased risk.\textsuperscript{79}

Congenital hypothyroidism is associated with at least a fourfold increased risk of congenital malformations, and represents yet another factor that may influence incidence/prevalence rates of congenital anomalies.\textsuperscript{80} A French study of 129 infants with congenital hypothyroidism noted that 15.5 percent had associated congenital anomalies.\textsuperscript{81} Nine of the infants had congenital heart defects (6.9 percent).

Women with epilepsy who are taking anticonvulsant medications have an increased risk of having offspring with gastroschisis, noted in one study as 2.7-fold greater than those without epilepsy.\textsuperscript{82} The possible reduction of other congenital malformations as a result of folic acid supplementation remains to be proved (see Chapter 3).

**Congenital malformations and infant morbidity and mortality**

The leading cause of infant death in the United States in 2011 was congenital malformations, deformations and chromosomal abnormalities, accounting for 20.9 percent of all infant deaths.\textsuperscript{83} Survival is clearly dependent on the severity or lethality of the congenital defect. The Centers for Disease Control and Prevention assessed mortality rates for infants born with trisomy 13 and trisomy 18. The authors identified 5,515 infants born with trisomy 13 and 8,750 born with trisomy 18. The median age at death for both trisomy 13 and trisomy 18 was 10 days. Survival to at least 1 year occurred in 5.6 percent of those born with trisomy 13 or trisomy 18.\textsuperscript{84} A regional study in the Netherlands noted lethal congenital malformations in 51 percent of stillbirths and 70 percent among those who died during the neonatal period.\textsuperscript{85} A Scottish study focused on the survival of 6,153 infants with congenital anomalies up to the age of 5 years, noted the following survival rates: chromosomal anomalies (48 percent), neural tube defects (72 percent), respiratory system anomalies (74 percent), congenital heart disease (75 percent), nervous system anomalies (77 percent) and Down syndrome (DS) (84 percent).\textsuperscript{86} The survival rate among males with congenital defects was 84 percent, compared with 97 percent in those born unaffected.\textsuperscript{24} Liu et al.\textsuperscript{87} examined temporal changes in fetal and infant deaths caused by congenital malformations in Canada, England, Wales, and the United States. They concluded that the major factor responsible for the accelerated decline in infant deaths was prenatal diagnosis and elective abortion of fetuses with abnormalities. Given the frequency of DS, a more detailed discussion follows.

**Down syndrome**

The special problems and associated defects in DS are well known, as is the increasing life expectancy. Studies from Japan,\textsuperscript{88} Denmark,\textsuperscript{89} England,\textsuperscript{90} Australia,\textsuperscript{91} and Canada\textsuperscript{92,93} highlight the increased life expectancy with DS. Baird and Sadovnick\textsuperscript{92} reported a large study of 1,610 individuals with DS identified in more than 1,500,000 consecutive livebirths in British Columbia from 1908 to 1981. They constructed survival curves and a life table for DS (Table 1.2) and for the general population.\textsuperscript{94} Their estimates show that 44.4 percent and 13.6 percent of liveborn individuals with DS will survive to 60 and 68 years, respectively, compared with 86.4 percent and 78.4 percent of the general population. In another report,\textsuperscript{95} these authors have analyzed the causes of death in DS, highlighting congenital defects and cardiovascular and respiratory illnesses as the most important. A UK population prevalence study noted a median life expectancy of 58 years in 2011.\textsuperscript{96}

Additional studies of mortality rates in individuals with DS revealed that those up to about 35 years of age were little different from others with intellectual disability. Thereafter, however, mortality rates in DS doubled every 6.4 years, compared with 9.6
Table 1.2 Life expectancy with Down syndrome, between 1908–1981, to age 68 years (excerpted from 92)

<table>
<thead>
<tr>
<th>Age</th>
<th>Total</th>
<th>Survival at start of age interval (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>1,020</td>
<td>81.05</td>
</tr>
<tr>
<td>10</td>
<td>841</td>
<td>78.40</td>
</tr>
<tr>
<td>20</td>
<td>497</td>
<td>75.34</td>
</tr>
<tr>
<td>30</td>
<td>91</td>
<td>72.12</td>
</tr>
<tr>
<td>40</td>
<td>136</td>
<td>69.78</td>
</tr>
<tr>
<td>50</td>
<td>57</td>
<td>60.68</td>
</tr>
<tr>
<td>55</td>
<td>31</td>
<td>53.96</td>
</tr>
<tr>
<td>60</td>
<td>16</td>
<td>44.44</td>
</tr>
<tr>
<td>68</td>
<td>1</td>
<td>13.57</td>
</tr>
</tbody>
</table>

Source: Baird and Sadovnick 1989. 94

years for other intellectually disabled individuals. 95 Life tables constructed by these authors indicated a life expectancy of 55 years for a 1-year-old patient with DS and mild/moderate developmental delay and a life expectancy of 43 years for a 1-year-old patient with DS more profoundly affected.

A study from the Centers for Disease Control and Prevention focused on the death certificates of 17,897 individuals with DS born between 1983 and 1997. 97 These authors reported that the median age at death for those with DS increased from 25 years in 1983 to 49 years in 1997 (Figure 1.1).

A 2009 Australian study found an overall survival figure for DS of 90 percent to at least 5 years of age. 98 The known comorbidity of DS 98–115 and earlier onset Alzheimer 99 disease casts a longer shadow. In DS individuals over 40 years of age, increasing neuropsychological dysfunction and loss of adaptive skills have been noted. 115 Between 50–70 percent of DS patients develop Alzheimer disease by 60 years of age, 105 and up to 84 percent of those with dementia develop seizures. 102 A French study between 1979 and 1999 found a sixfold decreased risk of death from urological cancer in those with DS. 112

Table 1.3 reflects the common associated defects that occur in DS 98–115 and the more common complications that can be anticipated, monitored, prevented, and treated. 116,117 A EUROCAT population-based register study between 2000 and 2010 in 12 countries analyzed 7,044 live births and fetal deaths with DS. This report 116 noted that 43.6 percent of births with DS had congenital heart disease while 15 percent had another congenital malformation. The National Society of Genetic Counselors published valuable guidelines for communicating both prenatal and postnatal diagnoses of DS. 104 A US population prevalence study estimated, in 2008, that there were 250,700 with DS. 118

Figure 1.1 Median age at death of people with Down syndrome by sex (upper), by racial group (middle) and with or without congenital heart defects (CHD) by racial group (lower).


The goal and purpose of prenatal diagnosis

The fundamental philosophy of prenatal genetic diagnosis is to provide reassurance to couples at risk so that they may selectively have unaffected children even if their procreative risk for having offspring with a genetic disorder is unacceptably
Table 1.3 Defects and complications associated with Down syndrome

<table>
<thead>
<tr>
<th>Defect or complication</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Neurologic</strong></td>
<td></td>
</tr>
<tr>
<td>Intellectual disability</td>
<td>100</td>
</tr>
<tr>
<td>Hypotonia</td>
<td>100</td>
</tr>
<tr>
<td>Alzheimer disease and dementia</td>
<td>&gt; 50</td>
</tr>
<tr>
<td>Obstructive sleep apnea</td>
<td>30–57</td>
</tr>
<tr>
<td>Behavior problems</td>
<td>18–38</td>
</tr>
<tr>
<td>Hearing impairment</td>
<td>12–78</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>12–46</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>11–30</td>
</tr>
<tr>
<td><strong>Heart</strong></td>
<td></td>
</tr>
<tr>
<td>Mitral valve prolapse</td>
<td>57</td>
</tr>
<tr>
<td>Congenital heart disease</td>
<td>±50</td>
</tr>
<tr>
<td>Aortic valve regurgitation</td>
<td>17</td>
</tr>
<tr>
<td><strong>Immune system</strong></td>
<td></td>
</tr>
<tr>
<td>Susceptibility to infection</td>
<td>100</td>
</tr>
<tr>
<td>Hearing impairment</td>
<td>12–78</td>
</tr>
<tr>
<td>Juvenile rheumatoid-like arthritis</td>
<td>1.2</td>
</tr>
<tr>
<td><strong>Gastrointestinal</strong></td>
<td></td>
</tr>
<tr>
<td>Congenital defects of the gastrointestinal tract</td>
<td>4–10</td>
</tr>
<tr>
<td>Celiac disease</td>
<td>2–20</td>
</tr>
<tr>
<td><strong>Endocrine/metabolic</strong></td>
<td></td>
</tr>
<tr>
<td>Obesity</td>
<td>30–35</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>7–50</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.4–10.6</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>1–3</td>
</tr>
<tr>
<td><strong>Ophthalmologic</strong></td>
<td></td>
</tr>
<tr>
<td>Eye disorders(^a)</td>
<td>80</td>
</tr>
<tr>
<td>Cataract</td>
<td>17–29</td>
</tr>
<tr>
<td>Keratoconus</td>
<td>8–10</td>
</tr>
<tr>
<td><strong>Hematologic/oncologic</strong></td>
<td></td>
</tr>
<tr>
<td>Leukemia</td>
<td>&gt; 20-fold excess</td>
</tr>
<tr>
<td>Testicular cancer</td>
<td>Standardized incidence ratio of 4.8</td>
</tr>
<tr>
<td>Transient myeloproliferative disorder</td>
<td>10</td>
</tr>
<tr>
<td>Retroperitoneal teratoma</td>
<td>Increased</td>
</tr>
<tr>
<td><strong>Musculoskeletal</strong></td>
<td></td>
</tr>
<tr>
<td>Atlantoaxial instability</td>
<td>10–30</td>
</tr>
<tr>
<td>Osteoarthritis</td>
<td>8–28</td>
</tr>
<tr>
<td>Atlantoaxial subluxation</td>
<td>1–2</td>
</tr>
<tr>
<td><strong>Dental</strong></td>
<td></td>
</tr>
<tr>
<td>Orthodontic problems</td>
<td>±all</td>
</tr>
<tr>
<td>Periodontal disease</td>
<td>±all</td>
</tr>
</tbody>
</table>

Table 1.3 (Continued)

<table>
<thead>
<tr>
<th>Defect or complication</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dermatologic</strong></td>
<td></td>
</tr>
<tr>
<td>Dermatologic disorders</td>
<td>1.9–39.2</td>
</tr>
<tr>
<td><strong>Urinary tract</strong></td>
<td></td>
</tr>
<tr>
<td>Urinary tract anomalies</td>
<td>3.2</td>
</tr>
</tbody>
</table>

Notes: \(^a\)Includes strabismus, nystagmus, refractive errors, glaucoma, and lens opacities.

Data from references 98, 99–103, 105–108

Fetal defects serious enough to warrant parental election of abortion are generally found in less than 5 percent of all cases studied, based on current indications for prenatal diagnosis. When couples are at risk for having a child with a serious or fatal disorder, common experience shows that those with risks between 10 and 25 percent or even greater most often avoid pregnancies unless prenatal diagnosis is available. The advent of prenatal diagnosis has made it possible for such high-risk couples to have children that they would otherwise never have conceived. As a consequence, the number of children born because of prenatal diagnosis is much higher than the very small number of pregnancies terminated because of the detection of grave fetal defects. Prenatal genetic studies are used in Western society virtually exclusively for the detection of defects generally characterized by irreparable intellectual disability and/or irremediable serious to fatal genetic disease. Sadly, at present, the ideal goal of prevention or treatment, rather than abortion after prenatal detection of a fetal defect, is achieved only rarely, with the exception of NTDs. Preimplantation genetic diagnosis (see Chapter 10) does, however, provide another option that avoids abortion.

All couples or individuals concerned about the risks of genetic disorders in their offspring should seek genetic counseling before conceiving. For the more common indications for prenatal diagnosis (such as a positive result on a noninvasive prenatal screen – see Chapter 11 – or advanced maternal age), the well informed obstetrician should be able to provide the necessary information.\(^{120, 121}\) However, a salutary observation in one study revealed that 43.3 percent of patients referred for amniocentesis exclusively for advanced maternal age, had additional mostly unrecognized genetic risks, or
significant concerns regarding one or more genetic or congenital disorders.\textsuperscript{122} Neither a questionnaire in the physician’s office nor limited consultation time is likely to reveal many of these disorders.

**Prerequisites for genetic counseling**

Genetic counseling is a communication process concerning the occurrence and the risk of recurrence of genetic disorders within a family. The aim of such counseling is to provide the counselee(s) with as complete an understanding of the disorder and/or problem as possible and of all the options and implications. The counseling process is also aimed at helping families cope with their problems and at assisting and supporting them in their decision-making.

The personal right to found a family is considered inviolable. Such reproductive autonomy is enhanced by genetic counseling, a process that both emphasizes freedom of choice and reviews the available options in order to enrich the decision-making process. All couples have a right to know whether they have an increased risk of having children with genetic disease and to know which options pertain to their particular situation. The physician and genetic counselor have a clear duty and obligation to communicate this information, to offer specific tests or to refer couples for a second or more expert opinion. In the United States, at least, the full force of law supports the prospective parents’ right to know.

As Kessler\textsuperscript{123} stated so succinctly, “Because genetic counselors work with people filled with uncertainty, fear of the future, anguish and a sense of personal failure” they have unusual challenges and opportunities “to understand clients, give them a sense of being understood and help them feel more hopeful, more valued and more capable of dealing with their life problems.” The physician and genetic counselor providing genetic counseling should have a clear perception of the necessary prerequisites, guiding principles and potential problems.

**Knowledge of disease**

The need for a counselor to have extensive factual knowledge about disease in general, as well as about the disease for which counseling is being provided, hardly needs emphasis. Such knowledge should include how the diagnosis is made and confirmed, the test accuracy and limitations, the important comorbidities, the recurrence risks, the mode of inheritance, the tests available to detect a carrier (and their detection rates), the heterogeneity and pleiotropic nature of the disease, the quality of life associated with survival, prognosis and the causes of death. When relevant, it is necessary to know about treatment and its efficacy.

The physician or genetic counselor who initiates genetic counseling for an apparently straightforward indication (e.g. advanced maternal age) may find one or more other familial conditions with which he or she has little or no familiarity. Such circumstances dictate referral for specialist consultation. A National Confidential Enquiry into counseling for genetic disorders by nongeneticists in the United Kingdom revealed that less than half of those with known high genetic risks were referred to medical geneticists.\textsuperscript{124} This study focused on a review of 12,093 “genetic events” involving potentially avoidable cases of DS, NTDs, cystic fibrosis, \(\beta\)-thalassemia, and multiple endocrine neoplasia. Medical record reviews were frustrated by the poor quality of clinical notes, which lacked evidence of counseling. An urgent call was made for genetic management to be at least as well documented as surgical operations, drug records and informed consent. A Dutch study evaluated the levels of knowledge, practical skills and clinical genetic practices of 643 cardiologists. They noted low levels of self-reported knowledge and that only 38 percent had referred patients to clinical geneticists.\textsuperscript{125} Other physicians, too, have been found lacking in the necessary knowledge and communication skills.\textsuperscript{126–129} Given the importance of genetic considerations in all specialties, these problems can be anticipated to become more problematic, more especially in family practice.\textsuperscript{130}

After the prenatal diagnosis of a serious genetic disorder, the physician should be able to inform the family fully about the anticipated burden and to detail the effects of this burden on an affected child, the family, other siblings, the family economics and marital relations, along with any other pros and cons of continuing pregnancy. The reality of early Alzheimer disease and other comorbidities in DS
and the care requirements that may devolve on the siblings should not be omitted from the discussion. Exact details should also be known about the risks of elective abortion (see Chapter 29).

**Expertise in genetic counseling**

Genetic counseling is best provided by board-certified clinical geneticists and genetic counselors. In countries with this specialization, such service is provided by a team composed of clinical geneticists (physicians) and genetic counselors, working in concert with clinical cytogeneticists, biochemical and molecular geneticists. It is, however, impractical and not cost effective to provide such formal counseling for every woman before prenatal diagnosis for advanced maternal age. It is necessary for the obstetrician to be fully informed about the indications for amniocentesis and to explain the techniques and requirements for obtaining the tissue or fluid, the limitations of the studies, the risks of chromosomal abnormality in the offspring of the patient being counseled, the risks of the procedure and, when pertinent, all matters concerned with elective abortion of an abnormal fetus.

Gordis et al. concluded that the way in which an obstetrician managed patients at risk regarding referral for genetic screening was closely related to that obstetrician's attitudes and education. Physicians in practice should be aware of the nuances and needs in the genetic counseling process, including the key psychologic aspects. Perhaps most important is the requirement that they recognize limitations in their knowledge of uncommon or rare genetic disorders and be alert to situations requiring referral. Obstetricians or family practitioners are not expected to have an extensive knowledge of all diseases but they should be able to recognize that a condition could be genetic. Concern about litigation should not act as a constant reminder to physicians of the need to consult or refer.

**Ability to communicate**

Many physicians are not born communicators and most have not had formal teaching and training to hone their communication skills. Recognizing these deficiencies, the American Academy of Pediatrics has provided valuable guidance and made specific recommendations for the development and teaching of communication skills, as have others.

Simple language, an adequate allocation of time, and care and sensitivity are keys to successful genetic counseling. Technical jargon, used with distressing frequency, is avoided only through conscious effort. How an issue requiring a decision is framed, and the nature of the language used, may influence the patient's choice. Counseling is facilitated when three key questions are asked: “Why did you come?” “What exactly do you hope to learn?” and “Have I answered all your questions and concerns?”

Although the explanation of exact statistical risks is important, patients often pay more attention to the actual burden or severity of the disease in question. How risks are explained and expressed is a skill to be mastered. Key to the exposition is the patient's educational level, cultural background, and the requirement of an interpreter (who may even be a counselor). The use of numeric probabilities, relative risk, risk reduction or simple numbers of chance (1 in 100) or words (almost never, negligible, sometimes, more often than not) are choices a counselor must make. Clearly, the simpler, the better and the more likely the information is understood. Patients' perceptions of risk not infrequently differ markedly from those of the counselor, a realization that should elicit no comment. An essential ingredient of the counseling process is time. The busy practitioner can hardly expect to offer genetic counseling during a brief consultation. Distress and misunderstanding are invariable sequelae of such hastily delivered counseling.

**Knowledge of ancillary needs**

For the couple at high risk of having a child with a serious genetic disorder, prenatal diagnosis is not the sole option. Even in situations in which a particular disease is diagnosable prenatally, it is important to be certain that other avenues are explored. Prospective parents who are known, for example, to be carriers of an autosomal recessive disorder may be unaware of the possibility of sperm or ovum donation, or may be unwilling to raise the question. This option may be viewed more favorably than prenatal diagnosis and elective abortion. Physicians should be certain that their patients are familiar...
with all the aforementioned important options, as well as with adoption, vasectomy, tubal ligation, treatments of the mother and/or fetus during pregnancy, and other methods of assisted reproduction (e.g. intracytoplasmic sperm injection, epididymal sperm aspiration, and preimplantation genetic diagnosis) (see Chapters 5 and 10).

**Empathy**

Empathy embodies the ability to not only understand the perspectives and emotions of others but to communicate that understanding. Much more than the communication of risk figures for a particular disorder is required in the genetic counseling process. Warmth, care, sympathy, understanding, and insight into the human condition are necessary for effective communication. The difficulty of assimilating information and making rational decisions in the face of anxiety should be recognized and vocalized. Empathy and sensitivity enable the counselor to anticipate and respond to unspoken fears and questions, and are qualities that make the counseling experience most beneficial and valuable to the counselee.

For example, a couple may have been trying to conceive for 10 years and, having finally succeeded, may be confronted by a callous physician who is impatient about their concerns regarding amniocentesis and elective abortion. Another couple may have lost their only child to a metabolic genetic disease and may be seeking counseling to explore the possibilities for prenatal diagnosis in a subsequent pregnancy or even treatment following prenatal diagnosis, as in the case of galactosemia. They may have in mind past problems encountered in prenatal diagnosis or may be aware of the uncertain outcome of treatment. Or worse still, after a long history of infertility, pregnancy is achieved only to find that the fetus has aneuploidy.

Sensitivity and awareness of the plight of prospective parents are critical prerequisites and include the need to recognize and address the usually unspoken fears and anxieties. They may have had a previous affected child with physical/mental deficits and experienced stigmatizing encounters, including intrusive inquiries, staring and pointing, devaluing remarks and social withdrawal.

Beyond the qualifications and factual knowledge of the counselor is the person, who is key to successful and effective counseling. Attitude, body language, warmth, manners, dress, tone of voice and personality are facets that seriously influence the credibility and acceptance of the counseling offered. Curiously, counselors rarely realize during their counseling session that they are simultaneously being assessed. Patients assess the apparent knowledge and credibility of the counselor, seek and are encouraged by evidence of experience, and consider the information provided in light of the counselor’s attitude, body language and other non-verbal characteristics. Staring at a computer screen while counseling conveys deep insensitivity.

Essential prerequisites for the empathetic genetic counselor include the following:

- Acknowledge the burden and empathize about the sadness or loss (e.g. a previous child; recurrent miscarriage; a deceased affected parent; a patient who has experienced mastectomy and chemotherapy for breast cancer with daughters at risk).
- Vocalize the realization of the psychologic pain and distress the person or couple has experienced (e.g. recurrent pregnancy loss followed by multiple IVF efforts and subsequently a successful pregnancy with a fetal defect).
- Compliment the coping that has been necessary, including the stress a couple might have to endure, despite sometimes conflicting feelings.
- Recognize (and explain) psychologic difficulties in decision making when faced with a prenatal diagnosis of the same disorder affecting one parent (discussion of self-extinction, self-image and issues of guilt and survival).
- Fulfill the patient’s need for hope and support and actively avoid any thoughtless comments that may erode these fundamental prerequisites. Well intentioned statements are frequently perceived in a very different way.

It is self-evident that empathy would engender greater patient satisfaction and may well be correlated with clinical competence.

**Sensitivity to parental guilt**

Feelings of guilt invariably invade the genetic consultation; they should be anticipated, recognized, and dealt with directly. Assurance frequently does not suffice; witness the implacable guilt of the obligate maternal carrier of a serious X-linked disease. Explanations that we all carry harmful
Genes often help. Mostly, however, encouragement to move anguish into action is important. This might also help in assuring any blame by the husband in such cases.\textsuperscript{151}

Guilt is not only the preserve of the obligate carrier. Affected parents inevitably also experience guilt on transmitting their defective genes.\textsuperscript{152,153} Frequently, parents express guilt about an occupation, medication or illegal drug that they feel has caused or contributed to their child’s problem. Kessler et al.\textsuperscript{153} advised that assuaging a parent’s guilt may diminish their power of effective prevention, in that guilt may serve as a defense from being powerless.

Guilt is often felt by healthy siblings of an affected child, who feel relatively neglected by their parents and who also feel anger toward their parents and affected sibling. “Survivor guilt” is increasingly recognized, as the new DNA technologies are exploited. Experience with Huntington disease and adult polycystic kidney disease\textsuperscript{154–160} confirm not only survivor guilt with a new reality (a future) but also problems in relationships with close family members. Huggins et al.\textsuperscript{157} found that about 10 percent of individuals receiving low-risk results experienced psychologic difficulties.

**Guiding principles for genetic counseling**

Eleven key principles are discussed that guide genetic counseling in the preconception, prenatal and perinatal periods. This section is in concert with consensus statements concerning ethical principles for genetics professionals\textsuperscript{161–163} and surveyed international guidelines.\textsuperscript{164}

**Accurate diagnosis**

Clinical geneticists, obstetricians or pediatricians are frequently the specialists most confronted by patients seeking guidance because of certain genetic diseases in their families. A previous child or a deceased sibling or parent may have had the disease in question. The genetic counseling process depends on an accurate diagnosis. Information about the exact previous diagnosis is important not only for the communication of subsequent risks but also for precise future prenatal diagnosis. Now whole exome or genome sequencing and the demonstrated potential diagnostic yield of 25–42 percent for previously undiagnosed patients with severe intellectual disability,\textsuperscript{10,165,166} introduce clinical demands to be up to date and well informed. It is not sufficient to know that the previous child had a mucopolysaccharidosis; exactly which type and even subtype must be determined because each may have different enzymatic deficiencies or genotypes (see Chapter 22). A history of limb-girdle muscular dystrophy will also not facilitate prenatal diagnosis because there are eight dominant types (1A–1H), at least 23 autosomal recessive types (2A–2W),\textsuperscript{167} and many are still to be molecularly identified. Similarly, a history of epilepsy gives no clear indication of which genes are involved.\textsuperscript{168} Birth of a previous child with craniosynostosis requires precise determination of the cause (where possible) before risk counseling is provided. Mutations in at least 13 genes are clearly associated with monogenic syndromic forms of craniosynostosis.\textsuperscript{169–171} Moreover, a chromosomal abnormality may be the cause.

Awareness of genetic heterogeneity and of intrafamily and interfamily phenotypic variation of a specific disorder (e.g. tuberous sclerosis)\textsuperscript{172} is also necessary. The assumption of a particular predominant genotype as an explanation for a familial disorder is unwarranted. The common adult-dominant polycystic kidney disease due to mutations in the ADPKD1 gene has an early infancy presentation in 2–5 percent of cases.\textsuperscript{173} Moreover, mutations in the ADPKD2 gene may result in polycystic kidney disease and perinatal death\textsuperscript{174} and, further, should not be confused with the autosomal recessive type due to mutations in the ARPKD gene. Awareness of contiguous gene syndromes, such as tuberous sclerosis and polycystic kidney disease (TSC2-PKD1) has become increasingly important, especially with the availability of microarrays.

Instead of simply accepting the patient’s naming of the disease (e.g. muscular dystrophy or a mucopolysaccharidosis), or that a test result was normal (or not), the counselor must obtain and document confirmatory data. The unreliability of the maternal history, in this context, is remarkable, a positive predictive value of 47 percent having been documented.\textsuperscript{175} Photographs of the deceased, autopsy reports, hospital records, results of carrier
detection or other tests performed elsewhere, and other information may provide the crucial confirmation or negation of the diagnosis made previously. Important data after miscarriage may also influence counseling. In a study of 91 consecutive, spontaneously aborted fetuses, almost one-third had malformations, most associated with increased risks in subsequent pregnancies.\textsuperscript{176} 

Myotonic muscular dystrophy type 1 (DM), the most common adult muscular dystrophy, with an incidence of about 1 in 8,000,\textsuperscript{177} serves as the paradigm for preconception, prenatal and perinatal genetic counseling. Recognition of the pleiomorphism of this disorder will, for example, alert the physician hearing a family history of one individual with DM, another with sudden death (cardiac conduction defect), and yet another relative with cataracts. Awareness of the autosomal dominant nature of this disorder and its genetic basis due to a dynamic mutation reflected in the number of trinucleotide (CTG) repeat units, raises issues beyond the 50 percent risk of recurrence in the offspring of an affected parent. As the first disorder characterized with expanding trinucleotide repeats, the observation linking the degree of disease severity to the number of triplet repeats was not long in coming.\textsuperscript{177} In addition, the differences in severity when the mutation was passed via a maternal rather than a paternal gene focused attention on the fact that congenital DM was almost always a sign of the greatest severity and originating through maternal transmission. However, at least one exception has been noted.\textsuperscript{178} There is about a 93–94 percent likelihood that the CTG repeat will expand on transmission. This process of genetic anticipation (increasing clinical severity over generations) is not inevitable. An estimated 6–7 percent of cases of DM are associated with a decrease in the number of triplet repeats or no change in number.\textsuperscript{179} Rare cases also exist in which complete reversal of the mutation occurs with spontaneous correction to a normal range of triplet repeats.\textsuperscript{180–183} 

There are also reports of patients born with a decreased number of triplet repeats who nevertheless show no decrease in the severity of their DM.\textsuperscript{184–186} It is unclear whether these cases in part reflect somatic or germline (either or both combined) mosaicism.\textsuperscript{179} Somatic mosaicism is certainly well documented in DM with, for example, larger expansions being observed in skeletal muscle than in peripheral blood.\textsuperscript{187} Discussion about potential complications of pregnancy in the prospective affected mother is crucial,\textsuperscript{188} and includes pregnancy loss, polyhydramnios, prolonged labor, uterine atony, postpartum hemorrhage, cardiac arrhythmias, increased sensitivity to anesthetic and relaxant agents, newborn apnea, neonatal death, arthrogryposis and intellectual disability.

Myotonic muscular dystrophy type 2 (DM 2), in contrast to DM 1, has more prominent proximal muscle weakness compared with distal weakness of DM 1. While multisystem involvement is similar in both types, neither congenital myotonic muscular dystrophy nor anticipation occurs in DM 2.\textsuperscript{189} Cardiac involvement in DM 2 also is less frequent and less severe than DM 1.\textsuperscript{190} DM 2 results from a large tetranucleotide repeat (CCTG) within an intron in CNBP gene. Again in contrast to DM 1, the DM 2 repeat number may contract rather than increase over generations.\textsuperscript{189} 

The lack of CAG triplet expansion among individuals presenting with Huntington disease-like symptoms and a family history of neurodegenerative disease has focused attention on phenocopies of Huntington disease.\textsuperscript{191} Estimates of such phenocopies range between 1 and 2.4 percent of patients manifesting Huntington disease-like signs with a family history of a neurodegenerative disorder.\textsuperscript{192} Among the reported phenocopies found thus far are a familial prion disease\textsuperscript{191} and a triplet expansion (CAG/CTG) in the junctophilin-3 gene on chromosome 16 in patients presenting with Huntington disease-like manifestations.\textsuperscript{193} The recognition in 2011 of a hexanucleotide repeat expansion in C9ORF72 as the cause of either or both amyotrophic lateral sclerosis (ALS) and frontotemporal dementia\textsuperscript{194,195} revealed a neurological spectrum clearly recognized previously.\textsuperscript{196} Between 40–50 percent of those affected by familial ALS have the characteristic expansion. About 15 percent of patients with ALS also have frontotemporal dementia, while 50 percent have some cognitive and/or behavioral dysfunction.\textsuperscript{196} Of those patients who present with frontotemporal lobe degeneration, the extreme end of the spectrum, 15 percent also have ALS. Hence, assessment of the family history in an effort to