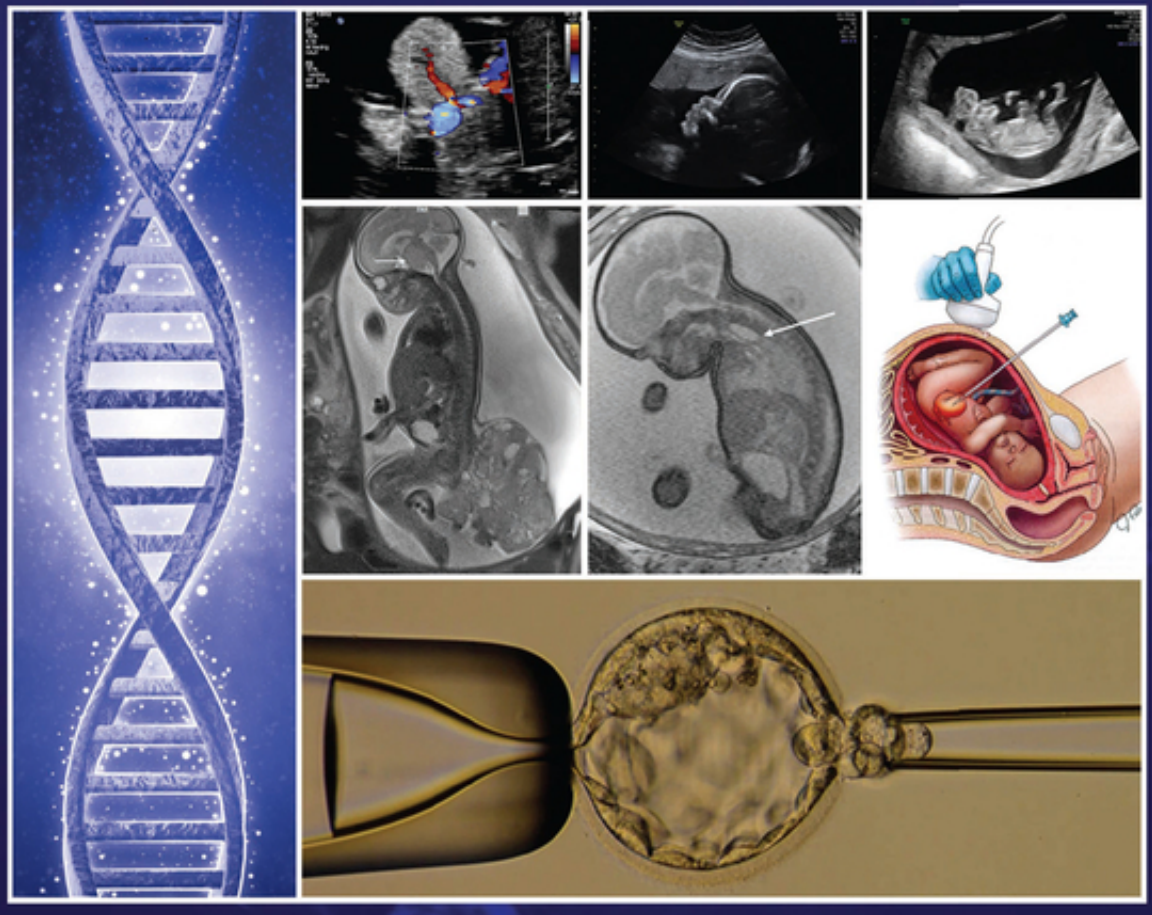
EIGHTH EDITION

Genetic Disorders and the Fetus

Diagnosis, Prevention, and Treatment



Edited by
Aubrey Milunsky and Jeff M. Milunsky

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Genetic Disorders and the Fetus

Dedicated to

Laura and Francia

For their love, support, and understanding

“Make assurance double sure.”
Shakespeare, *Macbeth*

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Diagnosis, Prevention, and Treatment

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Aubrey Milunsky, MB BCh, DSc, FRCP, FACMG, DCH

Professor of Obstetrics and Gynecology
Tufts University School of Medicine
Formerly Professor of Human Genetics, Pediatrics, Obstetrics and Gynecology
Boston University School of Medicine
Founder and Co-Director, Center for Human Genetics
Cambridge, MA, USA

Jeff M. Milunsky, MD, FACMG

Professor of Obstetrics and Gynecology
Tufts University School of Medicine
Formerly Professor of Genetics and Genomics, and Pediatrics
Boston University School of Medicine
Co-Director, Center for Human Genetics
Director, Clinical and Molecular Genetics
Cambridge, MA, USA

WILEY Blackwell

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Preface

Certainty and trust are the hallmarks of prenatal diagnosis where doubt and ambiguity are outlaws. At no time was that more apparent than when AM made his first prenatal genetic diagnosis over 50 years ago. "Are you sure?" were that patient's first words, intoned with deep anxiety. Those words underscored the still cogent need for accuracy in prenatal diagnosis, where mostly a single report would be final. That was a time when prenatal diagnosis depended on amniocentesis-based study, yielding an accuracy rate exceeding 99 percent. Few laboratory tests, then or now, concerned with profoundly important decision-making equal this enviable accuracy. Variants of uncertain significance had not yet entered the genetic lexicon.

Today, however, with the newer, beguiling, noninvasive technology, amniocentesis and chorionic villus sampling (CVS) use has declined dramatically. On the altars of convenience and expediency, women are choosing or simply encouraged to have noninvasive prenatal testing, often blissfully unaware that about half of all chromosomal abnormalities detectable through amniocentesis or CVS and authoritatively discussed, would be missed. There is room for concern given the current consensus that all women should be *offered* either of these two procedures.

Similarly, all women with risks of having offspring with a monogenic disorder and a known pathogenic variant should be informed about and offered the option of preimplantation genetic testing (PGT). The extensive and long-established experience of the authors with PGT enshrine this recommendation. Expanded carrier screening should make this a more frequently addressed option. Couples should, however, be carefully counseled about the limitations of such screening. All the facts, figures, guidelines, and recommendations have been updated in this edition, and will assist the expanded healthcare team in providing optimal care to all patients.

Coupled with remarkable advances in technology, prenatal diagnosis has undergone a revolution. Thus far, and continually increasing, more than 4,331 culprit genes and 6,739 associated phenotypes for an extensive array of genetic disorders have been identified. Consequently, since physicians in all medical specialties encounter genetic disorders for which a molecular diagnosis is available, awareness of the options for prenatal diagnosis or PGT has become especially important.

Pari passu with these technical advances has come the opportunity to avoid and prevent the occurrence of many lethal and seriously disabling genetic diseases. This progress means that physicians in all specialties incur responsibility (and inevitable liability) to acquire new knowledge of genetic disorders and offer appropriate tests or refer patients for evaluation and genetic counseling.

More than 60 million people worldwide are estimated to have DNA studies in the next 5 years. Expanded carrier testing, maternal cell-free plasma DNA testing, whole-exome sequencing, next-generation sequencing, single-cell molecular diagnosis, and advanced fetal imaging, all fully presented in this volume, now complement the well-established procedure for prenatal diagnosis and PGT. Whole-genome analysis for prenatal diagnosis (even if advisable) simply awaits further technical advances.

Chromosomal microarrays and whole-exome sequencing have propelled an even greater prenatal diagnostic reach, especially in the face of fetal structural, including skeletal, abnormalities, given the advances in ultrasound and magnetic resonance imaging, so expertly covered in this volume by authors from three European countries.

The fetal anomaly scan has to an important extent superseded amniotic fluid α-fetoprotein for

the diagnosis of neural tube defects. Nevertheless, the significant worldwide prevalence of neural tube defects makes maternal serum α-fetoprotein screening a continuing vital test, critically evaluated here by a pioneer. The diagnosis of neural tube defects and their consequences, as well as the frequently failed efforts at prevention, are thoroughly detailed.

Knowledge of the common sex chromosome aneuploidies and some of the rarer variants continues to expand. Up-to-date summaries of all these disorders are presented with specific recommendations for genetic counseling. Molecular prenatal diagnosis has now become routine and the multiple technologies utilized, with their benefits and limitations along with clinically based caveats and considerations, are presented in a significantly updated chapter.

The advent of next-generation sequencing has, by targeting panels or whole-exome approaches, resulted in more opportunities for avoidance and prevention through prenatal diagnosis. These widely available technologies not only address previously diagnosed childhood-onset disorders, but also those of adult onset, including cardiomyopathies, malignancies, and neurologic disorders.

Progress and refinement in the diagnosis and management of a wide range of metabolic disorders are fully and authoritatively updated, and equally complemented by the detailed in-depth advances in molecular diagnostics that include the hemoglobinopathies, fragile X syndrome, cystic fibrosis, disorders of folate metabolism, and the immunodeficiency diseases.

Pregnancy termination is a sad but fortunately uncommon consideration following prenatal diagnostic studies. The techniques and complications are fully discussed and complemented by insightful senior experience with the management of grief after pregnancy and perinatal loss. Discussion about the care and management of mothers with genetic disorders that affect fetal health and those who transmit infection to the fetus is sharply focused on diagnosis, prevention, avoidance, and treatment. Fetal health is doubly important given the known fetal origins of adult disease that go far beyond hypertension, obesity, and diabetes, to include the epigenetic phenomena induced by the maternal pregnancy environment. A thorough exposition on the importance of placental development, structure, function, genetics, and pathology on fetal growth and development is expertly presented in this edition. Steadily, but surely, fetal gene therapy via hematopoietic stem cell transplantation is taking root, while a remarkable chapter on fetal surgery by a leader in the field points to new brave surgical remedies.

While all authors acknowledge continuing progress in molecular genetics, inconclusive results due to variants of uncertain significance are not infrequent. Laboratory conclusions can be further compounded by a host of issues that potentially befuddle interpretation. Commonly encountered issues include delineation of normal variation or polymorphisms, difficulty determining the pathogenicity of variants, depth of sequencing coverage, regions of high GC content, mosaicism, DNA contamination, digenic inheritance, locus heterogeneity, and false-positive and false-negative results. The concurrence of an incidental (secondary) finding on fetal DNA analysis will predictably arouse great parental anxiety.

Current laws and public policy regarding prenatal diagnosis and PGT in 16 countries are examined in detail regarding international differences, with special reference to the guidelines relevant to the emerging technologies. A senior physician-lawyer, in reviewing the important principles in the torts of wrongful birth and wrongful life, focused on the potential liability of those involved in reproductive medicine. Professional ethics in obstetrics, with emphasis on the ethical principles of beneficence and autonomy and the ethical concept of the fetus as a patient, receive in-depth discussion by doyens in this field.

This volume is a major repository of facts about prenatal diagnosis and provides a critical analysis and synthesis of established and new knowledge based on the long experience of the senior contributing authorities in their respective fields. In addition, a broad international perspective is presented with contributions from recognized international experts from nine 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 or PGT.

This text is very well referenced and replete with evidence-based guidance and reflective of the lifetime experience and wisdom of distinguished senior authors. This edition encompasses 152 tables, 167 figures, and over 10,000 references. A valuable index will facilitate the reader's search for specific information.

The major technologic advances in genetics have made the requirement for preconception, prenatal, and perinatal genetic counseling of paramount importance. Even though the underlying principles and prerequisites are well established, the many advances have introduced a panoply of new challenges discussed in detail in a comprehensive, heavily referenced opening chapter. We are in the golden era of human genetics, and through new discoveries and insights have increased opportunities for the diagnosis, prevention, and treatment of many serious and lethal genetic disorders.

Aubrey Milunsky and Jeff M. Milunsky
Cambridge

Acknowledgments

This eighth edition marks the 42nd year of this text and reflects the continuing remarkable advances made in achieving accurate prenatal and preimplantation diagnoses. The first book on this subject (*The Prenatal Diagnosis of Hereditary Disease*) was published some 48 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, experience, and knowledge of these senior 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 nine countries.

Expert care in human genetics, maternal–fetal medicine, and perinatal medicine has demanded knowledge, up-to-date information, guidance, and expertise in each volume. This has been achieved only by the willingness of the 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 expert contributing authors to earlier editions. We remember them with pride and sadness: Bruno Brambati, MD, David J.H. Brock, PhD, Jacob A. Canick, PhD, Louis Dalliaire, MD, PhD, Sherman Elias, MD, H.J. Evans, PhD, FRSE, John C. Fletcher, PhD, Fredric Frigoletto, MD, Albert B. Gerbie, MD, Leonard A. Herzenberg, PhD, George Hug, MD, Lillian Y.F. Hsu, MD, Mary Z. Pelias, PhD, JD, Arthur Robinson, MD, Richard H. Schwarz, MD, Margery W. Shaw, MD, JD, Irving Umansky, MD, Yury Verlinsky, PhD, and Dorothy C. Wertz, PhD.

It is possible that we are unaware of the passing of a few authors and regret any omission. We remain eternally grateful to all these remarkable physicians and scientists.

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Aubrey Milunsky
Jeff M. Milunsky

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 L. Austin, MS, MA, CGC
Genetic Counsellor
Senior Research Program Leader
Division of Medical Genetics
Duke University
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

Deeksha Sarihyan Bali, PhD, FACMGG
Professor of Pediatrics
Laboratory Director Biochemical Genetics Laboratory
Division of Medical Genetics
Duke Health
Durham, NC, USA

Michael A. Belfort, MBBCH, D. Mid. COG(SA), D.A (SA), MD, PhD, FRCOG, FRCSC, FACOG
Professor and Ernst Bertner Chair, Department of Obstetrics and Gynecology
Secondary appointments: Departments of Anesthesiology, Surgery, Neurosurgery
Baylor College of Medicine
Obstetrician and Gynecologist-in-Chief
FB McGuyer and Family Chair in Fetal Surgery
Medical Director, Texas Children's Fetal Center
Texas Children's Hospital
Houston, TX, USA

Peter A. Benn, BSc, MSc, PhD, FACMG, DSc
Professor Emeritus
Department of Genetics and Genome Sciences
University of Connecticut Health Center
Farmington, CT, USA

Karin J. Blakemore, MD
Professor of Gynecology and Obstetrics, Oncology, and Medical Genetics
Director, Prenatal Genetics Center
Division of Maternal-Fetal Medicine
Department of Gynecology and Obstetrics
Johns Hopkins University School of Medicine
Baltimore, MD, USA

Natalie Chandler, FRCPath
Senior Clinical Scientist
North Thames Genomic Laboratory Hub
Great Ormond Street Hospital for Children NHS Foundation Trust
London, UK

Kathia Chaumoitre, MD, PhD
Professor of Paediatric Radiology
Imaging Department
North Hospital
Aix-Marseille University
Marseille, France

Frank A. Chervenak, MD, MMM
Professor and Chair
Department of Obstetrics and Gynecology
Associate Dean, International Medicine
Zucker School of Medicine at Hofstra/Northwell
Lenox Hill Hospital
New York, NY, USA

Lyn S. Chitty, PhD, MB, BS, MRCOG
Professor of Genetics and Fetal Medicine
Medical Director North Thames Genomic Laboratory Hub
Great Ormond Street Hospital for Children
Genetics and Genomic Medicine,
UCL Institute of Child Health
London, UK

Lorne A. Clarke, MDCM, FRCPC, FCCMG
Professor of Medical Genetics
University of British Columbia
Department of Medical Genetics
British Columbia Children's Hospital Research Institute
Vancouver, British Columbia, Canada

Howard Cuckle, MSc, DPhil
Professor
Faculty of Medicine, Tel Aviv University
Tel Aviv, Israel

James E. Davison, MBChB, PhD
Consultant in Paediatric Metabolic Medicine
Department of Metabolic Medicine
Great Ormond Street Hospital for Children NHS Foundation Trust
London, UK

Mina Desai, PhD
Associate Professor of Obstetrics & Gynecology
David Geffen School of Medicine at UCLA
Los Angeles, CA, USA
Director of Perinatal Research
The Lundquist Institute at Harbor-UCLA Medical Center
Torrance, CA, USA

Lorraine Dugoff, MD
Professor of Obstetrics and Gynecology
University of Pennsylvania School of Medicine
Chief, Reproductive Genetics Division
Department of Obstetrics and Gynecology
Hospital of the University of Pennsylvania
Philadelphia, PA, USA

Valentine Faure-Bardon
Lecturer in Obstetrics and Fetal Medicine
Department of Obstetrics and Fetal Medicine
Hôpital Necker-Enfants Malades, GH Paris-Centre
Université de Paris
Paris, France

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
Université de La Mediterranée
Head of Neuroradiology
Timone Hospital
Aix-Marseille University
Marseille, France

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

Andrea Gropman, MD, FAAP, FACMG
Professor of Neurology and Pediatrics
Chief, Neurogenetics and Neurodevelopmental Disabilities
Children's National Medical Center and the
George Washington University School of Medicine
Washington DC, USA

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

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

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

Marianne H. Hutti, PhD, WHNP-BC, FAANP, FAAN
Professor
College of Nursing
Senior Nurse Scientist
University of Kentucky Healthcare – Ambulatory Services
University of Kentucky
Lexington, KY, USA

Priya S. Kishnani, MD, FACMGG
C.L. and Su Chen Professor of Pediatrics and Professor of Molecular Genetics and Microbiology
Duke University School of Medicine
Medical Director, YT and Alice Chen Pediatrics Genetics and Genomics Center
Division Chief, Medical Genetics
Duke Health
Durham, NC, USA

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

Anver Kuliev, MD, PhD
Clinical Professor
Herbert Wertheim College of Medicine
Florida International University
Miami, FL
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, GH Paris Centre
Université de Paris
Paris, France

Brynn Levy, MSc(Med), PhD, FACMG
Professor of Pathology and Cell Biology, Columbia University Medical Center
Medical Director, Clinical Cytogenetics Laboratory
Co-Director, Laboratory of Personalized Genomic Medicine
Vagelos College of Physicians and Surgeons
Columbia University Irving Medical Center & the New York Presbyterian Hospital
New York, NY, USA

Malou A. Lugthart, MD
Research Fellow in Fetal Medicine
Department of Obstetrics
Amsterdam Reproduction and Development Research Institute
Amsterdam University Medical Centers
University of Amsterdam
Amsterdam, The Netherlands

Tippi C. MacKenzie, MD
Professor of Surgery
Co-Director, Center for Maternal-Fetal Precision Medicine
University of California, San Francisco
San Francisco, CA, USA

Laurence B. McCullough, PhD
Professor
Department of Obstetrics and Gynecology
Zucker School of Medicine at Hofstra/Northwell
Ethics Scholar
Department of Obstetrics and Gynecology
Lenox Hill Hospital
New York, NY, USA

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

Aubrey Milunsky, MD, DSc, FRCP, FACMG, DCH
Professor of Obstetrics and Gynecology
Tufts University School of Medicine, Boston, MA, USA
Formerly Professor of Human Genetics, Pediatrics, Obstetrics and Gynecology, and Pathology
Boston University School of Medicine
Founder and Co-Director, Center for Human Genetics
Cambridge, MA, USA

Jeff M. Milunsky, MD, FACMG
Professor of Obstetrics and Gynecology
Tufts University School of Medicine
Formerly Professor of Genetics and Genomics, and Pediatrics
Boston University School of Medicine
Co-Director, Center for Human Genetics
Director, Clinical Genetics and Molecular Genetics
Cambridge, MA, USA

Sara E. Mole, PhD
Professor in Molecular Cell Biology
UCL Great Ormond Street Institute of Child Health
MRC Laboratory of Molecular Cell Biology
Genetics and Genomics Medicine Research
& Teaching Department
Inborn Errors of Metabolism Section
University College London
London, UK

Minh Thu Minh Nguyen, LLM, LLB, BSc
Academic 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
Clinical Scientist
Emeritus Reader in Hematology
University of Oxford, Oxford, UK

Eva Pajkrt, MD, PhD
Professor of Obstetrics
Head of Obstetrics and Fetal Medicine
Department of Obstetrics
Amsterdam Reproduction and Development Research Institute
Amsterdam University Medical Centers
University of Amsterdam
Amsterdam, The Netherlands

Jennifer M. Puck, MD
Professor of Pediatrics
Division of Allergy/Immunology and Blood and Marrow Transplantation
University of California San Francisco
Department of Pediatrics
San Francisco, CA, USA

Svetlana Rechitsky, PhD
Clinical Associate Professor
Herbert Wertheim College of Medicine
Florida International University
Miami, FL, USA
President
Reproductive Genetic Innovations
Northbrook, IL, USA

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

David S. Rosenblatt, MDCM, FCCMG, FRCPSC, FAAP, FACMG
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

Michael G. Ross, MD, MPH
Distinguished Professor of Obstetrics and Gynecology and Public Health
Geffen School of Medicine at University of California Los Angeles
Fielding School of Public Health at UCLA
Los Angeles, CA, USA
Co-Director Institute for Women' and Children's Health
The Lundquist Institute at Harbor-UCLA Medical Center
Torrance, CA, USA

Marisa E. Schwab, MD
Surgery Resident
The Center for Maternal-Fetal Precision Medicine and Department of Surgery
University of California, San Francisco
San Francisco, CA, USA

Alireza A. Shamshirsaz
Associate Professor of Surgery, Obstetrics and Gynecology
Departments of Obstetrics and Gynecology and Surgery
Baylor College of Medicine
Chief, Division of Fetal Therapy and Surgery
Co-Chief, Maternal Fetal Surgery Section
Texas Children's Fetal Center
Texas Children's Hospital
Houston, TX, USA

Lee P. Shulman, MD, FACMG, FACOG
The Anna Ross Lapham Professor in Obstetrics and Gynecology
Feinberg School of Medicine of Northwestern University
Medical Director, Insight Medical Genetics
Medical Director, Reproductive Genetic Innovations
Chicago, IL, USA

Andrea Superti-Furga, MD
Professor of Pediatrics
University of Lausanne
Head, Division of Genetic Medicine
Lausanne University Hospital
Lausanne, Switzerland

Jan Traeger-Synodinos, DPhil (Oxon), ErCLG
Professor of Genetics
Director of the Laboratory of Medical Genetics
National and Kapodistrian University of Athens, Greece

Sheila Unger, MD, FRCPC
Chief
MER1 Division of Genetic Medicine
Lausanne University Hospital
Lausanne, Switzerland

Ignatia B. Van den Veyver, MD
Professor of Obstetrics and Gynecology and Molecular and Human Genetics
Baylor College of Medicine;
Director of Clinical Prenatal Genetics
Texas Children's Hospital
Houston, TX, USA

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

Liesbeth van Leeuwen, MD, PhD
Associate Professor
Department of Obstetrics
Amsterdam Reproduction and Development Research Institute
Amsterdam University Medical Centers
University of Amsterdam
Amsterdam, The Netherlands

Yves G. Ville, MD
Professor of Obstetrics and Fetal Medicine
Head of Department of Obstetrics and Fetal Medicine
Hôpital Necker-Enfants Malades, GH Paris-Centre
Université de Paris
Paris, France

Gerard Vockley, MD, PhD
Professor of Pediatrics and Human Genetics
Cleveland Family Endowed Professor of Pediatric Research
Department of Pediatrics
University of Pittsburgh School of Medicine and Graduate School of Public Health
Chief, Division of Medical Genetics
Director, Center for Rare Disease Therapy
Children's Hospital of Pittsburgh
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

Hans R. Waterham, PhD
Professor, Functional Genetics of Metabolic Diseases
Departments of Laboratory Medicine and Pediatrics
University of Amsterdam
Academic Medical Center
Laboratory for Genetic Metabolic Diseases
Amsterdam, The Netherlands

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

Bryan G. Winchester, MA, PhD
Emeritus Professor of Biochemistry
ULC Great Ormond Street 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

Ellen Wright Clayton, MD, JD
Craig-Weaver Professor of Pediatrics
Professor of Law
Center for Biomedical Ethics and Society
Vanderbilt University
Nashville, TN, USA

1 Genetic Counseling: Preconception, Prenatal, and Perinatal

Aubrey Milunsky[1,2] *and Jeff M. Milunsky*[1,2]

[1]Center for Human Genetics, Cambridge, MA, USA
[2]Tufts University School of Medicine, Boston, MA, USA

The time is fast approaching when virtually all the culprit genes and their mutations for >7,000 rare monogenic disorders[1] will be known. Thus far, causal single genes and their mutations have been determined for 5,673 genetic disorders,[2] enabling preimplantation genetic testing or prenatal genetic diagnosis. These advances using chromosomal microarrays, whole-exome sequencing and even whole-genome sequencing together with fetal imaging and noninvasive prenatal testing, expand the era in which all couples have the option of avoiding or preventing having children with irreversible, irremediable, crippling, or lethal monogenic disorders. Primary care physicians, and those in all medical specialties, will need to inform their patients of this key option. This imperative is already partly in current practice. Missing is the requirement of physicians to request and obtain the precise name of the genetic disorder in question or an existing DNA report on a family member, for prospective parents to benefit from available options.

Increasingly, couples are seeking prenatal diagnosis for adult-onset genetic disorders in which mutations have been determined. Huntington disease prenatal diagnosis has been in the vanguard for many years, but now there are requests for adult-onset dominantly transmissible disorders including breast and other malignancies, frontotemporal dementia, neurodegenerative disorders, and cardiomyopathies. The remarkable advances in genetics provide a cogent need to confer and refer. Physicians should not invite legal purview for a failure to inform, offer, refer, or provide genetic testing.

In context, couples at risk for having progeny with abnormalities expect to be informed about their risks 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.

The burden of genetic disorders and congenital malformations

A conservative estimate for the world population prevalence of rare diseases (71.9–80 percent considered as genetic) is 3.5–5.9 percent, equating to 263–446 million individuals affected at any point in time.[3, 4] In India, which has a quarter of the world's neonatal deaths (an estimated 753,000 in 2013), about 9 percent were due to congenital anomalies.[5] An estimated 7.9 million infants worldwide are born each year with a major congenital malformation according to a report in 2013.[6] The likelihood of having a child with a congenital malformation varies from 2 to 10 percent[7] due to multiple factors

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that complicate efforts to accurately diagnose and determine the incidence or prevalence of congenital anomalies or genetic disorders. Box 1.1 lists 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. Of the >7,000 rare genetic disorders, about 1 in 12 to 1 in 16 individuals are affected,[1] aware or unaware. Given a world population of 7.6 billion, an estimated 473 million are likely to have a rare disease.[1] More than 4,331 genes with phenotype-causing mutations have been identified, including 6,739 phenotypes with a known molecular basis.[2] Severe intellectual disability is considered to be largely genetic in origin[8, 9] with a global prevalence between 0.5 and 1.0 percent.[10] Despite continuing progress in the discovery of genes causally related to neurodevelopmental delay,[11] in less than 40 percent of cases is there a definitive recognition of cause. 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.[12] In the United States in 2013–2014,

Box 1.1 Factors that influence estimates of the incidence or prevalence in the newborn of a congenital malformation (CM) or genetic disorder

- Availability and use of expertise in prenatal diagnostic ultrasound and MRI
- Accuracy of diagnosis
- Age at diagnosis
- Case selection, bias, and ascertainment
- Congenital hypothyroidism
- Consanguinity
- Definitions of major and minor congenital anomalies
- Diagnostic DNA analysis
- Duration of follow-up
- Economic level in developed or developing world
- Environmental toxins
- Family history
- Frequency, inclusion, and exclusion of stillbirths, fetal deaths, and elective pregnancy termination
- Frequency of certain infectious diseases
- Frequency of *de novo* gene mutations
- History of recurrent spontaneous abortion
- *In vitro* fertilization
- Incidence and severity of prematurity
- Infertility
- Intracytoplasmic sperm injection
- Later manifestation or onset of disorder
- Maternal age
- Maternal alcohol abuse
- Maternal diabetes and gestational diabetes
- Maternal diet
- Maternal epilepsy, lupus erythematosus and other illnesses
- Maternal fever or use of hot tub in the first 6 weeks of pregnancy
- Maternal folic acid supplementation
- Maternal grandmother's age
- Maternal obesity
- Maternal serum screening for chromosome abnormalities
- Maternal smoking
- Maternal-specific susceptibility genes
- Maternal use of medication
- Mortality rates decreasing
- Multiple pregnancy rate
- Necropsy
- Noninvasive prenatal testing using cell-free fetal DNA for chromosomal abnormalities and monogenic disorders
- Parent with a congenital abnormality or genetic disorder
- Paternal age
- Previous affected child
- Previous maternal immunization/vaccination
- Season of the year
- Training and expertise in examination of newborns
- Use of chromosomal analysis
- Use of chromosomal microarray
- Use of whole-exome sequencing
- Use of whole-genome sequencing
- Use of death certificates
- Use of registry data

congenital malformations, deformations, and chromosomal abnormalities accounted for the most infant deaths – 4,746 (20.4 percent) out of 23,215 – in any category of causation.[13]

Incidence and prevalence of genetic disorders and congenital malformations

Estimates of aneuploidy in oocytes and sperm reach 25 percent and 3–4 percent, respectively.[14, 15] Estimates, especially for oocytes, vary widely (see Chapter 2). The effect of maternal age, among other factors, is important. At 25 years, early thirties, and >40 years of age, the rate of aneuploidy approximates 5 percent, 10–25 percent, and 50 percent, respectively.[15–19] Estimates of aneuploidy and structural chromosomal abnormalities in sperm vary from 7 to 14 percent.[20] Not surprisingly, then, about one in 13 conceptions results in a chromosomally abnormal conceptus,[21] while about 50 percent of first-trimester spontaneous abortions are associated with chromosomal anomalies.[22] One study of blastocysts 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.[23] Similar results have been reported by others.[24] 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 (see Chapters 11 and 13). Between 5.6 and 11.5 percent of stillbirths and neonatal deaths have chromosomal defects.[25]

Congenital malformations with obvious structural defects are found in about 2 percent of all births.[26] This was the figure in Spain among 710,815 livebirths,[27] with 2.25 percent in Liberia,[28] 2.03 percent in India,[29] and 2.53 percent among newborn males in Norway.[30] 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.[31] 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 (including anotia or microtia, cleft lip, trisomy 18, encephalocele, limb-reduction defect).[32] Factors that had an impact on the incidence/prevalence of congenital malformations are discussed later.

Over 25,500 entries for genetic disorders and traits have been catalogued.[2] 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).[33] Baseline birth prevalence of rare single-gene disorders for multiple countries are shown in Figure 1.1, which highlights the contribution of consanguinity-associated disorders.[34] Polygenic disorders occurred at a rate of 46.4 in 1,000 (Table 1.1). A key study of homozygosity in consanguineous patients with an autosomal recessive disease showed that, on average, 11 percent of their genomes were homozygous.[35] Each affected individual had 20 homozygous segments exceeding 3 cM.

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.[36, 37] If all congenital defects are considered, Baird et al.[33] 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.[38] 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.[39] About 27 percent suffer cardiovascular complications requiring surgery.[40, 41] Mitral valve prolapse affects 2–3 percent of the general population, involving more than 176 million people worldwide.[42] A Canadian study of 107,559 patients with congenital heart disease reported a prevalence of 8.21 per 1,000 livebirths, rising to an overall prevalence of 13.11 per 1,000 in adults.[43] 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 or malformations in the fetus are shown in Box 1.1. A metropolitan Atlanta study (1998–2005) showed an overall

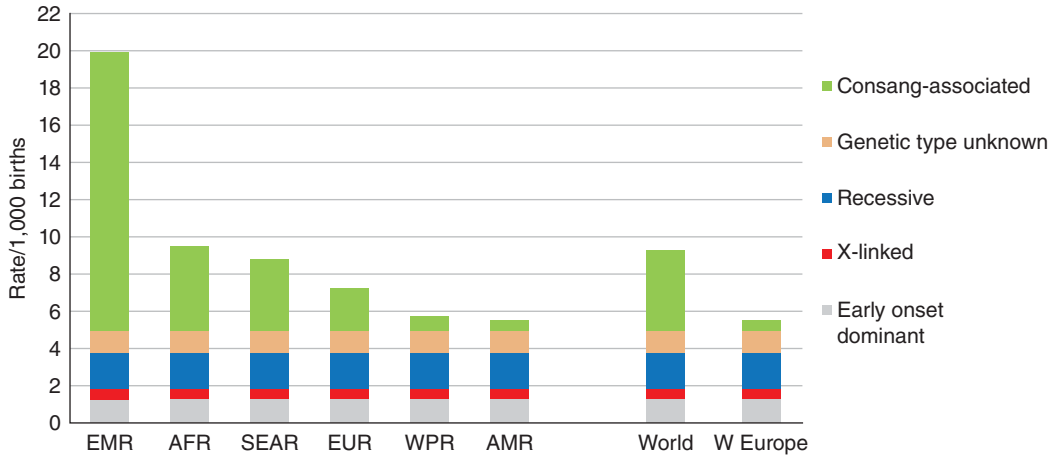

Figure 1.1 Total baseline birth prevalence of rare single-gene disorders by World Health Organization (WHO) region, highlighting the important contribution of consanguinity to monogenic disorders.
Source: Blencowe et al. 2018.[34] Reproduced with permission from Springer.

Table 1.1 The frequencies of genetic disorders in 1,169,873 births, 1952–1983[34].

Category	*Rate per million livebirths*	*Total births (percent)*
A		
Dominant	1,395.4	0.14
Recessive	1,665.3	0.17
X-linked	532.4	0.05
Chromosomal	1,845.4	0.18
Multifactorial	46,582.6	4.64
Genetic unknown	1,164.2	0.12
Total	53,175.3	5.32 [a]
B		
All congenital anomalies 740–759 [b]	52,808.2	5.28
Congenital anomalies with genetic etiology (included in section A)	26,584.2	2.66
C		
Disorders in section A plus those congenital anomalies not already included	79,399.3	7.94

[a] Sum is not exact owing to rounding.
[b] International Classification of Disease numbers.
Source: Blencowe et al. 2018.[34] With permission from Elsevier.

prevalence of 81.4 per 10,000 for congenital heart disease among 398,140 livebirths,[44] similar to a Belgian study of 111,225 live and stillborn infants ≥26 weeks of gestation with an incidence of 0.83 percent, chromosome abnormalities excluded.[45] A EUROCAT registry study found an increasing prevalence of severe congenital heart defects (single ventricle, atrioventricular septal defects, and tetralogy of Fallot) possibly due to increasing obesity and diabetes.[46] In a study of 8,760 patients with autism spectrum disorders and 26,280 controls, a statistically significant increase in the odds of concurrent congenital heart disease (odds ratio [OR] 1.32) was noted.[47] Atrial septal defects and ventricular septal defects were most common.

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[48] 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 newer genetic technologies, including chromosomal microarray, whole-exome sequencing, next-generation sequencing, and whole-genome sequencing, have helped unravel the causes of an increasing number of isolated or syndromic congenital heart defects.[49, 50] Identified genetic causes include monogenic disorders in 3–5 percent of cases, chromosomal abnormalities in 8–10 percent, and copy number variants in 3–25 percent of syndromic and 3–10 percent of isolated congenital heart defects.[49, 51] A next-generation sequencing study indicated that 8 percent and 2 percent of cases were due to *de novo* autosomal dominant and autosomal recessive pathogenic variants, respectively.[52]

Pregestational diabetes in 775 of 31,007 women was statistically significantly associated with sacral agenesis (OR 80.2), holoprosencephaly (OR 13.1), limb reduction defects (OR 10.1), heterotaxy (12.3), and severe congenital heart defects (OR 10.5–14.9).[53]

Maternal obesity is associated with an increased risk of congenital malformations.[54–65] The greater the maternal body mass index (BMI), the higher the risk, especially for congenital heart defects,[59, 60, 62, 65] with significant odds ratios between 2.06 and 3.5. In a population-based case–control study, excluding women with preexisting diabetes, Block et al.[66] 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). A Swedish study focused on 1,243,957 liveborn singletons and noted 3.5 percent with at least one major congenital abnormality.[64] These authors used maternal BMI to estimate risks by weight. The risk of having a child with a congenital malformation rose steadily with increasing BMI from 3.5 percent (overweight) to 4.7 percent (BMI ≥40). Our own[67, 68] and other studies[69] have implicated the prediabetic state or gestational diabetes as contributing to or causing the congenital anomalies in the offspring of obese women. In this context, preconception bariatric surgery seems not to reduce the risks of congenital anomalies.[61, 70–72] It appears that folic acid supplementation attenuates but does not eliminate the risk of spina bifida when associated with diabetes mellitus[73] or obesity[74] (see Chapter 10). In contrast, markedly underweight women reportedly have a 3.2-fold increased risk of having offspring with gastroschisis,[74] in all likelihood due to smoking and other acquired exposures.[75, 76] 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.[77] 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.[78] A Californian population-based study (1995–2012) recorded a prevalence for gastroschisis of 2.7 cases per 10,000 livebirths.[75]

The surveillance system of the National Network of Congenital Anomalies of Argentina reported a 2009–2016 study of 1,663,610 births with 702 born with limb reduction defects.[79] The prevalence was 4.22/10,000 births. In 15,094 stillbirths, the prevalence rose to 30.80/10,000. A Chinese study of 223 newborn deaths in a neonatal intensive care unit noted that 44 (19.7 percent) had a confirmed genetic disorder.[80] The National Perinatal Epidemiology Centre in Ireland in a study of fatal fetal anomalies recorded 2,638 perinatal deaths, 939 (36 percent) having a congenital anomaly, 43 percent of which were chromosomal.[81] More than a single anomaly was noted in 36 percent (333 of 938) of their cases. These numbers led to a significant genetic disease burden and have accounted for 28–40 percent of hospital admissions in North America, Canada, and England.[82–84] Notwithstanding their frequency, the causes of about 60 percent of congenital malformations remain obscure.[85, 86]

The effect of folic acid supplementation, via tablet or food fortification, on the prevalence of neural tube defects (NTDs), is now well known to reduce the frequency of NTDs by up to 70 percent[87, 88] (see Chapter 10). 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.[89]

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.[90] 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 birthweight infants. The mean gestational age overall was 28 weeks and the mean birthweight was 1,007 g.[91] A surveillance study of births, stillbirths, and fetuses for malformations in a single center with 289,365 births over 41 years noted 7,020 (2.4 percent) with one or more congenital abnormalities.[92] 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).[93] 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 California Twin Registry study of 20,803 twin pairs found an overall prevalence of selected anomalies of 38 per 1,000 persons.[94]

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.[95] 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 white (1.44 percent) was higher than in non-Hispanic black individuals (1.28 percent).[96] However, racial/ethnic disparities clearly exist for different types of congenital defects.[97]

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 and neurodevelopment.[98, 99] A French study of 129 infants with congenital hypothyroidism noted that 15.5 percent had associated congenital anomalies.[100] Nine of the infants had congenital heart defects (6.9 percent).

Women with epilepsy on anticonvulsant medications have an increased risk of having offspring with congenital malformations, noted in one study as 2.7-fold greater than those without epilepsy.[101] A Cochrane Epilepsy Group Registry meta-analysis of 31 studies of pregnant women on anticonvulsants concluded with increased, but variable RR of congenital malformations of 2.01–5.69, the latter figure being for valproate.[102]

There have been reports of an increased risk of congenital malformations following the use of assisted reproductive technology (ART) and negated by other studies.[103] A 2018 report using a Centers for Disease Control and Prevention (CDC) database of 11,862,780 livebirths (2011–2013) retrospectively analyzed the 71,050 pregnancies conceived by ART. Infants conceived by ART had an increased risk (77/10,000 vs. 25/10,000), an OR of 2.14.[103] The cause(s) of this increase – whether due to the ART or the patients' genetic predisposition – remains to be determined.

Lupo et al.[104] in a population-based registry study of over 10 million children in the United States assessed the association of cancer and congenital malformations. They reported that compared to children without congenital anomalies:

- children with chromosomal anomalies (n = 539,567) were 11.6 times more likely to be diagnosed with cancer and
- children with nonchromosomal congenital anomalies were 2.5 times more likely to have cancer before 18 years of age.

Congenital malformations and infant morbidity and mortality

The leading cause of infant death in the United States in 2014 was congenital malformations, deformations, and chromosomal abnormalities, accounting for 20.4 percent of 4,748 total infant deaths.[13] Survival is clearly dependent on the severity or lethality of the congenital defect. The CDC 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.[105] An international registry study (2019) from 18 countries revealed prevalence rates of 0.55 and 1.07 per 10,000 births for trisomies 13 and 18, respectively. Death in the first week of life occurred in 45 percent and 42 percent for trisomy 13 and trisomy 18, respectively. Reported mortality rates were 87 percent and 88 percent at 1 year for each of these trisomies.[106] 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.[107] A Scottish study focusing 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), NTDs (72 percent), respiratory system anomalies (74 percent), congenital heart disease (75 percent), nervous system anomalies (77 percent) and Down syndrome (84 percent).[108] The survival rate among males with congenital defects was 84 percent, compared with 97 percent in those born unaffected.[30] Liu et al.[109] 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 Down syndrome, a more detailed discussion follows.

Down syndrome

The availability of prenatal diagnosis and maternal serum screening for chromosomal abnormalities has also affected the birth frequency of Down syndrome. One French study of the impact of prenatal diagnosis over a 21-year period (1979–1999) in a well-defined population showed a drop of 80 percent in the birth prevalence of Down syndrome.[110] A later report from the Paris Registry of Congenital Anomalies (2001–2005) noted a "fairly stable prevalence of Down syndrome (7.1 per 10,000 livebirths) over time."[111] A Scottish study aimed to assess the impact of prenatal diagnosis on the prevalence of Down syndrome from 1980 to 1996. Both births and pregnancy terminations were included. Pregnancy terminations for Down syndrome rose from 29 percent to about 60 percent.[112] In contrast, the prevalence of Down syndrome 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.[113] In the United States, a prevalence rate of 8.27 per 10,000 was reported in 2013 with an estimated 250,700 individuals.[114, 115] In Europe, the 2009–2012 prevalence rate was 10.2 per 100,000 livebirths.[116] In Japan, the estimated prevalence rate approximates 22 per 10,000 births.[117] Many more babies with Down syndrome are born to women under rather than over 35 years of age. There is some evidence that the risk of having Down syndrome offspring in very young mothers is increased,[118–121] but not in twin pregnancies.[122]

The special problems and associated defects in Down syndrome are well known, as is the increasing life expectancy. Studies from Japan,[123] Denmark,[124] England,[125] Australia,[126] and Canada[127] highlight the increased life expectancy with Down syndrome. Baird and Sadovnick[127] reported a large study of 1,610 individuals with Down syndrome 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 Down syndrome (Table 1.2) and for the general population.[128] Their estimates show that 44.4 percent and 13.6 percent of liveborn individuals with Down syndrome will survive to 60 and 68 years, respectively, compared with 86.4 percent and 78.4 percent of the general population. In another report,[129] the authors have analyzed the causes of death in Down syndrome, highlighting congenital defects and cardiovascular and respiratory illnesses as the most important. A UK population

Table 1.2 Life expectancy with Down syndrome, between 1908–1981, to age 68 years.

Age	*Total*	*Survival at start of age interval (percent)*
5	1,020	81.05
10	841	78.40
20	497	75.34
30	91	72.12
40	136	69.78
50	57	60.68
55	31	53.96
60	16	44.44
68	1	13.57

Source: Baird and Sadovnick 1989.[127] With permission from John Wiley and Sons.

prevalence study noted a median life expectancy of 58 years in 2011.[130]

Additional studies of mortality rates in individuals with Down syndrome revealed that those up to about 35 years of age were little different from others with intellectual disability. Thereafter, however, mortality rates in Down syndrome doubled every 6.4 years, compared with 9.6 years for other intellectually disabled individuals.[129] Life tables constructed by these authors indicated a life expectancy of 55 years for a 1-year-old patient with Down syndrome and mild/moderate developmental delay and a life expectancy of 43 years for a 1-year-old patient with Down syndrome more profoundly affected.

A study from the CDC focused on the death certificates of 17,897 individuals with Down syndrome born between 1983 and 1997.[131] These authors reported that the median age at death for those with Down syndrome increased from 25 years in 1983 to 49 years in 1997 (Figure 1.2).

A 2009 Australian study found an overall survival figure for Down syndrome of 90 percent to at least 5 years of age.[132] The known comorbidities of Down syndrome[116, 133–149] and earlier onset Alzheimer disease[133] cast a longer shadow. In individuals with Down syndrome over 40 years of age, increasing neuropsychological dysfunction and loss of adaptive skills have been noted.[149] Between 50 and 70 percent develop Alzheimer disease by 60 years of age,[139] and up to 84 percent of those with dementia develop seizures.[136] People

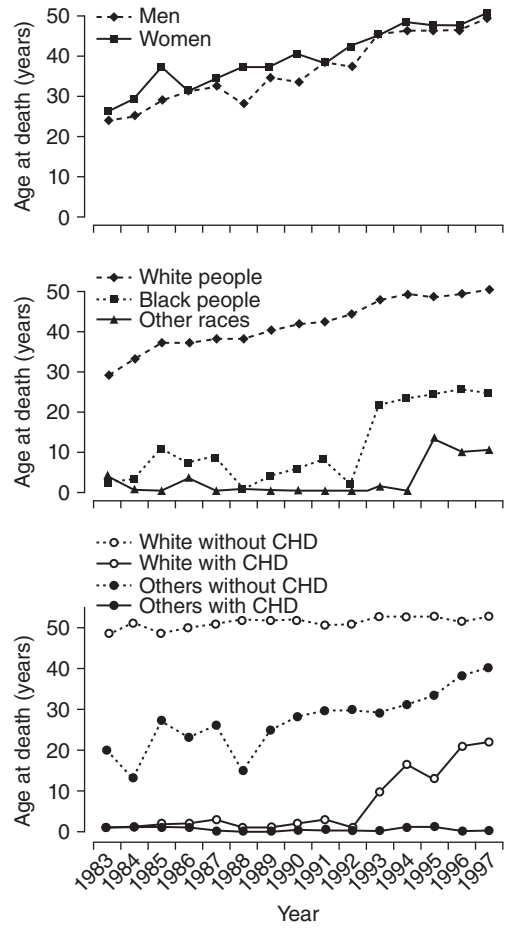

Figure 1.2 Median age at death of people with Down syndrome by sex (*upper*), by racial group (*middle*), and with or without congenital heart defects (CHD) by racial group (*lower*).
Source: Yang et al. 2002.[131] Reproduced with permission of Elsevier.

with Down syndrome who are APOEε4 carriers and/or have multiple comorbid disorders are at an increased risk of both dementia and death.[150] A French study between 1979 and 1999 found a sixfold decreased risk of death from urological cancer in those with Down syndrome.[146] People with Down syndrome have an overall decreased incidence of solid tumors.[151]

Table 1.3 reflects the common associated defects and complications that occur in Down syndrome, some of which can be anticipated, monitored, prevented, and treated.[132–165] A EUROCAT population-based register study between 2000 and 2010 in 12 countries analyzed 7,044 livebirths and

Table 1.3 Defects and complications associated with Down syndrome[132–165].

Defect or complication	*Prevalence (percent)*
Neurologic	
Intellectual disability	100
Hypotonia	100
Alzheimer disease and dementia	68–80
Sleep disorders	65
Autism	7–16
Hearing impairment	
Conductive	84
Sensorineural	2.7
Mixed	7.8
Epilepsy	5–13
Psychiatric disorders	11–30
ADHD	34
Moyamoya disease	3.8
Unexplained regression	Unknown
Heart	
Mitral valve prolapse	57
Congenital heart disease	44
Aortic valve regurgitation	17
Pulmonary hypertension	1.2–5.2
Respiratory	
Airway problems	>16
Immune system	
Susceptibility to infection	100
Juvenile rheumatoid-like arthritis	1.2
Gastrointestinal	
Congenital defects of the gastrointestinal tract	6
Celiac disease	5.4
Dysphagia	55
Endocrine/metabolic	
Overweight/obesity	23–70
Hypothyroidism	50
Diabetes mellitus	1.4–10.6
Hyperthyroidism	1–3
Ophthalmologic	
Eye disorders [a]	80
Cataract	17–29
Keratoconus	8–10
Hematologic/oncologic	
Leukemia	2–3 (>20-fold excess)
Testicular cancer	Standardized incidence ratio of 2.9
Transient myeloproliferative disorder	<10 (20–30% risk of AML)
Retroperitoneal teratoma	Increased
Anemia	2.6–10.5
Musculoskeletal	
Atlantoaxial instability	10–30
Osteoarthritis/low bone density	8–28
Atlantoaxial subluxation	1–2
Dental	
Tooth agenesis	54

Table 1.3 (Continued)

Defect or complication	*Prevalence (percent)*
Orthodontic problems	±all
Periodontal disease	±all
Dermatologic	
Hidradenitis suppurativa	2
Dermatologic disorders	1.9–39.2
Urinary tract	
Urinary tract anomalies	3.2

[a]Includes strabismus, nystagmus, refractive errors, glaucoma, and lens opacities.

fetal deaths with Down syndrome. That report[152] noted that 43.6 percent of *births* with Down syndrome 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 Down syndrome.[166]

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 high.[167] The goal is to reduce the risk of an adverse outcome to pregnancy and to secure the health of mother and fetus. Both the American Society for Reproductive Medicine and the American College of Obstetricians and Gynecologists recommend preconception counseling several times during a woman's reproductive lifespan.[168] 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 testing (see Chapter 2) does, however, provide an important 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 recognized carriers, a positive result on a noninvasive prenatal test [see Chapters 6–8] or advanced maternal age), the well-informed obstetrician should be able to provide the necessary information.[169, 170] 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.[171] Neither a questionnaire in the physician's office nor limited consultation time is likely to reveal many of these disorders. It is now vital that patients understand the importance of determining the *name* of a genetic disorder in the near or extended family. Since at least 6,739 monogenic phenotypes now have known genes,[2] prenatal diagnosis or preimplantation genetic testing is available for avoidance or prevention.

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[172] 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 explosive growth of information and data available in numerous gene databases stemming from gene discovery presents an overwhelming challenge for physicians and genetic counselors. Meeting the demand for excellence is best accomplished in tandem with a geneticist and team where possible. One important example concerns sudden unexpected death before 45 years of age.[173–175] A wide range of arrhythmia syndromes and cardiomyopathies with many known genes allow "molecular autopsies."[176] Where DNA was not obtained from inevitable autopsies, recovery of analyzable material can be achieved from retained tissue blocks. Pathologists increasingly recognize the importance of retaining tissue (e.g. liver) for freezing without preservative.

Another challenge is the growing list of syndromes or conditions due to discovery of an expanding long list of culprit neurodevelopmental genes and their pathogenic variants,[177, 178] a significant number being due to *de novo* variants.[179] The KBG syndrome serves as a typical example, with characteristic dysmorphic features, macrodontia of upper central incisors, skeletal abnormalities, short stature, and intellectual disability, confirmed by pathogenic variants in the *ANKRDII* gene.[180]

Recognition that highly variable phenotypes exemplified by the 22q11 deletion syndrome and confounded by changes with increasing age can make the family history difficult to interpret.[181–183]

Certain phenotypes may emerge as a consequence of environmental exposure or gene mutation, interpretation being further compounded by the presence or absence of ischemic encephalopathy at birth.[184, 185] Microcephaly serves as an ideal example with multiple known single genes and viruses (such as Zika) (see Chapter 34).[186–188] Online Mendelian Inheritance in Man (OMIM) has over 900 phenotype entries and almost 800 genes linked for microcephaly with variable expressivity.[188]

A not infrequent challenge is to determine whether a brain injury (hypoxia) or a genetic disorder was the cause of intellectual disability, presenting as cerebral palsy.[184, 185] Typical cerebral

palsy mimics include hereditary spastic paraplegia, dystonic disorders, and choreic movement disorders.[189] Multiple genes are known for the cerebral palsy mimics.[189–191]

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.[192] That study focused on a review of 12,093 "genetic events" involving potentially avoidable cases of Down syndrome, NTDs, cystic fibrosis, β-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.[193] Other physicians, too, have been found lacking in the necessary knowledge and communication skills.[184, 194–198] Given the importance of genetic considerations in all specialties, these problems can be anticipated to become increasingly problematic, more especially in family practice.[198, 199]

After the prenatal diagnosis of a serious genetic disorder, the geneticist/genetic counselor 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 Down syndrome 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 availability, options, and risks of elective abortion (see Chapter 32), as well as the possibility of adoption.

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 and 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 prenatal diagnosis and to explain the techniques and requirements for obtaining amniotic fluid or chorionic villi, 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.[200]

Gordis et al.[201] 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.[202] 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.[184, 203–205]

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,[206] as have others.[207, 208]

Simple language, an adequate allocation of time, care, and sensitivity are keys to successful genetic counseling. Technical jargon, used with

distressing frequency,[209] is avoided only through conscious effort. How an issue requiring a decision is framed[210] and the nature of the language used[211] may influence the patient's choice.[212] 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 bedevil a superb counselor). The use of numeric probabililties, relative risk, risk reduction or simple numbers of chance (1 in 100) or words (almost never, negligible, sometimes, more often than not)[213] are choices a counselor must make. Clearly, the simpler the better and the more likely the information will be 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,[214] epididymal sperm aspiration,[215] and preimplantation genetic testing) (see Chapter 2).

Empathy

Empathy embodies the ability to not only understand the perspectives and emotions of others but to communicate that understanding.[216, 217] 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[218] 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 counselees.

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.[219]

Beyond the qualifications and factual knowledge of the counselor is the person who is key to successful and effective counseling. A compassionate 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 nonverbal characteristics. Staring at a computer screen while counseling conveys deep insensitivity and engenders no trust.

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 *in vitro* fertilization (IVF) efforts and subsequently a successful pregnancy with a fetal defect).
- Acknowledge 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[172] that may erode these fundamental prerequisites. Well-intentioned statements are frequently perceived in a very different way.[206]

It is self-evident that empathy would engender greater patient satisfaction and may well be correlated with clinical competence.[220]

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.[221] Explanations that we all carry harmful genes often helps. Mostly, however, encouragement to move anguish into action is important. This might also help in assuaging any blame by the partner in such cases.[222]

Guilt is not only the preserve of the obligate carrier. Affected parents inevitably also experience guilt on transmitting their defective genes.[223, 224] 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.[224] 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[225–231] confirm not only survivor guilt with a new reality (a future) but also problems in relationships with close family members. Huggins et al.[228] 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[232–234] and surveyed international guidelines.[235]

Accurate diagnosis

Clinical geneticists, obstetricians, or pediatricians are frequently the specialists most confronted by patients seeking guidance because of genetic diseases in their families. Given the huge advances made in the recognition of thousands of culprit genes for genetic disorders seen in virtually all specialties, all physicians need to be aware of precise molecular diagnosis tests for monogenic disorders, and the opportunities for avoidance of recurrence. 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 options. Now whole-exome or genome sequencing and the

demonstrated potential diagnostic yield of 25–52 percent for previously undiagnosed patients with severe intellectual disability[236–240] 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 23). 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),[241] and many are still to be molecularly identified. Similarly, a history of epilepsy gives no clear indication of which genes are involved.[242] Birth of a previous child with craniosynostosis requires precise determination of the cause (~20 percent recognized as genetic)[243] before risk counseling is provided. Mutations in at least 13 genes are clearly associated with monogenic syndromic forms of craniosynostosis.[244–246] Moreover, a chromosomal abnormality may be the cause.

Awareness of genetic heterogeneity and of intra- and inter-family phenotypic variation of a specific disorder (e.g. tuberous sclerosis)[247] 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 caused by mutations in the *ADPKD1* gene has an early-infancy presentation in 2–5 percent of cases.[248] Moreover, mutations in the *ADPKD2* gene may result in polycystic kidney disease and perinatal death[249] and, further, should not be confused with the autosomal recessive type caused by mutations in the *ARPKD* gene. Awareness of contiguous gene syndromes, such as tuberous sclerosis and polycystic kidney disease (*TSC2-PKD1*) is 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.[250] 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.[251]

Myotonic muscular dystrophy type 1 (DM), the most common adult muscular dystrophy, with an incidence of about 1 in 8,000,[252] 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 in the *DMPK* gene 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 and earlier onset to the number of triplet repeats was not long in coming[252] (see Chapter 14). 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 when originating through maternal transmission. However, at least one exception has been noted.[253] 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.[254] Rare cases also exist in which complete reversal of the mutation occurs with spontaneous correction to a normal range of triplet repeats.[255–262]

Nondirective counseling

Physicians are accustomed to issuing therapeutic directives and, indeed, patients invariably depend on such instructions to improve their health status. Such directive approaches are not consistent with the overwhelming consensus of opinion that governs genetic counseling. Nondirective

genetic counseling has been endorsed by medical geneticists,[263] as well as by the World Health Organization Expert Committee on Genetic Counseling,[264] and in a multinational study focused on the attitudes of genetic counselors.[265, 266] In an analysis of nondirective genetic counseling, Kessler[267] proffered this definition: "Nondirectiveness describes procedures aimed at promoting the autonomy and self-directedness of the client." The role of the physician and genetic counselor is to provide the most complete information available, remaining impartial and objective in this communication process while recognizing a tenet of medicine as being to prevent disease. This might not be an easy task. Indeed there are some who believe that nondirective counseling is neither possible nor desirable.[268, 269] Not unexpectedly, significant differences in counseling techniques mirror the divergent views of counselors on the goals, content, and process of genetic counseling. Kessler[267] believes that the difficulties counselors have with answering direct questions and being nondirective reveal a lack of skill and an incompetence, which he lays at the door of inadequate training. In calling for correction of the major inadequacies in counseling, training, and skill, he emphasized that nondirectiveness is an "active strategy" aimed at "evoking the client's competence and ability for self-direction." The expansion of genetic counseling training and degree programs has ameliorated many of these issues.

Michie et al.[270] studied nondirectiveness in genetic counseling. They defined directiveness as advice and expressed views about or selective reinforcement of counselees' behavior, thoughts, or emotions. As expected, they concluded that genetic counseling as currently practiced was not characterized, either by counselors, counselees, or a standardized rating scale they used, as uniformly nondirective.

Clarke[271] remarkably argued that nondirective genetic counseling in the context of prenatal diagnosis is "inevitably a sham," largely because of the "structure of the encounter between counselor and client." He further contended "that an offer of prenatal diagnosis implies a recommendation to accept that offer, which in turn entails a tacit recommendation to terminate a pregnancy" if the fetus is abnormal. In 1970[272] it was emphasized that the offer of prenatal diagnosis was not associated with any explicit or implicit commitment to abort. Clarke[271] further opined that "nondirective counseling was unattainable, despite the counselor's motives, since the offer and acceptance of genetic counseling has already set up a likely chain of events in everyone's mind." Experienced clinical geneticists were taken aback by his views,[273–275] and rightly so. He regarded reproductive choice as part of the "1980s consumerism model of clinical genetics."[276] The personal values of geneticists/counselors may influence behavior in clinical practice and individual vigilance is necessary to abide by the nondirective principle. This may be less challenging than imagined given the reported highly valued benevolence, self-direction, and pattern of concern for the welfare of others.[276] Clarke ignored a fundamental tenet of genetic counseling founded in a free society, where choice is not a fad but a right. His ideas suggest contempt for the views (and hence choices) of the public, maintaining that respect for the handicapped is not achievable in a society that "makes judgments about what types of people are worthy of life."[276] Others have reported that people's decision-making processes are more rational than they might appear to be.[277] Simms[278] noted that, with hindsight, 80 percent of parents with handicapped children would have aborted their pregnancies. Later, in taking Clarke to task, she concluded that it was "his professional duty to advise parents to the best of his ability, not to make decisions for them. They will have to live with the consequences: he will not."[279]

The intrinsic danger of using a directive approach is the opportunity (even subconscious or inadvertent) for the physician/counselor to insinuate his or her own religious, racial, eugenic, or other beliefs or dictates of conscience into the counseling that is offered.[280] A breach of this principle, supported by some,[281] invites the provider to visit upon the patient unwarranted conscious or subliminal prejudices. Some obstetricians, for example, are known to have specifically not offered or referred patients for prenatal genetic studies because of their antiabortion views and have unconscionably exaggerated the specific risks of amniocentesis in order to discourage prenatal genetic studies. A Mexican study showed that physicians in specialties other than clinical genetics tend to counsel directively.[282]

The duty of the physician and genetic counselor is to communicate all the available information and then to assist a counselee to recognize his or her major priorities, beliefs, fears, and other concerns in order to make possible the counselee's rational decision making. To remain impartial is difficult and takes valuable time and conscious effort, but it is largely attainable. Time-pressed nongeneticists providing genetic counseling may easily experience slippage between choice and coercion.[283, 284] The difficulty lies mainly in trying to remain impartial while aiming to prevent the occurrence of genetic disease. Personality characteristics of the counselor may well influence the counseling provided.[285] The optimistic counselor may unwittingly color the texture of counseling provided in contrast to the depressed counselor. Hsia[286] validly observed that optimistic counselors may tell anxious individuals not to worry, whereas pessimistic ones might unwittingly exaggerate the significance of even small risks. The insinuation of the physician's prejudices into the decision-making process of the counselee constitutes a moral affront to individual privacy and reproductive autonomy.[287]

In rare instances, family circumstances may challenge the need to adhere to personal autonomy and nondirective counseling. The right of one monozygous twin at 50 percent risk for Huntington disease not to know information after predictive testing should be respected. If there is possible harm to the co-twin, Chapman suggested that testing should "be denied in the absence of mutual consent."[288] She further argued that in the interest of beneficence, directive counseling is acceptable for individuals at 50 percent risk of Huntington disease who suffer from depression, lack social support, and have a history of attempted suicide. For these patients, psychiatric evaluation and counseling, rather than predictive testing, have been recommended. In a 15-year experience offering predictive counseling for Huntington disease, the Canadian authors emphasized the importance of preparation for receiving test results.[289] In a study of counseling following prenatal diagnosis of Klinefelter syndrome, Marteau et al.[290] found that pregnancy was almost two-and-a-half times more likely to continue when counseling was provided by a geneticist.

Ever-increasing genetic testing using microarrays and whole-exome sequencing introduced the counseling challenge following determination of secondary findings. This issue of possible genomic uncertainty should be addressed prior to any sample being obtained. The American College of Medical Genetics and Genomics (ACMG) have a list of 59 actionable disorders which geneticists are directed to communicate because of potential health and life-saving opportunities (see Chapter 14). Patients may opt out of this potential directive counseling, and clearly have the right not to know.[291] More difficult, however, are discoveries of variants of uncertain or unknown significance (VOUS) (see Chapter 14). Recognition, for example, in a newborn with epileptic encephalopathy, macrosomia, hypotonia, hypoglycemia, and dysmorphic facies of unknown compound heterozygous, instead of known homozygous mutations[292] in the *HERC1* gene, would pose a serious challenge to remain nondirective regarding future recurrence risks and options. Further complicating nondirectiveness is the realization that pathogenic variants may occur in disease-free individuals.[293]

Fortunately, it is very uncommon to have two parents with totally opposing views regarding the option of an abortion of an affected fetus. A counseling experience with a couple, both of whom were FBI agents, brought this issue into stark relief. The emotional exchange and the vested positions of the parties invited the "nondirective directive" to return home for their decision making while ensuring that they were in the possession of all necessary facts upon which rationality could trump.

Incidental detection by ultrasound, for example, of a hypoplastic thymus,[294] following a maternal-age indicated amniocentesis of a 22q11.2 deletion provides another quandary when one parent with a few signs is found to harbor the same microdeletion. Certainty about the future phenotype would be unwise,[295] with the discussion about pregnancy termination requiring definitive nondirectiveness.

Concern for the individual

The ethical principles of beneficence, respect for autonomy, non-maleficence, and justice (see Chapter 37) underscore the approach to all patients. They are the focus of our concern, not the interests of the state. Although germs and genes occupy the province of the public health authorities, genetic

privacy is paramount. This attitude permeates the genetic counseling encounter where many challenging issues will be raised, including the frequent controversial issue of abortion.

Communication should not depend on questions posed by the patient, who may not be cognizant of the subject's dimensions or the available options. For example, in the case of a couple who are at risk of having a profoundly intellectually deficient child, the physician should explore the consequences for the interrelationships of the couple, the effects on their other children, the suffering of the affected child, the possible social stigma,[219] and the economic and other societal implications, as well as the need for contraception. Some may feel that the economic burden of a defective offspring on society should at least be mentioned as part of a comprehensive view of all issues being considered. However, our concern is for the individual, whose priorities, needs, and choices remain paramount. In the physician/counselor–patient relationship, concern for the individual should always override consideration of the needs of society. Many avenues exist for society to influence the actions of its citizens. In genetic counseling, the role of the physician/counselor is not that of an advocate for society.

A couple may elect to have an amniocentesis that is indeed indicated without making a commitment to pregnancy termination if the fetus is found to be abnormal. Some may deny such couples the opportunity for prenatal genetic studies. All couples have a right to have information about their fetus and prenatal diagnosis is a fundamentally reassuring technique. More than 95 percent of such couples do not need to consider elective abortion. The few who are initially ambivalent almost invariably move to terminate the pregnancy after the detection of a serious fetal defect. Nevertheless, abortion may be declined after the prenatal diagnosis of lethal or severe disorders such as anencephaly or trisomy 13. O'Connell et al. have described the profoundly emotional journey and the adaptive grieving process of four mothers who, after prenatal diagnoses of anencephaly, continued their pregnancies to delivery.[296] Concern for the individual includes providing ambivalent couples with the opportunity for reassurance or the choice to decline abortion with preparation for the consequences. Moreover, opportunities to save their offspring's life, or at least to improve the outcome, now exist in specific circumstances (see Chapters 29 and 30). The availability of adoption should always be discussed.

Quite often, a patient declines an otherwise clearly indicated amniocentesis. Today, the standard of care dictates the need for an explanatory note in the patient's record. A brief letter to the patient noting the indication for prenatal study and that such study was declined is also helpful. Litigation has ensued in which patients have maintained that no amniocentesis had been offered, while obstetricians (without notes in the records) have taken an opposite view.

The counseling session provides an opportunity to also contribute to the overall psychological health of the patient. Counselors should therefore spend significant time helping patients to apply the information to their lives and should not be wholly focused on communicating genetic information.[297]

Truth in counseling

Since the time of Hippocrates, physicians have often withheld the truth from their patients and, as Katz[298] emphasized in *The Silent World of Doctor and Patient*, defended the morality of this position. Sparing the patient emotional distress, removing hope, and/or diminishing the physician's personal esteem may have been some of the quintessential reasons for the lack of truth telling. While recognizing the modern change in moral sentiment, Lantos[299] acknowledged that truth telling has become "morally obligatory." Notwithstanding his preference that he "would not want a doctor judging the morality of my decision," he remained uncertain about the value of the "comforting lie."

Situations have arisen in genetic counseling where facts have been distorted, de-emphasized, or even hidden. Obstetricians opposed to abortion of an abnormal fetus have been known to provide incorrect or misleading information. That position is simply amoral, and flies in the face of the ethical principles of autonomy and beneficence. A physician or genetic counselor visiting their religious beliefs on a patient is totally unacceptable. In one medico-legal case, the mother had a 25 percent risk of having a second child with severe intellectual disability and microcephaly. The obstetrician purposefully delayed the required ultrasound study to 28 weeks of gestation, after which pregnancy termination was impermissible. The state court, in

addition to finding that physician negligent, levied a hefty punitive fine as well.

The enormous increase in DNA testing, including prenatal studies, has led to a corresponding increase in questions of nonpaternity. Prevalence estimates of nonpaternity vary widely,[300–302] with a meta-analysis noting a median of 4 percent in 17 studies.[301] Discovery of a potential chromosomal abnormality (e.g. an inversion), a microdeletion or a microduplication, or concerning DNA variant, may unexpectedly reveal nonpaternity. This observation may rest on a Y-chromosome karyotypic difference, haplotypes,[303] or a Y-deletion not found in the fetal DNA. A microarray may yield consanguinity (from runs of homozygosity) when the male partner is clearly not related (see Chapter 13). A biallelic DNA variant in the fetus may not be reflected in the putative allele of the "father of the fetus." Once the nonpaternity has been discovered the question arises about informing the male partner, and telling the truth.

Much has been written about this dilemma.[300, 304–308] Of course this potential family crisis could possibly be avoided when obtaining informed consent, at which time it should be made clear that paternity will be confirmed routinely if prenatal testing for other reasons is performed. Pregnant women given that information may decide to forego any testing.

The challenge providers face is the morality of nondisclosure, the potential for not only serious harm to the family unit but also, in some cultures, abandonment or potential serious injury or death to the mother.[304] Some have argued that clinical significance should determine whether disclosure should occur.[300] Where an inheritance pattern and explanation is necessary, for example, communication will be needed. In those circumstances the provider would be advised to first meet with the mother. However, clinical significance may not be immediately apparent. Avci recounts the poignant case of a 55-year-old father in kidney failure planning to receive a kidney transplant from his 35-year-old son.[304] The HLA matching pointed to nonpaternity. The physician in that case met with the parents and son, confabulating that tests on the son indicated that being a donor was highly risky for him! The position taken by this physician would be justifiable according to well regarded ethicists,[309] and in accord with the principle of beneficence. Other ethicists disagree, and maintain that veracity is an ethical principle[310, 311] and rather than a moral rule, it is a prima facie obligation.[304, 309] Like confidentiality, truth too is not absolute.

The paternalistic approach overrides all personal choices with the aim of protecting or benefitting the patient. Since this would occur without the patient's full knowledge or consent, it would be ethically unacceptable and in conflict with the principle of autonomy.[310] The Kantian philosophy holds that lying is always wrong, regardless of circumstances.[311]

In today's world, the question of nonpaternity disclosure automatically invites legal purview.[305, 306] Withholding information from the "father" directly violates the physician–patient "contract," and establishes a cause of action for malpractice. On the other hand, a woman attending genetic counseling alone (not infrequent) could maintain her rights to privacy,[312] the breach of which would inevitably end up in court. Much of enacted legislation in many states in the United States is focused on disclosures to third parties and not on the issue of concealing genetic information from a contracted party.[305]

Clearly, the discovery or realization of nonpaternity at the time of prenatal diagnosis is fraught with potentially serious personal, medical, social, and legal problems. The counseling provider has to be extremely adept in managing these cases. Warning about the potential discovery of nonpaternity as part of informed consent prior to testing[313, 314] may lead a pregnant woman to decline an indicated chorionic villus sample (CVS) or amniocentesis. Nondisclosure is ill advised when nonpaternity is discovered. In the effort to do no harm, we have requested a counseling session with the prospective mother alone. Her decision, taken in confidence, would govern further action. If, however, testing of the misattributed partner has genetic implications, nondisclosure becomes legally untenable.

Confidentiality and trust

Genetic counseling and testing always reveals much more about the patient's health status and often reveals risk information applicable to other family members. Ethical codes of practice enunciated by the American Medical Association (AMA) Code of Medical Ethics,[315] the American Society of

Human Genetics,[316] the National Society of Genetics Counselors,[317] and the President's Commission for the study of Ethical Problems in Medicine[318] have uniformly declared that it is impermissible to disclose confidential information without consent. While patient confidentiality was always thought of as inviolate, all[315–318] recognize exceptional circumstances. However, the promulgation of the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule (2003)[319] permits disclosures of health information if the individual to be warned is the subject of a threat of physical harm. This position harkens back to the infamous *Tarasoff* case in which an individual disclosed to his psychotherapist his intention to murder a former girlfriend who had spurned his affections.[320]

Much of the disclosure quandaries arise as a consequence of advances in the analysis of DNA. Relatives of a proband who is determined to be a carrier of a serious monogenic disorder or is actually affected, once informed, may be able to take life-saving measures (e.g. long QT syndrome, colon cancer). For colorectal cancer there is evidence that over 50 percent of families at risk do not receive the necessary information.[321, 322] Those in their reproductive years could choose options that include prenatal genetic diagnosis or preimplantation genetic testing. There are also relatives who exercise their right not to know, especially for degenerative neurological disorders for which no cure or effective therapy exists. Disclosure to third parties, other than relatives, also includes employers, insurance companies, and schools. It is hoped that the confidentiality of the physician–patient relationship and the patients' right to privacy and personal autonomy remain sacrosanct. The AMA has affirmed the importance of keeping genetic information confidential.[315]

Geneticists and genetic counselors may argue that they have no patient relationship with relatives in question. There is, however, a moral imperative to care. Practical issues inevitably supervene. If the patient is unwilling to transmit the information, the provider is stymied and cannot be expected to launch a search for the relative(s). Given the wide dispersal of families, frequently noted limited intrafamilial communication,[323] caregivers are left with the requirement to indicate in writing the need and importance for the patient to transmit the vital information.

Next-generation sequencing discovery of secondary findings applicable to the patient may also be of potential importance to close relatives (e.g. a mutation in *BRCA1* or *BRCA2*). In noncohesive noncommunicating families (sadly common), all good intentions may then come to naught. Some have argued that providers *may* owe a duty of care to relatives,[324] even though an international consensus holds that individuals have a moral obligation to communicate genetic information to their family members.[325] In France, a law requires direct disclosure to relatives about genetic risks of any serious disease that can affect their health.[326]

However, faced with an intractable patient, some guidance about disclosure is reflected in a statement issued by the American Society of Human Genetics in 1998.[316] When serious and foreseeable harm to at-risk relatives can be anticipated, when the disorder is preventable or treatable, or when reduction of risk through monitoring is achievable, disclosure is seen to be permissible. "The harm that may result from failure to disclose should outweigh the harm that may result from disclosure." In practice, few geneticists appear to have warned at-risk relatives without patient consent. The vast majority of medical geneticists who decided not to warn such relatives were concerned by patient confidentiality issues and legal liability.[327]

Timing of genetic counseling

Today, more than ever before, genetic counseling before conception or marriage[328] may provide opportunities for carrier detection, prenatal diagnosis, preimplantation genetic testing, or the presentation of other important options noted earlier. This is the time to review the family history, although it is startling that so many couples know so little about their relatives. Therefore, the optimal time to initiate counseling is not during pregnancy. Counselees whose first antenatal visits occur after the second missed menstrual period miss the critical period of organogenesis and patients referred well after conception have lost almost all their options except for selective abortion. Given the 70 percent protection afforded by periconceptional folic acid supplementation against the occurrence of an NTD[329, 330] (see Chapter 10), there is a need to advise women about the importance of preconception care.

Confronted by a fatally malformed newborn, the physician may attempt to counsel a couple on the very day of the birth of such a child or before the mother's discharge from the hospital. Although communication and support are both vital during those fateful days, the physician needs to recognize the great difficulty that anguished patients would have in assimilating or comprehending even the essence of any counseling.[279, 331, 332] The physician/counselor should share with the couple his or her awareness that it is difficult to remember all the important information in the face of emotional upset and that it would be normal and expected for them to raise all the same questions some weeks later, when the entire subject could be fully covered. Support for the parents should continue to be available for many months.

Parental counseling

Physicians/counselors have a duty to convey information about the known options, risks, benefits, and foreseeable consequences[203–205] to couples with increased risks of having children with genetic disorders. Such a duty may be difficult, if not impossible, to fulfill if only one member of the couple attends genetic counseling. The issues are usually complex and are frequently compounded by feelings of guilt and by ignorance, family prejudices, religious obstacles, fear, and serious differences of opinion between partners. Hence, when possible (at the time the appointment is made would seem to be best), the necessity that the couple attend together should be emphasized. Physicians/counselors have often seen an extremely anxious parent attend counseling alone and then have learned later of the counselee's incorrect interpretation to the partner, lack of appreciation of the true risk figures, and unnecessary emotional chaos. Not even letters written to couples after the counseling session[333] (a recommended procedure, to summarize the essence of the counseling provided) can safely substitute for face-to-face discussions with both, allowing for questions and interchange about the issues and an opportunity to examine the partner.

Genetic counselors should be cognizant of the complex interactive factors involved in parental reproductive decision making. Frets[334] confirmed the importance of the burden of the disease in question and found that the interpretation of risk (high or low) and the wish to have children were paramount factors. The absence of personal experience of the disease was also found to be a significant influence. Frets identified a number of factors that were independently and significantly associated with problems experienced by 43 percent of counseled couples. These included no postcounseling support, recognition of high risk, disapproval by relatives, having an affected child, and decisions not to have a (or another) child. Due diligence is necessary for the partners of genetic disease carriers, who clearly experience significant psychologic distress.[335]

Counselee education

Hsia et al.[332] emphasized that genetic counseling is an educational process in which the counselee acquires a set of facts and options. Fraser's[263] essential message was that genetic counseling does not involve telling families what they *should* do but rather what they *can* do. We maintain that members of the health professions should adopt as a guiding principle the critical imperative that the concept of genetic counseling be introduced in high school and in continuing public education[335–339] about genetic disease. Children sensitized in school about the importance of the family history, elements of heredity, concepts of individual susceptibility and risk, and opportunities for anticipatory prevention of unnecessary catastrophes are likely to better comprehend pregnancy risks and options.

Genetic counseling and prenatal diagnostic services are of little avail if many women attend for their first antenatal visit after 16 weeks of gestation. Currently, this is the case in many urban hospitals in the Western world, where between 20 and 40 percent of obstetric patients arrive at this late stage. Education beginning in high school and continued by public health authorities could effectively communicate the critical importance of preconception and prenatal care.

Duty to recontact

The enormous expansion of genetic testing, including expanded carrier testing, chromosomal microarrays, whole-exome sequencing, and whole-genome analysis, has further emphasized the continuing responsibility of communicating results. That obligation extends well after a clinical visit, given that the information may

inform a patient's risks or affect reproductive decisions.[336, 337]

Mersch et al.[340] reported that among 1.45 million people who received genetic testing for hereditary cancer risks between 2006 and 2016, further communications were necessary since 6.4 percent had unique variants reclassified. Some 7.7 percent of VOUS were reclassified and 8.7 percent were upgraded. As an aside, following genetic research and new meaningful results, an ethical duty to inform the patient has become apparent.[341]

In a study by Carrieri et al. most patients viewed recontact as desirable.[342] However, a range of barriers to implementation have been raised, including a lack of resources, potential negative psychological consequences, unclear operational definitions of contacting, policies that prevent healthcare professionals from recontacting, difficulties locating patients, intrusion into privacy, and a violation of a patient's interests and right not to know.[343–346]

To obviate any concern that failure to recontact could be construed as negligence,[346] patients need to be told as part of the informed consent for testing of their responsibility to be in contact, either annually or when childbearing is planned or in progress or if a relevant change has occurred in their family history. This is especially the case when sequencing or a chromosomal microarray reveals a VOUS. We have for decades appended a statement in our post-genetic counseling letter to the referring physician and the patient alike about the need to remain in contact. There is indeed a duty to recontact, but that duty is reciprocal, despite the objections of some.[347]

Medical genetics consultations frequently involve only one encounter and the requirement to contact that patient years later may be regarded as both irrational and unreasonable. Pelias pointed to a 1971 lawsuit[348] in which the University of Chicago failed to notify women who had been given diethylstilbestrol. The university had apparently become aware of the dangers of this drug but had delayed notification for 4–5 years. In yet another case, after a single visit to her gynecologist for insertion of an intrauterine device (a Dalkon shield), a woman sued this physician for failing to notify her of the subsequently recognized risks of this device.[349] In that case, as Pelias noted, the court allowed the case to proceed because of the continuing status of the physician–patient relationship and because the physician had a "separate duty to act."[350] Clearly, recommendations for recontact should be recorded in clinical notes and echoed in letters to referring physicians and patients alike. Initial ACMG guidelines regarding recontacting[351] were revised in 2008[352] and framed as "points to consider" in 2018.[353] These were the points:

1. Recontact is fundamentally a shared responsibility among the ordering healthcare provider, the clinical testing laboratory, and the patient.
2. As part of the informed consent process, the patient or family should be advised that:
   a) Changes in interpretation of clinical genomic test results are possible and recontact may be important for patient care.
   b) If the patient's medical history or family history changes, the patient should make the healthcare provider aware.
   c) Important times for the patient to request an update are at life cycle junctures such as preconception planning, pregnancy, and changes in family history information, including sudden unexpected death or the diagnosis of a major health issue in the person originally tested or a close relative.
   d) When seeking an updated variant interpretation, the patient or family should contact the provider who ordered the test, the clinical geneticist who interpreted the test result with the patient, and/or the clinical testing laboratory for an update on a result with an uncertain interpretation. Alternatively, the patient can request their primary care or specialty provider to contact a genetics provider.
   e) The patient or family has a right to decline recontact.
   f) The patient or family should register with the healthcare facility patient portal if available.
   g) It is the patient's obligation to provide updated contact information over time.
3. The ordering provider should emphasize, through discussion and in written explanation to the patient, that the ordering provider cannot promise that recontact regarding a revised interpretation will occur unless the patient initiates the recontact.
4. The discussion regarding recontact should be documented in the medical record. The patient or family ideally will be given a copy of the recontact policy.

5. The ordering provider should inform the patient of the specific tests performed and which laboratory performed the analysis, typically by providing a copy of the test report. The patient should be encouraged to keep the report with their important health information. The test report should be entered into the electronic health record (EHR) and should be provided to the referring physician.
6. The responsibility to inform the ordering physician of variant reclassification or discovery of a new gene–disease relationship rests with the clinical laboratory.
7. Medical geneticists need to inform referring providers that, even if the patient is referred to a medical geneticist for counseling regarding test results, the ordering physician will remain the primary contact for the laboratory.
8. If contacted by the laboratory with an updated result, the ordering physician should make reasonable efforts to recontact the patient.

Do no harm

The classic exhortation *primum non nocere* (first, do no harm) is as pertinent to clinical genetics as it is to medicine in all specialties. Attention to this principle arises particularly in the context of predictive genetic diagnosis, possible for a rapidly escalating number of neurodegenerative disorders (e.g. Huntington disease, frontotemporal dementia, Machado–Joseph disease), cardiovascular and other serious disorders including multiple endocrine neoplasia type 2B, and breast, colon, and other malignancies. Published recommendations and guidelines[354] urge rigorous pretest and post-test genetic counseling. Many factors impact the attempt at risk communication and prediction. Patients who attend for genetic counseling invariably have their own, possibly tentative idea, about their personal risks. Their perception of risks will vary according to their family history, educational level, socioeconomic status, psychological state of mind, life experience, gender, health status, language ability, culture, IQ, and comprehension of mathematics.[355–359] Those who initially thought their personal risks or risks of having an affected child were 50 percent and are informed that the risk only approximates 10 percent may be relieved and not even opt for any testing. Others may be startled to hear that all couples face a 3–4 percent risk on average for bearing a child with a birth defect, intellectual disability, or genetic disorder.

The inherent harm that could potentially be done by predictive testing is the potential for demoralization and depression with possible suicidal consequences (see later discussion). Extreme caution is recommended in considering predictive testing for a disorder without curative, let alone meaningful, palliative treatment. Although for certain dominant disorders some 50 percent of individuals at risk may receive good news, the other 50 percent face, effectively, a death sentence. A single consultation is inadvisable for a couple (or individual) considering predictive testing. During the counseling session with full information transfer, an assessment of emotional health should be made. For many, a consultation with a psychologist or psychiatrist would be wise before a follow-up visit to determine the decision to test or not, and to obtain informed consent.

Many at risk of developing Huntington disease choose not to be tested. In a study of 733 individuals who did not wish to learn if they harbored this fatal flaw, 66 percent pointed to lack of a cure or treatment, and 66 percent to the inability to undo information provided.[360] Only 12–17 percent of those at risk in North America and Europe pursue testing.[360–364] Family and extended family repercussions may occur as a consequence of a choice not to be tested in the face of a 50 percent risk.[365–367] Some family members may hold the untested who proceed to have children morally irresponsible.

There is of course the right of every person not to know their genetic status as potential carrier of a serious genetic disorder. It is not the duty of a counselor to state or hint that it is a moral imperative to have a predictive test. Rather, the responsibility is to provide a perspective on the testing, the various options, and the disparate pros and cons.

Predictive testing of children younger than 18 years of age is proscribed except in life-threatening disorders (e.g. long QT syndrome, multiple endocrine neoplasia type 2B). Given the remarkable pace of advances in human genetics, it may well be possible in the foreseeable future to develop a therapy that enhances the extant biologic mechanism already in place that delays the manifestations of later onset disease for decades after birth. No life should be ruined by severe depression or suicide

only to discover later that a critical palliative remedy has emerged.

No longer hypothetical is the prenatal diagnosis request by a pregnant mother for fetal Huntington disease without the knowledge of her at-risk partner who does not wish to know his genetic status. In preserving the partner's autonomy and recognizing maternal rights, we have in the past honored such requests. Mothers have, in these circumstances, faced with an affected fetus, elected to terminate the pregnancy, invoking miscarriage as the reason to her unknowing partner. Distressing as it is to contemplate such a marital relationship, textured on the one hand by extreme care and on the other hand by deceit born of sensitivity, consider our report of symptomatic juvenile Huntington disease at 18 months of age and diagnosed at the age of 3 years.[368] These cases pose challenging ethical, moral, and legal questions, but both prenatal and preimplantation genetic testing (see Chapter 2) are now well accepted in the Western world.[369–371] Certainly rigorous recommendations and guidelines are in place for the prenatal diagnosis and the preimplantation genetic testing for Huntington disease,[369] which would apply equally to other neurodegenerative disorders and serious/fatal adult-onset disorders.

In general, the post-prenatal testing behavior of the mother is not likely to escape the average paternal observer. In a study of 54 women whose fetal risks of being affected were 50 percent (that included spouses of an affected partner), after an initial unaffected pregnancy, 10 percent chose not to have prenatal testing in a subsequent pregnancy.[372]

Prenatal diagnosis is not recommended for couples who do not intend to terminate a pregnancy if the fetus is affected.[373] A contrary view holds that diagnosis of a fetal genetic disorder may well inform the subsequent management of labor and delivery. Continuation of that pregnancy would likely remove the autonomous right of that child to decide to be tested or not.[374] In a review of 15 such pregnancies, one guideline was to recommend that couples should not disclose the diagnosis in order to protect the confidentiality and autonomy of the future child.[374]

Clearly, there are extraordinarily difficult circumstances related to planned childbearing in the face of 50 percent risks for a neurodegenerative disorder coupled with a wish not to know. In these special circumstances, predictive testing can be regarded as acceptable only if performed with extreme care, concern, and professionalism.

Preconception care should begin during visits to the family physician after menarche. Reiterated and expanding discussions on personal health habits that will affect both the adolescent herself and a future child, provide a basis for promoting good health behavior, while a solid grounding in knowledge about the hazards of smoking, drugs, alcohol, sexually transmitted diseases, and nutrition is provided. Early adolescence is also a vital period during which to inculcate the importance of genes and the wisdom of assimilating and updating information on family history. Linkage of family history to the common experience of physical and mental handicap, outlined in the context of personal risk in childbearing, provides a compelling and cogent framework on which physicians, teachers, and parents can build.

This preparatory background may help educate all women about the importance of planning pregnancy. Over 50 percent of pregnancies in the United States are not planned and are often unintended.[375] Physicians also need to reorient their practices so that women of childbearing age understand that to optimize the chance of having a healthy child,[335] prenatal care is best initiated before conception and not after the second missed menstrual period, as is still anachronistically practiced so widely.

Duty to warn

Physicians and counselors traditionally owe no duty to individuals with whom they have never met or entered into any treatment relationship. However, following the decision of the California Supreme Court (in Tarasoff v. Regents of the University of California),[376] it has become clear that when a serious risk to the health or life of a third party is recognized, a duty of reasonable care evolves that demands protective action. Examples include contact with blood relatives at risk in situations of threatened violence, exposure to infection (HIV/AIDS), and now harmful genes. For colorectal cancer there is evidence that over 50 percent of families at risk do not receive the necessary information.[377–379] A salutary lesson is provided in the study of 43 families with at least one sudden unexplained death.[380] Identification of a genetic

cardiac disorder (e.g. long QT syndrome) was made in 40 percent of the families who harbored 151 presymptomatic carriers! The loss-of-chance legal doctrine makes it incumbent upon geneticists/counselors to impress on their patients the need to warn blood relatives if a serious genetic threat is determined. This counsel should be in writing and documented in the medical record. Litigated examples include failure to warn of the risk of medullary thyroid cancer, familial adenomatous polyposis with colon cancer, and the fragile X syndrome.[381] From the judicial opinions in these cases[382] we learned that: (i) moral duty is not equal to legal duty; (ii) the duty to one's family members of avertible risk serves the interests of justice; (iii) given precedents of third party disclosures in the fields of psychiatry and infectious disease, there has been a willingness to extend the duty to warn.

Sudden death as a consequence of a monogenic disorder invokes specific responsibilities not only by the pathologist performing the autopsy but also the geneticist or genetic counselor, if involved with the family. Determination of the cause of sudden death, if not clearly obvious, may be ascribed to an arrhythmia. Cost issues aside, there is the need to consider gene sequencing for the long QT syndrome, the Brugada syndrome, and catecholaminergic polymorphic ventricular tachycardia. At the very least, a tissue sample should be frozen without preservative for subsequent DNA studies. Where cardiac pathology points to a cardiomyopathy, similar considerations pertain. Counseling of next of kin in such cases is important, more especially since they may face a 50 percent personal risk. On occasion, a patient at high risk may refuse to be informed about a specific genetic test result. However, if that result implicates a specific disorder that not only places that individual at risk but as a consequence may cause harm to others, the ethical imperative would demand communication of that unwanted information.[383]

Important legal precedents serve as further guidance. In the *Pate v. Threlkel* case (1987),[384] the mother of Heidi Pate was diagnosed and treated for the autosomal dominant form of medullary thyroid cancer. Three years later, the same diagnosis was made for Heidi. She sued her mother's physicians asserting that they had had a duty to warn her and her siblings. The Florida Supreme Court held that a reasonably prudent physician had a legal duty to warn of a genetically transferable disease.

The case *Safer v. Estate of Pack*[385] followed a similar theme. The father of Donna Safer was diagnosed in 1956 and surgically treated for colon cancer associated with multiple polyposis. Despite a total colectomy, he died when Donna was only 10 years of age. Subsequently, at the age of 36 years, she was diagnosed with metastatic colon cancer due to autosomal dominant multiple polyposis. She sued her father's surgeon's estate (he died in 1969) for not warning *him* of the genetic nature and transmissibility of that cancer. The Appellate Court in New Jersey decided that a physician had a duty to warn those known to be at risk of a genetic disorder and went on to state that duty may not always be satisfied by warning the patient.[386] About 5 years later, in 2001, the New Jersey Legislature enacted a broad genetic privacy law[387] that without consent a physician is prohibited from disclosure of genetic information.[386, 388]

A failure to make a diagnosis of the fragile X syndrome in the symptomatic daughter of Kimberly Molloy was followed by her giving birth to a son with this disorder. She sued the three physicians who treated her daughter (*Molloy v. Meier*).[389] The Minnesota Supreme Court (2004) concluded that physicians owed a duty to a third party and that legal action was permissible for the failure to warn.[389]

More recently, and in the United Kingdom, the duty to warn came into sharp focus. A man with Huntington disease expressly forbade his doctor from informing his daughter of his diagnosis. She subsequently (and accidentally) learned of the diagnosis when she was already pregnant. She sued her father's physicians (*ABC v. St. Georges Healthcare NHS Trust*)[390] for failure to inform her, claiming she would have terminated her pregnancy. The High Court denied the claim, holding that there was no duty of care. However, the Court of Appeal (2017) overturned this decision, indicating that clinicians may owe a duty to warn a patient's relatives.[391]

The aforegoing cases, including the decision by the UK Court of Appeal, made it clear that confidentiality in genetics is not absolute[324, 392, 393] with some exceptions.

Following the ruling of the Court of Appeal, the case returned to the High Court for trial, where

the decision was against the claimant (ABC).[391] Notwithstanding that ruling the Court "introduced a novel legal duty of care owed by doctors to third parties in certain circumstances."[391]

Earlier, the UK General Medical Council regarded the transfer of genetic information as justified if failure to do so exposes others to a risk of death or serious harm.[324, 394] The Joint Committee on Genomics in Medicine concurred[393] and advised that if a breach of confidentiality is to be made, consent for disclosure should be sought, discussion should be held with professional colleagues (e.g. ethics committee), and disclosure should be kept to a minimum, and all actions documented.[395] Internationally, many authors have opined and wrestled with these issues and mostly saw the necessity of communicating with relatives of the proband.[396–400]

Preconception genetic counseling

It is an anachronism that preconception genetic counseling in the 21st century, despite being recognized as important, is not widely practiced.[401, 402] Expectations at the first preconception visit include routine documentation of the medical, obstetric, and family history, the latter regarded arguably as the most important "genetic test."[403] It is now possible to prenatally diagnose *all monogenic disorders* in which the culprit gene is known. Since 6,739 have phenotypes thus far with recognized single genes,[2] it is very important for the physician to obtain and record the exact name of the genetic disorder(s) in the family. A history of "muscular dystrophy," given numerous types, would, for example, not be useful. Patients need a brief explanation as to why they need to obtain the precise information, and the physician's request documented. Review of medical records, photographs (e.g. previous stillbirths), and pertinent autopsy reports, radiographs, brain scans, and chromosome or other special laboratory reports may be necessary, as well as referral for genetic counseling. Physical examination and necessary special tests also focus on acquired and genetic disorders that could, during pregnancy, threaten maternal and/or fetal welfare.

Previously undiagnosed/undetected disorders may be determined for the first time at this visit and may be important for planned childbearing and the selection of future prenatal diagnostic tests. There is a need to insist that the male partner attend the preconception visit (or absolutely the first prenatal visit), providing an opportunity to detect at least obvious genetic disorders and solidify information possibly provided earlier about his family history. The senior author recalls, over many years during prenatal diagnosis counseling for other issues, diagnosing various disorders in male partners who were wholly unaware of their conditions, including osteogenesis imperfecta, Treacher–Collins syndrome, tuberous sclerosis, neurofibromatosis, Charcot–Marie–Tooth (type 1A) disease, limb girdle muscular dystrophy, facioscapulohumeral muscular dystrophy, blepharophimosis, mitral valve prolapse, the XYY male, and spinocerebellar ataxia.

The first preconception visit also serves to instruct about the need for folic acid supplementation for the 70 percent avoidance of NTDs (see Chapter 10) and about diabetic control, management of obesity, cessation of illicit drugs, medications, smoking and alcohol. Referral to other specialists (e.g. neurologists), for tailoring medication requirements to safer and possibly less teratogenic agents (e.g. epilepsy, acne), is also recommended. This is also the time for specialists caring for the same patient to confer about the planned care of their patient through pregnancy and for documentation of that interaction to be made.

Indications for preconception genetic counseling

The indications for preconception genetic counseling should be determined at the first visit and can be considered in a few clear categories.

Advanced maternal age

An arbitrary age of 35 years has previously functioned in the United States as an expected standard of care, which requires that a prospective mother be informed of her increased risks of having a child with a chromosome defect, informed of the recommendation for prenatal diagnosis, and given an explanation of the risks of CVS or amniocentesis, with the associated details related to any problems, pitfalls or reservations. Now, given the very low procedural risks, all women should be offered

routine prenatal genetic studies that focus on chromosomal analysis and α-fetoprotein (see Chapter 17). Advances in fetal imaging and low risks of fetal loss following amniocentesis (0.1–0.4 percent) or CVS (0.2–0.4 percent)[404, 405] (see Chapter 9) have led to the policy change. The advent of noninvasive prenatal testing (see Chapters 6 and 7) has further decreased the need for CVS or amniocentesis.

Excluding infants with chromosome abnormalities, a prospective analysis of 102,728 pregnancies (including abortions, stillbirths, and livebirths) in Texas found that the incidence of congenital malformations increased significantly and progressively in women after 25 years of age.[406] The authors found that an additional age-related risk of nonchromosome malformations was approximately 1 percent in women 35 years of age or older. The odds ratio for cardiac defects was 3.95 in infants of women 40 years of age or older when compared with women aged 20–24 years.

Pregnancy outcomes related to maternal age were reported in a Danish study of 369,516 singleton cases.[407] Pregnancies were followed from 11–14 weeks to delivery or termination and the age groups (20–34, 35–39, and ≥40 years) compared. Adverse outcomes included chromosomal abnormalities, congenital malformations, miscarriage, stillbirth, and delivery prior to 34 weeks of gestation. Women ≥40 years had a 3.83 percent risk of chromosomal abnormality, compared with 0.56 percent in the younger age group. Other significant results were an odds ratio of 3.1 for miscarriage (1.68 percent vs. 0.42 percent) and an odds ratio of 1.66 (2.01 percent vs. 1.21 percent) for birth <34 weeks of gestation.

Paternal age

Paternal age has trended upwards in the United States, England, and elsewhere in recent years.[408, 409]

The current consensus view is that a male ≥40 years of age at the time of conception is defined as being of advanced age.[410] Advanced paternal age (≥40) in the United States for childbearing in the 35- to 49-year-old category has risen from 42.8/1000 to 69.1/1000 from 1980–2015.[411] This probably reflects increased divorce/remarriage rates and the increased use of assisted reproductive technologies.[409] Advanced paternal age is associated with increased infertility and miscarriage rates,[409, 412–415] as well as an increased risk of 0.3–0.5 percent of *de novo* autosomal dominant mutations that result in severe phenotypes.[416–421] Professional societies and others whose guidelines suggest that sperm donors be less than 50 years of age,[422, 423] might now reconsider given both new and established data.

Well-established data exist for a number of autosomal dominant disorders in the offspring of older fathers[408] (Table 1.4), with achondroplasia having a relative risk of 12. The causes are *de novo* mutations estimated to accumulate to 420 over a 20-year period.[408] An Israeli psychiatric disease registry study of 87,907 births, showed a 2.96-fold relative risk of schizophrenia among the offspring of fathers over 50 years of age compared with those aged 20–24 years.[424] A Swedish National Birth Registry study of the entire population of

Table 1.4 Single-gene dominant disorders in offspring that are associated with advanced paternal age and relevant to prenatal diagnosis.

Clinical condition	*Gene*	*Population risk*	*Relative risk*	*Adjusted risk*
Achondroplasia	*FGFR3*	1/15,000	12	1/1,250
Apert syndrome	*FGFR2*	1/50,000	9.5	1/5,263
Crouzon syndrome	*FGFR2*	1/50,000	8	1/6,250
Pfeiffer syndrome	*FGFR2*	1/100,000	6	1/16,666
Wilms tumor	*WT1*	1/10,000	2.1	1/4,761
Bilateral retinoblastoma	*RB1*	1/15,000	5	1/3,000
Neurofibromatosis 1	*NF1*	1/3,000	2.9	1/1,034
Osteogenesis imperfecta	*COL1A1/2*	1/10,000	2.5	1/4,000
Polycystic kidney disease	*PKD1/2*	1/1,000	1.2	1/833
Thanatophoric dysplasia	*FGFR3*	1/20,000	3.18	1/6,290

Source: Yatsenko et al.[408] Reproduced with permission of Springer Nature.

births (2,615,081) between 1973 and 2010 examined the link between autism and paternal age.[425] The authors observed a statistically significant 3.45-fold greater likelihood of autism for fathers age at conception of >45 years compared to fathers in the 20–24 age group. They also reported a 13.1-fold greater likelihood of developing attention deficit hyperactivity disorder and a 2.07-fold risk of psychosis. In a California study of 5,121 spontaneous abortions between 6 and 20 weeks of pregnancy, fathers over 50 years of age had double the likelihood of associated pregnancy loss.[415] A prospective Danish study of 23,821 pregnancies showed that fathers >50 years of age had associated risks of fetal death almost twice that of younger fathers.[426]

A Swiss population study found that the proportion of younger fathers was uniformly different between those with and without Down syndrome offspring. Young fathers had an almost twofold increased odds for siring a child with trisomy 21.[427] The authors stated the need for confirmation of their findings.

Paternal age should garner more attention during genetic counseling,[428] especially with the availability of molecular analysis of multiple genes susceptible to *de novo* mutations in both noninvasive prenatal testing (see Chapter 8) and prenatal diagnosis (see Chapter 14).

A previous fetus or child with a genetic disorder

A genetic evaluation and counseling are usually indicated when a previous fetus or child has or had a genetic disorder, unless the matter is straightforward (e.g. previous trisomy 21) and the obstetrician is well informed. Careful inquiry should be made about the health status of a previous child. Failure or delay in the diagnosis of a monogenic disorder leaves the parents without the option of prenatal diagnosis in a subsequent pregnancy. In addition, it deprives them of the option of preimplantation genetic testing for those disorders with known mutations. Failure to make an early diagnosis of a genetic disorder during the first 5 years of life is common. For example, the Rotterdam Clinical Genetics Group reported that 50 percent of children affected by neurofibromatosis had been treated for related symptoms before a specific diagnosis had been made.[429] Such delay has become problematic given that the *NF1* gene and genes for many other monogenic disorders are routinely sequenced for a precise diagnosis.

Frequently, distressed parents will select a different physician for a subsequent pregnancy and a new or more recent insight may shed light on the cause of the previous disorder. For example, confined placental mosaicism (see Chapter 4) may now serve to explain the discrepancy between reported chromosomal findings at the time of CVS and fetal tissues obtained at elective abortion. Confined placental mosaicism may also be associated with intrauterine growth restriction (see Chapter 4), requiring serial ultrasounds during the pregnancy.

Given the heterogeneous nature of genetic disease, being alert to alternative mechanisms of causation will on occasion be rewarding. For example, during a consultation with a patient who had previously delivered a child with the autosomal recessive Meckel–Gruber syndrome, preparatory discussions about establishing the specific mutation from each parent could reveal that the father is not a carrier of a mutation in the culprit gene. Although nonpaternity is more likely, a judicious approach would also include consideration of uniparental disomy.[430, 431] This mode of inheritance, in which an offspring can inherit two copies – part or all of a chromosome from one parent and no copy from the other parent – has been seen in a number of disorders, including Prader–Willi syndrome and Angelman syndrome (see discussion later and Chapter 14). About 25 percent of cases of Prader–Willi syndrome are caused by maternal uniparental disomy.[432] Involvement of chromosomes 7, 11, 14, and 15 have been notable. Uniparental disomy is caused primarily by meiotic nondisjunction events and followed by trisomy or monosomy "rescue." Most cases described have been associated with advanced maternal age and have been detected primarily in the process of prenatal genetic studies.[433, 434]

Recognition of the molecular basis of a disorder from which a previous child died may provide a couple with an opportunity for prenatal diagnosis in a subsequent planned pregnancy. A caveat would be the availability of analyzable tissue from the deceased child. In the recent past this was mostly not done, but with the escalation of new discoveries in genetics, tissues should now be frozen for potential future DNA analysis. The establishment

of the molecular basis of recognized syndromes, previously undetectable prenatally, now provides new opportunities for couples seeking prenatal diagnosis. Examples abound and include some of the craniosynostosis syndromes, certain skeletal dysplasias, and many other disorders.

In one of our cases, a father with metaphyseal dysplasia of Schmid, troubled by the indignities and hurts of growing up with severe short stature, elected prenatal diagnosis at a preconception visit. Subsequent mutation analysis of conceived twins yielded a normal prenatal diagnosis result confirmed postnatally.[435]

Heterogeneity and pleiotropism also require consideration in the context of a previous child's disorder and anticipation of future prenatal diagnosis. For example, a previous child with tuberous sclerosis or a fetus with a cardiac rhabdomyoma would prompt molecular analysis of the *TSC1* and *TSC2* genes for more precise future prenatal diagnosis.[436]

A parent with a genetic disorder

Physicians are now advised to determine whether a culprit gene has been found for a specific genetic disorder under discussion, since prenatal diagnosis would then be available for that couple or their children. Adult-onset genetic disorders (breast/ovarian cancer, colon cancer, hypertrophic cardiomyopathy, long QT syndrome) serve as examples where prenatal diagnosis is an option. The long-established prenatal diagnoses for both presymptomatic and symptomatic neurodegenerative disorders[437] continue to be expanded to include disorders such as amyotrophic lateral sclerosis and frontotemporal dementia by analysis of the *C9orf72* gene.[438] In prenatal diagnosis discussions for all adult-onset disorders, there is a natural focus on the tortured questions of personal existence and self-extinction. One example is that of a young father with CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy) who, faced with our prenatal diagnosis of this disorder, by mutation analysis of the *Notch3* gene, with his wife, elected termination.[439] Mutation analysis in a subsequent pregnancy assured an unaffected fetus.[440]

These consultations may invoke deep personal emotional conflict, especially when pleiomorphic genes are concerned. For example, a parent with tuberous sclerosis and normal intelligence could not be certain that an affected child would not have intellectual disability. This was especially evident in our series of 50 couples having prenatal diagnosis for tuberous sclerosis.[436] Discovery of fetal cardiac rhabdomyoma led to sequencing of both the *TSC1* and *TSC2* genes in the fetus and diagnosis in one of the asymptomatic parents. Parental decisions are neither simple nor predictable. In a UK study[441] of 644 deaf individuals and 143 with hearing impairment, 2 percent opined that they would prefer to have deaf children and would consider an elective abortion if the fetus was found to be hearing!

Prospective mothers with insulin-dependent diabetes mellitus (IDDM) could find their disorder harder to control during pregnancy. Diabetes should be well controlled before pregnancy. The better the control, the lower the risk of having a child with congenital defects.[442, 443] An Australian study noted that with good preconception care of type 1 IDDM, the major congenital malformation rate decreased from a high of 14 percent to 2.2 percent.[444] Notwithstanding extant knowledge about IDDM and pregnancy, a report of 273 women noted rates of stillbirth (1.85 percent), perinatal mortality (2.78 percent), and congenital anomalies (6 percent).[445] An important Stockholm study of 1,089 stillbirths usefully separated causes in preterm and term/post-term births.[446] Infection and intrauterine growth restriction/placental insufficiency accounted for over 44 percent of cases in about equal proportion.

The genetics of diabetes is complex with multiple types, both polygenic, multifactorial, syndromic, and monogenic in origin. The polygenic type 1 diabetes (T1DM) and type 2 diabetes (T2DM) have over 40 and 90 genes implicated, respectively. Between 1 and 5 percent of diabetes is monogenic and symptoms overlap with T1DM and T2DM diabetes.[447, 448] Affected monogenic type patients mostly do not have islet autoantibodies, often have endogenous insulin production, and are frequently misdiagnosed.[449, 450] Both T2DM and monogenic diabetes are often not insulin-dependent, have a family history of diabetes, and can occur in the young. Usually, insulin resistance does not occur, nor does acanthosis nigricans in monogenic diabetics, who are mostly not obese.[449]

Diabetes diagnosed in the first year of life is monogenic and due to K_{ATP} channel mutations.[451] There are multiple types of monogenic autosomal

dominant maturity-onset diabetes of the young (MODY), four subtypes predominating with mutations in *HNFIA* (52 percent), *GCK* (32 percent), *HNF4A* (10 percent), and *HNF1B* (6 percent).[452]

A precise preconception molecular diagnosis is important so as to direct appropriate treatment. No pharmacologic treatment is indicated for the GCK-MODY type, low dose sulfonylureas are prescribed for HNF1A-MODY and HNF4A-MODY, with high-dose sulfonylureas for K_{ATP} channel-related diabetes.[451]

Pregestational T1DM and T2DM are associated with poorer pregnancy outcomes, including up to a fourfold higher rate of perinatal mortality.[453] The poorer glycemic control at the time of conception and the first trimester, the higher the frequency of stillbirths, congenital abnormalities, perinatal morbidity and mortality, macrosomia, dystocia in labor, and maternal mortality.[454–458] Obesity, with its burden of obstetric complications and congenital anomalies[457] (as discussed earlier), compounds all the problems in the diabetic mother.

Pregnant women with the chronic multifactorial autoimmune disease systemic lupus erythematosus (SLE) face a host of complications. This disorder, with its predilection for women of childbearing age, is more prevalent in non-white populations and is characterized by involvement that includes renal, cardiovascular, musculoskeletal, neurological, rheumatological, and cutaneous systems.[459] Adverse pregnancy outcomes include fetal death, preterm births, intrauterine growth restriction, and neonatal lupus.[460] Women with anti-Ro/anti-La antibodies, the latter being specific for the diagnosis of SLE and Sjögren syndrome,[461] can be asymptomatic. Anti-Ro antibodies may precede the clinical manifestations of SLE by an average of 3.6 years.[462] Note, however, these antibodies are found in up to 3 percent of the general population.[463]

The prime consequences of having anti-Ro antibodies is the risk of fetal/neonatal heart block and neonatal lupus. In a study of 325 children with second- or third-degree heart block, the overall mortality rate was 17.5 percent. Death *in utero* occurred in 6 percent.[464] The risk of offspring being born with congenital heart block to a mother with anti-Ro antibodies is between 0.2 and 2.0 percent, but 15–20 percent if there has been a previously affected fetus or neonate.[464, 465] After two affected pregnancies, the subsequent pregnancy risk is 50 percent.[466] Complex therapeutic considerations include fluorinated glucocorticoids (dexamethasome and betamethasome) and maternal fetal echocardiography monitoring.[467, 468] Neonatal lupus with congenital heart block will usually require pacemaker implantation.[469, 470] For mothers with a previous affected pregnancy, hydroxychloroquine has been recommended as a pre-emptive treatment.[471, 472] Fortunately, only a third of mothers carrying fetuses with complete heart block have an identified autoimmune disorder such as lupus or Sjögren disease.[473]

Certain genetic disorders may threaten maternal and fetal health in pregnancy and are discussed in detail in Chapter 31.

A history of infertility

Beyond the issues of paternal age discussed earlier, there is the evidence that structural chromosomal abnormalities, which occur in 0.25 percent of births, more frequently have their origin in paternal chromosomes. In a 2006 report, 72 percent of *de novo* unbalanced chromosomal rearrangements were of paternal origin.[474] The likelihood of having a translocation doubled every 10 years after the age of 25.[475] An American Cancer Society Study of 2,532 cases of hematological cancers noted that men over 35 had a 63 percent higher risk of having affected offspring when compared with those under 25.[476] A small, but statistically significant increased risk of nonchromosomal congenital malformations associated with advanced paternal age was reported by the National Birth Defects Prevention Study.[477] Malformations included were cleft lip, diaphragmatic hernia, right ventricular outflow tract obstruction, and pulmonary stenosis.

About 10 percent of couples have infertility. A World Health Organization multicenter study concluded that the problem appeared predominantly in males in 20 percent of cases, predominantly in females in 38 percent, and in both partners in 27 percent. In the remaining 15 percent of cases, no definitive cause for the infertility was identified.[478] Care should be exercised in the preconception counseling of a couple with a history of infertility. In the absence of a recognizable cause, karyotyping of both is recommended. Unrecognized spontaneous abortions may have occurred without the patient's awareness, caused by overt structural

chromosome rearrangements or microdeletions or duplications (see Chapters 11 and 13). Microarrays performed after routine cytogenetics on products of conception in 2,389 cases revealed significant copy number changes or whole-genome uniparental disomy in 1.6 percent and 0.4 percent of cases, respectively.[479] A study of 1,300 infertile men revealed chromosomal abnormalities in 10.6 percent and Y-microdeletions in 4.0 percent.[480] Recognized habitual abortion due to the same causes would also require cytogenetic analysis. Such studies may reveal a parent (rarely both) with a chromosomal rearrangement with significant risks for bearing a child with intellectual disability and/or malformations, who could benefit from prenatal or preimplantation diagnosis.

Other examples of disorders characteristically associated with recurrent pregnancy loss or infertility include premature ovarian failure in fragile X syndrome carriers (see Chapter 16), and the X-linked disorders steroid sulfatase deficiency[481] and incontinentia pigmenti.[482] Thrombophilia as a significant cause remains uncertain.[483, 484] In about 8 percent of women experiencing recurrent abortion a mutation in the *SYCP3* gene (which encodes an essential component of the synaptonemal complex, key to the interaction between homologous chromosomes) was noted.[485] An extensive list of genes related to premature ovarian failure have been recognized,[486] especially noteworthy in a highly consanguineous population.[487] Consequently, next-generation sequencing[488] or whole-exome sequencing,[489–492] cost issues aside, would be indicated.

Although the investigation to determine the cause of male or female infertility can be extensive, several observations are pertinent here. We recognized that congenital bilateral absence of the vas deferens (CBAVD),[493] which occurs in 1–2 percent of infertile males, is primarily a genital form of CF (see Chapter 15). Men with CBAVD[494] should have CF gene analysis (sequencing, poly T variant analysis, deletion analysis). A meta-analysis concluded that among CBAVD patients, 78 percent had one recognizable *CFTR* gene mutation whereas 46 percent were noted to have two mutations.[495] The mutation detection rate is likely to exceed 92 percent including large gene rearrangements.[496] Of interest is the observation of Traystman et al.[497] that CF carriers may be at higher risk for infertility than the population at large. Men who test negative for a *CFTR* mutation should have the *ADGRG2* gene on the X chromosome sequenced.[498, 499]

Some patients with CBAVD (21 percent in one study[500]) also have renal malformations. These patients may have a normal sweat test and thus far no recognizable mutations in the CF gene.[500, 501] Renal ultrasound studies are recommended in all patients with CBAVD who have normal CFTR analyses. The partner of a male with CBAVD and a recognized mutation(s), after gene analysis, should routinely be offered sequencing and deletion analysis of the CFTR gene. Such couples frequently consider epididymal sperm aspiration,[502, 503] with pregnancy induced by IVF. Precise prenatal and/or preimplantation genetic testing can be achieved only if specific mutations have been recognized.

Significant male infertility is mainly associated with XXY males (see Chapter 12), autosomal translocations, Kallman syndrome, Y-microdeletions, autosomal inversions, CBAVD, mixed gonadal dysgenesis, and X-linked and autosomal gene mutations.[504] We reported a 28-year-old with azoospermia and bilateral congenital cataracts associated with a contiguous deletion including the Nance–Horan gene at Xp23.13 and implicating the *SCML1* gene.[505] The global prevalence of Yq microdeletions approximates 7.5 percent in infertile males.[506] Genes including *DAZ* ("deleted in azoospermia"), *YRRM* (Y chromosome RNA recognition motif),[507, 508] and others may be deleted singly or together in the region of Yq11.23.[509] Couples must be informed that male offspring of men with these interstitial deletions in the Y chromosome will have the same structural chromosome defect. The female partner of the male undergoing intracytoplasmic sperm injection (ICSI) needs explanations about procedures and medications for her that are not risk free. Patients should realize that ICSI followed by IVF is likely to achieve pregnancy rates between 20 and 24 percent,[510] a success rate not very different from the approximately 30 percent rate in a single cycle after natural intercourse at the time of ovulation.[510] Pregnancy follow-up data from cases culled from 35 different programs reported in a European survey[511] and a major American study of 578 newborns showed no increased occurrence of congenital malformations.[214] However, a statistically significant increase in sex chromosome

defects has been observed.[512] Prenatal diagnosis is recommended in all pregnancies following ICSI.

Even "balanced" reciprocal translocations in males may be associated with the arrest of spermatogenesis and resultant azoospermia.[513] In one series of 150 infertile men with oligospermia or azoospermia, an abnormal karyotype was found in 10.6 percent (16/180), 5.3 percent (8/150) had an AZF-c deletion, and 9.3 percent (14/150) had at least a single CF gene mutation.[514] This study revealed a genetic abnormality in 36/150 (24 percent) of men with oligospermia or azoospermia. A Turkish study of 1,696 males with primary infertility showed 8.4 percent with a chromosomal abnormality and 2.7 percent with a Y-chromosome microdeletion.[515]

Rarer disorders may need to be considered in the quest to determine the cause of infertility including, for example, the blepharophimosis, ptosis, epicanthus inversus syndrome, which may respond to treatment.[516]

In a study of 75,784 women to determine all-cause and cause-specific mortality, those with infertility had a 10 percent increased risk of death from any cause.[517] Death from breast cancer was more than doubled. In a major prospective Danish study, 3,356 women who had children born after frozen embryo transfer were compared with 910,291 fertile women. The incidence rate of childhood cancer was 17.5 per 100,000 for children born to fertile women, and 44.4 per 100,000 in children born after the use of frozen embryos.[518] The statistically significant increased risk was primarily leukemia and sympathetic nervous system tumors. The cause(s) remain unknown. A US study did not find a significant association, but had a shorter follow-up period (<5 years), follow-up loss, and incomplete maternal data.[519] In a retrospective study using insurance data, the records of 19,658 infertile women and 525,695 fertile women were examined to determine severe maternal morbidity.[520] The overall incidence of severe maternal morbidity among women receiving fertility treatment was 7.0 percent compared with 4.3 percent in fertile women.

Parental carrier of a genetic disorder

Prospective healthy parents are mostly unaware of their carrier status for a chromosomal or single-gene disorder, unless their medical or reproductive history has otherwise been informative. Studies to determine prenatal carrier status for a chromosomal disorder are recommended following a history of recurrent miscarriage, previous stillbirth, previous child with intellectual disability, or congenital abnormality, infertility, oligospermia, azoospermia, or a family history that is concerning for any of these outcomes. Chromosome analysis will mostly suffice in determining translocations, inversions, and somatic mosaicism. Chromosomal microarrays (see Chapter 13) for both parents are appropriate if no diagnosis was made for previous affected progeny, but will miss balanced translocations.

The first preconception visit is the time to establish the carrier status of a couple for either a chromosomal or monogenic disorder.[521] Among the many items to be considered during the preconception visit are the potential physical features indicative of sex-linked disorders that may manifest in female carriers (see discussion later). With or without a family history of the disorder in question, referral to a clinical geneticist would be appropriate for final evaluation of possible implications. Failure to recognize obvious features in a manifesting female may well result in a missed opportunity for prenatal genetic studies and an outcome characterized by a seriously affected male (or occasionally female) offspring. Recognition of the carrier status for Duchenne muscular dystrophy (DMD) of a prospective mother at the first preconception visit should immediately include consideration of her own future health. Some two-thirds of mothers are carriers of a DMD gene mutation. As X-linked carriers they may manifest symptoms and signs of this disorder, including muscle weakness, prominent but weak calf muscles, abnormal gait, fatigue, exercise intolerance, and, of greatest importance, heart involvement.[522] Up to 16.7 percent of DMD carriers develop dilated cardiomyopathy, with carriers of Becker muscular dystrophy (BMD) having up to a 13.3 percent risk.[523] The cardiomyopathy may also manifest with conduction defects and arrhythmias.[522, 524–527] While most carriers become symptomatic around puberty,[528] the risks and severity increase with age. Unfortunately, physicians are often unaware of the risks DMD carriers face,[529] despite having elevated levels of creatine phosphokinase.[530] In a study of 77 DMD and BMD carriers with a molecular confirmed diagnosis, 49

percent had myocardial fibrosis detected by cardiac MRI.[531] Irreversible heart failure maybe the final complication for which cardiac transplantation has been done.[532]

A report on 355 fragile X carrier women noted that >30 percent complained of anxiety, depression, and headaches.[533] Between 20 and 30 percent of carriers experience irregular or absent menses due to primary ovarian insufficiency.[534] This latter recognition during routine obstetric care often serves as an alert to check fragile X syndrome carrier status. We have also seen instances where recognition of carrier status has led to reversal of a putative diagnosis of parkinsonism or early dementia, instead of an actual diagnosis of the fragile X tremor ataxia syndrome manifesting in a grandfather over 60 years of age (see Chapter 16).

Carrier status for women with a family history of hemophilia A or B cannot be excluded by a normal activated partial thromboplastin time or normal factor VIII or factor IX levels.[535] A definitive molecular diagnosis combined with linkage analysis where necessary is needed, especially if prenatal or preimplantation diagnosis is sought. Determination of a pathogenic variant in the structurally complex factor VIII gene enables confirmation of carrier status.[536, 537] Prenatal diagnosis requests for hemophilia A are uncommon, but have been provided.[538–540] Preimplantation genetic testing (see Chapter 2) for hemophilia has also been accomplished.[541] Noninvasive prenatal diagnosis of hemophilia A and B in hemophilia carriers using maternal plasma and factor VIII and factor IX sequence variants has been demonstrated[542] (see Chapter 8).

We all carry a host of deleterious recessive genes (~100–300)[543] and technical advances have enabled routine simultaneous testing of hundreds of autosomal recessive and X-linked disorders which affect about 1 in 300 pregnancies.[544] Not well understood by patients is the fact that expanded carrier testing[545–555] examines only a few common mutations in each gene analyzed. The net effect is a significant reduction in the risk of being a carrier of the gene tested. Unfortunately, the refrain heard from patients having had expanded carrier testing is "I am not a carrier." Financial constraints prevent many couples benefitting from the extensive panel of carrier tests, leaving them with the previously required indications of ethnicity, affected offspring, or family history. This type of limited carrier testing, which includes CF and spinal muscular atrophy, misses about 70 percent of carriers of rare disorders.[556] For the most part carriers of autosomal recessive disorders are asymptomatic. An important exception are the carriers of the sickle cell disease gene mutation p.Glu6-Val in the β-globin chain of hemoglobin, who have an increased risk of both venous thromboembolism and chronic renal disease.[557] This is an important realization that should lead to care and surveillance, given that about 300 million worldwide have the sickle cell trait.

Autosomal recessive disease severity when due to compound heterozygous pathogenic variants will be a consequence of the variable expression of the two alleles (e.g. CF with the p.Phe508del and the p.Arg117His alleles resulting only in CBAVD) (see Chapter 15). Gene modifiers too will affect the phenotype. Variant interpretation remains a challenge as well as increasing the need and time taken for genetic counseling given that over 1,800 autosomal recessive genes are known.[543]

Clearly, the purpose of expanded carrier screening (see Chapter 14) for healthy couples enables them to benefit from available options that include preimplantation genetic testing, routine prenatal diagnosis, adoption, donor sperm or ova, or surrogacy. This approach has proved acceptable to the American College of Obstetricians and Gynecologists, the American College of Medical Genetics and Genomics, the Society for Maternal-Fetal Medicine, and the National Society of Genetic Counselors.[558, 559] The clinical utility and efficacy has been clearly demonstrated.[546, 549, 551, 558]

Johansen Taber et al.[560] reported on the actions and reproductive outcomes of 391 at-risk couples from a tested population of over 270,000 using a panel of 176 genetic disorders. Over 75 percent who had preconception testing, planned or acted to avoid having an affected progeny. More than 50 percent of at-risk couples terminated pregnancies. Relying on a survey study, the authors acknowledge, has limitations so far as memory, response bias, and selection (infertility problems) are concerned. In a smaller study, others[549] demonstrated the clear superiority of expanded carrier screening compared with ethnicity-based testing, with over threefold detection. Punj et al. offered preconception next-generation sequencing to determine

carriers and found 12/71 couples at risk.[548] Eight were carriers of hemochromatosis. These authors analyzed 728 genes in 202 individuals, 78 percent being determined to have at least one positive carrier result. In this exploratory study, which used a 148 gene-panel rather than the ACMG actionable panel of 59 genes, 3.5 percent of participants had a medically actionable variant[548] (see Chapter 14). Applying their analysis to the ACMG panel, 2.9 percent had an actionable variant.

Ethnicity-based carrier testing (Table 1.5) remains the only option for large swaths of the world's population. Selective Ashkenazi Jewish mutation carrier testing, for example, for disorders listed in Table 1.5 do provide valuable but limited information, leading to options noted above. A study of 6,805 Jewish patients (Ashkenazi, Sephardi, and Mizrahi) having expanded carrier screening showed that 64.6 percent were identified as a carrier of one or more of 96 disorders[562] (Table 1.6). The authors noted that >80 percent of the reported variants would have been missed by standard Ashkenazi Jewish screening protocols. One in 16 couples were identified as joint carriers with a 25 percent risk of having an affected child. A novel, likely pathogenic variant was seen in about 2.5 percent of patients tested. A whole-exome sequencing study of 123,136 cases examined carrier rates in six ethnic groups, focusing on 415 genes associated with severe recessive disorders.[563] These authors found that 32.6 percent (East Asian) and 62.9 percent (Ashkenazi Jewish) were variant carriers of at least one of the 415 genes. A pan-ethnic screen using these 415 genes would identify up to 2.52 percent of at-risk couples.

However, the limitations of ethnic-based carrier testing were revealed by a genetic ancestry analysis of >93,000 individuals having expanded carrier testing using a 96-gene panel.[565] Nine percent of those tested had an ancestry from a lineage inconsistent with self-reported ethnicity.

Multiple published reports on preconception or prenatal expanded carrier screening using large but variable-sized gene panels overwhelmingly support this approach above ethnicity-based testing.[545, 549, 566–572]

Although not currently required in preconception carrier screening, testing for hereditary cancer risk should be considered. A personal or family history of cancer as well as ethnicity currently serves as an indication for screening. Autosomal dominant disorders are otherwise not usually subject to screening. In a study of 26,906 individuals in the Healthy Nevada Project screened for *BRCA*-related breast and ovarian cancer, Lynch syndrome, and familial hypercholesterolemia, 1.33 percent were found to be carriers of pathogenic or likely pathogenic variants.[573] Moreover 90 percent of carriers had not been identified previously, and only 25.2 percent had a relevant family history. These three disorders determined by screening (not family history) are not usually considered for prenatal diagnosis or preimplantation genetic testing. However, other autosomal dominant disorders with manifestations in childhood (e.g. multiple endocrine neoplasia type 2B, familial adenomatous polyposis, long QT syndrome, cardiomyopathy) do qualify for preconception, preimplantation, and prenatal testing. A study of 23,179 individuals with a family history of cancer had next-generation sequencing using a 30-gene panel.[574] A total of 2,811 pathogenic variants were found in 2,698 individuals for an overall pathogenic frequency of 11.6 percent. For those of Ashkenazi Jewish descent three-quarters of the pathogenic variants in the *BRCA1* and *BRCA2* genes would have been missed if only the routine three common founder mutations were tested.

Geneticists and genetic counselors will attest to the frequent challenges they encounter faced by their patients' difficulty comprehending genetic test results, implications, and options. On the heels of the technologic advances in genetics have come commercialization in the form of direct-to-consumer (DTC) testing. Few patients are cognizant of the commercialization realities that include selling of their data, receiving misleading results, being faced with incorrect, false-positive or false-negative results, a lack of informed consent, confidentiality, and privacy.[575–580] There is a wide spectrum of laws that govern genetic testing in most countries, with special reference to laboratory accreditation, staff certification, genetic counseling requirements, and informed consent.

In one study of identical twins there was a lack of concordance between laboratories.[581] In an illustrative case, the result provided was actionable, but no action was taken by the recipient of the DTC communication.[582] Ethical breaches, including testing of children, further complicate DTC practices.[583]

Table 1.5 Genetic disorders in various ethnic groups.

Ethnic group	*Genetic disorder*
Africans (black)	Sickle cell disease and other disorders of hemoglobin
	α- and β-thalassemia
	Glucose-6-phosphate dehydrogenase deficiency
	Benign familial leucopenia
	High blood pressure (in females)
Afrikaners (white South Africans)	Variegate porphyria
	Fanconi anemia
American Indians (of British Columbia)	Cleft lip or palate (or both)
Amish/Mennonites	Ellis–Van Creveld syndrome
	Pyruvate kinase deficiency
	Hemophilia B
Armenians	Familial Mediterranean fever
Ashkenazi Jews	A-β-lipoproteinemia
	Bloom syndrome
	Breast cancer
	Canavan disease
	Colon cancer
	Congenital adrenal hyperplasia
	Dysferlinopathy (limb girdle muscular dystrophy 2B)
	Dystonia musculorum deformans
	Factor XI (PTA) deficiency
	Familial dysautonomia
	Familial hyperinsulinism
	Fanconi anemia (type C)
	Galactosemia
	Gaucher disease (adult form)
	Iminoglycinuria
	Joubert syndrome
	Maple syrup urine disease
	Meckel syndrome
	Niemann–Pick disease
	Pentosuria
	Retinitis pigmentosa [590]
	Tay–Sachs disease
	Warsaw Breakage syndrome [561]
Chinese	Thalassemia (α)
	Glucose-6-phosphate dehydrogenase deficiency (Chinese type)
	Adult lactase deficiency

Table 1.5 (Continued)

Ethnic group	*Genetic disorder*
Eskimos	E1 pseudocholinesterase deficiency
	Congenital adrenal hyperplasia
Finns	Aspartylglucosaminuria
	Congenital nephrosis
French Canadians	Neural tube defects
	Tay–Sachs disease
Irish	Neural tube defects
	Phenylketonuria
	Schizophrenia
Italians (northern)	Fucosidosis
Japanese and Koreans	Acatalasia
	Dyschromatosis universalis hereditaria
	Oguchi disease
Maori (Polynesians)	Clubfoot
Mediterranean peoples (Italians,	Familial Mediterranean fever
Greeks, Sephardic Jews, Armenians,	Glucose-6-phosphate dehydrogenase deficiency
Turks, Spaniards, Cypriots)	(Mediterranean type)
	Glycogen storage disease (type III)
	Thalassemia (mainly β)
Norwegians	Cholestasis-lymphedema
	Phenylketonuria
Yugoslavs (of the Istrian Peninsula)	Schizophrenia

Table 1.6 Residual risk values for diseases in Ashkenazi Jewish populations.

Disease	*100% Ashkenazi Jewish carrier frequency*	*Detectability*	*Residual risk*	*Probability of affected fetus if parents pos/neg*[a]
Gaucher disease	1 in 15	0.95	1 in 281	1 in 1,124
Cystic fibrosis	1 in 23	0.94	1 in 368	1 in 1,472
Tay–Sachs disease	1 in 27	0.98	1 in 1,301	1 in 5,204
Familial dysautonomia	1 in 31	>0.99	1 in 3,001	1 in 12,004
Canavan disease	1 in 55	>0.97	1 in 1,801	1 in 7,204
Glycogen storage disease type 1a	1 in 64	0.95	1 in 1,261	1 in 5,044
Hyperinsulinemic hypoglycemia	1 in 68	0.90	1 in 671	1 in 2,684
Mucolipidosis IV	1 in 89	0.95	1 in 1,761	1 in 7,044
Maple syrup urine disease	1 in 97	0.95	1 in 1,921	1 in 7,684
Fanconi anemia	1 in 100	0.99	1 in 9,901	1 in 39,604
Dihydrolipoamide dehydrogenase deficiency	1 in 107	>0.95	1 in 2,121	1 in 8,484
Niemann–Pick disease type A	1 in 115	0.97	1 in 3,801	1 in 15,204
Usher syndrome type 3	1 in 120	>0.95	1 in 2,381	1 in 9,524
Bloom syndrome	1 in 134	0.99	1 in 13,301	1 in 53,204
Usher syndrome type 1F	1 in 147	≥0.75	1 in 585	1 in 2,340
Nemaline myopathy	1 in 168	>0.95	1 in 3,341	1 in 13,364

[a]One parent is positive and one parent is negative by carrier screening.

Source: Modified from Scott et al.[564]

Professional organizations, aware of all these issues, have discouraged the use of DTC genetic testing. Position statements have accordingly been issued by the American College of Obstetricians and Gynecologists,[584] the American College of Medical Genetics and Genomics,[585] the Joint Society of Obstetricians and Gynecologists, and the Canadian College of Medical Genetics.[586] A range of laws exist in Europe, with France and Germany banning DTC genetic testing.[587] Serious concern has been expressed about the ethical, legal, and regulatory challenges of DTC testing in Ireland[588] and Europe.[589]

A family history of a genetic disorder

The explicit naming of a specific genetic disorder when the family history is being discussed facilitates evaluation and any possible testing. Difficulties are introduced when neither family nor previous physicians have recognized a genetic disorder within the family, sometimes revealed by expanded carrier screening[591] or whole-exome sequencing.[592] Such a disorder may be common (e.g. factor V Leiden deficiency) but nevertheless unrecognized. Clinical clues would include individuals in the family with deep-vein thrombosis, sudden death possibly due to a pulmonary embolus, and yet other individuals with recurrent pregnancy loss.[593] Venous thromboembolism is the third leading cause of cardiovascular death in the United States, and provides additional insights into the genetic basis of unprovoked pulmonary embolism. Using whole-exome sequencing in 393 affected individuals and 6,114 controls, Desch et al.[594] identified four genes (*PROS1*, *STAB2*, *PROC*, *SERPINC1*) with pathogenic variants, expanding the need for genetic testing given the history of thromboembolism.

For some families, individuals with quite different apparent clinical features may, in fact, have the same disorder. Seventeen cancers in different organs in family members may not be recognized as manifestations of the same common mutation. In hereditary nonpolyposis colon/rectal cancer, various family members may suffer from other cancers including the uterus, ovary, breast, stomach, small bowel, ureter, melanoma, or salivary glands. Analysis of the five culprit genes in the proband would enable detection of the mutation, which could then be assayed in other family members at risk. In another example, there may be two or more deceased family members who died from "kidney failure," and another one or two who died from a cerebral aneurysm or a sudden brain hemorrhage. Adult polycystic kidney disease (APKD) may be the diagnosis, which will require further investigation by both ultrasound and DNA analysis. Moreover, two different genes for APKD have been identified (about 85 percent of cases due to *APKD1* and close to 15 percent due to *APKD2*),[595] and a rare third locus is known. In yet other families, a history of hearing impairment/deafness in some members and sudden death in others may translate to the autosomal recessive Jervell and Lange–Nielsen syndrome.[596] This disorder is characterized by severe congenital deafness, a long QT interval, and large T waves, together with a tendency for syncope and sudden death due to ventricular fibrillation. Given that a number of genetic cardiac conduction defects have been recognized, a history of an unexplained sudden death in a family should lead to a routine electrocardiogram at the first preconception visit and possibly mutation analysis of at least 15 long QT syndrome genes.[597] Other disorders in which sudden death due to a conduction defect might have occurred, with or without a family history of cataract or muscle weakness, should raise the suspicion of myotonic muscular dystrophy (see Chapter 31).

Rare named disorders in a pedigree should automatically raise the question of the need for genetic counseling. We have seen instances (e.g. pancreatitis) in which, in view of its frequency, the disorder was simply ascribed to alcohol or idiopathic categories. Hereditary pancreatitis, although rare, is an autosomal dominant disorder for which several genes are known.[598]

Awareness of the clinical manifestations in carrier females of X-linked disorders is important given health and risk implications (Table 1.7). The pattern of inheritance of an unnamed disorder may signal a specific monogenic form of disease. For example, unexplained intellectual disability on either side of the female partner's family calls for fragile X DNA carrier testing. Moreover, unexpected segregation of a maternal premutation may have unpredicted consequences, including reversion of the triplet repeat number to the normal range.[671] Genetic counseling may be valuable, more especially because the phenomena

Table 1.7 Signs in females who are carriers of selected X-linked recessive disease pertinent to prenatal diagnosis.

Selected disorders	*Key feature(s) that may occur*	*Selected references*
Aarskog–Scott syndrome allelic with XLMR 16	Widow's peak or short stature	599
Achromatopsia	Decreased visual acuity and myopia	600
Adrenoleukodystrophy	Neurologic and adrenal dysfunction	601, 602
Alport syndrome	Microscopic hematuria and hearing impairment	603
Ameliogenesis imperfecta, hypomaturation type	Mottled enamel vertically arranged	604
Arthrogryposis multiplex congenita	Club foot, contractures, hyperkyphosis	605
ATRX syndrome α-thalessemia/ID syndrome	Mild intellectual disability, hemoglobin H inclusions	599, 606
Borjeson–Forssman–Lehmann syndrome	Tapered fingers, short, widely spaced, flexed toes, mild mental retardation	607
Choroideremia [a]	Chorioretinal dystrophy	608
Chondrodysplasia punctata 1	Mild intellectual disability, possible bone defects and short stature	599
Chronic granulomatous disease	Cutaneous and mucocutaneous lesions	609–611
Cleft palate	Bifid uvula	612
Conductive deafness with stapes fixation	Mild hearing loss	613
Deafness X-linked 1 allelic with Charcot-Marie-Tooth 5	Mild high-pitch hearing loss	599
Dilated cardiomyopathy	Cardiac failure	614
Duchenne/Becker muscular dystrophy	Pseudohypertrophy, muscle weakness, cardiomyopathy/conduction defects	615–618
Dyskeratosis congenita	Retinal pigmentation	619
Ectodermal dysplasia	Variable severity of skin, hair, nails, and teeth	599
Emery–Dreifuss muscular dystrophy	Cardiomyopathy/conduction defects	620–622
Fabry disease	Angiokeratomas, corneal dystrophy, "burning" hands and feet, rhabdomyolysis	623, 624
FG syndrome	Anterior displaced anus, facial dysmorphism	625
Fragile X syndrome	Mild-to-moderate intellectual disability, behavioral aberrations, schizoaffective disorder, premature ovarian failure, fragile X tremor ataxia syndrome, women and men premutation carriers	626–628 (see Chapter 16)
G6PD deficiency	Hemolytic crises, neonatal hyperbilirubinemia	629
Hemophilia A and B	Bleeding tendency	630
Hypohydrotic ectodermal dysplasia	Sparse hair, decreased sweating	631, 632
Ichthyosis	Ichthyosis	633
KDM5C gene disease	Intellectual disability	634
Lissencephaly and agenesis of the corpus callosum	Epilepsy with subcortical band heterotopia	599
Lowe syndrome	Lenticular cataracts	635
MASA syndrome/SPG1	Mild intellectual disability, abducted thumbs	599
McLeod neuroacanthocytosis syndrome	Chorea, late-onset cognitive decline	636
Menkes disease	Patchy kinky hair, hypopigmentation	637, 638
Myopia	Mild myopia	639
Nance–Horan syndrome [b]	Posterior Y-sutural cataracts and dental anomalies	640
Norrie disease	Retinal malformations	641
Ocular albinism type 1	Retinal/fundal pigmentary changes	642

Table 1.7 (Continued)

Selected disorders	*Key feature(s) that may occur*	*Selected references*
Oculofaciodigital syndrome (OFD1) allelic with Simson–Galabia–Beheld syndrome 2 and Joubert syndrome	Facial dysmorphism, abnormal digits, and polycystic kidneys	599
Oligodontia	Hypodontia	643
Opitz G/BBB syndrome	Hypertelorism	644
Opitz–Kaveggia syndrome	Mild intellectual disability, hypertelorism	599
Ornithine transcarbamylase deficiency	Hyperammonemia, psychiatric/neurologic manifestations	645, 646
Ovarian cancer	Ovarian cancer	647
Pelizaeus–Merzbacher	Possible mild spasticity	648
Retinoschisis	Peripheral retinal changes	649
Retinitis pigmentosa	Night blindness, concentric reduction of visual field, pigmentary fundal degeneration, extinction of electroretinogram, cone disruption, vision loss	650, 651
MECP2-duplication syndrome	Intellectual disability, neuropsychiatric features, endocrine abnormalities	652
Simpson–Golabi–Behmel syndrome	Extra lumbar/thoracic vertebrae, accessory nipples, facial dysmorphism	653, 654
Spinal and bulbar muscular atrophy	Muscle weakness and cramps	655
Split-hand/split-foot anomaly	Mild split-hand/split-foot anomaly	656
Spondyloepiphyseal dysplasia, late onset	Arthritis	657
Ulnar hypoplasia with lobster-claw deficiency of feet	Slight hypoplasia of ulnar side of hand and mild syndactyly of toes	658
Wiskott–Aldrich syndrome [a]	Abnormal platelets and lymphocytes	659, 660
X-linked intellectual disability	Mostly intellectual disability (many genes), occasional short stature, hypertension, psychiatric symptoms	661–663
X-linked mental retardation	Short stature, hypertelorism	599, 664, 665
X-linked mental retardation (OPHN1)	Cerebellar hypoplasia, distinctive facies	666, 667
X-linked myotubular myopathy	Weakness, respiratory problems	668
X-linked protoporphyria	Life-long photosensitivity; liver disease	669
X-linked retinitis pigmentosa	Retinal changes	670

[a] Uncertain.

[b] May be same disorder.

of pleiotropism (several different effects from a single gene) and heterogeneity (a specific effect from several genes) may confound interpretation in any of these families.

History of a previous child with intellectual disability with a diagnosis deemed "idiopathic" or of unknown cause after chromosomal, fragile X and biochemical analyses, is no longer tenable without whole-exome sequencing[672, 673] (see Chapter 14). Over 700 genes involved in intellectual disability of monogenic origin have been recognized.[674, 675] In a meta-analysis of 3,350 individuals with neurodevelopmental disorders[676–678] the diagnostic yield was 36 percent using whole-exome sequencing. More recently, whole-exome sequencing for patients sent for a chromosomal microarray yielded diagnoses in about 27 percent of intellectual disability cases.[676]

Consanguinity

A wide swath of the world's population have high rates of consanguinity (50–70 percent of births to

consanguineous parents). This especially applies to India, Pakistan, Bangladesh, the Middle East, and Africa. Medical literature is replete with examples of rare severe autosomal recessive disease in these populations. Where family history does not reveal unknown or hidden consanguinity, purposeful or incidental, significant runs of homozygosity seen on a chromosomal microarray (see Chapter 13) frequently will. In those instances, recognition of a shared gene and its mutation within a shared region may unexpectedly lead to a rare diagnosis. Not as well known, perhaps, is that shared variant homozygosity markedly reduces the fertility rate of close consanguineous couples.[679]

Consanguineous couples face increased risks of having children with autosomal recessive disorders; the closer the relationship, the higher the risks. A study in the United Arab Emirates of 2,200 women ≥15 years of age (with a consanguinity rate of 25–70 percent) concluded that the occurrence of malignancies, congenital abnormalities, intellectual disability, and physical handicap was significantly higher in the offspring of consanguineous couples.[680, 681] The pooled incidence of all genetic defects, regardless of the degree of consanguinity, was 5.8 percent, in contrast with a nonconsanguineous rate of 1.2 percent, similar to an earlier study.[681, 682] A Jordanian study also noted significantly higher rates of infant mortality, stillbirths, and congenital malformations among the offspring of consanguineous couples.[683] A Norwegian study of first-cousin Pakistani parents yielded a relative risk for birth defects of about twofold.[684] In that study, 28 percent of all birth defects were attributed to consanguinity. An observational study of 5,776 Indian newborns noted a birth defect prevalence of 11.4 per 1,000 births with a consanguinity rate of 44.74 percent.[685]

A study from Saudi Arabia, where the consanguinity rate exceeds 50 percent, focused on whole-exome sequencing of 2,219 families who had or had lost an affected fetus or child. The study group was constituted by 1,653 individual samples, 127 twosomes, 370 trios, 58 quads, and 11 others.[686] They resolved many cases by determining known causal recessive genes and their mutations, but also discovering multiple previously unknown pathogenic variants. In addition, they recognized some genes that also had a dominant rather than recessive mode of inheritance. Their prenatal diagnostic detection rate was 46.2 percent (30/65 cases), 87 percent of which were autosomal recessive.

Whole-exome sequencing following discovery of a fetal anomaly not resolved by karyotyping or chromosomal microarray may well provide a precise diagnosis. In a study of 102 anomalous fetuses, a definitive or probable diagnosis was made in 21 (20.6 percent).[687] A similar small study of 19 families with fetal anomalies yielded candidate variants in 12 (63 percent).[688] A systematic evidence-based review of exome and genome sequencing for congenital anomalies or intellectual disability on behalf of the ACMG concluded that a change in patient management was observed in nearly all studies, including an impact on reproductive outcomes.[689]

The occurrence of rare, unusual or unique syndromes invariably raises questions about potential consanguinity and common ancestral origins. Clinical geneticists will frequently be cautious in these situations, providing potential recurrence risks of 25 percent. Consanguineous couples may opt for the entire gamut of prenatal tests to diminish even their background risks, with special focus on their ethnic-specific risks.[690] Abnormal or concerning prenatal ultrasound observations in pregnancies by consanguineous couples may prompt prenatal whole-exome sequencing.[691]

Environmental exposures that threaten fetal health

Concerns about normal fetal development after exposure to medications, alcohol, illicit drugs, chemical, infectious or physical agents, and/or maternal illness are among the most common reasons for genetic counseling *during* pregnancy. Many of these anxieties and frequently real risks could be avoided through preconception care. Public health authorities, vested with the care of the underprivileged in particular, need to focus their scarce resources on preconception and prenatal care and on the necessary public education regarding infectious diseases, immunization, nutrition, and genetic disorders.

In preconception planning, careful attention to broadly interpreted fetal "toxins" is necessary, and avoidance should be emphasized. Alcohol, smoking, illegal drug use, certain medications, and X-ray exposure require discussion. Estimates of the prevalence of the fetal alcohol spectrum disorder

approximate 2 per 1,000 livebirths[692] in the United States but in certain regions and countries rates reach as high as 10 percent.[693–695] There is a limited list of known and proven human drug teratogens[696] (see Chapter 3). Maternal use of specific teratogenic medications,[697] such as isotretinoin, may be missed, unless the physician expressly inquires about them.

Preconception advice to avoid heat exposure in early pregnancy is appropriate. Our observations showed a 2.9 relative risk for having a child with a NTD in mothers who used a hot tub during the first 6 weeks of pregnancy.[698] High fever in the very early weeks of pregnancy is a potential teratogen[698] and should be avoided and treated promptly. Animal studies show that commonly used drugs enter the fetal brain.[699]

A report from the Spanish Collaborative Study of Congenital Malformations noted a 2.8-fold increased risk of Down syndrome in the offspring of women ≥35 years of age and who were taking oral contraceptives when they became pregnant.[700]

Identification of preconception options

The time to deal with unwanted risks is not during the second trimester of pregnancy, as is so often the case in practice. Preconception counseling will identify specific risks and attendant options, which include the following:

- Knowledge of family history
- Attention to maternal health (e.g. diabetes control,[701, 702] confirm cardiac and vascular normality)
- Decision not to have children (includes consideration of vasectomy or tubal ligation)
- Adoption
- *In vitro* fertilization
- Gamete intrafallopian tube transfer or allied techniques
- Artificial insemination by donor
- Ovum donation (includes surrogacy)
- Intracytoplasmic sperm injection
- Carrier detection tests
- Noninvasive prenatal screening by fetal DNA in the maternal circulation
- Naternal serum α-fetoprotein screening for NTDs
- Prenatal diagnosis (CVS, amniocentesis, cordocentesis, ultrasound, MRI)
- Preimplantation genetic testing
- Fetal treatment or surgery for selected disorders
- Folic acid supplementation in periconceptional period (see Chapter 10)
- Noninvasive prenatal testing (aneuploidy; monogenic disorders)
- Selective abortion

Genetic counseling as a prelude to prenatal diagnosis

The assumption that noninvasive prenatal testing for common chromosomal abnormalities (see Chapter 7) is a screening and not a diagnostic test, is unfortunately common. Many women receiving a normal report opt to avoid an amniocentesis. The vast majority will be vindicated, but some will complete pregnancy with a child having a disorder that could have been diagnosed in early gestation. Physicians and counselors are advised to remind women of this limitation, given that about half of all chromosomal abnormalities will be missed by the noninvasive screen.[703]

Prospective parents should understand their specific indication for prenatal tests and the limitations of such studies. Frequently, one or both members of a couple fail to appreciate how focused the prenatal diagnostic study will be. Either or both may have the idea that all causes of intellectual disability or congenital defects will be detected or excluded. It is judicious for the physician to urge that both members of a couple come for the consultation before CVS or amniocentesis. Major advantages that flow from this arrangement include a clearer perception by the partner regarding risks and limitations, a more accurate insight into his family history, and an opportunity to detect an obvious (although unreported or undiagnosed) genetic disorder of importance (e.g. Treacher–Collins syndrome, facioscapulohumeral dystrophy or one of the orofacial–digital syndromes). Women making an appointment for genetic counseling should be informed about the importance of having their partner with them for the consultation, avoiding subsequent misunderstanding about risks, options, and limitations.

Before prenatal genetic studies are performed, a couple should understand the inherent limitations both of the laboratory studies and, when relevant, of ultrasound. For detection of chromosomal

disorders, they should be aware of potential maternal cell admixture and mosaicism (see Chapter 11). When faced with potential X-linked hydrocephalus, microcephaly, or other serious X-linked disorders, and the realization of less than 100 percent certainty of diagnosis, couples may elect fetal sex determination as the basis for their decision to keep or terminate a pregnancy at risk. For some, neither chromosomal microarrays, biochemical assays, nor DNA analyses will provide results with 100 percent certainty.

The time taken to determine the fetal karyotype or other biochemical parameters should be understood before amniocentesis. The known anxiety of this period can be appreciably aggravated by a long, unexpected wait for a result. The need for a second amniocentesis is rarer nowadays but, in some circumstances, fetal blood sampling remains an additional option that may need discussion. Despite the very unlikely eventuality that no result may be obtained because of failed cell culture or contamination, this issue should be mentioned.

The potential possibility for false-positive or false-negative results should be carefully discussed when applicable. Any quandary stemming from the results of prenatal studies is best shared immediately with the couple. The role of the physician in these situations is not to cushion unexpected blows or to protect couples from information that may be difficult to interpret. All information available should be communicated, including the inability to accurately interpret the observations made. This is especially so with the use of the chromosomal microarray (see Chapter 13) and whole-exome sequencing (see Chapter 14). Cautions are appropriate with special reference to VOUS (see Chapter 14), that require in addition, parental samples to determine inherited or *de novo* changes.

Other key issues to be considered by the genetic counselor and discussed when appropriate with the consultand follow.

Informed consent

Consent for minor procedures including amniocentesis and CVS has been a requirement for decades and needs no repetition. However, the advent of chromosomal microarrays (see Chapter 13) and whole-exome sequencing for prenatal diagnosis (see Chapter 14) requires additional explanations and caveats. Informed consent for these two technologies is focused on the potential results, not sampling risks and procedures. The specific issues primarily involve the interpretation of results, their significance, the small possibility of uncertain findings, test limitations, and incidental results.

Chromosomal microarray testing adds up to 6–10 percent to a prenatal diagnosis result (see Chapter 13) beyond the 8–10 percent for routine karyotyping, and whole-exome sequencing when done after the ultrasound discovery of fetal structural abnormality adds an additional 6.2–80 percent.[691, 704–708] This absurd range reflects very small case series, varying indications, and the presence of single or multiple fetal abnormalities. A more likely detection range would be between 8.5 and 32 percent.[707, 708]

Prenatal diagnosis using whole-exome sequencing (see Chapter 14) is primarily focused on pregnancies in which fetal structural abnormality has been observed. A much less frequent indication would be a recent or late diagnosis of a parent with a likely monogenic disorder characterized by genetic heterogeneity. No matter the indication, the informed consent obtained incorporates and extends current practice for chromosomal microarray tests. The decision to offer whole-exome sequencing will almost inevitably come on the heels of the detection of fetal abnormality and in an atmosphere of tension and anxiety. Any center offering whole-exome sequencing will have, of necessity, established their informed consent procedure. The following list of pointers are likely to find common ground:

1. Pre- and postgenetic counseling by a geneticist or genetic counselor is a prerequisite, with strict adherence to ethical standards.[709, 710]
2. *Both* parents should be in attendance.
3. Explanations should use simple language, no jargon, and be in the language of the parents (with an interpreter, if needed).
4. The details of the fetal abnormality, effect on a child (pain; disability), a progressive disorder or not, and life expectancy.
5. The use of targeted sequencing, trios, and gene panels will need explanations, including the reason and need for prior or simultaneous chromosomal microarrays.
6. The time needed to obtain a result.

7. The likely detection rate and the limitations of whole-exome sequencing (e.g. repeat expansion disorder; mosaicism).
8. The occurrence of false positives, false negatives, or error.
9. The unexpected discovery of nonpaternity or consanguinity.
10. The detection of a variant of unknown significance.[709]
11. A "secondary finding"[711–714] unrelated to the original purpose of the analysis.
12. The opportunity for the parents to opt out of receiving "secondary findings"[715] which they should understand may have personal important health implications.
13. The choice to refuse testing.

Presymptomatic or predictive testing

Presymptomatic or predictive testing is available for a rapidly increasing number of disorders, especially neuromuscular and neurodegenerative (see Chapter 14). Huntington disease is the prototype, and predictive testing using guidelines promulgated by the World Federation of Neurology,[716–719] the International Huntington Association, and the European Huntington Disease Network[719] are well established. Various programs report that a majority of patients are able to cope when it is found that they are affected,[225–230, 720, 721] and, at least after a 1-year follow-up, potential benefit has been shown even in those found to be at increased risk.[722] A European collaborative study evaluated 180 known carriers of the Huntington disease gene mutation and 271 noncarriers, all of whom received a predictive test result. Although the follow-up was only 3 years for about half the group, pregnancies followed in 28 percent of noncarriers and only 14 percent of carriers.[723] Prenatal diagnosis was elected by about two-thirds of those who were carriers.

Genetic counseling for Huntington disease when intermediate alleles with 27–35 CAG repeats are determined, pose significant challenges.[724] Intermediate CAG repeats have been associated with behavioral, movement, and cognitive problems.[725–727] The concern is the unpredictable likelihood of expansion which might account for 7 percent of new mutations.[724] Providing counseling for those with low penetrance alleles (36–39 CAG repeats) is no less challenging. Repeats in this range are estimated to occur randomly in the general population with a frequency of about 1 in 400.[728] For patients with 36–39 repeats considering prenatal diagnosis, many factors will need to be addressed. These include all options discussed earlier and uncertainty, penetrance, anticipation, age of onset, and life expectancy. Experienced geneticists with an established program that includes predictive/presymptomatic testing for Huntington disease should preferably be consulted.

As others earlier,[729] we remain very concerned about the use of a test that can generate a "no hope" result. Even in sophisticated programs offering Huntington disease tests, fewer than expected at-risk individuals requested testing.[730] A multicenter Canadian collaborative study evaluated the uptake, utilization, and outcome of 1,061 predictive tests, 15 prenatal tests, and 626 diagnostic tests from 1987 to 2000. The uptake for predictive testing was about 18 percent (range 12.5–20.7 percent).[731] Of the 15 who had prenatal tests, 12 had an increased risk, which led to pregnancy termination in all but one.[731]

The motivations leading to the very difficult decision to have or not to have a predictive test are being recognized as extremely complex.[732] In a Danish study before DNA tests were available, one in 20 individuals *at risk* for Huntington disease committed suicide, more than double the population rate,[733] highlighting earlier reports of high suicide rates[734] and emphasizing the erosive effects of uncertainty. However, a worldwide assessment of suicide rates, suicide attempts, or psychiatric hospitalizations *after* predictive testing did not confirm a high rate of suicide.[735] In their worldwide questionnaire study sent to predictive testing centers, the authors noted that 44 individuals (0.97 percent) among 4,527 tested had five suicides, 21 suicide attempts, and 18 hospitalizations for psychiatric reasons. All those who committed suicide had signs of Huntington disease, while 11 (52.4 percent) of the 21 individuals who attempted suicide were symptomatic. Suicidal ideation or attempts remain a devastating reality for Huntington disease, especially given the psychopathology in those affected.[736, 737] Depression, anxiety, and bipolar disorder are not infrequent. Suicidal behavior may be about 12 times that in the population at large, reaching an estimated 20 percent.[738, 739] Others have written about the psychologic burden

created by knowledge of a disabling fatal disease decades before its onset.[740–742]

Hayden[743] warned that it is inappropriate to introduce a predictive test that "has the potential for catastrophic reactions" without a support program, including pretest and post-test counseling and specified standards for laboratory analyses. In one study, 40 percent of individuals tested for Huntington disease and who received DNA results required psychotherapy.[744] A 5-year longitudinal study of psychologic distress after predictive testing for Huntington disease focused on 24 carriers and 33 tested noncarriers. Mean distress scores for both carriers and noncarriers were not significantly different but carriers had less positive feelings.[745] A subgroup of tested persons were found to have long-lasting psychologic distress. An interview study of 20 who tested negative for Huntington disease revealed reactions that included obvious relief and gratitude, wishes to have (more) children, and life changes that included pursuit of a career and ending an unhappy relationship.[746] Negative reactions included survivor guilt with sadness and depression or a feeling of pressure to do something extraordinary with their lives.

Homozygotes for Huntington disease are rare[747, 748] and reported in one out of 1,007 patients (0.1 percent). Counseling a patient homozygous for Huntington disease about the 100 percent probability of transmitting the disorder to each child is equivalent to providing a nonrequested predictive test,[749] while failing to inform the patient of the risks would be regarded as the withholding of critical information. Pretest counseling in such cases would take into consideration a family history on both sides and therefore be able to anticipate the rare homozygous eventuality.

On the other hand, an increasing number of examples already exist (see Chapter 14) in which presymptomatic testing is possible and important to either the patient or future offspring or both. Uptake has been high by individuals at risk, especially for various cancer syndromes.[750] Use of DNA linkage or mutation analysis for ADPKD[751, 752] may lead to the diagnosis of an unsuspected associated intracranial aneurysm in 8 percent of cases (or 16 percent in those with a family history of intracranial aneurysm or subarachnoid hemorrhage[753]) and preemptive surgery, with avoidance of a life-threatening sudden cerebral hemorrhage. It is worth noting that a subgroup of families has features similar to Marfan syndrome and that haplo-insufficiency of the *PKD1* gene influences the transforming growth factor-β (TGFβ) signaling pathway.[754] In a study of 141 affected individuals, 11 percent decided against bearing children on the basis of the risk.[755] These authors noted that only 4 percent of at-risk individuals between 18 and 40 years of age would seek elective abortion for an affected fetus. The importance of accurate presymptomatic tests for potential at-risk kidney donors has been emphasized.[756] Organ donation by a sibling of an individual with ADPKD, later found to be affected, has occurred more than once. Since the *PKD1* gene abuts the tuberous sclerosis (*TSC2*) gene, heterozygous deletions may lead to a contiguous gene-deletion syndrome.[757]

Individuals at 50 percent risk for familial polyposis coli (with inevitable malignancy for those with this mutated gene) who undergo at least annual colonoscopy could benefit from a massive reduction in risk (from 50 percent to <1 percent) after DNA analysis. Individuals in whom this mutation was found with greater than 99 percent certainty may choose more frequent colonoscopies and eventually elective colonic resections, thereby saving the lives of the vast majority. The need for involvement of clinical geneticists is especially evident in this and other disorders in which complex results may emerge. Giardiello et al.[758] showed that physicians misinterpreted molecular test results in almost one-third of cases.

Families with specific cancer syndromes, such as multiple endocrine neoplasia, Li–Fraumeni syndrome, or von Hippel–Lindau disease, may also benefit by the institution of appropriate surveillance for those shown to be affected by molecular analysis when they are still completely asymptomatic, once again, in all likelihood, saving their lives. In one case, an evaluation using array comparative genomic hybridization to determine the cause of intellectual disability revealed a *de novo* deletion within 3p25.3 that included the von Hippel–Lindau gene.[759] For example, elective thyroidectomy is recommended for multiple endocrine neoplasia type 2B by 5 years of age in a child with this mutation, given the virtual 100 percent penetrance of this gene and the possible early appearance of cancer.[760] Predictive testing, even of children at high genetic risk, poses a

host of complex issues.[761] Where life-threatening early-onset genetic disorders are concerned, testing in early childhood still requires the exercise of parental prerogatives. However, failure to test because of parental refusal may invite the reporting of child neglect.[762]

Identification of specific mutations in the breast/ovarian cancer susceptibility genes (*BRCA1* and *BRCA2*) has led to us providing requested prenatal diagnosis. Mothers with such mutations who have seen their own mothers and sisters die have made the difficult personal decision to terminate pregnancy.[763] DudokdeWit et al. laid out a detailed and systematic approach to counseling and testing in these families.[764] In their model approach, important themes and messages emerge:

- Each person may have a different method of coping with threatening information and treatment options.
- Predictive testing should not harm the family unit.
- Special care and attention are necessary to obtain informed consent, protect privacy and confidentiality and safeguard "divergent and conflicting intrafamilial and intergenerational interests."

A French study noted that 87.7 percent of women who were first-degree relatives of patients with breast cancer were in favor of predictive testing.[765] Two specific groups of women are especially involved. The first are those who, at a young age, have already had breast cancer, with or without a family history, and in whom a specific mutation has been identified. Recognizing their high risk for breast and/or ovarian cancer,[766, 767] these women have grappled with decisions about elective bilateral mastectomy and oophorectomy and mastectomy of a contralateral breast. Current estimates of penetrance are 36–85 percent lifetime risk for breast cancer and 16–60 percent lifetime risk for ovarian cancer, depending upon the population studied.[768]

The second group of women are of Ashkenazi Jewish ancestry. These women have about a 2 percent risk of harboring two common mutations in *BRCA1* (c.68 69delAG and c.5266dupC) and one in *BRCA2* (c.5946delT) that account for the majority of breast cancers in this ethnic group.[768, 769] Regardless of a family history of breast or ovarian cancer, the lifetime risk of breast cancer among Jewish female mutation carriers was 82 percent in a study of 1,008 index cases.[770] Breast cancer risk by 50 years of age among mutation carriers born before 1940 was 24 percent, but 67 percent for those born after 1940.[770] Lifetime ovarian cancer risks were 54 percent for *BRCA1* and 23 percent for *BRCA2* mutation carriers.[770]

It can easily be anticipated that, with identification of mutations for more and more serious/fatal monogenic genetic disorders (including cardiovascular, cerebrovascular, neurodegenerative, connective tissue, and renal disorders, among others), prospective parents may well choose prenatal diagnosis in an effort to avoid at least easily determinable serious or fatal genetic disorders. Discovery of the high frequency (28 percent) of a mutation (T to A at *APC* nucleotide 3920) in the familial adenomatous polyposis coli gene among Ashkenazi Jews with a family history of colorectal cancer[771] is also likely to be followed by thoughts of avoidance through prenatal diagnosis. This mutation has been found in 6 percent of Ashkenazi Jews.[771] Because of the ability to determine whether a specific cancer will develop in the future, given identification of a particular mutation, much agonizing can be expected for many years. These quandaries will not and cannot be resolved in rushed visits to the physician's office as part of preconception or any other care. Moreover, developing knowledge about genotype–phenotype associations and many other aspects of genetic epidemiology will increasingly require referral to clinical geneticists.

Expansion mutations and anticipation

In 1991 the first reports appeared of dynamic mutations resulting from the unstable expansion of trinucleotide repeats.[772] Thus far, at least 40 proven disorders with these unstable repeats have been described (see Chapter 14).[773] All disorders described thus far are autosomal dominant or X-linked, except for Friedreich ataxia and progressive myoclonic epilepsy with myoclonic tremor,[774–776] which are autosomal recessive and also unique in having intronic involvement.[777] Typically for these disorders (except for Friedreich ataxia), the carrier will have one normal allele and a second expanded allele. The repeat expansion disorders, although diverse, share many basic features. They arise from normally existing polymorphic repeats, are unstable, changing size on

transmission, with longer repeats associated with severe and earlier onset disease, and highly variable phenotypes.[773]

These disorders (except for Friedreich ataxia and progressive myoclonic epilepsy type 1)[774] are also generally characterized by progressively earlier manifestations and/or more severe expression with succeeding generations. This genetic mechanism, called anticipation, is associated with further expansion (rarely contraction) of the specific triplet repeat (Box 1.2). These disorders characteristically have a direct relation between the number of repeats and the severity of disease with an inverse relation between the number of repeats and age of onset. These aspects of anticipation weigh heavily in preconception counseling when it becomes clear that the relatively mild-to-moderate status of a mother with myotonic muscular dystrophy type 1, for example, with a 50 percent risk, could have an affected child with severe congenital myotonic muscular dystrophy.[778] Triplet size in this disorder correlates significantly with muscular disability as well as intellectual and gonadal dysfunction.[779] These authors also noted that triplet repeat size did not correlate with the appearance of cataract, myotonia, gastrointestinal dysfunction, and cardiac abnormalities. For myotonic dystrophy type 2 there is no correlation between disease severity and tetranucleotide (CCTG) repeat length.[780] Women with myotonic dystrophy type 2 have an increased risk of ovarian and endometrial cancer.[781, 782] Somatic mosaicism with different amplification rates in various tissues may be one possible explanation for variable phenotypes. Fortunately, in very few repeat expansion disorders, including Huntington disease, do *de novo* mutations occur.[783] Parent-of-origin effects influencing anticipation are also recognized (see fragile X syndrome discussion in Chapter 16). The offspring of fathers with Huntington disease, spinocerebellar ataxias types 2 and 7, for example, may present clinically, and on occasion even before the father has become symptomatic.[784] For myotonic muscular dystrophy, paternally transmitted small expansions have

Box 1.2 Selected genetic disorders with anticipation

Disorders with anticipation

- All autosomal dominant disorders with repeat expansion mutations listed in Chapter 14 Table 14.2
- Charcot–Marie–Tooth disease type 1A
- Dyskeratosis congenita
- Familial amyloid polyneuropathy
- Hereditary nonpolyposis colorectal cancer (Lynch syndrome)

Disorders with suspected anticipation

- Ablepharon–macrostomia syndrome
- Adult-onset idiopathic dystonia
- Autosomal dominant acute myelogenous leukemia
- Autosomal dominant familial spastic paraplegia
- Autosomal dominant polycystic kidney disease (PKD1)
- Autosomal dominant rolandic epilepsy
- Behçet syndrome
- Bipolar affective disorder
- Crohn disease
- Facioscapulohumeral muscular dystrophy
- Familial adenomatous polyposis
- Familial breast cancer
- Familial chronic myeloproliferative disorders
- Familial Hodgkin lymphoma
- Familial intracranial aneurysms
- Familial pancreatic cancer
- Familial paraganglioma
- Familial Parkinson disease
- Familial primary pulmonary hypertension
- Familial rheumatoid arthritis
- Graves disease
- Hodgkin and non-Hodgkin lymphoma
- Holt–Oram syndrome
- Idiopathic pulmonary fibrosis
- Lattice corneal dystrophy type I (LCD1)
- Li–Fraumeni syndrome
- Ménière disease
- Obsessive–compulsive spectrum disorders
- Oculodentodigital syndrome
- Paroxysmal kinesigenic dyskinesia (PKD)
- Restless legs syndrome
- Schizophrenia
- Total anomalous pulmonary venous return
- Unipolar affective disorder

a higher risk of symptomatic offspring compared with females.[785] Rarely, two triplet repeat disorders occur concurrently, as reported in a patient with both oculopharyngeal muscular dystrophy and Huntington disease.[786] Anticipation does occur in Huntington disease, but not in oculopharyngeal muscular dystrophy. It is well documented that the paradoxical effects of repeat interruptions in the ATTCT expansion alleles in spinocerebellar ataxia type 10 result in a contraction in intergenerational repeat size.[787] *De novo* repeat interruptions may also be associated with less somatic instability and few or no symptoms and signs in myotonic muscular dystrophy type 1.[788, 789] Spinocerebellar ataxia type 2 has also been associated with Parkinsonism and an increased risk for amyotrophic lateral sclerosis (ALS).[790] Almost all of the 59 autosomal recessive spinocerebellar ataxias[791] are not characterized by repeat expansions. Marked heterogeneity in the clinical features are common.

Recognition in the last decade of hexanucleotide repeat expansions in the *C9orf72* gene reveal additional challenges that have raised consideration of prenatal diagnosis, as discussed under "Accurate diagnosis." Mutations in *C9orf72* have been reported in 40–50 percent of cases with familial amyotrophic lateral sclerosis, between 3.5 percent and 8 percent of sporadic ALS cases,[792–795] and in 25 percent of familial frontotemporal lobar degeneration, with about 7 percent in sporadic cases.[793, 794] The clinical spectrum includes patients with frontotemporal dementia and ALS as well as those with a corticobasal syndrome.[796] The real burden and likely involvement of prenatal diagnosis is the recognition of *C9orf72* expansions noted in Western Europe as occurring in 18.52 percent of familial cases and 6.26 percent in sporadic cases of frontotemporal lobar degeneration.[797] Overall frequencies of these expansions in Finland, Sweden, and Spain were much higher, being 29.33 percent, 20.73 percent, and 25.49 percent, respectively.[797] A further distressing aspect of the *C9orf72* expansion is the symptomatology that extends to family members who *do not* have the expansion. In a study of 1,414 first- and second-degree relatives, a statistically significant number had an increased risk of schizophrenia (hazard ratio of 4.9), late-onset psychosis, and suicide.[798] There is also evidence of anticipation.[799]

Preimplantation genetic testing (see Chapter 2) has been successful for many repeat expansion disorders including fragile X syndrome (see Chapter 16), Huntington disease, myotonic muscular dystrophy, and spinocerebellar ataxias types 2 and 12.[800–802]

Imprinting and uniparental disomy

All that is genetic is not necessarily Mendelian. Developing gametes or early embryonic cells may have genes deleted or silenced, with such primal events being of a single parent origin and lifelong. Moreover, these occurrences may be a consequence of an environmental (epigenetic) factor or influence. Notwithstanding this epigenetic phenomenon, the genomic change, termed "imprinting," is heritable with potentially serious clinical implications. Epigenetics does not alter DNA sequence, but it does alter its expression.

The expectation is that each pair of autosomes have an equal matched allele from each parent. Infrequently, a pair may be constituted by alleles from one parent, termed uniparental disomy (UPD). If those two are chromosome 7 alleles from one parent and harbor a mutation in the *CFTR* gene, and the chromosome 7 from the other parent is lost during meiosis, the offspring will have autosomal recessive cystic fibrosis.[803, 804] Multiple different disorders are known to be a consequence of UPD and influenced by parent of origin (see Chapter 14).

Relatively rarely, with biparental alleles, one gene (or a cluster) on one allele may be silenced (imprinted). If it is the paternally only expressed region on chromosome 15q, the consequence would be Prader–Willi syndrome, and if it is the maternally expressed *UBE3A* gene, Angelman syndrome would be the consequence. Silencing occurs through a process of DNA methylation. The repressed allele is methylated; the functional allele is unmethylated. Various assays are available to determine methylation status.[805, 806] Multilocus imprinting may also occur, and result in a phenotypic spectrum.[807] Accurate detection of UPD can also be determined by whole-exome sequencing.[808] Imprinted gene clusters are primarily found on chromosomes 6, 7, 11, 14, 15, and 20.[809]

Recommendations made by the ACMG[810] for prenatal UPD testing include the following:

- Multiple-cell pseudomosaicism or true mosaicism for trisomy or monosomy of chromosomes 6, 7, 11, 14, 15, or 20 from amniocentesis or CVS.
- Multiple-cell pseudomosaicism or true mosaicism for trisomy or monosomy of chromosomes 6, 7, 11, 14, 15, or 20 in CVS followed by normal karyotype in amniocentesis.
- In the context of preimplantation genetic screening (PGS), a transfer of mosaic embryos with trisomy or monosomy of chromosomes 6, 7, 11, 14, 15, or 20 should be followed by prenatal studies including UPD testing.
- Prenatal imaging anomalies consistent with a UPD phenotype. The classic example is the pathognomonic coat-hanger sign in paternal UPD14.
- Familial or *de novo* balanced Robertsonian translocation or isochromosome involving chromosome 14 or 15 based on CVS or amniocentesis. Both familial and *de novo* translocations are associated with an increased risk for UPD.
- *De novo* small supernumerary marker chromosome with no apparent euchromatic material in the fetus.
- Non-Robertsonian translocation between an imprinted chromosome with possible 3:1 disjunction that can lead to trisomy or monosomy rescue or gamete complementation. Although every chromosome abnormality that increases the occurrence of nondisjunction in theory would increase the risk of UPD of the chromosomes involved, there are only very few cases reported.

Imprinting disorders are the results of abnormal expression of imprinted genes at seven imprinted domains on the six chromosomes noted above. These disorders are due to different molecular changes that include copy number variation (loss or gain), UPD, point mutation in the active allele, an epimutation resulting in gain or loss of DNA methylation at the imprinting control region, a microdeletion or microduplication at an imprinting control region interfering with DNA methylation, and structural chromosome rearrangements.[811] Recurrence risks for imprinting disorders vary according to the molecular alteration. For example, copy number variations or point mutations may occur *de novo* or come from one parent, who may or may not be affected, depending upon which grandparent transmitted the mutant allele.[811] For Angelman syndrome and the Prader–Willi syndrome genetic alterations are almost invariably *de novo*, resulting in extremely low risks of recurrence. The expectation, however, is a point mutation in the culprit *UBE3A* gene that causes Angelman syndrome, with a recurrence rate of 50 percent when inherited from an unaffected mother. Fortunately, only about 1 percent of our genes find expression from one or other parent.[812]

Multilocus imprinting disorders with maternal effect genes (including *NLRP2*, *NLRP7*, and *PADI6*) can affect oocytes and resulting offspring, who may manifest with atypical imprinting disorders.[813, 814] Multilocus imprinting disturbance in methylation may affect growth and development. Epigenetic effects are evident in sperm, oocyte, and zygote genomes.[815, 816] It is no surprise then, that mutations in *NLRP* genes may result in early miscarriages, hydatidiform moles, and apparent infertility.[813] Most imprinted genes express in the placenta, and loss of imprinting can affect placental weight, fetal growth, and development,[817–821] and the regulation of placental hormones.[821]

Potential imprinting disturbances at the sperm, oocyte, or zygote stages are associated with ART and preimplantation procedures. Cogent evidence exists of an increased incidence of imprinting disorders following ART.[822–828] In the most extensive report to date, Hattori et al.[822] in a nationwide study in Japan, reported on 931 patients with imprinting disorders. These included 117 cases of Beckwith–Weidemann syndrome, 67 with Silver–Russel syndrome, 520 with Prader–Willi syndrome, and 227 with Angelman syndrome. Most were conceived through ART including intracytoplasmic sperm injection. They noted a 4.46- and 8.91-fold increased frequency of Beckwith–Weidemann syndrome and Silver–Russel syndrome respectively. Cortessis et al.,[828] in a meta-analysis of 23 studies on ART and the occurrence of imprinting disorders, reported significant odds ratios of 4.7 for Angelman syndrome, 5.8 for Beckwith–Weidemann syndrome, 2.2 for Prader–Willi syndrome, and 11.3 for Silver–Russel syndrome.

Mutations in imprinted genes that occur after fertilization can result in somatic mosaicism.[829] An interesting example is represented by discordant monozygotic twins in which only one has the disorder (Beckwith–Weidemann syndrome)[830–832]

or Silver–Russel syndrome,[829, 833] pointing to epigenetic disturbances in early development.[829]

About 1.7 percent of births in the United States result from ART.[834] Although the frequency of imprinting disorders is increased, the actual risks are very low, but should be discussed.

Genotype–phenotype associations

DNA mutation analysis has slowly clarified genotype–phenotype associations requiring extensive databases and definitive phenotyping[835, 836] (see Chapter 14). Notwithstanding this limitation, mutation analysis does provide precise prenatal diagnosis opportunities and detection of affected fetuses even with compound heterozygosity. Simple logic might have concluded that genotype at a single locus might predict phenotype. For monogenic disorders this is frequently not the case. Allelic combinations of missense, nonsense, and compound heterozygous mutations within different genes could result in overlapping clinical phenotypes as exemplified for the Kabuki syndrome and Schinzel–Giedion syndrome.[837] Now that clinical diagnostic criteria have been established[838] and two genes (*KMT2D* and *KDM6A*) recognized, syndrome identification has been facilitated.[839] Additional novel pathogenic variants continue to be discovered.[840] It appears that hyperinsulinism, long halluces, large central incisors, and hypertrichosis are more common in Kabuki syndrome due to *KDM6A* mutations,[841, 842] while the classic Kabuki facial features and renal/palatal anomalies are more commonly found with *KMT2D* mutations.[839, 843] In the autosomal dominant Marfan syndrome (due to mutations in *FBN1*), family members with the same mutation may have severe ocular, cardiovascular, and skeletal abnormalities, while siblings or other close affected relatives with the same mutation may have mild effects in only one of these systems.[844] In Gaucher disease with one of the common Ashkenazi Jewish mutations, only about one-third of homozygotes have significant clinical disease.[845] At least two-thirds have mild or late-onset disease or remain asymptomatic (see Chapter 21). Compound heterozygotes for this disorder involving mutations p.L444P and p.N370S have included a patient with mild disease first diagnosed at 73 years of age, while another requiring enzyme replacement therapy was diagnosed at the age of 4 years.[846]

In cystic fibrosis, a strong correlation exists between genotype and pancreatic function but only a weak association has been noted with the respiratory phenotype[847] (see Chapter 15). Although individuals who are homozygous for the common cystic fibrosis mutation (ΔF508) can be anticipated to have classic cystic fibrosis, those with the less common mutation (p.R117H) are likely to have a milder disease.[848] On occasion, an individual who is homozygous for the "severe" ΔF508 mutation might unexpectedly exhibit a mild pancreatic-sufficient phenotype. Illustrating the complexity of genotype–phenotype associations is the instance noted by Dork et al.[849] of a mildly affected ΔF508 homozygote whose one chromosome 7 carried both the common ΔF508 mutations and a cryptic p.R553Q mutation. Apparently, a second mutation in the same region may modify the effect of the common mutation, permitting some function of the chloride channel[850] and thereby ameliorating the severity of the disease. Modifying genes in cystic fibrosis are being increasingly recognized[851–853] (see Chapter 15).

The extensive mutational heterogeneity in hemophilia A[854–856] is related not only to variable clinical severity but also to the increased likelihood of antifactor VIII antibodies (inhibitors) developing. Miller et al.[857] found about a fivefold higher risk of inhibitors developing in hemophiliac males with gene deletions compared with those without deletions. In Netherton syndrome, a severe autosomal recessive ichthyosis that affects skin, hair, and immune system, upstream mutations in the *SPINK5* gene correlate with more severe phenotypes.[858]

The many mutations and wide phenotypic range seen in neurofibromatosis type 1 is well known, and characterized by variable expressivity and age-dependent clinical features. This variability makes phenotype prediction difficult. Among the few thousand constitutional variants in the *NF1* gene, recurrent pathogenic missense variants at p.Met1149, p.Arg1276 or p.Lys1423 have been associated with a Noonan-like phenotype.[859] Moreover, these authors also found that mutations at p.Arg1276 was associated with spinal neurofibromas, and that mutations at both p.Lys1423 and p.Arg1276 were associated with a high prevalence of cardiovascular abnormalities, including pulmonic stenosis.

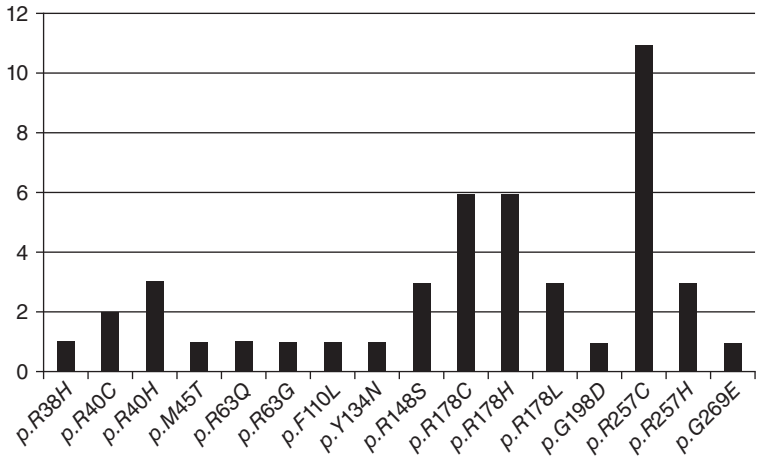

Figure 1.3 Shown are the 16 pathogenic variants reported in the *ACTG2* gene and the number of times each mutation was observed in 45 probands.[863]

Chronic intestinal pseudo-obstruction (CIPO), also known as megacystis–microcolon–intestinal–hypoperistalsis syndrome, is a severe debilitating visceral myopathy involving enteric smooth muscle.[860–863] Mutations in the *ACTG2* gene account for about 44–50 percent of cases. We noted in a whole-exome sequencing study a mutational hotspot in the *ACTG2* gene (Figure 1.3).[863] We subsequently determined somatic *ACTG2* mosaicism,[864] further complicating genotype–phenotype determination.

Japanese authors have assembled mutation data for the *NOTCH3* gene and recognized three mutations as major contributors to the phenotype of CADASIL.[865] They also recognized gender differences in symptomatology (worse in males) that included migraines, stroke, psychiatric problems, cognitive impairments, and dementia. Although CADASIL is mostly adult onset, we have provided prenatal diagnosis for a family with an affected young father, as noted earlier.

Given the history of a previously affected offspring with a genetic disorder, the preconception visit serves as an ideal time to refocus on any putative diagnosis (or lack thereof), to check constantly updated databases where prior alterations are or are not considered pathogenic, and to perform newly available mutation analyses when applicable.

Recognition of genotype–phenotype associations remains challenging for reasons that include expressivity, penetrance, multiple causal genes, modifier alleles, compound heterozygosity, locus heterogeneity, interacting polymorphisms of small effect, and digenic inheritance. For the vast majority of monogenic disorders, even without known epigenetic influence (such as epilepsy, microcephaly, holoprosencephaly, hydrocephalus, craniosynostosis), definitive genotype–phenotype associations remain unknown.

Somatic mosaicism

We are all somatic postzygotic mosaics, either born that way or later as a consequence of spontaneously occurring mutations during our lifetimes. Using single-cell whole-genome sequencing of B lymphocytes, Zhang et al.[866] found that the number of somatic mutations increases from <500 per cell in newborns to >3,000 per cell in centenarians. These dynamic changes involving other tissues as well, are likely to be associated with cancer and aging,[867] and many disorders (Table 1.8).

Somatic mosaicism has been described in almost all autosomal dominant disorders. Tissue- or organ-specific segmental mosaicism explains certain overgrowth syndromes exemplified by the PIK_3CA-associated developmental disorders that result in focal overgrowth, brain overgrowth, or capillary malformations with overgrowth.[868–870]

A remarkable example of focal growth due to somatic mosaicism was the hyperinsulinism noted in an infant without any signs of the Beckwith–Wiedemann syndrome. Following removal of 80 percent of the pancreas, atypical histological features with enlarged hyperchromatic nuclei in islets were observed. Methylation analysis, a chromosomal microarray, and short tandem repeat markers led to a diagnosis of mosaic segmental paternal uniparental disomy

Table 1.8 Selected examples of monogenic disorders with established somatic mosaicism with DNA confirmation.

Disorder	*Gene*	*Reference*
Achondrogenesis type 2	*COL2A1*	885
Aicardi–Goutières syndrome	*TREX1*	886
Alport syndrome	*COL4A5*	887
Alzheimer disease, early-onset	*PS1*	888
Androgen insensitivity	*AR*	888
Atelostegenesis type I	*FLNB*	889
Beta-propeller protein-associated neurodegeneration	*WDR45*	890
Campomelic dysplasia	*SOX9*	888
Catecholaminergic polymorphic ventricular tachycardia	*RYR2*	891
Centronuclear myopathy	*DNM2*	892
Charcot–Marie–Tooth disease type 1E	*PMP22*	893
CHARGE syndrome	*CHD7*	888
Chronic infantile neurologic, cutaneous, articular syndrome	*NLRP3*	894, 895
Chronic intestinal pseudo-obstruction	*ACTG2*	864
Cleidocranial dysplasia	*RUNX2*	888
COL2A1 disorders	*COL2A1*	896
Congenital central hypoventilation syndrome	*PHOX2B*	897
Congenital contractural arachnodactyly	*FBN2*	888
Congenital disorder of glycosylation	*SLC35A2*	898
Congenital lipomatous overgrowth with vascular, epidermal and skeletal anomalies	*PIK3CA*	899
Cornelia de Lange syndrome	*CdLS*	900
Costello syndrome	*HRAS*	901
Creutzfeldt–Jakob disease	*PRNP*	902
Crouzon syndrome	*FGFR2*	903
Duchenne muscular dystrophy	*DMD*	888, 904
Ectrodactyly	*SHFM3*	905
EEC (ectrodactyly, ectodermal dysplasia, and orofacial clefts)	*P63*	888
Epidermal nervus, rhabdomyosarcoma, polycystic kidneys and growth restriction	*KRAS*	906
Epidermolysis bullosa simplex	*KRTS 5*	888
Epilepsy with mental retardation in females	*PCDH19*	907, 908
Facial infiltrating lipomatosis	*PIK3CA*	909
Familial polymicrogyria	*TUBA1A*	910
Fanconi anemia	*FANCD2*	911
Fascioscapular humeral muscular dystrophy	*D4Z4*	888
Freeman–Sheldon syndrome	*TNNI2*	912
Gardner syndrome	*APC*	913
Hemi-megalencephaly	*PIK3CA*	914
Hemophilia A and B	*F8* and *F9*	888
Hereditary hemorrhagic telangiectasia associated with pulmonary arterial hypertension	*ACVRL1*	915
Hereditary nonpolyposis colon cancer (Lynch syndrome)	*MLH1*	916
Hereditary spastic paraplegia	*SPG4*	888
Hunter syndrome	*IDS*	888
Hyper-IgE syndrome	*STAT3*	917
Hypocalcemia	*CASR*	888
Infantile spinal muscular atrophy	*SMN1*	888
Intellectual disability	*GATAD$_2$B*	918
Isolated growth hormone deficiency	*GH1*	919

(Continued)

Table 1.8 (Continued)

Disorder	*Gene*	*Reference*
Juvenile myelomonocytic leukemia	*NRAS*	920
Keratinocyte epidermal nevi	*RAS*	921
Lesch–Nyhan syndrome	*HPRT1*	888
Li–Fraumeni syndrome	*TP53*	922
Loeys–Dietz syndrome	*TGFBR2*	888
Lone atrial fibrillation	*Cx43*	923
Maffuci syndrome	*IDHI*	924
Marfan syndrome	*FBN1*	888
McCune–Albright syndrome	*GNAS1*	888
Metaphyseal chondromatosis with D-2-hydroxyglutaric aciduria	*IDH1*	925
MYH9 disorders	*MYH9*	888
Myoclonic epilepsy	*SCN1A*	888
Myofibrillar myopathy	*BAG3*	926
Myotonic dystrophy type 2	*ZNF9*	927
Nail–patella syndrome	*LMX1B*	928
Neonatal diabetes	*KCNJ11*	888
Neurofibromatosis type 1 (generalized and segmental)	*NF1*	929
Neurofibromatosis type 2	*NF2*	930
Ohtahara syndrome	*STXBP1*	931
Ollier disease	*IDHI*	924
Ornithine transcarbamylase deficiency	*OTC*	888
Osteochondromas	*EXT*	932
Osteogenesis imperfecta II	*COL1A1*, COL1A2	888
Osteopathia striata	*AMER1*	933
Otopalatodigital syndrome	*FLNA*	888
Paroxsysmal nocturnal hemoglobinuria	*PIGA*	888
Phenylketonuria	*PAH*	888
Pheochromocytomas and hemihyperplasia	UPD 11p15	934
Pitt–Hopkins syndrome	*TCF4*	935
Polycythemia–paraganglioma syndrome	*HIF2A*	936
Progeria	*LMNA*	937
Proteus syndrome	*AKT1*	938
Pseudohypoparathyroidism type 1a	*GNAS*	939
Pyruvate dehydrogenase complex disorder	*PDHA1*	940
Retinitis pigmentosa	*RPGR*	941
Retinoblastoma	*RB1*	942
Rett syndrome in males	*MECP2*	943
Rett syndrome, atypical	*CDKL5*	944
Rubinstein–Taybi syndrome	*CREBBP*	945, 946
Shprintzen–Goldberg syndrome	*SKI*	947
Sotos syndrome	*NSD1*	948
Spondyloperipheral dysplasia	*COL2A1*	949
Stickler syndrome	*COL2A1*	896
Subcortical band heterotopia and pachygyria	*LIS1*	950
Testicular dysgenesis syndrome	*SRY*	951
Thanatophoric dysplasia	*FGFR3*	888
Timothy syndrome type 1	*CACNA1C*	952
Townes–Brock syndrome	*SALL1*	888
Uniparental disomies	–	953

(Continued)

Table 1.8 (Continued)

Disorder	*Gene*	*Reference*
Von Hippel–Lindau	*VHL*	888
Wiskott–Aldrich syndrome	*WASP*	954
X-linked anhidrotic ectodermal dysplasia with immunodeficiency	*NEMO*	955
X-linked chronic granulomatous disease	*CYBB*	956
X-linked craniofrontonasal syndrome	*EFNB1*	957
X-linked creatine deficiency	*SLC6A8*	958
X-linked Danon disease	*LAMP2*	959
X-linked dilated cardiomyopathy	*DMD*	960
X-linked dyskeratosis congenita	*DKC1*	888
X-linked focal dermal hypoplasia	*PORCN*	961, 962
X-linked hypophosphatemia	*PHEX*	888
X-linked incontinentia pigmenti	*NEMO*	963
X-linked Menkes disease	*ATP7A*	964
X-linked mental retardation	*ARX*	888
X-linked osteopathia striata with cranial sclerosis and developmental delay	*WTX*	965
X-linked periventricular nodular heterotopia	*FLNA*	966
X-linked protoporphyria	*XLDPP*	967
X-linked subcortical band heterotopia	*DCX*	968

11p15.5-p15.1 in pancreatic tissue, but not in the infant's blood.[871]

Brain somatic mutations occurring during cortical development may result in sporadic intractable epilepsy.[872] One study focused on the parents of children with Dravet syndrome due to *SCN1A* mutations.[873] *SCN1A* mosaicism was found in 5.2 percent (30 out of 575) of families with affected children. Discovery of an oncogene (e.g. *RB1*) for retinoblastoma occurring in the absence of a family history, will inevitably lead to examination of the parents to determine recurrence risk. An analysis using targeted deep sequencing of the parents of 124 offspring with bilateral retinoblastoma revealed only one parent with somatic mosaicism for the deleterious *RB1* mutation, a 0.4 percent risk of recurrence.[874]

Over 700 genes are linked to neurodevelopmental disorders, some with epilepsy. Discovery of a putative *de novo* mutation now invariably leads to genomic evaluation of both parents in a search for somatic mosaicism. Disorders in this category include intellectual disability, epileptic encephalopathies, cerebral cortical malformations, and autism spectrum disorders.[875, 876]

In a study of 10,362 consecutive patients, over 1 in 200 were shown to have somatic mosaicism.[877] In that study, mosaicism was detected for aneuploidy, ring or marker chromosomes, microdeletion/duplication copy number variations, exonic copy number variations, and unbalanced translocations. Examples include hypomelanosis of Ito, other syndromes with patchy pigmentary abnormalities of skin associated with intellectual disability, and some patients with asymmetric growth restriction.[878, 879] Gonadal mosaicism (see Chapter 14) should be distinguished from somatic cell mosaicism in which there is also gonadal involvement. In such cases, the patient with somatic cell mosaicism is likely to have some signs, although possibly subtle, of the disorder in question, while those with gonadal mosaicism are not expected to show any signs of the disorder. Current methodologies for clinical and prenatal diagnosis invariably list detection of very low degrees of mosaicism in a caveat that accompanies the reports. Additional examples of somatic and gonadal mosaicism include autosomal dominant osteogenesis imperfecta,[880, 881] Huntington disease,[882] and spinocerebellar ataxia type 2.[883] Lessons from these and the other examples quoted

for gonadal mosaicism indicate a special need for caution in genetic counseling for disorders that appear to be sporadic (see Chapter 14).

Very careful examination of both parents for subtle indicators of the disorder in question is necessary, particularly in autosomal dominant and sex-linked recessive conditions. The autosomal dominant disorders are associated with 50 percent risks of recurrence, while the sex-linked disorders have 50 percent risk for males and 25 percent risk for recurrence in families. Pure gonadal mosaicism would likely yield risks considerably lower than these figures, such as 4–8 percent for females with gonadal mosaicism and X-linked DMD. A second caution relating to counseling such patients with an apparent sporadic disorder is the offer of prenatal diagnosis (possibly limited) despite the inability to demonstrate the affected status of the parent.

Chromosomal mosaicism is discussed in Chapter 11 but note can be taken here of a possibly rare (and mostly undetected) autosomal trisomy. A history of subfertility with mostly mild dysmorphic features and normal intelligence has been reported in at least ten women with mosaic trisomy 18.[884]

Genetic counseling when the fetus is affected

The fateful day when the anxious, waiting couple hears the grim news that their fetus has a malformation or genetic disorder will live on in their memories forever. Cognizance of this impact should inform the thoughts, actions, and communications of the physician or counselor called on to exercise consummate skill at such a poignant time. Couples may have traveled the road of hope and faith for many years, battling infertility only to be confronted by the devastating reality of a fetal anomaly. With hopes and dreams so suddenly dashed, distress, doubt, anger, and denial surface rapidly. The compassionate physician or counselor will need to be fully armed with all the facts about the defect or be ready to obtain an immediate expert clinical genetics consultation for the couple.

Care should be taken in selecting a quiet, comfortable, private location that is safe from interruption. The language used should be clear and without jargon. Attention to a patient's cultural background and possible need for an interpreter is important. This is a communication not to be rushed but characterized by sensitivity and empathy. Informing a couple with bad news about the fetus by telephone or email is unacceptable. Arrangements for a follow-up visit and support where needed is advisable. Ptacek and Eberhardt[969] and others,[970] in reviewing the literature, noted consensus recommendations in breaking bad news that included the aforegoing and sitting close enough for eye contact without physical barriers. Identifying a support person, if the partner cannot/will not attend the consultation, is important and knowledge of available resources is valuable. All of the above points are preferences that have been vocalized by parents receiving bad news during pregnancy or about their infants.[971]

Almost all couples would have reached this juncture through maternal serum screening, noninvasive prenatal testing, an ultrasound or MRI study, or amniocentesis/CVS for maternal age, for established known carriers, because of a previously affected child, being an affected parent, or having a family history of a specified disorder. More recently, prenatal diagnosis using whole-exome sequencing[972] has led to the diagnosis of unexpected genetic disorders, and in the process introduced ethical issues and challenging quandaries.[973, 974] Commonly, an anxious patient insists on a prenatal study. Physicians are advised not to dissuade patients from prenatal diagnosis but rather to inform them about the risks of fetal loss balanced against the risk of fetal abnormality, distinctly different from recommendations for accepted indications. Given the low risks, prenatal diagnosis can be offered to all couples (see Chapter 9).

Recognition of a fetal abnormality by imaging, molecular, or cytogenetic study may reveal, for the first time, the genetic disorder in an affected asymptomatic parent. Robyr et al.[975] described 20 such parents with disorders including spinal muscular atrophy, DiGeorge syndrome, osteogenesis imperfecta, arthrogryposis, and Noonan-like syndrome.

Frequently, second-trimester ultrasound studies reveal fetal abnormalities of uncertain etiology with a subsequent normal karyotype. A chromosomal microarray may enable a precise diagnosis in 6–8.1 percent[976, 977] (see Chapter 13). In a legal case, sequential observations noted prominent lateral cerebral ventricles, multiple thoracic hemivertebrae, and intrauterine growth restriction. Amniocyte chromosome studies were normal. The

parents were not counseled about the potential for intellectual disability despite no definitive diagnosis. The child was born with holoprosencephaly with marked psychomotor delay. Diagnostic uncertainty must be shared with parents at risk. Uncertainty should not and cannot be suppressed for the patient's sake. Expressing uncertainty does not imply ignorance or incompetence. An honest accounting of the problems at hand, the offer of a second opinion, and an empathetic approach all go a long way in averting a catastrophic outcome and aggravating litigation. Moreover, responsibility shared is anxiety halved.

Decision making

The presence of both parents for the consultation concerning possible elective abortion for a fetal anomaly is critical in this situation. All the principles governing the delivery of genetic counseling and discussed earlier apply when parents need to decide whether or not to continue their pregnancy. A brief explanation of some of the key issues follows, culled from over 50 years of experience in this very subject.

Doubt and disbelief crowd the parental senses in the face of such overwhelming anxiety. Was there a sample mix up? How accurate is this diagnosis? How competent is the laboratory? Have they made errors in the past? How can we be certain that there has been no communication failure? Is there another couple with the same name? There are endless questions and endless doubts. Each and every one needs to be addressed carefully, slowly and deliberately, with painstaking care to provide the necessary assurance and reassurance. Needless to say, the clinical geneticist or counselor must have thoroughly checked all the logistics and potential pitfalls before initiating this consultation. Errors have indeed occurred in the past.[184, 185]

The central portion of the communication will focus on the nature of the defect and the physician or counselor providing the counseling should be fully informed about the disorder, its anticipated burden, the associated prognosis, life expectancy, and the possible need for lifetime care. A clear understanding of the potential for pain and suffering is necessary, and an exploration concerning the effect on both parents and their other children is second only to a discussion about the potential effects on the child who is born with the condition in question. Any uncertainties related to diagnosis, prognosis, pleiotropism, or heterogeneity should emerge promptly. Questions related to possible future pregnancies should be discussed, together with recurrence risks and options for prenatal diagnosis.

The question concerning a repeat prenatal study is invariable, at least if not stated then certainly in the mind of the parents. There are occasions when a repeat test might be appropriate, especially if there is a failure to reconcile cytogenetic or molecular results with expected high-resolution ultrasound observations. Maternal cell contamination (see Chapters 9, 11, and 14), while extremely unlikely in almost all circumstances, requires exclusion in some others. Some prenatal diagnoses may not easily be interpretable and a phenotype may not be predictable with certainty. A *de novo* supernumerary chromosome fragment in the prenatal cytogenetic analysis (see Chapter 11) or a microdeletion or microduplication (see Chapter 13) are key examples. VOUS, especially in a gene known to harbor pathogenic mutations, is unnerving. Where a VOUS is uninterpretable, decision making reverts to the fetal anomaly seen or biochemical abnormality observed. The sensitive counselor should offer a second opinion to anxious parents facing an uncertain prenatal diagnosis. The "compleat physician" anticipates virtually all of the patient's questions, answers them before they are asked, and raises all the issues without waiting for either parent to vocalize them.

Occasionally, there are powerful disparate attitudes to abortion between the spouses as discussed earlier. Such differences would best be considered during the preconception period, rather than for the first time when faced with a serious fetal defect. Resolution of this conflict is not the province of the physician or counselor, nor should either become arbitrator in this highly charged and very personal dispute, in which religious belief and matters of conscience may collide. The physician's or counselor's duty is to ensure that all facts are known and understood and that the pros and cons of various possible scenarios are identified in an impartial manner. A return appointment within days should be arranged. Questions of paternity have also suddenly emerged in this crisis period and can then be settled, sometimes with painful certainty.

Elective abortion: decision and sequel

Among the greatest challenges clinical geneticists and genetic counselors face is the consultation in which the results of prenatal studies indicating a serious fetal defect are communicated to parents for the first time. These appointments must not be rushed. It is important that the many variables influencing parental decisions about pregnancy termination be recognized.[978, 979] The quintessential qualities a counselor will need include maturity, experience, warmth and empathy, sensitivity, knowledge, communication skill, and insight into the psychology of human relationships, pregnancy, and grieving. Personal experience with loss or bereavement is likely to influence the emotional guidance provided.[980] Certainly there is a wealth of literature suggesting inadequate preparation for those who ultimately care for individuals facing bereavement or death.[980, 981] An in-depth understanding of the disability that the affected child and parents could anticipate is of obvious importance. The principles and prerequisites for counseling discussed earlier apply fully in these circumstances and the fact that this is a parental decision, not a medical "recommendation," should not need reiteration.

Anticipatory counseling in these consultations has been characterized by in-depth discussions of two areas: first, all medical and scientific aspects of the prenatal diagnosis made (and discussed earlier), and second, recognition and vocalization of emotional responses and reference to experiences (preferably published) of other couples in like circumstances when it was helpful. These sessions have then included explorations concerning guilt, a possible feeling of stigma (because of abortion), anger, upset, family pressures, and how other couples have coped. All of this anticipatory counseling should be tinctured with support and hope when possible.

It is important that the many variables influencing parental decisions about pregnancy termination when faced with a serious disability and/or life-threatening or limiting disorder or anomaly be recognized and understood.[979, 982–985] Parents will automatically bring their moral and religious beliefs to bear on their decision making. So too will their experience of disability and what they had seen in families with affected children. A mother's age, prior periods of infertility, previous miscarriages, a history of an elective abortion or fetal abnormality, all factor into their decisions. Fortunately, not common is the painful quandary of uncertainty concerning severity of the prenatally diagnosed genetic disorder. One example is the mildly affected mother with a 22q11.2 deletion informed about a conotruncal cardiac anomaly in her fetus and uncertain future intellectual disability, the risk for which approximates 30 percent, further compounded by up to 30 percent risk of developing schizophrenia in young adulthood, and autism/autism-spectrum disorders in about 20 percent.[986–991]

Longing for and imagining becoming a parent anew or again may also have been bolstered by unexpected bonding that occurred when the mother saw fetal features and/or movements on obstetric ultrasound. A frequent expressed concern is the effect a disabled child would have on the family's other child or children. Worse still, would that child have the burden of caring for the affected sibling after the death of the parents. Would some stigma attach and eventually have an effect on a potential marriage mate for their child or children. Would they have to devote so much time and energy to the needs of a disabled child that it would result in relative neglect of their other children. To what degree, if any, would there be pain or suffering (including psychological) for the affected child.

Perhaps not surprising is the influence of their own parents and their belief in the couple's ability to parent a child with a serious disability. Economic issues also loom large, depending upon the pressures and circumstances of their lives. On occasion, there is an unwillingness to continue pregnancy when a partner has suffered from the same later onset disorder. Marital ambiguity about the abortion decision can dominate the process and destroy a relationship. Any argument should be relegated to the couple's home, with a request to return when a decision has been made.

The importance of continuing follow-up visits with couples who have terminated pregnancy for fetal defects cannot be overemphasized. In an important study on the psychosocial sequelae in such cases, White-van Mourik et al.[992] showed the long-range effects. Displays of emotional and somatic symptoms 1–2 years after abortion were not rare and included partners. Although

some couples grew closer in their relationships, separations, especially because of failed communication, increased irritability, and intolerance, were noted in 12 percent of the 84 patients studied.[993] Marital discord in these circumstances has been noted previously.[993, 994] At least 50 percent of couples admitted to having problems in their sexual relationship. In addition, many couples indicated changed behavior toward their existing children, including overprotectiveness, anxiety, irritability, and subsequent guilt and indifference (Table 1.9).[992] Women with secondary infertility and those younger than 21 years of age (or immature women) had the most prolonged emotional, physical, and social difficulties.[992] After a loss of a child, with or without an anomaly, between 10 and 25 percent of distressed parents have disturbed emotional stability and adverse mental and physical health effects.[995] Anticipated grief experienced by mothers, especially those faced with a third-trimester diagnosis of a lethal fetal abnormality, requires psychological help with preparedness. Empathy and sensitivity are critical at these intensely painful times and mature counseling and nonjudgmental support are vital to help parents cope.

Grief counseling becomes part of the consultation after elective termination, in which full recognition of bereavement is necessary (see Chapter 33). Compassion fatigue, characterized as feeling overwhelmed by experiencing patients' suffering,[996] mainly in cancer genetic counseling, is not likely to be an issue in prenatal genetic counseling. The psychology of mourning has been thoroughly explored[997–999] (see Chapter 33). Worden emphasized how important it is for a bereaved individual to complete each of four stages in the mourning process:[998]

Table 1.9 The frequency of emotions and somatic symptoms of 84 women and 68 men: overall and 24 months after terminating a pregnancy for fetal abnormality.

	Overall		*24 months after termination*	
	Women (%)	*Men (%)*	*Women (%)*	*Men (%)*
Feeling				
Sadness	95	85	60	47
Depression	79	47	12	6
Anger	78	33	27	7
Fear	77	37	46	17
Guilt	68	22	33	7
Failure	61	26	24	14
Shame	40	9	18	4
Vulnerability	35	0	18	0
Relief	30	32	16	16
Isolation	27	20	11	6
Numbness	23	0	0	0
Panic spells	20	0	5	0
Withdrawal	0	32	0	13
Left out	0	12	0	0
Somatic symptom				
Crying	82	50	22	5
Irritable	67	38	19	3
No concentration	57	41	7	1
Listlessness	56	17	2	0
Sleeplessness	47	19	2	1
Tiredness	42	21	6	3
Loss of appetite	31	10	0	0
Nightmares	24	7	5	0
Palpitations	17	-	6	0
Headaches	9	8	2	0

Source: White-van Mourik et al. 1992.[992] Rproduced with permission of John Wiley and Sons.

1. Acceptance of the loss.
2. Resolving the pain of grieving.
3. Adjusting to life without the expected child.
4. Placing the loss in perspective.

The importance of allowing parents the option of holding the fetus (or later, the child), when appropriate, is well recognized.[1000, 1001] These authors have also called attention to the complex tasks of mourning for a woman who is faced with one abnormal twin when pregnancy reduction or birth might occur.

Notwithstanding anticipated loss and grief, Seller et al.,[1001] reflecting our own experience, emphasized that many couples recover from the trauma of fetal loss "surprisingly quickly." Insinuation of this reality is helpful to couples in consultations both before and after elective termination. Moreover, couples' orientation toward the grieving process achieves an important balance when they gain sufficient insight into the long-term emotional, physical, economic, and social consequences they might have needed to contemplate if prenatal diagnosis had not been available.

Testing the other children

Invariably, parents faced with the news of their affected fetus question the need to test their other children. Answers in the affirmative are appropriate when diagnosis of a disorder is possible. Carrier detection tests, however, need careful consideration and are most appropriately postponed until the late teens, when genetic counseling should be offered. Given the complex dilemmas and far-reaching implications of testing asymptomatic children for disorders that may manifest many years later, parents would best be advised to delay consideration of such decisions while in the midst of dealing with an existing fetal defect. In later consultations, the thorny territory of predictive genetic testing of children can be reviewed at length.[1002–1005] Fanos[1002] emphasized that testing adolescents "may alter the achievement of developmental tasks, including seeking freedom from parental figures, establishment of personal identity, handling of sexual energies and remodeling of former idealizations of self and others." Fanos also emphasized that parental bonding may be compromised by genetic testing when the child's genetic health is questionable. Parents may react to the possible loss or impairment of a child by developing an emotional distance, recognized as the vulnerable child syndrome.[1006] Other aspects, including interference with the normal development of a child's self-concept, introduce issues of survivor guilt or increase levels of anxiety already initiated by family illnesses or loss.[1006] Predictive testing of children for later manifesting neurodegenerative or other disorders would rarely be recommended, except in circumstances in which early diagnosis could offer preventive or therapeutic benefit.

Perinatal genetic counseling

A similar spectrum of issues and concerns is faced after the detection and delivery of a child with a genetic disorder or an anomaly. Pregnancy with a defective fetus may have been continued from the first or second trimester or a diagnosis may be made in the third trimester or at the delivery of a living or stillborn child. The principles and prerequisites for genetic counseling discussed earlier apply equally in all these circumstances.[1007] Special attention should be focused on assuaging aspects of guilt and shame (see Chapter 33). Difficult as it may be for some physicians,[1008, 1009] close rapport, patient visitation, and sincerity are necessary at these times, even when faced with commonly experienced anger. A misstep by the physician in these circumstances in failing to continue (it is to be hoped) the rapport already established during pregnancy care provides the spark that fuels litigation.[184]

The rate of stillbirth in the United States in 2013 was 5.96/1,000 livebirths, occurring in 1 in 160 deliveries,[1010] with about 23,600 cases ≥20 weeks of gestation. For twin pregnancies, the rate is about 2.5 times higher. Chromosomal abnormalities occur in 6–13 percent of stillbirths,[1011–1013] but is greater than 20 percent in those with malformations. The risk of recurrence following unexplained stillbirth is between 2.5 and 4.18 percent.[1010] In comparison, stillbirth rates in 2010–2016 in Pakistan were 56.9/1,000 births, 25.3/1,000 in India, 21.3/1,000 in Zambia and Kenya, and 19.9/1,000 in Guatemala.[1014] Using whole-exome sequencing in 246 stillbirths, 15 (6.1 percent) had a molecular diagnosis in one report.[1015] The genetic cause of most stillbirths remains unknown. Women with a history of stillbirth have an increased risk of

long-term chronic kidney disease and end-stage renal disease.[1016]

Despite anger, grief, and the gamut of expected emotions, the attending physician (not an inexperienced healthcare provider) should take care to urge an autopsy when appropriate. Diagnosis of certain disorders (e.g. congenital nephrosis) can be made by promptly collected and appropriately prepared tissue, and by subsequent DNA studies (see Chapter 10) including whole-exome sequencing (see Chapter 14). In circumstances in which parents steadfastly withhold permission for autopsy, radiographs, MRI, computed tomography, and needle liver biopsy for DNA could provide important information when a precise diagnosis has yet to be made.[1017–1019] In most stillbirths, the cause(s) is not determined. In the long QT syndrome, which has rarely been diagnosed *in utero*,[1020] and which we have diagnosed in the first month of life,[1021] affected mothers have an increased risk of fetal death, not only due to an arrhythmia, but also to putative placental or myometrial dysfunction.[1022] Moreover, stillbirth at ≥23 weeks of gestation in these mothers is associated with an increased risk of severe maternal morbidity, especially among those with comorbidities.[1023] MRI could provide a useful acceptable alternative when fetal anomalies are expected.[1017] The autopsy is the last opportunity parents will have to determine causation, which may ultimately be critical in their future childbearing plans and also for their previous children. A formal protocol for evaluating the cause of stillbirth or perinatal death is important (Box 1.3) to secure a definitive diagnosis, thereby laying the foundation for providing accurate recurrence risks and future precise prenatal diagnosis. In the emotional chaos that invariably follows stillbirth, necessary actions may be forgotten. An action checklist (Box 1.4) serves to orient the process. In addition, in the face of known or suspected genetic disorders in which mutation analysis now or in the future may be critical, care should be taken to obtain tissue for DNA banking or for establishing a cell line. Later, parents may return and seriously question the failure of the physician to secure tissues or DNA that would have been so meaningful in future planning (e.g. X-linked intellectual disability).

Psychologic support is important for couples who have lost an offspring from any cause – a situation compounded by fetal or congenital abnormality.[1024, 1025] The birth (or prenatal detection) of twins discordant for a chromosomal disorder is not rare, given the increased frequency of multiple pregnancy associated with advanced maternal age and the use of assisted reproductive techniques. Pregnancy reduction[1026] (see Chapter 32), or the death of one twin, or delivery of both, evokes severely conflicting emotions that may well affect the mother's care for the surviving child.[1027] Considerable psychologic skill must be marshaled by physicians if meaningful care and support are to be provided.[1028]

Supporting telephone calls from doctor and staff, and encouragement to attend appointments every 6 weeks, or more frequently when appropriate, are often appreciated by patients. Review of the autopsy report and discussion with reiterative counseling should be expected of all physicians. Frequently, parents receive an autopsy report by mail without further opportunity for explanation and discussion. In one study, 27 percent failed to receive autopsy results.[1029] Providing contact with support groups whose focus is the disorder in question is also valuable. In the United States, the vast majority of these groups have combined to form the Alliance of Genetic Support Groups, which acts as a central clearinghouse and referral center.

Family matters

Beyond all the "medical" steps taken in the wake of stillbirth or perinatal death due to fetal defects are critical matters important to the family and its future. Active, mature, and informed management is necessary in these difficult and frequently poignant situations. Regardless of the cause of the child's defect(s), maternal guilt is almost invariable and sometimes profound. Recognition of a definitive cause unrelated to a maternal origin should be explained in early discussions and reiterated later. For autosomal recessive disorders or with even more problematic X-linked disorders, maternal "culpability" is real and not easily assuaged. The fact that we all carry harmful genes, some of which we may have directly inherited, while others may have undergone mutation, will need in-depth discussion. Mostly, it is possible and important to reassure mothers that the outcome was not due to something they did wrong. Where the converse is true, much effort will be needed for management of

Box 1.3 Elements of a stillbirth evaluation

Key components	*Details*	*Comments*
Patient history	Family history • Recurrent spontaneous abortions • Stillbirths • Monogenic disorder(s) • Congenital malformations or syndromes • Chromosomal disorders • Ethnicity • Consanguinity • Neurodevelopmental delay Maternal history: • Previous venous thromboembolism • Diabetes mellitus • Chronic hypertension • Thrombophilia • Systemic lupus erythematosus • Autoimmune disease • Epilepsy • Severe anemia • Heart disease • Tobacco, alcohol, drug or medication use Obstetric history: • Recurrent miscarriages • Previous child with congenital malformation, syndrome or genetic disorder • Previous child with intrauterine growth restriction • Previous gestational hypertension or preeclampsia • Previous gestational diabetes mellitus • Previous placental abruption • Previous fetal demise Current pregnancy: • Maternal age • Paternal age • Gestational age at stillbirth • Medical conditions complicating pregnancy • Cholestasis • Pregnancy weight gain and body mass index • Complications of multifetal gestation, such as twin–twin transfusion syndrome, twin reversed arterial perfusion syndrome, and discordant growth • Placental abruption • Abdominal trauma • Preterm labor or rupture of membranes • Gestational age at onset of prenatal care • Intrauterine growth restriction • Abnormalities seen on an ultrasound image • Infections or chorioamnionitis	

Box 1.3 Continued

Key components	*Details*	*Comments*
Fetal autopsy	If patient declines, external evaluation by a trained perinatal pathologist. Other options include photographs, X-ray imaging, ultrasonography, magnetic resonance imaging, and sampling of tissues, such as blood or skin.	Provides important information in approximately 30% of cases
	Freeze tissue for future DNA study	
	If macerated tissue, request permission for needle biopsy of liver for DNA study	
Placental examination	Includes evaluation for signs of viral or bacterial infection. Discuss available tests with pathologist	Provides additional information in 30% of cases. Infection is more common in preterm stillbirth (19 vs. 2% at term)
Fetal karyotype/ microarray	Amniocentesis before delivery provides the greatest yield. Umbilical cord proximal to placenta if amniocentesis declined	Abnormalities found in approximately 8% of cases
	Whole-exome or whole-genome sequencing/from frozen tissue or needle biopsy	
Maternal evaluation at time of demise	• Fetal–maternal hemorrhage screen: Kleihauer–Betke test or flow cytometry for fetal cells in maternal circulation • Syphilis • Lupus anticoagulant • Anticardiolipin antibodies • β_2 glycoprotein antibodies	Routine testing for inherited thrombophilias is not recommended. Consider in cases with a personal or family history of thromboembolic disease
In selected cases	Indirect Coombs	If not performed previously in pregnancy
	Glucose screening (oral glucose tolerance test, hemoglobin A_{1C})	In the large-for-gestational-age baby
	Toxicology screen	In cases of placental abruption or when drug use is suspected

Source: Modified from American College of Obstetricians and Gynecologists, Society for Maternal-Fetal Medicine.[1010]

guilt[1030] and shame, and for planning actions that promise a better future with ways to avert another adverse outcome.

Attention to details that have a very important role in the mourning process (see Box 1.4 checklist) include ensuring that the child be given a name and, in the case of the death of an abnormal fetus in the third trimester, that the parents' wishes for a marked grave be determined. As noted earlier, most caretakers feel that parents are helped by both seeing and holding the baby.[1000, 1001, 1031] Although some may experience initial revulsion when the subject is mentioned, gentle coaxing and explanations about the experiences of other couples may help grieving parents. Even with badly disfigured offspring, it is possible for parents to cradle a mostly covered baby whose normal parts, such as hands and feet, can be held. Important mementos that parents should be offered are photographs,[1032] a lock of hair, the baby's name band

Box 1.4 Action checklist following stillbirth

DATE OF BIRTH _____ NURSE IN CHARGE _____
ATTENDING PHYSICIAN _____ PHONE# _____
NAME OF CLERGY _____ PHONE# _____

☐ FAMILY PRIVACY SECURED ☐ CARD ON DOOR ☐ PHYSICIAN CALLED ☐ FAMILY MET WITH PHYSICIAN

PARENTAL OPTIONS	PARENTAL DECISIONS		COMMENTS
Infant viewing	Yes ☐	No ☐	
Infant holding	Yes ☐	No ☐	
Naming of infant	Yes ☐	No ☐	Name: _____
Photographs	Yes ☐	No ☐	
Autopsy permission (signature)	Yes ☐	No ☐	
Genetic studies	Yes ☐	No ☐	N/A ☐
Burial	Yes ☐	No ☐	
Cremation	Yes ☐	No ☐	
Family members allowed to visit/hold	Yes ☐	No ☐	
Religious rites	Yes ☐	No ☐	
Lock of baby's hair	Yes ☐	☐	No
Tissue for DNA Study obtained and frozen	Yes ☐	☐	No

BABY: Weight _____ Length _____
Bathed ☐ Dressed ☐ Footprints ☐ Photos ☐ Parents viewed ☐
Death certificate ☐
MRI of brain ☐
(if autopsy decline)

HOSPITAL DISCHARGE:					
	Memory envelop given (baby items)	Yes ☐	No ☐		
	Grief packed with references given	Yes ☐	No ☐		
	Grief counseling referral	Yes ☐	No ☐	Declined ☐	
	Genetic counseling referral	Yes ☐	No ☐		
	Follow up consultation (and to discuss autopsy results)	Yes ☐	No ☐		

Nurse Completing Form: Name _____ Signature _____ Date _____

or clothing.[1027, 1028] Ultimately, these concrete emblems of the baby's existence assist parents in the mourning process, although the desperate emptiness that mothers especially feel is not easily remedied.[1033] Photos may also be helpful in providing comfort for other children and for grandparents. Parents will also vary in their choice of traditional or small, private funerals. Physicians should ensure that parents have the time to make these various decisions and assist by keeping the child in the ward for some hours when necessary.

Both parents should be encouraged to return for continuing consultations during the mourning period.[1034] Follow-up contact after pregnancy has ended includes calls, condolences cards,

and recommendation for further bereavement counseling. This appointment will also enable further discussion about causation, future risks, and options, as well as coping strategies. Parents confirm that anxiety blocks the assimilation and comprehension of facts and recommendations. Vocalizing the realization is helpful while repeating information provided previously. Mourning may run its course for 6–24 months. These consultations will serve to explore aspects of depression, guilt, anger, denial, possible marital discord, and physical symptoms such as frigidity or impotence. Impulsive decisions for sterilization should be discouraged in the face of overwhelming grief. Advice should be given about safe, reliable, and relatively long-term contraception.[1035] Similarly, parents should be fully informed about the consequences of having a "replacement child" very soon after their loss.[1036, 1037] That child may well become a continuing vehicle of grief for the parents, who may then become overanxious and overprotective. Subsequently, they may bedevil the future of the replacement child with constant references to the lost baby, creating a fantasy image of perfection that the replacement child could never fulfill. Such a child may well have trouble establishing his or her own identity.

The surviving children

Distraught parents frequently seek advice about how to tell their other children. Responses should be tailored to the age of the child in question, to the child's level of understanding, and against a background of the religious and cultural beliefs of the family. A key principle to appreciate is that having reached the stage of cognizance regarding the loss, a child needs and seeks personal security. Hence, the parents' attention should be focused on love, warmth, and repetitive reassurance, especially about (possibly) unstated feelings of previous wrongdoing and personal culpability. Advice about grieving together instead of being and feeling overwhelmed in front of their children is also helpful. Focusing on the children's thoughts and activities is beneficial rather than lapsing into a state of emotional paralysis, which can only serve to aggravate the family's psychodynamics adversely.

The efficacy of genetic counseling

Genetic counseling is a communication process that aims to achieve as complete an understanding by the counselee(s) as possible, thereby enabling nondirective rational decision making. Studies examining the efficacy of genetic counseling in various settings and using different modalities (e.g. telephone versus in-person) and self-efficacy of genetic counselors and students continue.[1038–1041] Anxiety, distress, uncertainty, guilt, decisional conflict, and a deficient knowledge of science, together with difficulty in understanding a balance of risks, influence the ultimate efficacy of genetic counseling. Parental decisions to have additional affected progeny should not be viewed as a failure of genetic counseling. Although the physician's goal is the prevention of genetic disease, the orientation of the prospective parents may be quite different. A fully informed couple, both of whom had achondroplasia, requested prenatal diagnosis with the expressed goal of aborting a normal unaffected fetus so as to be able to raise a child like themselves. Would this be construed as a failure in genetic counseling? Would continued pregnancy with an anencephalic fetus after genetic counseling be considered a failure of genetic counseling?

Clarke et al.[1042] considered three prime facets that could possibly evaluate the efficacy of genetic counseling: (i) recall of risk figures and other relevant information by the counselee(s); (ii) the effect on reproductive planning; and (iii) actual reproductive behavior. Their conclusions, reflecting a Western consensus, were that there are too many subjective and variable factors involved in the recall of risk figures and other genetic counseling information to provide any adequate measure of efficacy. Further, assessing reproductive intentions may prejudge the service the counselee wishes as well as the fact that there are too many confounding factors that have an impact on reproductive planning. Moreover, how many years after counseling would be required to assess the impact on reproductive planning? They regarded evaluation of reproductive plans as "a poor proxy for reproductive behavior." In dispensing with assessments of actual reproductive behavior in the face of counseling about such risks, they pointed to the complex set of social and other factors

that confound the use of this item as an outcome measure. They did, however, recommend that efficacy be assessed against the background goals of genetic counseling aimed at evaluation of the understanding of the counselee(s) of their own particular risks and options. A questionnaire study from the Netherlands questioned 1,479 counselees about their experience of genetic counseling. Questionnaires were administered before and after counseling and for the third time after results were disclosed.[1043] They noted improvement in the level of empowerment, personal control, and anxiety after the whole process.

Evaluation of the efficacy of genetic counseling should not only include the degree of knowledge acquired (including the retention of the counselee(s) with regard to the indicated probabilities), the rationality of decision making (especially concerning further reproduction), but also the potential personal influences outlined in the Netherlands' study. Frequent contraceptive failures in high-risk families highlight the need for very explicit counseling. A further measure of efficacy is the frequency and accuracy of a proband's communication of important risk information to close relatives. It appears that communication of test results may be selective, with male relatives and parents less likely to be informed.[1044]

Important points made by Emery et al.[1045] in their prospective study of 200 counselors, included the demonstrated need for follow-up after counseling, especially when it is suspected that the comprehension of the counselee(s) is not good. This seemed particularly important in chromosomal and X-linked recessive disorders. They noted that the proportion deterred from having children increased with time and that more than one-third of their patients opted for sterilization within 2 years of counseling.

A number of studies[1045–1048] document the failure of comprehension by the counselee(s). Such failures are increasingly likely with genome sequencing resulting in secondary findings and revelations of unknown significance.[1048] The reports do not reflect objective measures of the skill or adequacy of genetic counseling and the real value of a summary letter to the patient of the information provided after the counseling visit. Sorenson et al.[1049] prospectively studied 2,220 counselees who were seen by 205 professionals in 47 clinics located in 25 states and the District of Columbia. They gathered information not only on the counselees but also on the counselors and the clinics in which genetic counseling was provided. They, too, documented that 53 percent of counselees did not comprehend their risks later, while 40 percent of the counselees given a specific diagnosis did not appear to know it after their counseling. They thoroughly explored the multiple and complex issues that potentially contributed to the obvious educational failure that they (and others) have observed. In another study of parents with a Down syndrome child, Swerts[1050] noted that of those who had genetic counseling, 45 percent recalled recurrence risks accurately, 21 percent were incorrect, and 34 percent did not remember their risks.

In considering the effectiveness of genetic counseling, Sorenson et al.[1049] summarized the essence of their conclusion:

> In many respects, an overall assessment of the effectiveness of counseling, at least the counseling we assessed in this study, is confronted with the problem of whether the glass is half full or half empty. That is, about half of the clients who could have learned their risk did but about half did not. And, over half of the clients who could have learned their diagnosis did but the remainder did not. In a similar vein, clients report that just over half of their genetic medical questions and concerns were discussed, but about half were not. The picture for socio-medical concerns and questions was markedly worse, however. And, reproductively, just over half of those coming to counseling to obtain information to use in making their reproductive plans reported counseling influenced these plans, but about half did not. Any overall assessment must point to the fact that counseling has been effective for many clients, but ineffective for an almost equal number.

A critical analysis of the literature by Kessler[1051] concluded that published studies on reproductive outcome after genetic counseling revealed no major impact of counseling. Moreover, decisions made before counseling largely determined reproduction after counseling.

A study of patients' expectations of genetic counseling revealed that the majority had their

expectations fulfilled, especially with perceived personal control.[1052] When patients' expectations for reassurance and advice were met, they were subsequently less concerned and had less anxiety when compared with such expectations that were not fulfilled, similar to the Netherlands report.[1043]

The limited efficacy of genetic counseling revealed in the study by Sorenson et al.[1049] reflects the consequences of multiple factors, not the least of which were a poor lay understanding of science.[1036] Efficacy, of course, is not solely related to counselee satisfaction. Efforts to educate the public about the importance of genetics in their personal lives have been made by one of us in a series of books (one translated into nine languages) over 50 years.[184, 331, 335, 337, 338, 1053] In addition to public education and its concomitant effect of educating physicians generally, formal specialist certification in the United States, Canada, the United Kingdom, and elsewhere, acceptance of clinical genetics as a specialty, and degree programs for genetic counselors certified by the National Board of Genetic Counselors, has undoubtedly improved the efficacy of genetic counseling. There remains, however, a pressing need to better educate practicing physicians about the "new genetics"[184, 185, 199, 1054, 1055] in this, the golden era of human genetics.

References

1. Ferreira CR. The burden of rare diseases. Am J Med Genet A 2019;179A:885.
2. Online Mendelian Inheritance in Man, OMIM®. McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University (Baltimore, MD), 2008. https://www.researchgate.net/publication/23307013_McKusick%27s_online (accessed September 18, 2020).
3. Nguengang Wakap S, Lambert DM, Olry A, et al. Estimating cumulative point prevalence of rare diseases: analysis of the Orphanet database. Eur J Hum Genet 2020;28:165.
4. Bick D, Jones M, Taylor SL, et al. Case for genome sequencing in infants and children with rare, undiagnosed or genetic diseases. J Med Genet 2019;56:783.
5. Bhide P, Kar A. A national estimate of the birth prevalence of congenital anomalies in India: systematic review and meta-analysis. BMC Pediatrics 2018;18:175.
6. Chaabane S, Bérard A. Epidemiology of major congenital malformations with specific focus on teratogens. Curr Drug Saf 2013;8:128.
7. Straub L, Huybrechts KF, Bateman BT, et al. The impact of technology on the diagnosis of congenital malformations. Am J Epidemiol 2019;188:1892.
8. Ropers H. Genetics of early onset cognitive impairment. Hum Genet 2010;11:161.
9. Mefford HC, Batshaw ML, Hoffman EP. Genomics, intellectual disability, and autism. N Engl J Med 2012;366:733.
10. Coffman KA, Borgatti R. Finding a common path to the assessment of persons with intellectual development disorders. Neurology 2020;94:507.
11. Kvarnung M, Nordgen A. Intellectual disability and rare disorders: a diagnostic challenge. Adv Exp Med Biol 2017;1031:39.
12. European Organisation for Rare Disease (EURORDIS). What is a rare disease? http://www.eurordis.org
13. Murphy SL, Mathews TJ, Martin JA, et al. Annual summary of vital statistics: 2013–2014. Pediatrics 2017;139:e20163239.
14. Martin RH, Ko E, Rademaker A. Distribution of aneuploidy in human gametes: comparison between human sperm and oocytes. Am J Med Genet 1991;39:321.
15. Fragouli E, Alfarawati S, Goodall NN, et al. The cytogenetics of polar bodies: insights into female meiosis and the diagnosis of aneuploidy. Mol Hum Reprod 2011;17:286.
16. Pellestor F, Andreo B, Arnal F, et al. Maternal aging and chromosomal abnormalities: New data drawn from in vitro unfertilized human oocytes. Hum Genet 2003;112:195.
17. Fragouli E, Escalona A. Gutierrez-Mateo C., et al. Comparative genomic hybridization of oocytes and first polar bodies from young donors. Hum Genet Reprod Biomed Online 2009;19:228.
18. Fragouli E, Katz-Jaffe M, Alfarawati S, et al. Comprehensive chromosome screening of polar bodies and blastocysts from couples experiencing repeated implantation failure. Fertil Steril 2010;94:875.
19. Hassold T, Hall H, Hunt P. The origin of human aneuploidy: Where we have been, where we are going? Hum Mol Genet 2007;16:R203.

20. Martin RH, Ko E, Barclay L. Human sperm karyotypes. In: Verma RS, Babu A, eds. Human chromosomes: manual of basic techniques. New York: McGraw-Hill, 1994:56.
21. Plachot M. Chromosome analysis of oocytes and embryos. In: Verlinsky Y, Kuliev A, eds. Preimplantation genetics. New York: Plenum Press, 1991:103.
22. Boué J, Boué A, Lazar P. Retrospective and prospective epidemiological studies of 1500 karyotyped spontaneous human abortions. Teratology 1975;12:11.
23. Liu J, Wang W, Sun X, et al. DNA microarray reveals that high proportions of human blastocysts from women of advanced maternal age are aneuploid and mosaic. Biol Reprod 2012;87:148.
24. Mertzanidou A, Wilton L, Cheng J, et al. Microarray analysis reveals abnormal chromosomal complements in over 70% of 14 normally developing human embryos. Hum Reprod 2013;28:256.
25. Alberman ED, Creasy MR. Frequency of chromosomal abnormalities in miscarriages and perinatal deaths. J Med Genet 1977;14:313.
26. Holmes-Seidle M, Ryyvanen M, Lindenbaum RH. Parental decisions regarding termination of pregnancy following prenatal detection of sex chromosome abnormality. Prenat Diagn 1987;7:239.
27. Martinez-Frias ML, Bermejo E, Cereijo A, et al. Epidemiological aspects of Mendelian syndromes in a Spanish population sample. II. Autosomal recessive malformation syndromes. Am J Med Genet 1991;38:626.
28. Njoh J, Chellaram R, Ramas L. Congenital abnormalities in Liberian neonates. West Afr J Med 1991;10:439.
29. Verma IC. Burden of genetic disorders in India. Indian J Pediatr 2001;67:893.
30. Lie RT, Wilcox AJ, Skjaerven R. Survival and reproduction among males with birth defects and risk of recurrence in their children. JAMA 2001;285:755.
31. Queisser-Luft A, Stolz G, Wiesel A, et al. Malformations in newborn: results based on 30,940 infants and fetuses from the Mainz congenital birth defect monitoring system (1990–1998). Arch Gynecol Obstet 2002;266:163.
32. Canfield MA, Mai CT, Wang Y, et al. The association between race/ethnicity and major birth defects in the United States, 1999–2007. Am J Public Health 2014;104:e14.
33. Baird PA, Anderson TW, Newcombe HB, et al. Genetic disorders in children and young adults: a population study. Am J Hum Genet 1988;42:677.
34. Blencowe H, Moorthie S, Petrou M, et al. Rare single gene disorders: estimating baseline prevalence and outcomes worldwide. J Community Genet 2018;9:397.
35. Woods CG, Cox J, Springell K, et al. Quantification of homozygosity in consanguineous individuals with autosomal recessive disease. Am J Hum Genet 2006;78:889.
36. Milunsky A. The prevention of genetic disease and mental retardation. Philadelphia: WB Saunders, 1975.
37. Myrianthopoulos NC. Malformations in children from one to seven years. New York: Alan R. Liss, 1985.
38. Braverman AC, Güven H, Beardslee MA, et al. The bicuspid aortic valve. Curr Probl Cardiol 2005;30:470.
39. Williams DS. Bicuspid aortic valve. J Insur Med 2006;38:72.
40. Debiec R, Sall H, Samani NJ, et al. Genetic insights into bicuspid aortic valve disease. Cardiol Rev 2017;25:158.
41. Freeze SL, Landis BJ, Ware SM, et al. Bicuspid aortic valve: A review with recommendations for genetic counseling. J Genet Counsel 2016;25:1171.
42. Delling FN, Vasan RS. Epidemiology and pathophysiology of mitral valve prolapse: new insights into disease progression, genetics and molecular basis. Circulation 2014;129:2158.
43. Marelli AJ, Ionescu-Ittu R, Mackie AS, et al. Lifetime prevalence of congenital heart disease in the general population from 2000 to 2010. Circulation 2014;130:749.
44. Reller MD, Strickland MJ, Riehle-Colarusso T, et al. Prevalence of congenital heart defects in metropolitan Atlanta, 1998–2005. J Pediatr 2008;153:807.
45. Moons P, Sluysmans T, De Wolf D, et al. Congenital heart disease in 111,225 births in Belgium: birth prevalence, treatment and survival in the 21st century. Acta Paediatr 2009;98:472.
46. Morris JK, Wellesley DG, Barisic I, et al. Epidemiology of congenital cerebral anomalies in Europe: a multicentre, population-based EUROCAT study. Arch Dis Child 2019;104:1181.
47. Sigmon ER, Kelleman M, Susi A, et al. Congenital heart disease and autism: a case-control study. Pediatrics 2019;144:pii e20184114.
48. Hoffman JI, Kaplan S. The incidence of congenital heart disease. J Am Coll Cardiol 2002;39:1890.
49. Pierpont ME, Brueckner M, Chung WK, et al. Genetic basis for congenital heart disease: revisited: a scientific statement from the American Heart Association. Circulation 2018;138:e653.
50. Wang Y, Cao L, Liang D, et al. Prenatal chromosomal microarray analysis in fetuses with congenital heart disease: a prospective cohort study. Am J Obstet Gynecol 2018;218(2):244.e1.

51. Cowan JR, Ware SM. Genetics and genetic testing in congenital heart disease. Clin Perinatol 2015;42:373.
52. Jin SC, Homsy J, Zaidi S, et al. Contribution of rare inherited and de novo variants in 2,871 congenital heart disease probands. Nat Genet 2017;49:1593.
53. Tinker SC, Gilboa SM, Moore CA, et al. Specific birth defects in pregnancies of women with diabetes: National Birth Defects Prevention Study, 1997–2011. Am J Obstet Gynecol 2020;222:176.e1.
54. Stothard KJ, Tennant PW, Bell R, et al. Maternal overweight and obesity and the risk of congenital anomalies: a systematic review and meta-analysis. JAMA 2009;301:636.
55. Watkins ML, Rasmussen SA, Honein MA, et al. Maternal obesity and risk for birth defects. Pediatrics 2003;111:1152.
56. Moore LL, Singer MR, Bradlee ML, et al. A prospective study of the risk of congenital defects associated with maternal obesity and diabetes mellitus. Epidemiology 2000;11:689.
57. Moore LL, Bradlee ML, Singer MR, et al. Chromosomal anomalies among the offspring of women with gestational diabetes. Am J Epidemiol 2002;155:719.
58. Correa A, Marcinkevage J. Prepregnancy obesity and the risk of birth defects: an update. Nutr Rev 2013;71(Suppl 1):S68.
59. Gao LJ, Wang ZP, Lu QB, et al. Maternal overweight and obesity and the risk of neural tube defects: a casecontrol study in China. Birth Defects Res A Clin Mol Teratol 2013;97:161.
60. Madsen NL, Schwartz SM, Lewin MB, et al. Prepregnancy body mass index and congenital heart defects among offspring: a population-based study. Congenit Heart Dis 2013;8:131.
61. Josefsson A, Bladh M, Wiréhn A-B, et al. Risk for congenital malformations in offspring of women who have undergone bariatric surgery: a national cohort. BJOG 2013;120:1477.
62. McMahon DM, Liu J, Zhang H, et al. Maternal obesity, folate intake, and neural tube defects in offspring. Birth Defects Res A Clin Mol Teratol 2013;97:115.
63. Mills JL, Troendle J, Conley MR, et al. Maternal obesity and congenital heart defects: a population-based study. Am J Clin Nutr 2010;91:1543.
64. Persson M, Cnattingius S, Villamor E, et al. Risk of major congenital malformation in relation to maternal overweight and obesity severity: cohort study of 1.2 million singletons. BMJ 2017;357:j2563.
65. Zheng Z, Yang T, Chen L, et al. Increased maternal body mass index is associated with congenital heart defects: an updated meta-analysis of observational studies. Int J Cardiol 2018;273:112.
66. Block SR, Watkins SM, Salemi JL, et al. Maternal prepregnancy body mass index and risk of selected birth defects: evidence of a dose–response relationship. Paediatr Perinat Epidemiol 2013;27:521.
67. Cai GJ, Sun XX, Zhang L, et al. Association between maternal body mass index and congenital heart defects in offspring: a systematic review. Am J Obstet Gynecol 2014;211:91.
68. Milunsky A. Glucose intolerance in the parents of children with Down's syndrome. Am J Mental Def 1970;74:475.
69. Biggio JR Jr, Chapman V, Neely C, et al. Fetal abnormalities in obese women: the contribution of diabetes. Obstet Gynecol 2010;115:290.
70. Auger N, Bilodeau-Bertrand M, Tith RM, et al. Bariatric surgery and the risk of congenital anomalies in subsequent pregnancies. Am J Clin Nutr 2019;110:1168.
71. Benjamin RH, Littlejohn S, Mitchell LE. Bariatric surgery and birth defects: a systematic literature review. Paediatr Perinat Epidemiol 2018;32:533.
72. Neovius M, Pasternak B, Näslund I, et al. Association of maternal gastric bypass surgery with offspring birth defects. JAMA 2019;322:1515.
73. Wang M, Wang, ZP, Gao LJ, et al. Maternal body mass index and the association between folic acid supplements and neural tube defects. Acta Paediatr 2013;102:908.
74. Lam PK, Torfs C, Brand RJ. A low pregnancy body mass index is a risk factor for an offspring with gastroschisis. Epidemiology 1999;10(6):717.
75. Anderson JE, Galganski LA, Cheng Y, et al. Epidemiology of gastroschisis: a population-based study in California from 1995–2012. J Pediatr Surg 2018;53:2399.
76. Perry MF, Mulcahy H, DeFranco EA. Influence of periconception smoking behavior on birth defect risk. Am J Obstet Gynecol 2019;220:588.e1.
77. Hackshaw A, Rodeck C, Boniface S. Maternal smoking in pregnancy and birth defects: a systemic review based on 173,687 malformed cases and 11.7 million controls. Hum Reprod Update 2011;17:589.
78. Vu LT, Nobuhara KK, Laurent C, et al. Increasing prevalence of gastroschisis: population-based study in California. J Pediatr 2008;152:807.
79. Alberto G, Barbero P, Liascovich R, et al. Congenital limb reduction defects in 1.6 million births in Argentina. Am J Med Genet A 2020;182:1084.
80. Yang L, Liu X, Li Z, et al. Genetic aetiology of early infant deaths in a neonatal intensive care unit. J Med Genet 2020;57:169.

81. Power S, Meaney S, O'Donoghue K. The incidence of fatal anomalies associated with perinatal mortality in Ireland. Prenat Diagn 2020;40:549.
82. Galjaard H. Genetic metabolic diseases: early diagnosis and prenatal analysis. Amsterdam: Elsevier/North-Holland, 1980.
83. Scriver CR, Neal JL, Saginur R, et al. The frequency of genetic disease and congenital malformation among patients in a pediatric hospital. Can Med Assoc J 1973;108:1111.
84. Khokha MK, Mitchell LE, Wallingford JB. White paper on the study of birth defects. Birth Defects Res 2017;109:180.
85. Brent RL. The magnitude of the problem of congenital malformations. In: Marois M, ed. Prevention of physical and mental congenital defects. Part A: The scope of the problem. New York: Alan R. Liss, 1985:55.
86. Brent R. Environmental causes of human congenital malformations. Prog Obstet Gynecol 2008;5:61.
87. Milunsky A, Jick H, Jick SS, et al. Multivitamin/folic acid supplementation in the earliest weeks of pregnancy reduces the prevalence of neural tube defects. JAMA 1989;262:2847.
88. MRC Vitamin Study Research Group. Prevention of neural tube defects: results of the Medical Research Council Vitamin Study. Lancet 1991;338:131.
89. Ray JG, Meier C, Vermeulen MJ, et al. Association of neural tube defects and folic acid food fortification in Canada. Lancet 2002;360:2047.
90. Rasmussen SA, Moore CA, Paulozzi LJ, et al. Risk for birth defects among premature infants: a population based study. J Pediatr 2001;138:668.
91. Adams-Chapman I, Hensen NI, Shankaran S, et al. Ten-year review of major birth defects in VLBW infants. Pediatrics 2013;132:49.
92. Toufaily MH, Westgate M, Lin AE, et al. Causes of congenital malformations. Birth Defects Res 2018;110:87.
93. Glinianaia SV, Rankin J, Wright C. Congenital anomalies in twins: a register-based study. Hum Reprod 2008;23:1306.
94. Yu Y, Cozen W, Hwang AE, et al. Birth anomalies in monozygotic and dizygotic twins: results from the California Twin Registry. J Epidemiol 2019;29:18.
95. Lie RT, Wilcox AJ, Skjaerven R. Survival and reproduction among males with birth defects and risk of recurrence in their children. JAMA 2001;285:755.
96. Mangones T, Manhas A, Visintainer P, et al. Prevalence of congenital cardiovascular malformations varies by race and ethnicity. Int J Cardiol 2010;143:317.
97. Kucik JE, Alverson CJ, Gilboa SM, et al. Racial/ethnic variations in the prevalence of selected major birth defects, metropolitan Atlanta, 1994–2005. Public Health Rep 2012;127:52.
98. Su PY, Huang L, Hao JH, et al. Maternal thyroid function in the first twenty weeks of pregnancy and subsequent fetal and infant development: a prospective population-based cohort study in China. J Clin Endocrinol Metab 2011;96:3234.
99. Huget-Penner S, Feig DS. Maternal thyroid disease and its effects on the fetus and perinatal outcomes. Prenatal Diag 2020;40:1077.
100. Stoll C, Dott B, Alembik Y, et al. Congenital anomalies associated with congenital hypothyroidism. Ann Genet 1999;42:17.
101. Olafsson E, Hallgrimsson JT, Hauser WA, et al. Pregnancies of women with epilepsy: a population-based study in Ireland. Epilepsia 1998;39:887.
102. Weston J, Bromley R, Jackson CF, et al. Monotherapy treatment of epilepsy in pregnancy: congenital malformation outcomes in the child. Cochrane Database Syst Rev 2016;11:CD010224.
103. Shechter-Maor G, Czuzoj-Shulman N, Spence AR, et al. The effect of assisted reproductive technology on the incidence of birth defects among livebirths. Arch Gynecol Obstet 2018;297:1397.
104. Lupo PJ, Schraw JM, Desrosiers TA, et al. Association between birth defects and cancer risk among children and adolescents in a population-based assessment of 10 million live births. JAMA Oncol 2019;5:1150.
105. Rasmussen SA, Wong LY, Yang Q, et al. Population based analyses of mortality in trisomy 13 and trisomy 18. Pediatrics 2003;111:777.
106. Goel N, Morris JK, Tucker D, et al. Trisomy 13 and 18 – prevalence and mortality – a multi-registry population based analysis. Am J Med Genet A 2019;179:2382.
107. DeGalan-Roosen AE, Kuijpers JC, Meershoek AP, et al. Contribution of congenital malformations to perinatal mortality: a 10 years prospective regional study in The Netherlands. Eur J Obstet Gynecol Reprod Biol 1998;80:55.
108. Dastgiri S, Gilmour WH, Stone DH. Survival of children born with congenital anomalies. Arch Dis Child 2003;88:391.
109. Liu S, Joseph KS, Wen SW. Trends in fetal and infant deaths caused by congenital anomalies. Semin Perinatol 2002;26:268.
110. Stoll C, Alembik Y, Dott B, et al. Impact of prenatal diagnosis on livebirth prevalence of children with congenital anomalies. Ann Genet 2002;45;115.

111. de Vigan C, Khoshnood B, Cadio E, et al. Prenatal diagnosis and prevalence of Down syndrome in the Parisian population, 2001–2005. Gynecol Obstet Fertil 2008;36:146.
112. Iliyasu Z, Gilmour WH, Stone DH. Prevalence of Down syndrome in Glasgow, 1980–96: the growing impact of prenatal diagnosis on younger mothers. Health Bull (Edinb) 2002;60:20.
113. Weijerman ME, van Furth AM, Vonk Noordegraaf A, et al. Prevalence, neonatal characteristics and first-year mortality of Down syndrome: a national study. J Pediatr 2008;152:15.
114. de Graaf G, Buckley F, Skotko BG. Estimation of the number of people with Down Syndrome in the United States. Genet Med 2017;19:439.
115. Presson AP, Partyka G, Jensen KM, et al. Current estimate of Down syndrome population prevalence in the United States. J Pediatr 2013;163:1163.
116. Stoll C, Dott B, Alembik Y, et al. Associated congenital anomalies among cases with Down syndrome. Eur J Med Genet 2015;58:674.
117. Sasaki A, Sago H. Equipoise of recent estimated Down syndrome live births in Japan. Am J Med Genet 2019;179A:1815.
118. Migliore L, Migheli F, Coppedè F. Susceptibility to aneuploidy in young mothers of Down syndrome children. Scientific World Journal 2009;9:1052.
119. Lie RT, Heuch I, Irgens LM. A temporary increase of Down syndrome among births of young mothers in Norway: an effect of risk unrelated to maternal age? Genet Epidemiol 1991;8:217.
120. Erickson JD. Down syndrome, paternal age, maternal age and birth order. Ann Hum Genet 1978;41:289.
121. Egan JF, Smith K, Timms D, et al. Demographic differences in Down syndrome livebirths in the US from 1989 to 2006. Prenat Diagn 2011;31:389.
122. Sparks TN, Norton ME, Flessel M, et al. Observed rate of Down syndrome in twin pregnancies. Obstet Gynecol 2016;128:1127.
123. Masaki M, Higurashi M, Iijima K, et al. Mortality and survival for Down syndrome in Japan. Am J Hum Genet 1981;33:629.
124. Dupont A, Vaeth M, Videbech P. Mortality and life expectancy of Down's syndrome in Denmark. J Ment Defic Res 1986;30:111.
125. Fryers T. Survival in Down's syndrome. J Ment Defic Res 1986;30:101.
126. Malone Q. Mortality and survival of the Down's syndrome population in Western Australia. J Ment Defic Res 1988;32:59.
127. Baird PA, Sadovnick AD. Life expectancy in Down syndrome adults. Lancet 1988;2:1354.
128. Baird PA, Sadovnick AD. Life tables for Down syndrome. Hum Genet 1989;82:291.
129. Strauss D, Eyman RK. Mortality of people with mental retardation in California with and without Down syndrome, 1986–1991. Am J Ment Retard 1996;100:643.
130. Wu J, Morris JK. The population prevalence of Down's syndrome in England and Wales in 2011. Eur J Hum Genet 2013;21:1016.
131. Yang Q, Rasmussen SA, Friedman JM. Mortality associated with Down's syndrome in the USA from 1983 to 1997: a population-based study. Lancet 2002;359:1019.
132. Hasle H, Clemmensen IH, Mikkelsen M. Risks of leukemia and solid tumours in individuals with Down's syndrome. Lancet 2000;355:165.
133. Roizen NJ, Patterson D. Down's syndrome. Lancet 2003;361:1281.
134. Matsunaga S, Imakiire T, Koga H, et al. Occult spinal canal stenosis due to C-1 hypoplasia in children with Down syndrome. J Neurosurg 2007;107:457.
135. Anwar AJ, Walker JD, Frier BM. Type 1 diabetes mellitus and Down's syndrome: prevalence, management and diabetic complications. Diabet Med 1998;15:160.
136. Menéndez M. Down syndrome, Alzheimer's disease and seizures. Brain Dev 2005;27:246.
137. Patja K, Pukkala E, Sund R, et al. Cancer incidence of persons with Down syndrome in Finland: a population-based study. Int J Cancer 2006;118:1769.
138. Hill DA, Gridley G, Cnattingius S, et al. Mortality and cancer incidence among individuals with Down syndrome. Arch Intern Med 2003;163:705.
139. Malt EA, Dahl RC, Haugsand TM, et al. Health and disease in adults with Down syndrome. Tidsskr Nor Laegeforen 2013;133:290.
140. Kosashvili Y, Taylor D, Backstein D, et al. Total hip arthroplasty in patients with Down syndrome. Orthopedics 2010;33:629.
141. Weijerman ME, de Winter JP. The care of children with Down syndrome. Eur J Pediatr 2010;169:1445.
142. Kobayashi T, Sakemi Y, Yamashita H. Increased incidence of retroperitoneal teratomas and decreased incidence of sacrococcygeal teratomas in infants with Down syndrome. Pediatr Blood Cancer 2014;61:363.
143. De Simone R, Puig XS, Gélisse P, et al. Senile myoclonic epilepsy: delineation of a common condition associated with Alzheimer's disease in Down syndrome. Seizure 2010;19:383.
144. Tenenbaum A, Chavkin M, Wexler I, et al. Morbidity and hospitalizations of adults with Down syndrome. Res Dev Disabil 2012;33:435.

145. Mårlid K, Stephansson O, Grahnquist L, et al. Down syndrome is associated with elevated risk of celiac disease: a nationwide case-control study. J Pediatr 2013;163:237.
146. Satgé D, Sasco AJ, Day S, et al. A lower risk of dying from urological cancer in Down syndrome: clue for cancer protecting genes on chromosome 21. Urol Int 2009;82:296.
147. Hasle H, Friedman JM, Olsen JH, et al. Low risk of solid tumors in persons with Down syndrome. Genet Med 2016;18(11):1151.
148. Määttä T, Määttä J, Tervo-Määttä T, et al. Healthcare and guidelines: a population based survey of recorded medical problems and health surveillance for people with Down syndrome. J Intellect Dev Disabil 2011;36:118.
149. de Carvalho M, Swash M. Neurologic complications of craniovertebral dislocation. Handb Clin Neurol 2014;119:435.
150. Hithersay R, Startin CM, Hamburg S, et al. Association of dementia with mortality among adults with Down syndrome older than 35 years. JAMA Neurol 2019;76:152.
151. Satgé D, Seidel MG. The pattern of malignancies in Down syndrome and its potential context with the immune system. Front Immunol 2018;9:3058.
152. Morris JK, Garne E, Wellesley D, et al. Major congenital anomalies in babies born with Down syndrome: a EUROCAT population-based registry study. Am J Med Genet 2014;164A:2979.
153. Ghezzo A, Salvioli S, Solimando MC, et al. Age related changes of adaptive and neuropsychological features in persons with Down syndrome. PLoS One 2014;9:e113111.
154. Hartley D, Blumenthal T, Carrillo M, et al. Down syndrome and Alzheimer's disease: common pathways, common goals. Alzheimers Dement 2015;11:700.
155. Kinnear D, Morrison J, Allan L, et al. Prevalence of physical conditions and multimorbidity in a cohort of adults with intellectual disabilities with and without Down syndrome: cross-sectional study. BMJ Open 2018;8:e018292.
156. Ludvigsson JF, Lebwohl B, Green PHR, et al. Celiac disease and Down syndrome mortality: a nationwide cohort study. BMC Pediatr 2017;17:41.
157. Oxelgren UW, Myrelid A, Annerén G, et al. Prevalence of autism and attention-deficit-hyperactivity disorder in Down syndrome: a population-based study. Dev Med Child Neurol 2017;59:276.
158. Palaska PK, Antonarakis GS. Prevalence and patterns of permanent tooth agenesis in individuals with Down syndrome: a meta-analysis. Eur J Oral Sci 2016;124:317.
159. Santoro SL, Cannon S, Capone G, et al. Unexplained regression in Down syndrome: 35 cases from an international Down syndrome database. Genet Med 2020;22(4):767.
160. Cuoghi OA, Topolski F, de Faria LP, et al. Prevalence of dental anomalies in permanent dentition of Brazilian individuals with Down syndrome. Open Dent J 2016;10:469.
161. Garg A, Strunk A, Midura M, et al. Prevalence of hidradenitis suppurativa among patients with Down syndrome: a population-based cross-sectional analysis. Br J Dermatol 2018;178:697.
162. Giménez S, Videla L, Romero S, et al. Prevalence of sleep disorders in adults with Down syndrome: a comparative study of self-reported, actigraphic, and polysomnographic findings. J Clin Sleep Med 2018;14:1725.
163. Hamilton J, Yaneza MMC, Clement WA, et al. The prevalence of airway problems in children with Down's syndrome. Int J Pediatr Otorhinolaryngol 2016;81:1.
164. Sinai A, Mokrysz C, Bernal J, et al. Predictors of age of diagnosis and survival of Alzheimer's disease in Down syndrome. J Alzheimers Dis 2018;61:717.
165. Whooten R, Schmitt J, Schwartz A. Endocrine manifestations of Down syndrome. Curr Opin Endocrinol Diabetes Obes 2018;25:61.
166. Sheets KB, Crissman BG, Feist CD, et al. Practice guidelines for communicating a prenatal or postnatal diagnosis of Down syndrome: recommendations of the National Society of Genetic Counselors. J Genet Counsel 2011;20:432.
167. Milunsky A. The prenatal diagnosis of hereditary disorders. Springfield, IL: Charles C. Thomas, 1973.
168. American Society for Reproductive Medicine, American College of Obstetricians and Gynecologists' Committee on Gynecologic Practice. Prepregnancy counseling: Committee Opinion No. 762. Fertil Steril 2019;111:32.
169. American College of Obstetricians and Gynecologists. Family history as a risk assessment tool. Obstet Gynecol 2011;117:747.
170. Wilson RD. Genetic considerations for a woman's preconception evaluation. J Obstet Gynaecol Can 2011;33:57.
171. Rubin SP, Malin J, Maidman J. Genetic counseling before prenatal diagnosis for advanced maternal age: an important medical safeguard. Obstet Gynecol 1983;62:155.

172. Kessler S. Psychological aspects of genetic counseling. XIII. Empathy and decency. J Genet Couns 1999;8:333.
173. Scheiper S, Ramos-Luis E, Blanco-Verea A, et al. Sudden unexpected death in the young – value of massive parallel sequencing in postmorten genetic analyses. Forensic Sci Int 2018;293:70.
174. Spoonamore KG, Ware SM. Genetic testing and genetic counseling in patients with sudden death risk due to heritable arrhythmias. Heart Rhythm 2019;13:789.
175. Tang Y, Williams N, Sampson BA. Genetic testing in sudden unexpected natural death in the young: New York City Office of Chief Medical Examiner's experience and perspective. Forensic Sci Med Pathol 2019;15:481.
176. Tester DJ, Ackerman MJ. Evaluating the survivor or the relatives of those who do not survive: the role of genetic testing. Cardiol Young 2017;27:S19.
177. Tejada MI, Ibarluzea N. Non-syndromic X-linked intellectual disability: current knowledge in light of the recent advances in molecular and functional studies. Clin Genet 2020;97:677.
178. Neri G, Schwartz CE, Lubs HA, et al. X-linked intellectual disability update 2017. Am J Med Genet Part A 2018;00:1.
179. López-Rivera JA, Pérez-Palma E, Symonds J, et al. A catalogue of new incidence estimates of monogenic neurodevelopmental disorders caused by de novo variants. Brain 2020;143(4):1099.
180. Gnazzo M, Lepri FR, Dentici ML, et al. KBG syndrome: common and uncommon clinical features based on 31 new patients. Am J Med Genet A 2020;182:1073.
181. McNeill A, Lewis R, Freeth M. Views of adults with 22q11 deletion syndrome on reproductive choices. Am J Med Genet A 2020;182:1284.
182. Van L, Heung T, Graffi J, et al. All-cause mortality and survival in adult with 22q11.2 deletion syndrome. Genet Med 2019;21:2328.
183. Palmer LD, Butcher NJ, Boot E, et al. Elucidating the diagnostic odyssey of 22q11.2 deletion syndrome. Am J Med Genet A 2018;176:936.
184. Milunsky A. I didn't know, I didn't know: avoidable deaths and harm due to medical negligence. Amazon Createspace, 2018.
185. Milunsky A. Obstetrics, genetics and litigation. (in press).
186. Jayaraman D, Bae B, Walsh CA. The genetics of primary microcephaly. Annu Rev Genomics Hum Genet 2018;19:177.
187. Shaheen R, Maddirevula S, Ewida N, et al. Genomic and phenotypic delineation of congenital microcephaly. Genet Med 2019;21:545.
188. Boonsawat P, Joset P, Steindl K, et al. Elucidation of the phenotypic spectrum and genetic landscape in primary and secondary microcephaly. Genet Med 2019;21:2043.
189. Zouvelou V, Yubero D, Apostolakopoulou L, et al. The genetic etiology in cerebral palsy mimics: the results from a Greek tertiary care center. Eur J Paediatr Neurol 2019;23:427.
190. Matthews AM, Blydt-Hansen I, Al-Jabri B, et al. Atypical cerebral palsy: Genomics analysis enables precision medicine. Genet Med 2019;21:1621.
191. Pearson TS, Pons R, Ghaoui R, et al. Genetic mimics of cerebral palsy. Mov Disord 2019;34:625.
192. Harris R, Lane B, Harris H, et al. National Confidential Enquiry into counseling for genetic disorders by non-geneticists: general recommendations and specific standards for improving care. Br J Obstet Gynaecol 1999;106:658.
193. van Langen IM, Birnie E, Leschot NJ, et al. Genetic knowledge and counseling skills of Dutch cardiologists: sufficient for the genomics era? Eur Heart J 2003;24:560.
194. Rosas-Blum E, Shirsat P, Leiner M. Communicating genetic information: a difficult challenge for future pediatricians. BMC Med Educ 2007;7:17.
195. Harvey EK, Fogel CE, Peyrot M, et al. Providers' knowledge of genetics: a survey of 5915 individuals and families with genetic conditions. Genet Med 2007;9:259.
196. Baars MJ, Henneman L, Ten Kate LP. Deficiency of knowledge of genetics and genetic tests among general practitioners, gynecologists and pediatricians: a global problem. Genet Med 2005;7:605.
197. Shaer CM, Chescheir N, Erickson K, et al. Obstetrician-gynecologists' practice and knowledge regarding spina bifida. Am J Perinatol 2006;23:355.
198. Haga SB, Burke W, Ginsburg GS, et al. Primary care physicians' knowledge of and experience with pharmacogenetic testing. Clin Genet 2012;82:388.
199. Milunsky A. The "new genetics" in clinical practice: a brief primer. J Am Board Fam Med 2017;30(3):377.
200. Committee on Genetics. Committee Opinion No. 693: Counseling about genetic testing and communication of genetic test results. Obstet Gynecol 2017;129:e96.
201. Gordis L, Childs B, Roseman MG. Obstetricians' attitudes toward genetic screening. Am J Public Health 1977;67:469.

202. Kessler S. Psychological aspects of genetic counseling. XII. More on counseling skills. J Genet Couns 1998;7:263.
203. Milunsky A, Annas GJ. Genetics and the law. New York: Plenum Press, 1976.
204. Milunsky A, Annas GJ. Genetics and the law II. New York: Plenum Press, 1980.
205. Milunsky A, Annas GJ. Genetics and the law III. New York: Plenum Press, 1985.
206. Levetown M and the Committee on Bioethics. Communicating with children and families: from everyday interactions to skill in conveying distressing information. Pediatrics 2008;121:e1441.
207. Forrest LE, Delatycki MB, Skene L, et al. Communicating genetic information in families – a review of guidelines and position papers. Eur J Hum Genet 2007;15:612.
208. Phillips A, Niemiec E, Howard HC, et al. Communicating genetic information to family members: analysis of consent forms for diagnostic genomic sequencing. Eur J Hum Genet 2020;28:1160.
209. Farrell M, Deuster L, Donovan J, et al. Pediatric residents' use of jargon during counseling about newborn genetic screening results. Pediatrics 2008;122:243.
210. Welkenhuysen M, Evers-Kiebooms G, d'Ydewalle G. The language of uncertainty in genetic risk communication: framing and verbal versus numerical information. Patient Educ Couns 2001;43:179.
211. Benkendorf JL, Prince MB, Rose MA, et al. Does indirect speech promote nondirective genetic counseling? Results of a sociolinguistic investigation. Am J Med Genet 2001;106:199.
212. Abramsky L, Fletcher O. Interpreting information: what is said, what is heard – a questionnaire study of health professionals and members of the public. Prenat Diagn 2002;22:1188.
213. O'Doherty K, Suthers GK. Risky communication: pitfalls in counseling about risk and how to avoid them. J Genet Couns 2007;16:409.
214. Palermo GD, O'Neill CL, Chow S, et al. Intracytoplasmic sperm injection: state of the art in humans. Reproduction 2017;154(6):F93.
215. Hibi H, Sumitomo M, Fukunaga N, et al. Superior clinical pregnancy rates after microsurgical epididymal sperm aspiration. Reprod Med Biol 2018;17(1):59.
216. Decety J. Empathy in medicine: what it is, and how much we really need it. Am J Med 2020;133:561.
217. Looi JCL. Empathy and competence. Med J Aust 2008;188:414.
218. Eden OB, Black I, MacKinlay GA, et al. Communication with parents of children with cancer. Palliat Med 1994;8:105.
219. Turner J, Biesecker B, Leib J, et al. Parenting children with Proteus syndrome: experiences with, and adaptation to, courtesy stigma. Am J Med Genet A 2007;143A:2089.
220. Hojat M, Mangione S, Nasca TJ, et al. The Jefferson Scale of Physician Empathy: development and preliminary psychometric data. Educ Psychol Meas 2001;61:349.
221. Lehmann A, Speight BS, Kerzin-Storrar L. Extended family impact of genetic testing: the experiences of X-linked carrier grandmothers. J Genet Couns 2011;20:365.
222. James CA, Hadley DW, Holtzman NA, et al. How does the mode of inheritance of a genetic condition influence families? A study of guilt, blame, stigma and understanding of inheritance and reproductive risks in families with X-linked and autosomal recessive diseases. Genet Med 2006;8:234.
223. Targum SD. Psychotherapeutic considerations in genetic counseling. Am J Med Genet 1981;8:281.
224. Kessler S, Kessler H, Ward P. Psychological aspects of genetic counseling. III. Management of guilt and shame. Am J Med Genet 1984;17:673.
225. Hayden MR, Canadian Collaborative Study of Predictive Testing for HD. Predictive medicine for late onset disorders: the experience for Huntington disease. Am J Hum Genet 1991;49:50.
226. Tibben A, Vegter-van der Vlis M, Skraastad MI, et al. Presymptomatic DNA-testing for Huntington disease in The Netherlands. Am J Hum Genet 1991;49:316.
227. Craufurd D, Dodge A, Kerzin-Storrar L, et al. Psychosocial impact of presymptomatic predictive testing for Huntington's disease. Am J Hum Genet 1991;49:311.
228. Huggins M, Bloch M, Kanani S, et al. Ethical and legal dilemmas arising during predictive testing for adult-onset disease: the experience of Huntington disease. Am J Hum Genet 1990;47:4.
229. Folstein SE. Presymptomatic testing for Huntington's disease: outcome of 136 at-risk persons who requested testing. Am J Hum Genet 1991;49:62.
230. Wiggins S, Whyte P, Hayden M, et al. No harm, potential benefit: the one year follow-up of participants in the Canadian Collaborative Study of Predictive Testing for Huntington's Disease. Am J Hum Genet 1991;49:317.
231. Ravine D, Walker RG, Sheffield JL, et al. Experience of family screening for autosomal dominant polycystic kidney disease. Am J Hum Genet 1991;49:50.

232. Baumiller RC, Comley S, Cunningham G, et al. Code of ethical principles for genetics professionals. Am J Med Genet 1996;65:177.
233. Baumiller RC, Cunningham G, Fisher N, et al. Code of ethical principles for genetics professionals: an explication. Am J Med Genet 1996:65:179.
234. Langfelder-Schwind E, Kloza E, Sugerman E, et al. Cystic fibrosis prenatal screening in genetic counseling practice: recommendations of the National Society of Genetic Counselors. J Genet Couns 2005;14:1.
235. Rantanen E, Hietala M, Kristoffersson U, et al. What is ideal genetic counseling? A survey of current international guidelines. Eur J Hum Genet 2008;16:445.
236. Yang Y, Muzny DM, Xia F, et al. Molecular findings among patients referred for clinical whole-exome sequencing. JAMA 2014;312:1870.
237. Lee H, Deignan JL, Dorrani N, et al. Clinical exome sequencing for genetic identification of rare Mendelian disorders. JAMA 2014;312:1880.
238. Tan TY, Dillon OJ, Stark Z, et al. Diagnostic impact and cost-effectiveness of whole-exome sequencing for ambulant children with suspected monogenic conditions. JAMA Pediatr 2017;171:855.
239. Li R, Fu F, Yu Q, et al. Prenatal exome sequencing in fetuses with congenital heart defects. Clin Genet 2020;98:215.
240. Sabbagh R, Van den Veyver IB. The current and future impact of genome-wide sequencing on fetal precision medicine. Hum Genet 2020;139:1121.
241. Nigro V, Savarese M. Genetic basis of limb-girdle muscular dystrophies: the 2014 update. Acta Myol 2014;33:1.
242. Thomas RH, Berkovic SF. The hidden genetics of epilepsy – a clinically important new paradigm. Nat Rev Neurol 2014;10:283.
243. Armand T, Schaefer E, Di Rocco F, et al. Genetic bases of craniosynostoses: an update. Neurochirurgie 2019;65(5):196.
244. Passos-Bueno MR, Serti Eacute AE, Jehee FS, et al. Genetics of craniosynostosis: genes, syndromes, mutations and genotype-phenotype correlations. Front Oral Biol 2008;12:107.
245. Paumard-Hernandez B, Berges-Soria J, Barroso E. Expanding the mutation spectrum in 182 Spanish probands with craniosynostosis: identification and characterization of novel TCF12 variants. Eur J Hum Genet 2015;23(7):907.
246. Jezela-Stanek A, Krajewska-Walasek M. Genetic causes of syndromic craniosynostoses. Eur J Paediatr Neurol 2013;17:22.
247. Curatolo P, Bombardieri R, Jozwiak S. Tuberous sclerosis. Lancet 2008;372:657.
248. Rossetti S, Harris PC. Genotype–phenotype correlations in autosomal dominant and autosomal recessive polycystic kidney disease. J Am Soc Nephrol 2007;18:1374.
249. Bergmann C, Brüchle NO, Frank V, et al. Perinatal deaths in a family with autosomal dominant polycystic kidney disease and a PKD2 mutation. N Engl J Med 2008;359:318.
250. Rasmussen SA, Mulinare J, Khoury MJ, et al. Evaluation of birth defect histories obtained through maternal interviews. Am J Hum Genet 1990;46:478.
251. Haxton MJ, Bell J. Fetal anatomical abnormalities and other associated factors in middle-trimester abortion and their relevance to patient counseling. Br J Obstet Gynaecol 1983;90:501.
252. Harper PS. Myotonic dystrophy, 2nd edn. London: WB Saunders, 1989.
253. Bergoffen J, Kant J, Sladky J, et al. Paternal transmission of congenital myotonic dystrophy. J Med Genet 1994;31:518.
254. Wieringa B. Myotonic dystrophy reviewed: back to the future? Hum Mol Genet 1994;3:1.
255. Shelbourne P, Winqvist R, Kunert E, et al. Unstable DNA may be responsible for the incomplete penetrance of the myotonic dystrophy phenotype. Hum Mol Genet 1992;1:467.
256. Brunner HG, Jansen G, Nillesen W, et al. Reverse mutation in myotonic dystrophy. N Engl J Med 1993;328:476.
257. O'Hoy KL, Tsilfidis C, Mahadevan MS, et al. Reduction in size of the myotonic dystrophy trinucleotide repeat mutation during transmission. Science 1993;259:809.
258. Brook JD. Retreat of the triplet repeat? Nat Genet 1993;3:279.
259. Hunter AG, Jacob P, O'Hoy K, et al. Decrease in the size of the myotonic dystrophy CTG repeat during transmission from parent to child: implications for genetic counseling and genetic anticipation. Am J Med Genet 1993;45:401.
260. Ashizawa T, Anvret M, Baiget M, et al. Characteristics of intergenerational contractions of the CTG repeat in myotonic dystrophy. Am J Hum Genet 1994;54:414.
261. Abeliovich D, Lerer I, Pashut-Lavon I, et al. Negative expansion of the myotonic dystrophy unstable sequence. Am J Hum Genet 1993;52:1175.
262. Ashizawa T, Dunne PW, Ward PA, et al. Effects of the sex of myotonic dystrophy patients on the unstable triplet repeat in their affected offspring. Neurology 1994;44:120.
263. Fraser FC. Genetic counseling. Am J Hum Genet 1974;26(5):636.

264. World Health Organization Expert Committee. Genetic counseling. WHO Tech Rep 1969;416:1.
265. Wertz DC, Fletcher JC. Attitudes of genetic counselors: a multinational survey. Am J Hum Genet 1988;42:592.
266. Wertz DC, Fletcher JC, Mulvihill JJ. Medical geneticists confront ethical dilemmas: cross-cultural comparisons among 18 nations. Am J Hum Genet 1990;46:1200.
267. Kessler S. Psychological aspects of genetic counseling. XI. Nondirectiveness revisited. Am J Med Genet 1997;72:164.
268. Vanstone M, Kinsella EA, Nisker J. Information-sharing to promote informed choice in prenatal screening in the spirit of the SOGC clinical practice guideline: a proposal for an alternative model. J Obstet Gynecol Can 2012;34:269.
269. Pennacchini M, Pensieri C. Is non-directive communication in genetic counseling possible? Clin Ter 2011;162:e141.
270. Michie S, Bron F, Bobrow M, et al. Nondirectiveness in genetic counseling: an empirical study. Am J Hum Genet 1997;60:40.
271. Clarke A. Is non-directive genetic counseling possible? Lancet 1991;338:998.
272. Milunsky A, Littlefield JW, Kanfer JN, et al. Prenatal genetic diagnosis. N Engl J Med 1970;283:1370, 1441, 1498.
273. Super M. Non-directive genetic counseling. Lancet 1991;338:1266.
274. Pembrey M. Non-directive genetic counseling. Lancet 1991;338:1267.
275. Harris R, Hopkins A. Non-directive genetic counseling. Lancet 1991;338:1268.
276. Clarke A. Non-directive genetic counseling. Lancet 1991;338:1524.
277. Einhorn HJ, Hogarth RM. Behavioral decision theory: processes of judgment and choice. Annu Rev Psychol 1981;32:53.
278. Simms M. Informed dissent: the view of some mothers of severely mentally handicapped young adults. J Med Ethics 1986;12:72.
279. Simms M. Non-directive genetic counseling. Lancet 1991;338:1268.
280. Chang BS, Lowenstein DH. Epilepsy. N Engl J Med 2003;349:1257.
281. Keeling SL. Duty to warn of genetic harm in breach of patient confidentiality. J Law Med 2004;12:235.
282. Carnevale A, Lisker R, Villa AR, et al. Counseling following diagnosis of a fetal abnormality: comparison of different clinical specialists in Mexico. Am J Med Genet 1997;69:23.
283. Williams C, Alderson P, Farsides B. Is nondirectiveness possible within the context of antenatal screening and testing? Soc Sci Med 2002;54:339.
284. Johnston J, Farrell R, Parens E. Supporting women's autonomy in prenatal testing. N Engl J Med 2017;377(6):505.
285. Wiering BM, Albada A, Bensing JM, et al. The influence of dispositional optimism on post-visit anxiety and risk perception accuracy among breast cancer genetic counselees. Psychooncology 2013;22:2419.
286. Hsia YE. Choosing my children's genes: genetic counseling. In: Lipkin M, Rowley PT, eds. Genetic responsibility. New York: Plenum Press, 1974:43.
287. Pergament E, Pergament D. Reproductive decisions after fetal genetic counseling. Best Pract Res Clin Obstet Gynaecol 2012;26:517.
288. Chapman MA. Predictive testing for adult-onset genetic disease: ethical and legal implications of the use of linkage analysis for Huntington disease. Am J Hum Genet 1990;47:1.
289. Dufrasne S, Roy M, Galvez M, et al. Experience over fifteen years with a protocol for predictive testing for Huntington disease. Mol Genet Metab 2011;102:494.
290. Marteau TM, Nippert I, Hall S, et al. Outcomes of pregnancies diagnosed with Klinefelter syndrome: the possible influence of health professionals. Prenat Diagn 2002;22:562.
291. Isidor B, Julia S, Saugier-Veber P, et al. Searching for secondary findings: considering actionability and preserving the right not to know. Eur J Hum Genet 2019;27:1481.
292. Ortega-Recalde O, Beltrán OI, Gálvez JM, et al. Biallelic HERC1 mutations in a syndromic form of overgrowth and intellectual disability. Clin Genet 2015;88:e1.
293. Chen R, Shi L, Hakenberg J, et al. Analysis of 589,306 genomes identifies individuals resilient to severe Mendelian childhood diseases. Nat Biotechnol 2016;34:531.
294. Schindewolf E, Khalek N, Johnson MP, et al. Expanding the fetal phenotype: prenatal sonographic findings and perinatal outcomes in a cohort of patients with confirmed 22q11.2 deletion syndrome. Am J Med Genet A 2018;176:1735.
295. Rose NC, Benn P, Milunsky A. Current controversies in prenatal diagnosis: should NIPT routinely include microdeletions/microduplications? Prenat Diagn 2016;36:10.
296. O'Connell O, Meaney S, O'Donoghue K. Anencephaly: the maternal experience of continuing with the pregnancy. Incompatible with life but not with love. Midwifery 2019;71:12.

297. Skirton H. More than an information service: are counselling skills needed by genetic professionals in the genomic era? Eur J Hum Genet 2018;26:1239.
298. Katz J. The silent world of doctor and patient. New York: Free Press, 1984.
299. Lantos JD. Should we always tell children the truth? Perspect Biol Med 1996;40:78.
300. Wright CF, Parker M, Lucassen AM. When genomic medicine reveals misattributed genetic relationships – the debate about disclosure revisited. Genet Med 2019;21:97.
301. Nuffield Council on Bioethics. Donor conception: ethical aspects of information sharing. London: Nuffield Council on Bioethics, 2013.
302. Bellis MA, Hughes K, Hughes S, et al. Measuring paternal discrepancy and its public health consequences. J Epidemiol Community Health 2005;59:749.
303. Kayser M. Forensic use of Y-chromosome DNA: a general overview. Hum Genet 2017;136:621.
304. Avci E. Should physicians tell the truth without taking social complications into account? A striking case. Med Health Care Philos 2018;21:23.
305. Brown K. Genetic counseling: legal issues surrounding nondisclosure of paternity. J Leg Med 2008;29:345.
306. Hercher L, Jamal L. An old problem in a new age: revisiting the clinical dilemma of misattributed paternity. Appl Transl Genom 2016;8:36.
307. Lowe G, Pugh J, Kahane G, et al. How should we deal with misattributed paternity? A survey of lay public attitudes. AJOB Empir Bioeth 2017;8:234.
308. Prero MY, Strenk M, Garrett J, et al. Disclosure of misattributed paternity. Pediatrics 2019;143:e20183899.
309. Beauchamp T, Childress J. Principles of biomedical ethics. Oxford: Oxford University Press, 2013.
310. Gert B, Culver CM, Clouser KD. Bioethics: a systematic approach, 2nd edn. New York: Oxford University Press, 2006.
311. Josen AR, Siegler M, Winslade WJ. Clinical ethics: a practical approach to ethical decisions in clinical medicine. New York: McGraw Hill, 2010.
312. Chico V. Reasonable expectations of privacy in non-disclosure of familial genetic risk: what is it reasonable to expect? Eur J Med Genet 2019;62:308.
313. Lucast EK. Informed consent and the mis attributed paternity problem in genetic counseling. Bioethics 2007;21:41.
314. Weil J, Ormond K, Peters J, et al. The relationship of nondirectiveness to genetic counseling: report of a workshop at the 2003 NSGC Annual Education Conference. J Genet Couns 2006;15:85.
315. American Medical Association. Code of Medical Ethics § 2.131 Disclosure of familial risk in genetic testing, 2014–2015. Chicago, IL: American Medical Association, 2015.
316. American Society of Human Genetics, Social Issues Subcommittee on Familial Disclosure. Professional disclosure of familial genetic information. Am J Hum Genet 1998;62:474.
317. National Society of Genetic Counselors. NSGC Code of Ethics sec. II, pt. 7.
318. President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research. Screening and counseling for genetic conditions. Washington, DC: US Government Printing Office, 1983:478.
319. US Department of Health and Human Services, Office for Civil Rights. Standards for privacy of individually identifiable health information. Code of Federal Regulations vol. 45, parts 160, 164 (2002), as amended (2013).
320. Capron AM. Autonomy, confidentiality and quality care in genetic counseling. In: Capron AM, Lappe M, Murray RF, et al., eds. Genetic counseling: facts, values and norms. New York: Alan R. Liss, 1979:307.
321. Menko FH, Aalfs CM, Henneman L, et al. Informing family members of individuals with Lynch syndrome: a guideline for clinical geneticists. Fam Cancer 2013;12:319.
322. Lacroix M, Nycum G, Godard B, et al. Should physicians warn patients' relatives of genetic risk? Can Med Assoc J 2008;178:593.
323. Van den Heuvel LM, Huisinga MJ, Hoedemaekers YM, et al. Informing relatives at risk of inherited cardiac conditions: experiences and attitudes of healthcare professionals and counselees. Eur J Hum Genet 2019;27:1341.
324. Dove ES, Chico V, Fay M, et al. Familial genetic risks: How can we better navigate patient confidentiality and appropriate risk disclosure to relatives? J Med Ethics 2019;45:504.
325. Dufrasne S, Roy M, Galvez M, et al. Experience over fifteen years with a protocol for predictive testing for Huntington disease. Mol Genet Metab 2011;102:494.
326. Van Haecke DD, de Montgolfier S. Genetic diseases and information to relatives: practical and ethical issues for professionals after introduction of a legal framework in France. Eur J Hum Genet 2018;26:786.
327. Falk MJ, Dugan RB, O'Riordan MA, et al. Medical geneticists' duty to warn at-risk relatives for genetic disease. Am J Med Genet 2003;120A:374.

328. Milunsky A. Genetic disorders and the fetus: diagnosis, prevention, and treatment, 2nd edn. New York: Plenum Press, 1986.
329. Milunsky A, Jick H, Jick SS, et al. Multivitamin/folic acid supplementation in the earliest weeks of pregnancy reduces the prevalence of neural tube defects. JAMA 1989;262:2847.
330. MRC Vitamin Study Research Group. Prevention of neural tube defects: results of the Medical Research Council Vitamin Study. Lancet 1991;338:131.
331. Milunsky A. Know your genes. Boston, MA: Houghton-Mifflin, 1977.
332. Hsia YE, Hirschhorn K, Silverberg RL, et al. Counseling in genetics. New York: Alan R. Liss, 1979.
333. Lewis C, Mehta P, Kent A, et al. An assessment of written patient information provided at the genetic clinic and relating to genetic testing in seven European countries. Eur J Hum Genet 2007;15:1012.
334. Frets PG, Duivenvoorden HJ, Verhage F, et al. Factors influencing the reproductive decision after genetic counselling. Am J Med Genet 1990;35:496.
335. Milunsky A. How to have the healthiest baby you can. New York: Simon & Schuster, 1987.
336. Kung JT, Gelbart, ME. Getting a head start: the importance of personal genetics education in high schools. Yale J Biol Med 2012;85:87.
337. Milunsky A. Choices, not chances: an essential guide to your heredity and health. Boston, MA: Little, Brown, 1989.
338. Milunsky A. Heredity and your family's health. Baltimore, MD: Johns Hopkins University Press, 1992.
339. Milunsky A. Your genes, your health: a critical family guide that could save your life. Oxford: Oxford University Press, 2012.
340. Mersch J, Brown N, Pirzadeh-Miller S, et al. Prevalence of variant reclassification following hereditary cancer genetic testing. JAMA 2018;320(12):1266.
341. Cantebury v. Spence, 464 F.2d 772 (D.C. Cir. 1972).
342. Carrieri D, Dheensa S, Doheny S, et al. Recontacting in clinical practice: the views and expectations of patients in the United Kingdom. Eur J Hum Genet 2017;25:1106.
343. Laurie G. Privacy and the right not to know: a plea for conceptual clarity. In: Ruth C, Mairi L, Darren S, eds. The right to know and the right not to know: genetic privacy and responsibility. Cambridge: Cambridge University Press, 2014:38.
344. Committee of the International Huntington Association and the World Federation of Neurology. Guidelines for the molecular genetics predictive test in Huntington's disease. J Med Genet 1994;31:555.
345. Hunter AGW, Sharpe NF, Mullen M, et al. Ethical, legal, and practical concerns about recontacting patients to inform them of new information. In: Sharpe NF, Carter RF, eds. Genetic testing. care, consent and liability. New York: John Wiley & Sons, 2006.
346. Sirchia F, Carrieri D, Dheensa S, et al. Recontacting or not recontacting? A survey of current practices in clinical genetics centres in Europe. Eur J Hum Genet 2018;26:946.
347. Bombard Y, Mighton C. Recontacting clinical genetics patients with reclassified results: equity and policy challenges. Eur J Hum Genet 2019;27:505.
348. Mink v. University of Chicago, 460F. Supp. 713 (N.D.Ill.1978).
349. Tresemer v. Barke, 86 Cal. App.3d 656, 150 Cal. Rptr 384 (1978).
350. Pelias MZ. Duty to disclose in medical genetics: a legal perspective. Am J Med Genet 1991;39:347.
351. Hirschhorn K, Fleischer LD, Godmilow L, et al. Duty to re-contact. Genet Med 1999;1:171.
352. Shirts BH, Parker LS. Changing interpretations, stable genes: responsibilities of patients, professionals, and policy makers in the clinical interpretation of complex genetic information. Genet Med 2008;10:778.
353. David KL, Best RG, Brenman LM, et al. Patient re-contact after revision of genomic test results: points to consider – a statement of the American College of Medical Genetics and Genomic (ACMG). Genet Med 2019;21:769.
354. Nance MA. Genetic counseling and testing for Huntington's disease: a historical review. Am J Med Genet B Neuropsychiatr Genet 2017;174:75.
355. Borle K, Morris E, Inglis A, et al. Risk communication in genetic counseling: Exploring uptake and perception of recurrence numbers, and their impact on patient outcomes. Clin Genet 2018;94:239.
356. Stuttgen K, Dvoskin R, Bollinger J, et al. Risk perception before and after presymptomatic genetic testing for Huntington's disease: not always what one might expect. Mol Genet Genomic Med 2018;6:1140.
357. Ibisler A, Ocklenburg S, Stemmler S, et al. Prospective evaluation of predictive DNA testing for Huntington's disease in a large German center. J Genet Couns 2017;26:1029.
358. Smit AK, Newson AJ, Best M, et al. Distress, uncertainty, and positive experiences associated with receiving information on personal genomic risk of melanoma. Eur J Hum Genet 2018;26:1094.
359. McGarry A, McDermott MP, Kieburtz K, et al. Risk factors for suicidality in Huntington disease. Neurology 2019;92:e1643.

360. Anderson KE, Eberly S, Marder KS, et al. The choice not to undergo genetic testing for Huntington disease: results from the PHAROS study. Clin Genet 2019;96:28.
361. Tassicker RJ, Teltscher B, Trembath MK, et al. Problems assessing uptake of Huntington's disease predictive testing and a proposed solution. Eur J Hum Genet 2009;17(1):66.
362. Morrision PJ, Harding-Lester S, Bradley A. Uptake of Huntington disease predictive testing in a complete population. Clin Genet 2011;80(3):281.
363. Baig SS, Strong M, Quarrell OWJ. The global prevalence of Huntingtons disease: a systematic review and discussion. Neurodegener Dis Manag 2016;6(4):331.
364. Baig SS, Strong M, Rosser E, et al. 22 Years of predictive testing for Huntington's disease: the experience of the UK Huntington's Prediction Consortium. Eur J Hum Genet 2017;25(11):1290.
365. Mendes Á, Paneque M, Clarke A, et al. Choosing not to know: accounts of non-engagement with pre-symptomatic testing for Machado-Joseph disease. Eur J Hum Genet 2019;27:353.
366. Cowley L. What can we learn from patients' ethical thinking about the right 'not to know' in genomics? Lessons from cancer genetic testing for genetic counselling. Bioethics 2016;30:628.
367. Stark Z, Wallace J, Gillam L, et al. Predictive genetic testing for neurodegenerative conditions: how should conflicting interests within families be managed? J Med Ethics 2016;42:640.
368. Milunsky JM, Maher TA, Loose BA, et al. XL PCR for the detection of large trinucleotide expansions in juvenile Huntington's disease. Clin Genet 2003;64:70.
369. MacLeod RTA, Frontali M, Evers-Kiebooms G, et al. Recommendations for the predictive genetic test in Huntington's disease. Clin Genet 2013;23:221.
370. Tassicker R, Savulescu J, Skene L, et al. Prenatal diagnosis requests for Huntington's disease when the father is at risk and does not want to know his genetic status: clinical, legal and ethical viewpoints. BMJ 2003;326:331.
371. Van Rij MC, De Rademaeker M, Moutou C, et al. Preimplantation genetic diagnosis (PGD) for Huntington's disease: the experience of three European centres. Eur J Hum Genet 2012;20:368.
372. Bouchghoul H, Clément SF, Vauthier D, et al. Prenatal testing in Huntington disease: after the test, choices recommence. Eur J Hum Genet 2016;24:1535.
373. Duncan RE, Foddy B, Delatycki MB. Refusing to provide a prenatal test: can it ever be ethical? BMJ 2006;333:1066.
374. Wadrup F, Holden S, MacLeod R, et al. A case-note review of continued pregnancies found to be at a high risk of Huntington's disease: considerations for clinical practice. Eur J Hum Genet 2019;27:1215.
375. Jones EF, Forrest JD, Henshaw SK, et al. Unintended pregnancy, contraceptive practice and family planning services in developed countries. Fam Plann Perspect 1988;20:53.
376. Tarasoff v. Regents of the University of California, 551 P.2d 334 (Cal. 1976).
377. Stol YH, Menko FH, Westerman MJ, et al. Informing family members about a hereditary predisposition to cancer: attitudes and practices among clinical geneticists. J Med Ethics 2010;36:391.
378. Menko FH, Aalfs CM, Henneman L, et al. Informing family members of individuals with Lynch syndrome: a guideline for clinical geneticists. Fam Cancer 2013;12:319.
379. Lacroix M, Nycum G, Godard B, et al. Should physicians warn patients' relatives of genetic risk? Can Med Assoc J 2008;178:593.
380. Tan HL, Hofman N, van Langen IM, et al. Sudden unexplained death. Heritability and diagnostic yield of cardiological and genetic examination in surviving relatives. Circulation 2005;112:207.
381. Offit K, Groeger E, Turner S, et al. The "duty to warn" a patient's family members about hereditary disease risks. JAMA 2004;292:1469.
382. Marta MR. Genetic testing: do healthcare professionals have a duty to tell a patient's family members that they may be at risk. J Healthc Risk Manag 1999;19:26.
383. Elger BS, Michaud K, Fellmann F, et al. Sudden death: ethical and legal problems of post-mortem forensic genetic testing for hereditary cardiac diseases. Clin Genet 2010;77:287.
384. Pate v. Threlkel, 661 So. 2d 278, 282 (Fla. 1995).
385. Safer v. Estate of Pack, 677 A.2d 1188, 1192-1193. (N.J. Super. Ct. App. Div.), cert. denied, 683 A.2d 1163 (N.J. 1996).
386. Rothstein MA. Reconsidering the duty to warn genetically at-risk relatives. Genet Med 2018;20:285.
387. N.J. State. Ann § 10:5-47 (2001).
388. Wolf SM, Crock BN, Van Ness B, et al. Managing incidental findings and research reslts in genomic research involving biobanks and archived data sets. Genet Med 2012;14:361.
389. Molloy v. Meier, 679 N.W.2d 711 (Minn. 2004).
390. ABC V. St. George's Healthcare NHS Trust [2015] EWHC 1394
391. ABC V. St. George's Healthcare NHS Trust [2015] EWCA 336. (QB).

392. Lucassen A, Gilbar R. Disclosure of genetic information to relatives: Balancing confidentiality and relatives' interests. J Med Genet 2018;55:285.
393. Royal College of Physicians, Royal College of Pathologists and British Society for Human Genetics. Contest and confidentiality in clinical genetic practice: guidance on genetic testing and sharing genetic information. Report of the Joint Committee on Medical Genetics, 2nd edn. London: Royal College of Physicians/Royal College of Pathologists, 2011.
394. General Medical Council. Confidentiality: good practice in handling patient information. London: General Medical Council, 2017, revised in May 2018.
395. Middleton A, Milne R, Robarts L, et al. Should doctors have a legal duty to warn relatives of their genetic risks? Lancet 2019;394:2133.
396. Wouters RHP, Bijlsma RM, Ausems MGEM, et al. Am I my family's keeper? Disclosure dilemmas in next-generation sequencing. Hum Mutat 2016;37:1257.
397. Gilbar R, Foster C. Doctors' liability to the patient's relatives in genetic medicine: ABC v. St. George's Healthcare NHS trust [2015] EWHC 1394 (QB). Med Law Rev 2016;24:112.
398. Suter S. Legal challenges in genetics, including duty to warn and genetic discrimination. Cold Spring Harb Perspect Med 2020;10:a036665.
399. Meggiolaro N, Barlow-Stewart K, Dunlop K, et al. Disclosure to genetic relatives without consent – Australian genetic professionals' awareness of the health privacy law. BMC Med Ethics 2020;21:13.
400. Perry TJ, Patton SI, Farmer MB, et al. The duty to warn at-risk relatives- The experience of genetic counselors and medical geneticists. Am J Med Genet A 2020;182:314.
401. Heyes T, Long S, Mathers N. Preconception care: practice and beliefs of primary care workers. Fam Pract 2004;21:22.
402. Czeizel AE, Gasztonyi Z, Kuliev A. Periconceptional clinics: a medical health care infrastructure of new genetics. Fetal Diagn Ther 2005;20:515.
403. Solomon BD, Jack BW, Feero WG. The clinical content of preconception care: genetics and genomics. Am J Obstet Gynecol 2008;199(6 Suppl 2):S340.
404. Enzensberger C, Pulvermacher C, Degenhardt J, et al. Fetal loss rate and associated risk factors after amniocentesis, chorionic villus sampling and fetal blood sampling. Ultraschall Med 2012;33:e75.
405. Akolekar R, Beta J, Picciarelli, et al. Procedure-related risk of miscarriage following amniocentesis and chorionic villus sampling: a systematic review and meta-analysis. Ultrasound Obstet Gynecol 2015;45(1):16.
406. Hollier LM, Leveno KJ, Kelly MA, et al. Maternal age and malformations in singleton births. Obstet Gynecol 2000;96:701.
407. Frederiksen LE, Ernst A, Brix N, et al. Risk of adverse pregnancy outcomes at advanced maternal age. Obstet Gynecol 2018;131:457.
408. Yatsenko AN, Turek PJ. Reproductive genetics and the aging male. J Assist Reprod Genet 2018;35:933.
409. Brandt JS, Cruz Ithier MA, Rosen T, et al. Advanced paternal age, infertility, and reproductive risks: a review of the literature. Prenat Diagn 2019;39:81.
410. Bray I, Gunnell D, Davey Smith G. Advanced paternal age: how old is too old?. J Epidemiol Community Health 2006;60;851.
411. Martin JA, Hamilton BE, Osterman MJ, et al. Births: final data for 2015. Natl Vital Stat Rep 2017;66:1.
412. Ford WC, North K, Taylor H, et al. Increasing paternal age is associated with delayed conception in a large population of fertile couples: evidence for declining fecundity in older men. The ALSPAC study team (Avon longitudinal study of pregnancy and childhood). Hum Reprod 2000;15(8):1703.
413. Hassan MA, Killick SR. Effect of male age on fertility: evidence for the decline in male fertility with increasing age. Fertil Steril 2003;79(Suppl 3):1520.
414. Belloc S, Cohen-Bacrie P, Benkhalifa M, et al. Effect of maternal and paternal age on pregnancy and miscarriage rates after intrauterine insemination. Reprod Biomed Online 2008;17(3):392.
415. Slama R, Bouyer J, Windham G, et al. Influence of paternal age on the risk of spontaneous abortion. Am J Epidemiol 2005;161(9):816.
416. Orioli IM, Castilla EE, Scarano G, et al. Effect of paternal age in achondroplasia, thanatophoric dysplasia, and osteogenesis imperfecta. Am J Med Genet 1995;59(2):209.
417. Risch N, Reich EW, Wishnick MM, et al. Spontaneous mutation and parental age in humans. Am J Hum Genet 1987;41(2):218.
418. Crow JF. The high spontaneous mutation rate: is it a health risk? Proc Natl Acad Sci U S A 1997;94(16):8380.
419. Glaser RL, Jabs EW. Dear old dad. Sci Aging Knowledge Environ 2004;3:re1.
420. Friedman JM. Genetic disease in the offspring of older fathers. Obstet Gynecol 1981;57(6):745.
421. Taylor JL, Debost JPG, Morton SU, et al. Parental-age-related de novo mutations and risk for five disorders. Nat Commun 2019;10:3043.

422. Toriello HV, Meck JM. Statement on guidance for genetic counseling in advanced paternal age. Genet Med 2008;10(6):457.
423. Practice Committee of American Society for Reproductive Medicine;Practice Committee of Society for Assisted Reproductive Technology. Recommendations for gamete and embryo donation: a committee opinion. Fertil Steril 2013;99(1):47.
424. Malaspina D, Harlap S, Fennig S, et al. Advancing paternal age and the risk of schizophrenia. Arch Gen Psychiatry 2001;58(4):361.
425. D'Onofrio BM, Rickert ME, Frans E, et al. Paternal age at childbearing and offspring psychiatric and academic morbidity. JAMA Psychiatry 2014;71(4):432.
426. Nybo Andersen AM, Hansen KD, Andersen PK, Davey SG. Advanced paternal age and risk of fetal death: a cohort study. Am J Epidemiol 2004;160(12):1214.
427. Steiner B, Masood R, Rufibach K, et al. An unexpected finding: younger fathers have a higher risk of offspring with chromosomal aneuploidies. Eur J Hum Genet 2015;23(4):466.
428. Jennings MO, Owen RC, Keefe D, et al. Management and counseling of the male with advanced paternal age. Fertil Steril 2017;107:324.
429. Cnossen MH, Smit FJ, deGoede-Bolder A, et al. Diagnostic delay in neurofibromatosis type 1. Eur J Pediatr 1997;156:482.
430. Bruechle NO, Steuernagel P, Zerres K, et al. Uniparental disomy as unexpected cause of Meckel-Gruber syndrome: report of a case. Pediatr Nephrol 2017;32:1989.
431. Nakka P, Smith SP, O'Donnell-Luria AH, et al. Characterization of prevalence and health consequences of uniparental disomy in four million individuals from the general population. Am J Hum Genet 2019;105:921.
432. Matsubara K, Murakami N, Nagai T, et al. Maternal age effect on the development of Prader-Willi syndrome resulting from upd(15)mat through meiosis I errors. J Hum Genet 2011;56:566.
433. Hoffmann K, Heller R. Uniparental disomies 7 and 14. Best Pract Res Clin Endocrinol Metab 2011;25:77.
434. Cho SY, Ki CS, Sohn YB, et al. The proportion of uniparental disomy is increased in Prader-Willi syndrome due to an advanced maternal childbearing age in Korea. J Hum Genet 2013;58:150.
435. Milunsky JM, Maher T, Lebo R, et al. Prenatal diagnosis for Schmid metaphyseal chondrodysplasia in twins. Fetal Diagn Ther 1998;13:167.
436. Milunsky A, Ito M, Maher TA, et al. Prenatal molecular diagnosis of tuberous sclerosis complex. Am J Obstet Gynecol 2009;200(3):321.
437. Piña-Aguilar RE, Simpson SA, Alshatti A, et al. 27 years of prenatal diagnosis for Huntington disease in the United Kingdom. Genet Med 2019;21:1639.
438. Robberecht W, Philips T. The changing scene of amyotrophic lateral sclerosis. Nat Rev Neurosci 2013;14:248.
439. Milunsky A, Konialis C, Shim SH, et al. The prenatal diagnosis of cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) by mutation analysis. Prenat Diagn 2005;25:1057.
440. Konialis C, Hagnefelt B, Kokkali G, et al. Pregnancy following preimplantation genetic diagnosis of cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL). Prenat Diagn 2007;27:1079.
441. Middleton A, Hewison J, Mueller R. Prenatal diagnosis for inherited deafness: what is the potential demand? J Genet Couns 2001;10:121.
442. Milunsky A, Alpert E, Kitzmiller JL, et al. Prenatal diagnosis of neural tube defects. VIII. The importance of serum α-fetoprotein screening in diabetic pregnant women. Am J Obstet Gynecol 1982;142:1030.
443. Miller E, Hare JW, Cloherty JP, et al. Elevated maternal HbA1c in early pregnancy and major congenital anomalies in infants of diabetic mothers. N Engl J Med 1981;304:1331.
444. McElvy SS, Miodovnik M, Rosenn B, et al. A focused preconceptional and early pregnancy program in women with type 1 diabetes reduces perinatal mortality and malformation rates to general population levels. J Matern Fetal Med 2000;9:14.
445. Penney GC, Mair G, Pearson DW, et al. Outcomes of pregnancies in women with type 1 diabetes in Scotland: a national population-based study. Br J Obstet Gynaecol 2003;110:315.
446. Stormdal Bring H, Hultén Varli IA, Kublickas M, et al. Causes of stillbirth at different gestational ages in singleton pregnancies. Acta Obstet Gynecol Scand 2014;93:86.
447. Kropff J, Selwood MP, McCarthy MI, et al. Prevalence of monogenic diabetes in young adults: a community-based, cross-sectional study in Oxfordshire, UK. Diabetologia 2011;54:1261.
448. Pihoker C, Gilliam LK, Ellard S, et al. Prevalence, characteristics and clinical diagnosis of maturity onset diabetes of the young due to mutations in HNF1A, HNF4A, and glucokinase: results from the

SEARCH for Diabetes in Youth. J Clin Endocrinol Metab 2013;98:4055.
449. Kleinberger JW, Maloney KA, Pollin TI. The genetic architecture of diabetes in pregnancy: implications for clinical practice. Am J Perinatol 2016;33:1319.
450. Stein SA, Maloney KL, Pollin TI. Genetic counseling for diabetes mellitus. Curr Genet Med Rep 2014;2:56.
451. Dickens LT, Naylor RN. Clinical management of women with monogenic diabetes during pregnancy. Curr Diab Rep 2018;188:12.
452. Shields BM, Hicks S, Shepherd MH, et al. Maturity-onset diabetes of the young (MODY): how many cases are we missing? Diabetologia 2010;53(12):2504.
453. Colstrup M, Mathiesen ER, Damm P, et al. Pregnancy in women with type 1 diabetes: have the goals of St. Vincent declaration been met concerning foetal and neonatal complications? J Matern Fetal Neonatal Med 2013;26:1682.
454. Schaefer-Graf U, Napoli A, Nolan CJ. Diabetes in pregnancy: a new decade of challenges ahead. Diabetologia 2018;61:1012.
455. Parimi M, Nitsch D. A systemic review and meta-analysis of diabetes during pregnancy and congenital genitourinary abnormalities. Kidney Int Rep 2020;5:678.
456. Mackin ST, Nelson SM, Kerssens JJ, et al. Diabetes and pregnancy: national trends over 15 year period. Diabetologia 2018;61:1081.
457. Helle E, Priest JR. Maternal obesity and diabetes mellitus as risk factors for congenital heart disease in the offspring. J Am Heart Assoc 2020;9:e011541.
458. Stogianni A, Lendahls L, Landin-Olsson M, et al. Obstetric and perinatal outcomes in pregnancies complicated by diabetes, and control pregnancies, in Kronoberg, Sweden. BMC Pregnancy Childbirth 2019;19:159.
459. Fava A, Petri M. Systemic lupus erythematosus: diagnosis and clinical management. J Autoimmun 2019;96:1.
460. Limaye MA, Buyon JP, Cuneo BF, et al. A review of fetal and neonatal consequences of maternal systemic lupus erythematosus. Prenat Diagn 2020;40:1066.
461. Popescu MR, Dudu A, Jurcut C, et al. A broader perspective on Anti-Ro antibodies and their fetal consequences – a case report and literature review. Diagnostics (Basel) 2020;10:478.
462. Arbuckle MR, McClain MT, Rubertone MV, et al. Development of autoantibodies before the clinical onset of systemic lupus erythematosus. N Engl J Med 2003;349:1526.
463. Satoh M, Chan EK, Ho LA, et al. Prevalence and sociodemographic correlates of antinuclear antibodies in the United States. Arthritis Rheum 2012;64:2319.
464. Wainwright B, Bhan R, Trad C, et al. Autoimmune-mediated congenital heart block. Best Pract Res Clin Obstet Gynaecol 2020;64:41.
465. Panaitescu AM, Nicolaides K. Maternal autoimmune disorders and fetal defects. J Matern Fetal Neonatal Med 2018;31:1798.
466. Brito-Zerón P, Izmirly PM, Ramos-Casals M, et al. The clinical spectrum of autoimmune congenital heart block. Nat Rev Rheumatol 2015;11:301.
467. Clowse ME, Eudy AM, Kiernan E, et al. The prevention, screening and treatment of congenital heart block from neonatal lupus:a survey of provider practices. Rheumatology 2018;57(Suppl S5):v9.
468. Rein AJJT, Mevorach D, Perles Z, et al. Early diagnosis and treatment of atrioventricular block in the fetus exposed to maternal anti-SSA/Ro-SSB/La antibodies a prospective, observational, fetal kinetocardiogram-based study. Circulation 2009;119:1867.
469. Kusumoto FM, Schoenfeld MH, Barrett C, et al. 2018 ACC/AHA/HRS Guideline on the evaluation and management of patients with bradycardia and cardiac conduction delay: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2019;74:932.
470. Stanner C, Horndasch M, Vitanova K, et al. Neonates and infants requiring life-long cardiac pacing: How reliable are epicardial leads through childhood? Int J Cardiol 2019;297:43.
471. Izmirly PM, Costedoat-Chalumeau N, Pisoni CN, et al. Maternal use of hydroxychloroquine is associated with a reduced risk of recurrent anti-SSA/ro-antibody – Associated cardiac manifestations of neonatal lupus. Circulation 2012;126:76.
472. Hansahiranwadee W. Diagnosis and management of fetal autoimmune atrioventricular block. Int J Womens Health 2020;12:633.
473. Pruetz JD, Miller JC, Loeb GE, et al. Prenatal diagnosis and management of congenital complete heart block. Birth Defects Res 2019;111:380.
474. Thomas NS, Durkie M, Van Zyl B, et al. Parental and chromosomal origin of unbalanced de novo structural chromosome abnormalities in man. Hum Genet 2006;119(4):444.
475. Thomas NS, Morris JK, Baptista J, et al. De novo apparently balanced translocations in man are predominantly paternal in origin and associated with

a significant increase in paternal age. J Med Genet 2010;47(2):112.
476. Teras LR, Gaudet MM, Blase JL, Gapstur SM. Parental Age at birth and risk of hematological malignancies in older adults. Am J Epidemiol 2015;182(1):41.
477. Green RF, Devine O, Crider KS, et al. Association of paternal age and risk for major congenital anomalies from the National Birth Defects Prevention Study, 1997 to 2004. Ann Epidemiol 2010;20(3):241.
478. World Health Organization. Towards more objectivity in diagnosis and management of male infertility. Int J Androl 1987;7:1.
479. Levy B, Sigurjonsson S, Pettersen B, et al. Genomic imbalance in products of conception: single-nucleotide polymorphism chromosomal microarray analysis. Obstet Gynecol 2014;124(2 Pt 1):202.
480. Abur U, Gunes S, Asci R, et al. Chromosomal and Y-chromosome microdeletion analysis in 1,300 infertile males and the fertility outcome of patients with AZFc microdeletions. Andrologia 2019;51(11):e.13402.
481. Scriver CR, Beaudet AL, Sly WS, et al. The metabolic and molecular bases of inherited disease, vol. II, 7th edn. New York: McGraw-Hill, 1995:B3008.
482. Turnpenny PD, Gunasegaran R, Smith NC, et al. Recurrent miscarriage, cystic hygroma and incontinentia pigmenti. Br J Obstet Gynaecol 1992;99:920.
483. Poursadegh Zonouzi A, Chaparzadeh N, Ghorbian S, et al. The association between thrombophilic gene mutations and recurrent pregnancy loss. J Assist Reprod Genet 2013;30:1353.
484. Bouvier S, Cochery-Nouvellon E, Lavigne-Lissalde G, et al. Comparative incidence of pregnancy outcomes in thrombophilia-positive women from the NOH-APS observational study. Blood 2014;123:414.
485. Bolor H, Mori T, Nishiyama S, et al. Mutations of the SYCP3 gene in women with recurrent pregnancy loss. Am J Hum Genet 2009;84:14.
486. Tucker EJ, Grover SR, Bachelot A, et al. Premature ovarian insufficiency: new perspectives on genetic cause and phenotypic spectrum. Endocr Rev 2016;37(6):609.
487. Maddirevula S, Awartani K, Coskun S, et al. A genomics approach to females with infertility and recurrent pregnancy loss. Hum Genet 2020;139:605.
488. Patel B, Parets S, Akana M, et al. Comprehensive genetic testing for female and male infertility using next level generation sequencing. J Assist Reprod Genet 2018;35(8):1489.
489. AlAsiri S, Basit S, Wood-Trageser MA, et al. Exome sequencing reveals MCM8 mutation underlies ovarian failure and chromosomal instability. J Clin Invest 2015;125(1):258.
490. Wood-Trageser MA, Gurbuz F, Yatsenko SA, et al. MCM9 mutations are associated with ovarian failure, short stature, and chromosomal instability. Am J Hum Genet 2014;95(6):754.
491. Kasippillai T, MacArthur DG, Kirby A, et al. Mutations in eIF4ENIF1 are associated with primary ovarian insufficiency. J Clin Endocrinol Metab 2013;98(9):E1534.
492. de Vries L, Behar DM, Smirin-Yosef P, et al. Exome sequencing reveals SYCE1 mutation associated with autosomal recessive primary ovarian insufficiency. J Clin Endocrinol Metab 2014;99(10):E2129.
493. Anguiano A, Oates RD, Amos JA, et al. Congenital bilateral absence of the vas deferens: a primarily genital form of cystic fibrosis. JAMA 1992;267:1794.
494. Bieth E, Hamdi SM, Mieusset R. Genetics of the congenital absence of the vas deferens. Hum Genet 2020 Feb 5. DOI: 10.1007/s00439-020-02122-w. Online ahead of print.
495. Yu J, Chen Z, Ni Y, et al. CFTR mutations in men with congenital bilateral absence of the vas deferens (CBAVD): a systemic review and meta-analysis. Hum Reprod 2012;27:25.
496. Taulan M, Girardet A, Guittard C, et al. Large genomic rearrangements in the CFTR gene contribute to CBAVD. BMC Med Genet 2007;8:22.
497. Traystman MD, Schulte NA, MacDonald M, et al. Mutation analysis for cystic fibrosis to determine carrier status in 167 sperm donors from the Nebraska Genetic Semen Bank. Hum Mutat 1994;4:271.
498. Patat O, Pagin A, Siegfried A, et al. Truncating mutations in the adhesion G protein-coupled receptor G2 gene ADGRG2 cause an X-Linked congenital bilateral absence of vas deferens. Am J Hum Genet 2016;99:437.
499. Wu H, Gao Y, Ma C, et al. A novel hemizygous loss-of-function mutation in ADGRG2 causes male infertility with congenital bilateral absence of the vas deferens. J Assist Reprod Genet 2020;37(6):1421.
500. Augarten A, Yahav Y, Kerem BS, et al. Congenital bilateral absence of vas deferens in the absence of cystic fibrosis. Lancet 1994;344:1473.
501. Schwarzer JU, Schwarz M. Significance of CFTR gene mutations in patients with congenital aplasia of vas deferens with special regard to renal aplasia. Andrologia 2012;44:305.
502. Temple-Smith PD, Southwick GJ, Yates CA, et al. Human pregnancy by IVF using sperm aspirated from the epididymis. J In Vitro Fertil Embryo Transfer 1985;2:119.

503. Silber SJ, Ord T, Balmaceda J, et al. Congenital absence of the vas deferens: the fertilizing capacity of human epididymal sperm. N Engl J Med 1990;7:147.
504. Flannigan R, Schlegel PN. Genetic diagnosis of male infertility in clinical practice. Best Pract Res Clin Obstet Gynaecol 2017;44:26.
505. Milunsky A, Milunsky JM, Dong W, et al. A contiguous microdeletion syndrome at Xp23.13 with non-obstructive azoospermia and congenital cataracts. J Assist Reprod Genet 2020;37:471.
506. Colaco S, Modi D. Genetics of the human Y chromosome and its association with male infertility. Reprod Biol Endocrinol 2018;16:14
507. Najmabadi H, Huang V, Yen P, et al. Substantial prevalence of microdeletions of the Y chromosome in infertile men with idiopathic azoospermia and oligospermia detected using a sequence-tagged site-based mapping strategy. J Clin Endocrinol Metab 1996;71:1347.
508. Ma K, Inglis JD, Sharkey A, et al. A Y chromosome gene family with RNA-binding protein homology: candidates for the azoospermia factor AZF controlling human spermatogenesis. Cell 1993;73:1287.
509. Reijo R, Alagappan RK, Patrizio P, et al. Severe oligo-zoospermia resulting from deletions of azoospermia factor gene on Y chromosome. Lancet 1996;347:1290.
510. de Kretser DM. Male infertility. Lancet 1997;349:787.
511. Bonduelle M, Hamberger L, Joris H, et al. Assisted reproduction by intracytoplasmic sperm injection: an ESHRE survey of clinical experiences until December 1993. Hum Reprod Update 1995;1:3.
512. Meschede D, Horst J. Sex chromosomal anomalies in pregnancies conceived through intracytoplasmic sperm injection: a case for genetic counseling. Hum Reprod 1997;12:1125.
513. Chandley AC. Meiotic studies and fertility in human translocation carriers. In: Daniel A, ed. The cytogenetics of mammalian autosomal rearrangements. New York: Alan R. Liss, 1988:370.
514. Dohle GR, Halley DJ, van Hemel JO, et al. Genetic risk factors in infertile men with severe oligo-zoospermia and azoospermia. Hum Reprod 2002;17:13.
515. Özdemir TR, Özyilmaz B, Çakmak Ö, et al. Evaluation of chromosomal abnormalities and Y-chromosome microdeletions in 1696 Turkish cases with primary male infertility: a single-center study. Turk J Urol 2020;46:95.
516. Bunyan DJ, Thomas NS. Screening of a large cohort of blepharophimosis, ptosis, epicanthus inversus syndrome patients reveals a very strong paternal inheritance bias and a wide spectrum of novel FOXL2 mutations. Eur J Med Genet 2019:62.
517. Stentz NC, Koelper N, Barnhart KT, et al. Infertility and mortality. Am J Obstet Gynecol 2020;222:251e.1.
518. Hargreave M, Jensen A, Hansen MK, et al. Association between fertility treatment and cancer risk in children. JAMA 2019;322:2203.
519. Spector LG, Brown MB, Wantman E, et al. Association of in vitro fertilization without childhood cancer in the United States. JAMA Pediatr 2019;0392(6):e1903392.
520. Murugappan G, Li S, Lathi RB, et al. Increased risk of severe maternal morbidity among infertile women: analysis of US claims data. Am J Obstet Gynecol 2020;223(3):404.e1.
521. Committee on Genetics. Committee opinion no. 691: carrier screening for genetic conditions. Obstet Gynecol 2017;129:e41.
522. Lim KRQ, Sheri N, Nguyen Q, et al. Cardiac involvement in dystrophin-deficient females: current understanding and implications for the treatment of dystrophinopathies. Genes 2020;11(7):765.
523. Ishizaki M, Kobayashi M, Adachi K, et al. Female dystrophinopathy: review of current literature. Neuromuscul Disord 2018;28:572.
524. Hoogerwaard EM, Van Der Wouw PA, Wilde AAM, et al. Cardiac involvement in carriers of Duchenne and Becker muscular dystrophy. Neuromuscul Disord 1999;9:347.
525. Viggiano E, Ergoli M, Picillo E, et al. Determining the role of skewed X-chromosome inactivation in developing muscle symptoms in carriers of Duchenne muscular dystrophy. Hum Genet 2016;135:685.
526. Finsterer J, Stollberger C. Muscle, cardiac, and cerebral manifestations in female carriers of dystrophin variants. J Neurol Sci 2018;388:107.
527. Tunteeratum A, Witoonpanich R, Phudhichareonrat S, et al. Congestive heart failure with rhabdomyolysis and acute renal failure in a manifesting female carrier of Duchenne muscular dystrophy with duplication of dystrophin gene. J Clin Neuromuscul Dis 2009;11:49.
528. Martinez HR, Pignatelli R, Belmont JW, et al. Childhood onset of left ventricular dysfunction in a female manifesting carrier of muscular dystrophy. Am J Med Genet Part A 2011;155:3025.
529. Eekhoff L, Edwards J, Martin A, et al. Assessing the barriers to cardiac care in carriers of Duchenne and Becker muscular dystrophy. J Genet Couns 2019;28:993.
530. Papa R, Madia F, Bartolomeo D, et al. Genetic and early clinical manifestations of females heterozygous

for Duchenne/Becker muscular dystrophy. Pediatr Neurol 2016;55:58.

531. Mah ML, Cripe L, Slawinski MK, et al. Duchenne and Becker muscular dystrophy carriers: evidence of cardiomyopathy by exercise and cardiac MRI testing. Int J Cardiol 2020;316:257.
532. Papa AA, D'Ambrosio P, Petillo R, et al. Heart transplantation in patients with dystrophinopathic cardiomyopathy: review of the literature and personal series. Intractable Rare Dis Res 2017;6:95.
533. Allen EG, Charen K, Hipp HS, et al. Clustering of comorbid conditions among women who carry an FMR1 premutation. Genet Med 2020;22:758.
534. Allen EG, Sullivan AK, Marcus M, et al. Examination of reproductive aging milestones among women who carry the FMR1 premutation. Hum Reprod 2007;22:2142.
535. Plug I, Mauser-Bunschoten EP, Bröcker-Vriends AHJT, et al. Bleeding in carriers of hemophilia. Blood 2006;108:52.
536. Konkle BA, Huston H, Fletcher SN. Hemophilia A. GeneReviews® [internet]. Seattle (WA): University of Washington, Seattle, 1993–2020, 2000 Sep 21 [updated 2017 Jun 22].
537. Konkle BA, Huston H, Fletcher SN. Hemophilia B. GeneReviews® [internet]. Seattle (WA): University of Washington, Seattle, 1993–2020, 2000 Oct 2 [updated 2017 Jun 15].
538. Balak DM, Gouw SC, Plug I, et al. Prenatal diagnosis for haemophilia: a nationwide survey among female carriers in the Netherlands. Haemophilia 2012;18:584.
539. Chuansumrit A, Sasanakul W, Promsonthi P, et al. Prenatal diagnosis for haemophilia: the Thai experience. Haemophilia 2016;22:880.
540. Kessler L, Adams R, Mighion L, et al. Prenatal diagnosis in haemophilia A: experience of the genetic diagnostic laboratory. Haemophilia 2014;20:e384.
541. Chen M, Chang S-P, Ma G-C, et al. Preimplantation genetic diagnosis of hemophilia A. Thromb J 2016;14(Suppl 1):33.
542. Hudecova I, Jiang P, Davies J, et al. Noninvasive detection of F8 int22h-related inversions and sequence variants in maternal plasma of hemophilia carriers. Blood 2017;130:340.
543. Antonarakis SE. Carrier screening for recessive disorders. Nat Rev Genet 2019;20:549.
544. Hogan GJ, Vysotskaia VS, Beauchamp KA, et al. Validation of an expanded carrier screen optimizes sensitivity via full-exon sequencing and panel-wide copy number variant identification. Clin Chem 2018;64:1063.
545. Hernandez-Nieto C, Alkon-Meadows T, Lee J, et al. Expanded carrier screening for preconception reproductive risk assessment: prevalence of carrier status in Mexican population. Prenat Diagn 2020;40:635.
546. Kraft S, Duenas D, Wilfond B, et al. The evolving landscape of expanded carrier screening: challenges and opportunities. Genet Med 2019;21:790.
547. Franasiak J, Olcha M, Bergh P, et al. Expanded carrier screening in an infertile population: how often is clinical decision making affected? Genet Med 2016;18:1097.
548. Punj S, Akkari Y, Huang J, et al. Preconception carrier screening by genome sequencing: results from the clinical laboratory. Am J Hum Genet 2018;102:1078.
549. Peyser A, Singer T, Mullin C, et al. Comparing ethnicity-based and expanded carrier screening methods at a single fertility center reveals significant differences in carrier rates and carrier couple rates. Genet Med 2019;21:1400.
550. Haque IS, Lazarin GA, Kang HP, et al. Modeled fetal risk of genetic diseases identified by expanded carrier screening. JAMA 2016;316:734.
551. Beauchamp K, Johansen Taber K, Muzzey D. Clinical impact and cost-effectiveness of a 176-condition expanded carrier screen. Genet Med 2019;21:1948.
552. Johansen Taber K, Beauchamp K, Lazarin G, et al. Clinical utility of expanded carrier screening: results-guided actionability and outcomes. Genet Med 2019;21:1041.
553. Van der Hout S, Holtkamp K, Henneman L, et al. Advantages of expanded universal carrier screening: what is at stake? Eur J Hum Genet 2016;25:17.
554. Hogan GJ, Vysotskaia VS, Beauchamp KA, et al. Validation of an expanded carrier screen that optimizes sensitivity via full-exon sequencing and panel-wide copy number variant identification. Clin Chem 2018;64:1063.
555. King J, Klugman S. Ethnicity-based carrier screening. Obstet Gynecol Clin North Am 2018;45:83.
556. Lazarin GA, Haque IS, Nazareth S, et al. An empirical estimate of carrier frequencies for 400+ causal Mendelian variants. Genet Med 2013;15:178.
557. Wilson RD, De Bie I, Armour CM, et al. Joint SOGC-CCMG opinion for reproductive genetic carrier screening: an update for all Canadian providers of maternity and reproductive healthcare in the era of direct-to-consumer testing. J Obstet Gynaecol Can 2016;38:742.e3.
558. American College of Obstetricians and Gynecologists. Committee opinion no. 690: carrier screening in the age of genomic medicine. Obstet Gynecol 2017;129:e35.

559. Edwards JG, Feldman G, Goldberg J, et al. Expanded carrier screening in reproductive medicine – points to consider. Obstet Gynecol 2015;125:653.
560. Johansen Taber K, Beauchamp K, Lazarin G, et al. Clinical utility of expanded carrier screening: results-guided actionability and outcomes. Genet Med 2019;21:1041.
561. Rabin R, Hirsch Y, Johansson MM, et al. Study of carrier frequency of Warsaw breakage syndrome in the Ashkenazi Jewish population and presentation of two cases. Am J Med Genet A 2019;179:2144.
562. Akler G, Birch AH, Schreiber-Agus N, et al. Lessons learned from expanded reproductive carrier screening in self-reported Ashkenazi, Sephardi, and Mizrahi Jewish patients. Mol Genet Genomic Med 2020;8:e1053.
563. Guo MH, Gregg AR. Estimating yields of prenatal carrier screening and implications for design of expanded carrier screening panels. Genet Med 2019;21(9):1940.
564. Scott SA, Edelmann L, Liu L, et al. Experience with carrier screening and prenatal diagnosis for 16 Ashkenazi Jewish genetic diseases. Hum Mutat 2010;31:1240.
565. Kaseniit KE, Haque IS, Goldberg JD, et al. Genetic ancestry analysis on >93,000 individuals undergoing expanded carrier screening reveals limitations of ethnicity-based medical guidelines. Genet Med 2020;22(10):1694.
566. Singer A, Sagi-Dain L. Impact of a national genetic carrier-screening program for reproductive purposes. Acta Obstet Gynecol Scand 2020;99:802.
567. Shi L, Webb BD, Birch AH, et al. Comprehensive population screening in the Ashkenazi Jewish population for recurrent disease-causing variants. Clin Genet 2017;91:599.
568. Baskovich B, Hiraki S, Upadhyay K, et al. Expanded genetic screening panel for the Ashkenazi Jewish population. Genet Med 2016;18:522.
569. Bristow SL, Morris JM, Peyser A, et al. Choosing an expanded carrier screening panel: comparing two panels at a single fertility centre. Reprod Biomed Online 2019;38:225.
570. Rosenblum LS, Zhu H, Zhou Z, et al. Comparison of pan-ethnic and ethnic-based carrier screening panels for individuals of Ashkenazi Jewish descent. J Genet Couns 2020;29:56.
571. Arjunan A, Litwack K, Collins N, et al. Carrier screening in the era of expanding genetic technology. Genet Med 2016;18:1214.
572. Gregg AR, Edwards JG. Prenatal genetic carrier screening in the genomic age. Semin Perinatol 2018;42:303.
573. Grzymski JJ, Elhanan G, Morales Rosado JA, et al. Population genetic screening efficiently identifies carriers of autosomal dominant diseases. Nat Med 2020;26(8):1235.
574. Neben CL, Zimmer AD, Stedden W, et al. Multi-gene panel testing of 23,179 individuals for hereditary cancer risk identifies pathogenic variant carriers missed by current genetic testing guidelines. J Mol Diagn 2019;21:646.
575. Tandy-Connor S, Guiltinan J, Krempely K, et al. False-positive results released by direct-to-consumer genetic tests highlight the importance of clinical confirmation testing for appropriate patient care. Genet Med 2018;20:1515.
576. Petersen LM, Lefferts JA. Lessons learned from direct-to-consumer genetic testing. Clin Lab Med 2020;40:83.
577. Laestadius LI, Rich JR, Auer PL. All of your data (effectively) belongs to us: data practices among direct-to-consumer genetic testing firms. Genet Med 2017;19:513.
578. de Pauw A, Schwartz M, Colas C, et al. Direct-to-consumer misleading information on cancer risks calls for an urgent clarification of health genetic testing performed by commercial companies. Eur J Cancer 2020;132:100.
579. Horton R, Crawford G, Freeman L, et al. Direct-to-consumer genetic testing. BMJ 2019;367:I5688.
580. Millward M, Tiller J, Bogwitz M, et al. Impact of direct-to-consumer genetic testing on Australian clinical genetic services. Eur J Med Genet 2020;63:103968.
581. Huml AM, Sullivan C, Figueroa M, et al. Consistency of direct-to-consumer genetic testing results among identical twins. Am J Med 2020;133:143.e2.
582. Garmany R, Lee CJ, Sharp RR, et al. Failure to follow up on a medically actionable finding from direct to consumer genetic testing: a case report. Mol Genet Genomic Med 2020;8:e.1252.
583. Niemiec E, Kalokairinou L, Howard HC. Current ethical and legal issues in health-related direct-to-consumer genetic testing. Per Med 2017;14:433.
584. Committee on Genetics. Committee opinion no. 724: consumer testing for disease risk. Obstet Gynecol 2017;130:e270.
585. ACMG Board of Directors. Direct-to-consumer genetic testing: a revised position statement of

the American College of Medical Genetics and Genomics. Genet Med 2016;18:207.
586. Wilson RD, De Bie I, Armour CM, et al. Joint SOGC-CCMG opinion for reproductive genetic carrier screening: an update for all Canadian providers of maternity and reproductive healthcare in the era of direct-to-consumer testing. J Obstet Gynaecol Can 2016;38:742.e3.
587. Kalokairinou L, Howard HC, Slokenberga S, et al. Legislation of direct-to-consumer genetic testing in Europe: a fragmented regulatory landscape. J Community Genet 2018;9:117.
588. de Paor A. Direct to consumer genetic testing-law and policy concerns in Ireland. Ir J Med Sci 2018;187:575.
589. Rafiq M, Ianuale C, Ricciardi W, et al. Direct-to-consumer genetic testing: a systematic review of European guidelines, recommendations, and position statements. Genet Test Mol Biomarkers 2015;19:535.
590. Tatour Y, Tamaiev J, Shamaly S, et al. A novel intronic mutation of PDE6B is a major cause of autosomal recessive retinitis pigmentosa among Caucasus Jews. Mol Vis 2019;25:155.
591. Sparks TN. Expanded carrier screening: counseling and considerations. Hum Genet 2020;139:1131.
592. Tayoun AA, Mason-Suares H. Considerations for whole exome sequencing unique to prenatal care. Hum Genet 2020;139:1149.
593. Simioni P, Prandoni P, Lensing AW, et al. The risk of recurrent venous thromboembolism in patients with an Arg5066Glnmutation in the gene for factor V (factor V Leiden). N Engl J Med 1997;336:399.
594. Desch KC, Ozel AB, Halvorsen M, et al. Whole-exome sequencing identifies rare variants in STAB2 associated with venous thromboembolic disease. Blood 2020;136:533.
595. Veldhuisen B, Saris JJ, deHaij S, et al. A spectrum of mutations in the second gene for autosomal dominant polycystic kidney disease (PKD2). Am J Hum Genet 1997;61:547.
596. Neyroud N, Tesson F, Denjoy I, et al. A novel mutation in the potassium channel gene KVLQT1 causes the Jervell and Lange–Nielsen cardioauditory syndrome. Nat Genet 1997;15:186.
597. Wallace E, Howard L, Liu M, et al. Long QT syndrome: genetics and future perspective. Pediatr Cardiol 2019;40:1419.
598. Rebours V, Boutron-Ruault MC, Schnee M, et al. The natural history of hereditary pancreatitis: a national series. Gut 2009;58:97.
599. Migeon BR. X-linked diseases: susceptible females. Genet Med 2020;22:1156.
600. Pinckers A. X-linked progressive cone dystrophy. Doc Ophthalmol Proc Ser 1982;33:399.
601. El-Deiry SS, Naidu S, Blevins LS, et al. Assessment of adrenal function in women heterozygous for adrenoleukodystrophy. J Clin Endocrinol Metab 1997;82:856.
602. Menage P, Carreau V, Tourbah A, et al. Les adrenoleucodystrophies heterozygotes symptomatiques de l'adulte: 10 cas. Rev Neurol 1993;149:445.
603. Hasstedt SJ, Atkin CL, San Juan AC Jr., Genetic heterogeneity among kindreds with Alport syndrome. Am J Hum Genet 1986;38:940.
604. Patel RR, Hovijitra S, Kafrawy AH, et al. X-linked (recessive) hypomaturation amelogenesis imperfecta: a prosthodontic, genetic and histopathologic report. J Prosthet Dent 1991;66:398.
605. Hennekam RC, Barth PG, van Lookeren Campagne W, et al. A family with severe X-linked arthrogryposis. Eur J Pediatr 1991;150:656.
606. Gibbons RJ, Suthers GK, Wilkie AOM, et al. X-linked alpha-thalassemia/mental retardation (ATR-X) syndrome: location to Xq12–q21.31 by X inactivation and linkage analysis. Am J Hum Genet 1992;51:1136.
607. Mathews KD, Ardinger HH, Nishimura DY, et al. Linkage localization of Borjeson–Forssman–Lehmann syndrome. Am J Med Genet 1989;34:470.
608. Karna J. Choroideremia: a clinical and genetic study of 84 Finnish patients and 126 female carriers. Acta Ophthalmol 1986;176(Suppl):1.
609. Romera MG, Martin MM, Gonzalez E. Chronic granulomatous disease: a case study of a symptomatic carrier. J Invest Allerg Clin Immunol 1997;7:57.
610. Lovas JG, Issekutz A, Walsh N, et al. Lupus erythematosus-like oral mucosal and skin lesions in a carrier of chronic granulomatous disease. Chronic granulomatous disease carrier genodermatosis. Oral Surg Oral Med Oral Pathol Oral Rad Endod 1995;80:78.
611. Marciano BE, Zerbe CS, Falcone EL, et al. X-linked carriers of chronic granulomatous disease: illness, lyonization, and stability. J Allergy Clin Immunol 2018;141:365.
612. Rollnick BR, Kaye CI. Mendelian inheritance of isolated nonsyndromic cleft palate. Am J Med Genet 1986;24:465.
613. Cremers CWRJ, Huygen PLM. Clinical features of female heterozygotes in the X-linked mixed deafness syndrome (with perilymphatic gusher during stapes surgery). Int J Pediatr Otorhinolaryngol 1983;6:179.
614. Kamdar F, Garry DJ. Dystrophin-deficient cardiomyopathy. J Am Coll Cardiol 2016;67:2533.

615. Politano L, Nigro V, Nigro G, et al. Development of cardiomyopathy in female carriers of Duchenne and Becker muscular dystrophies. JAMA 1996;275:1335.
616. Matthews PM, Benjamin D, van Bakel I, et al. Muscle X-inactivation patterns and dystrophin expression in Duchenne muscular dystrophy carriers. Neuromuscul Disord 1995;5:209.
617. Azofeifa J, Voit T, Hubner C, et al. X-chromosome methylation in manifesting and healthy carriers of dystrophinopathies: concordance of activation ratios among first degree female relatives and skewed inactivation as cause of the affected phenotypes. Hum Genet 1995;96;167.
618. Darras BT, Urion DK, Ghosh PS. Dystrophinopathies. In: Adam MP, Ardinger HH, Pagon RA, et al., eds. GeneReviews® [internet]. Seattle (WA): University of Washington, Seattle, 1993–2020, September 5, 2000.
619. Schnur RE, Heymann WR. Reticulate hyperpigmentation. Semin Cutan Med Surg 1997;16:72.
620. Emery AEH. Emery–Dreifuss syndrome. J Med Genet 1989;26:637.
621. Viggiano E, Madej-Pilarczyk A, Carboni N, et al. X-linked Emery-Dreifuss muscular dystrophy: study of X-chromosome inactivation and its relation with clinical phenotypes in female carriers. Genes (Basel) 2019;10:919.
622. Kong D, Zhan Y, Liu C, et al. A novel mutation of the EMD gene in a family with cardiac conduction abnormalities and a high incidence of sudden cardiac death. Pharmgenomics Pers Med 2019;12:319.
623. Ropers HH, Wienker TF, Grimm T, et al. Evidence for preferential X-chromosome inactivation in a family with Fabry disease. Am J Hum Genet 1977;29:361.
624. Berger JR. Misdiagnosis of multiple sclerosis in a female heterozygote with Fabry's disease. Mult Scler Relat Disord 2019;30:45.
625. Thompson EM, Baraitser M, Lindenbaum RH, et al. The FG syndrome: seven new cases. Clin Genet 1985;27:582.
626. Vianna-Morgante AM, Costa SS, Pares AS, et al. FRAXA premutation associated with premature ovarian failure. Am J Med Genet 1996;64:373.
627. Sobesky WE, Taylor AK, Pennington BF, et al. Molecular/clinical correlations in females with fragile X. Am J Med Genet 1996;64:340.
628. Franke P, Maier W, Hautzinger M, et al. Fragile-X carrier females: evidence for a distinct psychopathological phenotype? Am J Med Genet 1996;64:334.
629. Meloni T, Forteleoni G, Dore A, et al. Neonatal hyperbilirubinaemia in heterozygous glucose-6-phosphate dehydrogenase deficient females. Br J Haematol 1983;53:241.
630. Mauser Bunchoten EP, van Houwelingen JC, Sjamsoedin Visser EJ, et al. Bleeding symptoms in carriers of hemophilia A and B. Thromb Haemost 1988;59:349.
631. Vabres P, Larregu M. X-linked genodermatoses. Ann Dermatol Venereol 1995;122:154.
632. Rahbaran M, Doabsari MH, Salavitabar S, et al. A novel frameshift mutation in the EDA gene in an Iranian patient affected by X-linked hypohidrotic ectodermal dysplasia. Call Mol Biol Lett 2019;24:54.
633. Afzal S, Ramzan K, Ullah S, et al. A novel nonsense mutation in the STS gene in a Pakistani family with X-linked recessive ichthyosis: including a very rare case of two homozygous female patients. BMC Med Genet 2020;21:20.
634. Carmignac V, Nambot S, Lehalle D, et al. Further delineation of the female phenotype with KDM5C disease causing variants: 19 new individuals and review of the literature. Clin Genet 2020;98:43.
635. Endres W. Inherited metabolic diseases affecting the carrier. J Inherit Metab Dis 1997;20:9.
636. Jung HH, Danek A, Walker RH, et al. McLeod neuroacanthocytosis syndrome. GeneReviews®. Seattle (WA): University of Washington, Seattle, 1993–2020, 2004 [updated 2019 May 23].
637. Lorette G, Toutain A, Barthes M, et al. Menkes syndrome: an unusual pigmentation anomaly in a mother and three sisters. Ann Pediatr 1992;39:453.
638. Collie WR, Moore CM, Goka TJ, et al. Pili torti as marker for carriers of Menkes disease. Lancet 1978;1:607.
639. Bartsocas CS, Kastrantas AD. X-linked form of myopia. Hum Hered 1981;31:199.
640. Nance WE, Warburg M, Bixler D, et al. Congenital X-linked cataract, dental anomalies and brachymetacarpalia. Birth Defects Orig Artic Ser 1974;10:285.
641. Kellner U, Fuchs S, Bornfeld N, et al. Ocular phenotypes associated with two mutations (R121W, C126X) in the Norrie disease gene. Ophthalmol Genet 1996;17:67.
642. Charles SJ, Moore AT, Zhang Y, et al. Carrier detection in X-linked ocular albinism using linked DNA polymorphisms. Br J Ophthalmol 1994;78:539.
643. Erpenstein H, Pfeiffer RA. Geschlechsgebunden-dominant erbliche Zahnunterzahl. Humangenetik 1967;4:280.
644. Meroni G. X-linked Opitz G/BBB syndrome. GeneReviews® Seattle (WA): University of

Washington, Seattle, 1993–2020, 2004 [updated 2018 Apr 5].

645. Herinklake S, Boker K, Manns M. Fatal clinical course of ornithine transcarbamylase deficiency in an adult heterozygous female patient. Digestion 1977;58:83.
646. Fries MH, Kuller JA, Jurecki E, et al. Prenatal counseling in heterozygotes for ornithine transcarbamylase deficiency in an adult heterozygous female patient. Digestion 1997;58:83.
647. Etter JL, Moysich K, Kohli S, et al. Transmission of X-linked ovarian cancer: characterization and implications. Diagnostics (Basel) 2020;10:90.
648. Warshawsky I, Rudick RA, Staugaitis SM, et al. Primary progressive multiple sclerosis as a phenotype of a PLP1 gene mutation. Ann Neurol 2005;58:470.
649. Kaplan J, Pelet A, Hentari H, et al. Contribution to carrier detection and genetic counseling in X linked retinoschisis. J Med Genet 1991;28:383.
650. Souied E, Segues B, Ghazi I, et al. Severe manifestations in carrier females in X linked retinitis pigmentosa. J Med Genet 1997;34:793.
651. Kurata K, Hosono K, Hayashi T, et al. X-linked retinitis pigmentosa in Japan: clinical and genetic findings in male patients and female carriers. Int J Mol Sci 2019;20:1518.
652. Ramocki MB, Peters SU, Tavyev YJ, et al. Autism and other neuropsychiatric symptoms are prevalent in individuals with MeCP2 duplication syndrome. Ann Neurol 2009;66:771.
653. McKusick VA. Mendelian inheritance in man, 11th edn. Baltimore, MD: Johns Hopkins University Press, 1994:2530.
654. Sajorda BJ, Gonzalez-Gandolfi CX, Hathaway ER, et al. Simpson-Golabi-Behmel syndrome type 1. GeneReviews® Seattle (WA): University of Washington, Seattle, 1993–2020, 2006 [updated 2018 Nov 29].
655. Ishihara H, Kanda F, Nishio H, et al. Clinical features and skewed X-chromosome inactivation in female carriers of X-linked recessive spinal and bulbar muscular atrophy. J Neurol 2001;248:856.
656. Ahmad M, Abbas H, Haque S, et al. X-chromosomally inherited split-hand/split foot anomaly in a Pakistani kindred. Hum Genet 1987;75:169.
657. McKusick VA. Mendelian inheritance in man, 11th edn. Baltimore, MD: Johns Hopkins University Press, 1994:2535.
658. van den Berghe H, Dequeker J, Fryns JP, et al. Familial occurrence of severe ulnar aplasia and lobster claw feet: a new syndrome. Hum Genet 1978;42:109.
659. Wengler G, Gorlin JB, Williamson JM, et al. Nonrandom inactivation of the X chromosome in early lineage hematopoietic cells in carriers of Wiskott–Aldrich syndrome. Blood 1995;85:2471.
660. Peacocke M, Siminovitch KA. The Wiskott–Aldrich syndrome. Semin Dermatol 1993;12:247.
661. Ziats CA, Schwartz CE, Gecz J, et al. X-linked intellectual disability: phenotypic expression in carrier females. Clin Genet 2019;97:418.
662. Uliana V, Bonatti F, Zanatta V, et al. Spectrum of X-linked intellectual disabilities and psychiatric symptoms in a family harbouring a Xp22.12 microduplication encompassing the RPS6KA3 gene. J Genet 2019;98:10.
663. Jackson MR, Loring KE, Homan CC, et al. Heterozygous loss of function of IQSEC2/ Iqsec2 leads to increased activated Arf6 and severe neurocognitive seizure phenotype in females. Life Sci Alliance 2019;2:e.201900386.
664. Stoll C, Geraudel A, Chauvin A. New X-linked syndrome of mental retardation, short stature and hypertelorism. Am J Med Genet 1991;39:474.
665. Atkin JF, Flaitz K, Patil S, et al. A new X-linked mental retardation syndrome. Am J Med Genet 1985;21:697.
666. Barresi S, Tomaselli S, Athanasiadis A, et al. Oligophrenin-1 (OPHN1), a gene involved in X-linked intellectual disability, undergoes RNA editing and alternative splicing during human brain development. PLoS One 2014;9:e91351.
667. Al-Owain M, Kaya N, Al-Zaidan H, et al. Novel intragenic deletion in OPHN1 in a family causing XLMR with cerebellar hypoplasia and distinctive facial appearance. Clin Genet 2011;79:363.
668. Dowling JJ, Lawlor MW, Das S. X-linked myotubular myopathy. GeneReviews® Seattle (WA): University of Washington, Seattle, 1993–2020, 2002 [updated 2018 Aug 23].
669. Brancaleoni V, Balwani M, Granata F, et al. X-chromosomal inactivation directly influences the phenotypic manifestation of X-linked protoporphyria. Clin Genet 2016;89:20.
670. Nowakowski R. Ocular manifestations in female carriers of X-linked disorders. J Am Optom Assoc 1995;66:352.
671. Mornet E, Chateau C, Taillandier A, et al. Recurrent and unexpected segregation of the FMR1 CGG repeat in a family with fragile X syndrome. Hum Genet 1996;97:512.
672. Bowling KM, Thompson ML, Amaral MD, et al. Genomic diagnosis for children with intellectual disability and/or developmental delay. Genome Med 2017;9:43.

673. Sun Y, Ruivenkamp CAL, Hoffer MJV, et al. Next-generation diagnostics: gene panel, exome, or whole genome? Hum Mutat 2015;36:648.
674. Vissers LELM, Gilissen C, Veltman JA. Genetic studies in intellectual disability and related disorders. Nat Rev Genet 2016;17:9.
675. Mir YR, Kuchay RAH. Advances in identification of genes involved in autosomal recessive intellectual disability: a brief review. J Med Genet 2019;56:567.
676. Linstrand A, Eisfeldt J, Pettersson M, et al. From cytogenetics to cytogenomics: whole-genome sequencing as a first-line test comprehensively captures the diverse spectrum of disease-causing genetic variation underlying intellectual disability. Genome Med 2019;11:68.
677. Miller DT, Adam MP, Aradhya S, et al. Consensus statement: chromosomal microarray is a first-tier clinical diagnostic test for individuals with developmental disabilities or congenital anomalies. Am J Hum Genet 2010;86(5):749.
678. Waggoner D, Wain KE, Dubuc AM, et al. Yield of additional genetic testing after chromosomal microarray for diagnosis of neurodevelopmental disability and congenital anomalies: a clinical practice resource of the American College of Medical Genetics and Genomics (ACMG). Genet Med 2018;20(10):1105.
679. Clark DW, Okada Y, Moore KHS, et al. Associations of autozygosity with a broad range of human phenotypes. Nat Commun 2019;10:4957.
680. Abdulrazzaq YM, Bener A, Al-Gazali LI, et al. A study of possible deleterious effects of consanguinity. Clin Genet 1997;51:167.
681. Saadallah AA, Rashed MS. Newborn screening: experiences in the Middle East and North Africa. J Inherit Metab Dis 2007;30:482.
682. Bundey S, Alam H, Kaur A, et al. Race, consanguinity and social features in Birmingham babies: a basis for prospective study. J Epidemiol Commun Health 1990;44:130.
683. Khoury SA, Massad DF. Consanguinity, fertility, reproductive wastage, infant mortality and congenital malformations in Jordan. Saudi Med J 2000;21:150.
684. Stoltenberg C, Magnus P, Lie RT, et al. Birth defects and parental consanguinity in Norway. AmJ Epidemiol 1997;145:439.
685. Perveen F, Tyyab S. Frequency and pattern of distribution of congenital anomalies in the newborn and associated maternal risk factors. J Coll Physicians Surg Pak 2007;17:340.
686. Monies D, Abouelhoda M, Assoum M, et al. Lessons learned from large-scale, first-tier clinical exome sequencing in a highly consanguineous population. Am J Hum Genet 2019;104(6):1182.
687. Vora NL, Gilmore K, Brandt A, et al. An approach to integrating exome sequencing for fetal structural anomalies into clinical practice. Genet Med 2020;22(5):954.
688. Meier N, Bruder E, Lapaire O, et al. Exome sequencing of fetal anomaly syndromes: novel phenotype-genotype discoveries. Eur J Hum Genet 2019;27:730.
689. Malinowski J, Miller DT, Demmer L, et al. Systematic evidence-based review: outcomes from exome and genome sequencing for pediatric patients with congenital anomalies or intellectual disabilities. Genet Med 2020;22(6):986.
690. Milunsky A. Heredity and your family's health. Baltimore, MD: Johns Hopkins University Press, 1992.
691. Greenbaum L, Pode-Shakked B, Eisenberg-Barzilai S, et al. Evaluation of diagnostic yield in fetal whole-exome sequencing: a report on 45 consecutive families. Front Genet 2019;10:425.
692. Goh YI, Chudley AE, Clarren SK, et al. Development of Canadian screening tools for fetal alcohol spectrum disorder. Can J Clin Pharmacol 2008;15:e344.
693. Memo L, Gnoato E, Caminiti S, et al. Fetal alcohol spectrum disorders and fetal alcohol syndrome: the state of the art and new diagnostic tools. Early Hum Dev 2013;89(Suppl 1):S40.
694. Chudley AE. Fetal alcohol spectrum disorder: counting the invisible – mission impossible? Arch Dis Child 2008;93:721.
695. Clarren SK, Randels SP, Sanderson M, et al. Screening for fetal alcohol syndrome in primary schools: a feasibility study. Teratology 2001;63:3.
696. Holmes LB. Human teratogens: update 2010. Birth Defects Red A Clin Mol Teratol 2011;91:1.
697. Gheysen W, Kennedy D. An update on maternal medication-related embryopathies. Prenat Diagn 2020;40:1168.
698. Milunsky A, Ulcickas M, Rothman KJ, et al. Maternal heat exposure and neural tube defects. JAMA 1992;268:882.
699. Saunders NR, Dziegielewska KM. Medications for pregnant women: A balancing act between the interests of the mother and of the fetus. Prenat Diagn 2020;40:1156.
700. Martinez-Frias ML, Bermejo E, Rodriguez-Pinilla E, et al. Periconceptional exposure to contraceptive pills and risk for Down syndrome. J Perinatol 2001;21:288.
701. Shub A, Lappas M. Pregestational diabetes in pregnancy: complications, management, surveillance, and

mechanisms of disease – a review. Prenat Diagn 2020;40:1092.
702. Murray SR, Reynolds RM. Short- and long-term outcomes of gestational diabetes and its treatment on fetal development. Prenat Diagn 2020;40:1085.
703. Evans MI, Andriole S, Curtis J, et al. The epidemic of abnormal copy number variant cases missed because of reliance upon noninvasive prenatal screening. Prenat Diagn 2018;38(10):730.
704. Vora NL, Powell B, Brandt A, et al. Prenatal exome sequencing in anomalous fetuses: new opportunities and challenges. Genet Med 2017;19:1207.
705. Jelin AC, Vora N. Whole exome sequencing: applications in prenatal genetics. Obstet Gynecol Clin North Am 2018;45:69.
706. Best S, Wou K, Vora N, et al. Promises, pitfalls and practicalities of prenatal whole exome sequencing. Prenat Diagn 2018;38:10.
707. Normand EA, Braxton A, Nassef S, et al. Clinical exome sequencing for fetuses with ultrasound abnormalities and suspected Mendelian disorder 2018;10:74.
708. Lord J, McMullan DJ, Eberhardt RY, et al. Prenatal exome sequencing analysis in fetal structural anomalies detected by ultrasonography (PAGE): a cohort study. Lancet 2019;393:747.
709. Horn R, Parker M. Opening Pandora's box?: ethical issues in prenatal whole genome and exome sequencing. Prenat Diagn 2018;38:20.
710. Bunnik EM, de Jong A, Nijsingh N, et al. The new genetics and informed consent: differentiating choice to preserve autonomy. Bioethics 2013;27:348.
711. ACMG Board of Directors. Points to consider in the clinical application of genomic sequencing. Genet Med 2012;14:759.
712. Committee on Genetics and the Society for Maternal-Fetal Medicine. Committee opinion no. 682: microarrays and next-generation sequencing technology: the use of advanced genetic diagnostic tools in obstetrics and gynecology. Obstet Gynecol 2016;128:e262.
713. Kalia SS, Adelman K, Bale SJ, et al. Recommendations for reporting of secondary findings in clinical exome and genome sequencing, 2016 update (ACMG SF v2.0): a policy statement of the American College of Medical Genetics and Genomics. Genet Med 2017;19:249.
714. Johnston JJ, Rubinstein WS, Facio FM, et al. Secondary variants in individuals undergoing exome sequencing: screening of 572 individuals identifies high-penetrance mutations in cancer-susceptibility genes. Am J Hum Genet 2012;91:97.
715. Pinxten W, Howard HC. Ethical issues raised by whole genome sequencing. Best Pract Res Clin Gastroenterol 2014;28:269.
716. Committee of the International Huntington Association and the World Federation of Neurology. Guidelines for the molecular genetics predictive test in Huntington's disease. J Med Genet 1994;31:555.
717. International Huntington Association and World Federation of Neurology. Guidelines for the molecular genetics predictive test in Huntington's disease. Neurology 1994;44:1533.
718. Skirton H, Goldsmith L, Jackson L, et al. Quality in genetic counseling for presymptomatic testing-clinical guidelines for practice across the range of genetic conditions. Eur J Hum Genet 2013;21:256.
719. MacLeod RTA, Frontali M, Evers-Kiebooms G, et al. Recommendations for the predictive genetic test in Huntington's disease. Clin Genet 2013;23:221.
720. Tibben A, Duivenvoorden J, Niermeijer MF, et al. Psychological effects of presymptomatic DNA testing for Huntington's disease in theDutch program. Psychosom Med 1994;56:526.
721. Lawson K, Wiggins S, Green T, et al. Adverse psychological events occurring in the first year after predictive testing for Huntington's disease. J Med Genet 1996;33:856.
722. Wiggins S, Whyte P, Huggins M, et al. The psychological consequences of predictive testing for Huntington's disease. N Engl J Med 1992;327:1401.
723. Evers-Kiebooms G, Nys K, Harper P, et al. Predictive DNA-testing for Huntington's disease and reproductive decision making: a European collaborative study. Eur J Hum Genet 2002;10:167.
724. Migliore S, Jankovic J, Squitieri F. Genetic counseling in Huntington's disease: potential new challenges on horizon? Front Neurol 2019;10:453.
725. Kenney C, Powell S, Jankovic J. Autopsy-proven Huntington's disease with 29 trinucleotide repeats. Mov Dis 2007;22:127.
726. Killoran A, Biglan KM, Jankovic J, et al. Characterization of the Huntington intermediate CAG repeat expansion phenotype in PHAROS. Neurology 2013;80:2022.
727. Cubo E, Ramos-Arroyo MA, Martinez-Horta S, et al. Intermediate CAG repeats in Huntington' s disease. A longitudinal analysis of the European Huntington' s Disease Network Registry Cohort (S25. 003). Neurology 2016;86:571.
728. Kay C, Collins JA, Miedzybrodzka Z, et al. Huntington disease reduced penetrance alleles occur at

high frequency in the general population. Neurology 2016;87:282.
729. Perry TL. Some ethical problems in Huntington's chorea. Can Med Assoc J 1981;125:1098.
730. Quaid KA, Brandt J, Faden RR, et al. Knowledge, attitude and the decision to be tested for Huntington's disease. Clin Genet 1989;36:431.
731. Moore RC, Xiang F, Monaghan J, et al. Huntington disease phenocopy is a familial prion disease. Am J Hum Genet 2001;69:1385.
732. Evers-Kiebooms G, Swerts A, Cassimann JJ, et al. The motivation of at-risk individuals and their partners in deciding for or against predictive testing for Huntington's disease. Clin Genet 1989;35:29.
733. Sorenson SA, Fenger K. Suicide in patients with Huntington's disease and their sibs. Am J Hum Genet 1991;49:316.
734. Schoenfeld M, Myers RH, Cupples LA, et al. Increased rate of suicide among patients with Huntington's disease. J Neurol Neurosurg Psychiatry 1984;47:1283.
735. Almqvist EW, Bloch M, Brinkman R, et al., on behalf of an International Huntington Disease Collaborative Group. A worldwide assessment of the frequency of suicide, suicide attempts or psychiatric hospitalization after predictive testing for Huntington disease. Am J Hum Genet 1999;64:1293.
736. van Duijn E, Kingma EM, van der Mast RC. Psychopathology in verified Huntington's disease gene carriers. J Neuropsychiatry Clin Neurosci 2007;19:441.
737. Kachian ZR, Cohen-Zimerman S, Bega D, et al. Suicidal ideation and behavior in Huntington's disease: systematic review and recommendations. J Affect Disord 2019;250:319.
738. McGarry A, McDermott MP, Kieburtz K, et al. Risk factors for suicidality in Huntington disease. Neurology 2019;92:e1643.
739. Wesson M, Boileau NR, Perlmutter JS, et al. Suicidal ideation assessment in individuals with premanifest and manifest Huntington disease. J Huntingtons Dis 2018;7:239.
740. Markel DS, Young AB, Penney JB. At-risk persons' attitudes toward presymptomatic and prenatal testing of Huntington's disease in Michigan. Am J Med Genet 1987;26:295.
741. Lamport AN. Presymptomatic testing for Huntington's chorea: ethical and legal issues. Am J Med Genet 1987;26:307.
742. Taylor CA, Myers RH. Long-term impact of Huntington disease linkage testing. Am J Med Genet 1997:70:365.
743. Hayden MR. Predictive testing for Huntington disease: are we ready for widespread community implementation? Am J Med Genet 1991;40:515.
744. Nance MA, Leroy BS, Orr HT, et al. Protocol for genetic testing in Huntington disease: three years of experience in Minnesota. Am J Med Genet 1991;40:518.
745. Decruyenaere M, Evers-Kiebooms G, Cloostermans T, et al. Psychological distress in the 5-year period after predictive testing for Huntington's disease. Eur J Hum Genet 2003;11:30.
746. Winnberg E, Winnberg U, Pohlkamp L, et al. What to do with a second chance in life? Long-term experiences of non-carriers of Huntington's disease. J Genet Couns 2018;27:1438.
747. Gusella JF, McNeil S, Persichetti F, et al. Huntington's disease. Cold Spring Harb Symp Quant Biol 1996;61:615.
748. Kremer B, Goldberg P, Andrew SE. A worldwide study of the Huntington's disease mutation: the sensitivity and specificity of measuring CAG repeats. N Engl J Med 1994;330:1401.
749. Alonso ME, Yescas P, Rasmussen A, et al. Homozygosity in Huntington's disease: new ethical dilemma caused by molecular diagnosis. Clin Genet 2002;61:437.
750. Evans DGR, Maher EF, Macleod R, et al. Uptake of genetic testing for cancer predisposition. J Med Genet 1997;34:746.
751. Veldhuisen B, Saris JJ, deHaij S, et al. A spectrum of mutations in the second gene for autosomal dominant polycystic kidney disease (PKD2). Am J Hum Genet 1997;61:547.
752. Deltas CC, Christodoulou K, Tjakouri C, et al. Presymptomatic molecular diagnosis of autosomal dominant polycystic kidney disease using PKD1- and PKD2-linked markers in Cypriot families. Clin Genet 1996;50:10.
753. Pirson Y, Chaveau D. Intracranial aneurysms in autosomal dominant polycystic kidney disease. In: Watson ML, Torres VE, eds. Polycystic kidney disease. Oxford: Oxford University Press, 1996:530.
754. Liu D, Wang CJ, Judge DP, et al. A Pkd1-Fbn1 genetic interaction implicates TGF-β signaling in the pathogenesis of vascular complications in autosomal dominant polycystic kidney disease. J Am Soc Nephrol 2014;25:81.
755. Sujansky E, Kreutzer SB, Johnson AM, et al. Attitudes of at-risk and affected individuals regarding presymptomatic testing for autosomal dominant polycystic kidney disease. Am J Med Genet 1990;35:510.

756. Hannig VL, Hopkins JR, Johnson HK, et al. Presymptomatic testing for adult onset polycystic kidney disease in at-risk kidney transplant donors. Am J Med Genet 1991;40:425.
757. Oyazato Y, Iijima K, Emi M, et al. Molecular analysis of TSC2/PKD1 contiguous gene deletion syndrome. Kobe J Med Sci 2011;57:E1.
758. Giardiello FM, Brensinger JD, Petersen GM, et al. The use and interpretation of commercial APC gene testing for familial adenomatous polyposis. N Engl J Med 1997;336:823.
759. Hogan J, Turner A, Tucker K, et al. Unintended diagnosis of Von Hippel-Lindau syndrome using Array Comparative Genomic Hybridization (CGH): counseling challenges arising from unexpected information. J Genet Couns 2013;22:22.
760. Telander RL, Zimmerman D, Sizemore GW, et al. Medullary carcinoma in children: results of early detection and surgery. Arch Surg 1989;124:841.
761. Ross LF. Predictive genetic testing for conditions that present in childhood. Kennedy Inst Ethics J 2002;12:225.
762. Wertz DC, Fanos JH, Reilly PR. Genetic testing for children and adolescents: who decides? JAMA 1994;272:875.
763. Lancaster JM, Wiserman RW, Berchuk A. An inevitable dilemma: prenatal testing for mutations in the BRCA1 breast-ovarian cancer susceptibility gene. Obstet Gynecol 1996;87:306.
764. DudokdeWit AC, Tibben A, Frets PG, et al. BRCA1 in the family: a case description of the psychological implications. Am J Med Genet 1997;71:63.
765. Julian-Reynier C, Eisinger F, Vennin P, et al. Attitudes towards cancer predictive testing and transmission of information to the family. J Med Genet 1996;33:731.
766. Lancaster JM, Wiseman RW, Berchuck A. An inevitable dilemma: prenatal testing for mutations in the BRCA1 breast-ovarian cancer susceptibility gene. Obstet Gynecol 1996;87:306.
767. Antoniou A, Pharoah PD, Narod S, et al. Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case series unselected for family history: a combined analysis of 22 studies. Am J Hum Genet 2003;72:1117.
768. National Comprehensive Cancer Network. Practice guidelines in oncology. Genetic/familial high-risk assessment: breast and ovarian. Version 1. Fort Washington, PA: National Comprehensive Cancer Network, 2008.
769. Burke W, Daly M, Garber J, et al. Recommendations for follow-up care of individuals with an inherited predisposition to cancer. II. BRCA1 and BRCA2. Cancer Genetics Studies Consortium. JAMA 1997;277:997.
770. King M-C, Marks JH, Mandell JB. Breast and ovarian cancer risks due to inherited mutations in BRCA1 and BRCA2. Science 2003:302;643.
771. Laken SJ, Petersen GM, Gruber SB, et al. Familial colorectal cancer in Ashkenazim due to a hypermutable tract in APC. Nat Genet 1997;17:79.
772. Verkerk AJ, Pieretti M, Sutcliffe JS, et al. Identification of a gene (FMR-1) containing a CGG repeat coincident with a breakpoint cluster region exhibiting length variation in fragile X syndrome. Cell 1991;65:905.
773. Paulson H. Repeat expansion diseases. Handb Clin Neurol 2018;147:105.
774. Lehesjoki A-E, Kälviäinen R. Progressive myoclonic epilepsy type 1. GeneReviews® [internet]. Seattle (WA): University of Washington, Seattle, 1993–2020, 2004 Jun 24 [updated 2020 Jul 2].
775. Ishikawa K, Dürr A, Klopstock T, et al. Pentanucleotide repeats at the spinocerebellar ataxia type 31 (SCA31) locus in Caucasians. Neurology 2011;77:1853.
776. Corbett MA, Kroes T, Veneziano L, et al. Intronic ATTTC repeat expansions in STARD7 in familial adult myoclonic epilepsy linked to chromosome 2. Nat Commun 2019;10:4920.
777. Campuzano V, Montermini L, Molot MD, et al. Friedreich's ataxia: autosomal recessive disease caused by an intronic GA triplet repeat expansion. Science 1996;271:1423.
778. Yum K, Wang ET, Kalsotra A. Myotonic dystrophy: disease repeat range, penetrance, age of onset, and relationship between repeat size and phenotypes. Curr Opin Genet Dev 2017;44:30.
779. Jaspert A, Fahsold R, Grehl H, et al. Myotonic dystrophy: correlation of clinical symptoms with the size of the CTG trinucleotide repeat. J Neurol 1995;242:99.
780. Schoser B. Myotonic dystrophy type 2. GeneReviews® [internet]. Seattle (WA): University of Washington, Seattle, 1993–2020, 2006 Sep 21 [updated 2020 Mar 19].
781. Higgs C, Hilbert JE, Wood L, et al. Reproductive cancer risk factors in women with myotonic dystrophy (DM): survey data from the US and UK DM registries. Front Neurol 2019;10:1071.
782. Alsaggaf R, Pfeiffer RM, Wang Y, et al. Diabetes, metformin and cancer risk in myotonic dystrophy type 1. Int J Cancer 2020;147:785.
783. Myers RH, MacDonald ME, Koroshetz WJ et al. De novo expansion of a (CAG)n repeat in sporadic Huntington's disease. Ann Neurol 1992;32:707.

784. Trottier Y, Briancalana V, Mandel JL. Instability of CAG repeats in Huntington's disease: relation to parental transmission and age of onset. J Med Genet 1994;31:377.
785. Joosten IBT, Hellebrekers DMEI, de Greef BTA, et al. Parental repeat length instability in myotonic dystrophy type 1 pre- and protomutations. Eur J Hum Genet 2020;28(7):956.
786. Margolesky J, Starosta-Rubenstein S, Verma A, et al. A co-occurrence of trinucleotide repeat disorders. Mov Disord Clin Pract 2018;5(6):643.
787. McFarland KN, Liu J, Landrian I, et al. Paradoxical effects of repeat interruptions on spinocerebellar ataxia type 10 expansions and repeat instability. Eur J Hum Genet 2013;21:1272.
788. Cumming SA, Hamilton MJ, Robb Y, et al. De novo repeat interruptions are associated with reduced somatic instability and mild or absent clinical features in myotonic dystrophy type 1. Eur J Hum Genet 2018;26(11):1635.
789. Pešović J, Perić S, Brkušanin M, et al. Repeat interruptions modify age at onset in myotonic dystrophy type 1 by stabilizing DMPK expansions in somatic cells. Front Genet 2018;9:601.
790. Laffita-Mesa JM, Rodriguez Pupo JM, Moreno Sera R, et al. De novo mutations in ataxin-2 gene and ALS risk. PLoS One 2013;8:e70560.
791. Beaudin M, Matilla-Dueñas A, Soon B, et al. The classification of autosomal recessive cerebellar ataxias: a consensus statement from the society for research on the cerebellum and ataxias task force. Cerebellum 2019;18(6):1098.
792. Robberecht W, Philips T. The changing scene of amyotrophic lateral sclerosis. Nat Rev Neurosci 2013;14:248.
793. Majounie E, Renton AE, Mok K, et al. Frequency of the C9orf72 hexanucleotide repeat expansion in patients with amyotrophic lateral sclerosis and frontotemporal dementia: a cross-sectional study. Lancet Neurol 2012;11:323.
794. Beck J, Poulter M, Hensman D, et al. Large C9orf72 hexanucleotide repeat expansions are seen in multiple neurodegenerative syndromes and are more frequent than expected in the UK population. Am J Hum Genet 92:345.
795. Williams KL, Fifita JA, Vucic S, et al. Pathophysiological insights into ALS with C9orf72 expansions. J Neurol Neurosurg Psychiatry 2013;84:931.
796. Lindquist SG, Duno M, Batbayli M, et al. Corticobasal and ataxia syndromes widen the spectrum of C9orf72 hexanucleotide expansion disease. Clin Genet 2013;83:279.
797. van der Zee J, Gijselinck I, Dillen L, et al. A pan-European study of the C9orf72 repeat associated with FTLD: geographic prevalence, genomic instability, and intermediate repeats. Hum Mutat 2013;34:363.
798. Devenney EM, Ahmed RM, Halliday G, et al. Psychiatric disorders in C9orf72 kindreds: study of 1,414 family members. Neurology 2018;91:e.1498.
799. Esselin F, Mouzat K, Polge A, et al. Clinical phenotype and inheritance in patients with C9ORF72 hexanucleotide repeat expansion: results from a large French cohort. Front Neurosci 2020;14:316.
800. Shi D, Xu J, Niu W, et al. Live births following preimplantation genetic testing for dynamic mutation diseases by karyomapping: a report of three cases. J Assist Reprod Genet 2020;37:539.
801. Fernández RM, Lozano-Arana MD, Sánchez B, et al. Preimplantation genetic diagnosis for myotonic dystrophy type 1 and analysis of the effect of the disease on the reproductive outcome of the affected female patients. Biomed Red Int 2017;2017:9165363.
802. Milunsky A, Baldwin C, Milunsky J. Molecular genetics and prenatal diagnosis. In: Milunsky A, Milunsky J, eds. Genetic disorders and the fetus: diagnosis, prevention and treatment, 7th edn. Hoboken, NJ: John Wiley & Sons, 2016:380.
803. Gerbrands LC, Haarman EG, Hankel MA, et al. Cystic fibrosis and Silver-Russell syndrome due to a partial maternal isodisomy of chromosome 7. Clin Case Rep 2017;5(10):1697.
804. Sotomayor FV, Abarca-Barriga HH. Homozygous deletion of the CFTR gene caused by interstitial maternal isodisomy in a Peruvian child with cystic fibrosis. J Pediatr Genet 2019;8(3):147.
805. Ammerpohl O, Martín-Subero JI, Richter J, et al. Hunting for the 5th base: techniques for analyzing DNA methylation. Biochim Biophys Acta 2009;1790:847.
806. Dedeurwaerder S, Defrance M, Calonne E, et al. Evaluation of the Infinium methylation 450K technology. Epigenomics 2011;3:771.
807. Begemann M, Rezwas FI, Beygo J, et al. Maternal variants in NLRP and other maternal effect proteins are associated with multilocus imprinting disturbance in offspring. J Med Genet 2018;55:497.
808. Yauy K, de Leeuw N, Yntema HG, et al. Accurate detection of clinically relevant uniparental disomy from exome sequencing data. Genet Med 2020;22:803.
809. Bhoj EJ, Rajabi F, Baker SW, et al. Imprinted genes in clinical exome sequencing: Review of 538 cases and exploration of mouse-human conservation in the

identification of novel human disease loci. Eur J Med Genet 2020;63:103903.
810. del Gaudio D, Shinawi M, Astbury C, et al. Diagnostic testing for uniparental disomy: a points to consider statement from the American College of Medical Genetics and Genomics (ACMG). Genet Med 2020;22:1133.
811. Court F, Martin-Trujillo A, Romanelli V, et al. Genome-wide allelic methylation analysis reveals disease-specific susceptibility to multiple methylation defects in imprinting syndromes. Hum Mutat 2013;34:595.
812. Elbracht M, Mackay D, Begemann M, et al. Disturbed genomic imprinting and its relevance for human reproduction: causes and clinical consequences. Hum Reprod Update 2020;26:197.
813. Docherty LE, Rezwan FI, Poole RL, et al. Mutations in NLRP5 are associated with reproductive wastage and multilocus imprinting disorders in humans. Nat Commun 2015;6:8086.
814. Soellner L, Begemann M, Degenhardt F, Geipel A, et al. Maternal heterozygous NLRP7 variant results in recurrent reproductive failure and imprinting disturbances in the offspring. Eur J Hum Genet 2017;25:924.
815. Lee MT, Bonneau AR, Giraldez AJ. Zygotic genome activation during the maternal-to-zygotic transition. Annu Rev Cell Dev Biol 2014;30:581.
816. Zhou LQ, Dean J. Reprogramming the genome to totipotency in mouse embryos. Trends Cell Biol 2015;25:82.
817. Vicenz C, Lovett JL, Wu W, et al. Loss of imprinting in human placentas is widespread, coordinated, and predicts birth phenotypes. Mol Biol Evol 2020;37:429.
818. Giabicani É, Brioude F, Le Bouc Y, et al. Imprinted disorders and growth. Ann Endocrinol (Paris) 2017;78:112.
819. Rhon-Calderon EA, Vrooman LA, Riesche L, et al. The effects of assisted reproductive technologies on genomic imprinting in the placenta. Placenta 2019;84:37.
820. Litzky JP, Deyssenroth MA, Everson TM, et al. Prenatal exposure to maternal depression and anxiety on imprinted gene expression in placenta and infant neurodevelopment and growth. Pediatr Res 2018;83(5):1075.
821. John RM. Imprinted genes and the regulation of placental endocrine function: pregnancy and beyond. Placenta 2017;56:86.
822. Hattori H, Hiura H, Kitamura A, et al. Association of four imprinting disorders and ART. Clin Epigenetics 2019;11:21.
823. Uk A, Collardeau-Frachon S, Scanvion Q, et al. Assisted reproductive technologies and imprinting disorders: results of a study from a French congenital malformations registry. Eur J Med Genet 2018;61:518.
824. Mackay DJG, Temple IK. Human imprinting disorders: principles, practice, problems, and progress. Eur J Med Genet 2017;60:618.
825. Henningsen AA, Gissler M, Rasmussen S, et al. Imprinting disorders in children born after ART: a Nordic study from CoNARTaS group. Hum Reprod 2020;35:1178.
826. Johnson JP, Beischel L, Schwanke C, et al. Overrepresentation of pregnancies conceived by artificial reproductive technology in prenatally identified fetuses with Beckwith-Wiedemann syndrome. J Assist Reprod Genet 2018;35:985.
827. Mussa A, Molinatto C, Cerrato F, et al. Assisted reproductive techniques and risk of Beckwith-Wiedemann syndrome. Pediatrics 2017;140:e20164311.
828. Cortessis VK, Azadian M, Buxbaum J, et al. Comprehensive meta-analysis reveals association between multiple imprinting disorders and conception by assisted reproductive technology. J Assist Reprod Genet 2018;35:943.
829. Monk D, Mackay DJG, Eggermann T, et al. Genomic imprinting disorders: lessons on how genome, epigenome and environment interact, Nat Rev Genet 2019;20:235.
830. Court F, Tayama C, Romanelli V, et al. Genome-wide parent-of-origin DNA methylation analysis reveals the intricacies of human imprinting and suggests a germline methylation-independent mechanism of establishment. Genome Res 2014;24:554.
831. Weksberg R, Shuman C, Caluseriu O, et al. Discordant KCNQ1OT1 imprinting in sets of monozygotic twins discordant for Beckwith-Wiedemann syndrome. Hum Mol Genet 2002;11:1317.
832. Bliek J, Alders M, Maas SM, et al. Lessons from BWS twins: complex maternal and paternal hypomethylation and a common source of haematopoietic stem cells. Eur J Hum Genet 2009;17:1625.
833. Riess A, Binder G, Ziegler J, et al. First report on concordant monozygotic twins with Silver-Russell syndrome and ICR1 hypomethylation. Eur J Med Genet 2016;59:1.
834. DeAngelis AM, Martini AE, Owen CM. Assisted reproductive technology and epigenetics. Semin Reprod Med 2018;36:221.
835. Bragin E, Chatzimichali EA, Wright CF, et al. DECIPHER: database for the interpretation of phenotype-linked plausibly pathogenic sequence

and copynumber variation. Nucleic Acids Res 2014;42(Database issue):D993.
836. Johnston JJ, Biesecker LG. Databases of genomic variation and phenotypes: existing resources and future needs. Hum Mol Genet 2013;22(R1):R27.
837. Lu J, Campeau P, Lee B. Genotype-phenotype correlation – promiscuity in the era of next generation sequencing. N Engl J Med 2014;371:593.
838. Adam MP, Banka S, Bjornsson HT, et al. Kabuki syndrome: international consensus diagnostic criteria. J Med Genet 2019;56:89.
839. Bögershausen N, Gatinois V, Riehmer V, et al. Mutation update for Kabuki syndrome genes KMT2D and KDM6A and further delineation of X-linked Kabuki syndrome subtype 2. Hum Mutat 2016;37:847.
840. Shangguan H, Su C, Ouyang Q, et al. Kabuki syndrome: novel pathogenic variants, new phenotypes and review of the literature. Orphanet J Rare Dis 2019;14:255.
841. Banka S, Lederer D, Benoit V, et al. Novel KDM6A (UTX) mutations and a clinical and molecular review of the X-linked Kabuki syndrome (KS2). Clin Genet 2015;87:252.
842. Yap KL, Johnson AEK, Fischer D, et al. Correction: "Congenital hyperinsulinism as the presenting feature of Kabuki syndrome: clinical and molecular characterization of 10 affected individuals". Genet Med 2019;21:262.
843. Courcet JB, Faivre L, Michot C, et al. Clinical and molecular spectrum of renal malformations in Kabuki syndrome. J Pediatr 2013;163:742.
844. Pyeritz RE, McKusick VA. The Marfan syndrome: diagnosis and management. N Engl J Med 1979;300:772.
845. Beutler E, Nguyen NJ, Henneberger MW, et al. Gaucher disease: gene frequencies in the Ashkenazi Jewish population. Am J Hum Genet 1993;53:85.
846. Lewis BD, Nelson PV, Robertson EF, et al. Mutation analysis of 28 Gaucher disease patients: the Australasian experience. Am J Med Genet 1994;49:218.
847. Kerem E, Corey M, Kerem B, et al. The relationship between genotype and phenotype in cystic fibrosis: analysis of the most common mutation. N Engl J Med 1990;323:1517.
848. Cystic Fibrosis Genotype-Phenotype Consortium. Correlation between genotype and phenotype in patients with cystic fibrosis. N Engl J Med 1993;329:1308.
849. Dork T, Wulbrand U, Richter T, et al. Cystic fibrosis with three mutations in the cystic fibrosis transmembrane regulator gene. Hum Genet 1991;87:441.
850. Le C, Ramjeesingh M, Reys E, et al. The cystic fibrosis mutation (F508) does not influence the chloride channel activity of CFTR. Nat Genet 1993;3:311.
851. Cutting GR. Modifier genes in Mendelian disorders: the example of cystic fibrosis. Ann NY Acad Sci 2010;1214:57.
852. Bradley GM, Blackman SM, Watson CP, et al. Genetic modifiers of nutritional status in cystic fibrosis. Am J Clin Nutr 2012;96:1299.
853. Blackman SM, Commander CW, Watson C. Genetic modifiers of cystic fibrosis-related diabetes. Diabetes 2013;62:3627.
854. Tuddenham EGD. Factor VIII and haemophilia A. Baillière's Clin Haematol 1989;2:849.
855. McVey JH, Rallapalli PM, Kemball-Cook G, et al. The European association for haemophilia and allied disorders (EAHAD) coagulation factor variant databases: important resources for haemostasis clinicians and researchers. Haemophilia 2020;26:306.
856. Atik T, Işik E, Onay H, et al. Factor 8 gene mutation spectrum of 270 patients with haemophilia A: identification of 36 novel mutations. Turk J Haematol 2020;37(3):145.
857. Miller DS, Steinbrecher RA, Wieland K, et al. The molecular genetic analysis of haemophilia A: characterization of six partial deletions in the factor VIII gene. Hum Genet 1990;86:219.
858. Sarri CA, Roussaki-Schulze A, Vasilopoulos Y, et al. Netherton syndrome: a genotype-phenotype review. Mol Diagn Ther 2017;21:137.
859. Koczkowska M, Callens T, Chen Y, et al. Clinical spectrum of individuals with pathogenic NF1 missense variants affecting p. Met1149, p.Arg1276, and p.Lys1423: genotype-phenotype study in neurofibromatosis type 1. Hum Mutat 2020;41:299.
860. Lehtonen HJ, Sipponen T, Tojander S, et al. Segregation of a missense variant in entire smooth muscle actin gamma-2 with autosomal dominant familial visceral myopathy. Gastroenterology 2012;143:1482.
861. Berdon W, Baker D, Blanc W, et al. Megacystis-microcolon-intestinal hypoperistalsis syndrome: a new cause of intestinal obstruction in the newborn. Report of radiologic findings in five newborn girls. AJR Am J Roentgenol 1976;126:957.
862. Puri P, Shinkai M. Megacystis-microcolon-intestinal-hypoperistalsis syndrome. Semin Pediatr Surg 2005;14:58.
863. Milunsky M, Baldwin C, Zhang X, et al. Diagnosis of chronic intestinal pseudo-obstruction & megacystis by sequencing the ACTG2 gene. J Pediatr Gastroenterol Nutr 2017;65:384.

864. Milunsky A, Lazier J, Baldwin C, et al. Prenatal diagnosis of chronic intestinal pseudo-obstruction and paternal somatic mosaicism for the ACTG2 pathogenic variant. Prenat Diagn 2017;37:1254.
865. Xiromerisiou G, Marogianni C, Dadouli K, et al. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy revisited: genotype-phenotype correlations of all published cases. Neurol Genet 2020;6:e434.
866. Zhang L, Dong X, Lee M, et al. Single-cell whole-genome sequencing reveals the functional landscape of somatic mutations in B lymphocytes across human lifespan. Proc Natl Acad Sci U S A 2019;116:9014.
867. Vijg J. Somatic mutations, genome mosaicism, cancer and aging. Curr Opin Genet Dev 2014;26:141.
868. Mirzaa G, Timms AE, Conti V, et al. PIK3CA-associated developmental disorders exhibit distinct classes of mutations with variable expression and tissue distribution. JCI Insight 2016;1:e.87623.
869. Lalonde E, Ebrahimzadeh J, Rafferty K, et al. Molecular diagnosis of somatic overgrowth conditions: a singular-center experience. Mol Genet Genomic Med 2019;7:e536.
870. Quinlan-Jones E, Williams D, Bell C, et al. Prenatal detection of PIK3CA-related overgrowth spectrum in cultured amniocytes using long-range PCR and next-generation sequencing. Pediatr Dev Pathol 2017;20(1):54.
871. Tung JY, Lai SHY, Au SLK, et al. Coexistence of paternally-inherited ABCC8 mutation and mosaic paternal uniparental disomy 11p hyperinsulinism. Int J Pediatr Endocrinol 2020;2020:13.
872. Koh HY, Lee JH. Brain somatic mutations in epileptic disorders. Mol Cells 2018;41:881.
873. Liu AJ, Yang XX, Wu QX, et al. Study on mosaicism of SCN1A gene mutation in parents of children with Dravet syndrome. Zhonghua Er Ke Za Zhi 2017;55:818.
874. Dehainault C, Golmard L, Millot GA, et al. Mosaicism and prenatal diagnosis options: insights from retinoblastoma. Eur J Hum Genet 2017;25:381.
875. D'Gama AM, Walsh CA. Somatic mosaicism and neurodevelopmental disease. Nat Neurosci 2018;21:1504.
876. Rodin RE, Walsh CA. Somatic mutation in pediatric neurological diseases. Pediatr Neurol 2018;87:20.
877. Pham J, Shaw C, Pursley A, et al. Somatic mosaicism detected by exon-targeted, high resolution aCGH in 10362 consecutive cases. Eur J Hum Genet 2014;22:969.
878. Donnai D, Read AP, McKeown C, et al. Hypomelanosis of Ito-A manifestation of mosaicism or chimerism. J Med Genet 1988;25:809.
879. Thomas IT, Frias JL, Cantu ES, et al. Association of pigmentary anomalies with chromosomal and genetic mosaicism and chimerism. Am J Hum Genet 1989;45:193.
880. Raghunath M, Mackay K, Dalgleish R, et al. Genetic counseling on brittle grounds: recurring osteogenesis imperfecta due to parental mosaicism for a dominant mutation. Eur J Pediatr 1995;154:123.
881. Lund AM, Nicholls AC, Schwartz M, et al. Parental mosaicism and autosomal dominant mutations causing structural abnormalities of collagen I are frequent in families with osteogenesis imperfecta type III/IV. Acta Paediatr 1997;86:711.
882. Telenius H, Kremer B, Goldberg YP, et al. Somatic and gonadal mosaicism of the Huntington disease gene CAG repeat in brain and sperm. Nat Genet 1994;6:409.
883. Cancel G, Durr A, Didierjean O, et al. Molecular and clinical correlations in spinocerebellar ataxia 2: a study of 32 families. Hum Mol Genet 1997;6:709.
884. Satge D, Geneix A, Goburdhun J, et al. A history of miscarriages and mild prognathism as possible mode of presentation of mosaic trisomy 18 in women. Clin Genet 1996;50:470.
885. Comstock JM, Putnam AR, Sangle N, et al. Recurrence of achondrogenesis type 2 in sibs: additional evidence for germline mosaicism. Am J Med Genet A 2010;152A;1822.
886. Abe J, Nakamura K, Nishikomori R, et al. A nationwide survey of Aicardi-Goutières syndrome patients identifies a strong association between dominant TREX1 mutations and chilblain lesions: Japanese cohort study. Rheumatology (Oxford) 2014;53:448.
887. Bruttini M, Vitelli F, Meloni I, et al. Mosaicism in Alport syndrome with genetic counselling. J Med Genet 2000;37:717.
888. Erickson RP. Somatic gene mutation and human disease other than cancer: an update. Mutat Res 2010;705:96.
889. Meira JGC, Sarno MAC, Faria ÁCO, et al. Diagnosis of Atelosteogenesis type I suggested by fetal ultrasonography and atypical paternal phenotype with mosaicism. Rev Bras Ginecol Obstet 2018;40(9):570.
890. Haack TB, Hogarth P, Kruer MC, et al. Exome sequencing reveals de novo WDR45 mutations causing a phenotypically distinct, X-linked dominant form of NBIA. Am J Hum Genet 2012;91:1144.

891. Roux-Buisson N, Egéa G, Denjoy I, et al. Germline and somatic mosaicism for a mutation of the ryanodine receptor type 2 gene: implication for genetic counseling and patient caring. Europace 2011;13:120.
892. Catteruccia M, Fattori F, Codemo V, et al. Centronuclear myopathy related to dynamin 2 mutations: clinical, morphological, muscle imaging and genetic features of an Italian cohort. Neuromuscul Disord 2013;23:229.
893. Taioli F, Bertolasi L, Ajena D, et al. Parental mosaicism of a novel PMP22 mutation with minimal neuropathic phenotype. J Peripher Nerv Syst 2012;17:414.
894. Omoyinmi E, Melo Gomes S, Standing A, et al. Brief report: whole-exome sequencing revealing somatic NLRP3 mosaicism in a patient with chronic infantile neurologic, cutaneous, articular syndrome. Arthritis Rheumatol 2014;66:197.
895. Tanaka N, Izawa K, Saito MK, et al. High incidence of NLRP3 somatic mosaicism in patients with chronic infantile neurologic, cutaneous, articular syndrome: results of an International Multicenter Collaborative Study. Arthritis Rheum 2011;63:3625.
896. Nagendran S, Richards AJ, McNinch A, et al. Somatic mosaicism and the phenotype expression of COL2A1 mutations. Am J Med Genet A 2012;158A:1204.
897. Meguro T, Yoshida Y, Hayashi M, et al. Inheritance of polyalanine expansion mutation of PHOX2B in congenital central hypoventilation syndrome. J Hum Genet 2012;57:335.
898. Ng BG, Buckingham KJ, Raymond K, et al. Mosaicism of the UDP-galactose transporter SLC35A2 causes a congenital disorder of glycosylation. Am J Hum Genet 2013;92:632.
899. Kurek KC, Luks VL, Ayturk UM, et al. Somatic mosaic activating mutations in PIK3CA cause CLOVES syndrome. Am J Hum Genet 2012;90:1108.
900. Baquero-Montoya C, Gil-Rodríguez MC, Braunholz D, et al. Somatic mosaicism in a Cornelia de Lange syndrome patient with NIPBL mutation identified by different next generation sequencing approaches. Clin Genet 2014;86:595.
901. Girisha KM, Lewis LE, Phadke SR, et al. Costello syndrome with severe cutis laxa and mosaic HRAS G12S mutation. Am J Med Genet A 2010;152A:2861.
902. Alzualde A, Moreno F, Martinez-Lage P, et al. Somatic mosaicism in a case of apparently sporadic Creutzfeldt-Jakob disease carrying a de novo D178n mutation in the PRNP gene. Am J Med Genet B Neuropsychiatr Genet 2010;153B:1283.
903. Goriely A, Lord H, Lim J, et al. Germline and somatic mosaicism for FGFR2 mutation in the mother of a child with Crouzon syndrome: implications for genetic testing in "paternal age-effect" syndromes. Am J Med Genet A 2010;152:2067.
904. Zampatti S, Mela J, Peconi C, et al. Identification of Duchene/Becker muscular dystrophy mosaic carriers through a combined DNA/RNA analysis. Prenat Diagn 2018;38(13):1096.
905. Filho AB, Souza J, Faucz FR, et al. Somatic/gonadal mosaicism in a syndromic form of ectrodactyly, including eye abnormalities, documented through array-based comparative genomic hybridization. Am J Med Genet A 2011;155A:1152.
906. Bourdeaut F, Hérault A, Gentien D, et al. Mosaicism for oncogenic G12D KRAS mutation associated with epidermal nevus, polycystic kidneys and rhabomyosarcoma. J Med Genet 2010;47:859.
907. Terracciano A, Specchio N, Darra F, et al. Somatic mosaicism of PCDH19 mutation in a family with low-penetrance EFMR. Neurogenetics 2012;13:341.
908. Dibbens LM, Kneen R, Bayly MA, et al. Recurrence risk of epilepsy and mental retardation in females due to parental mosaicism of PCDH19 mutations. Neurology 2011;76:1514.
909. Maclellan RA, Luks VL, Vivero MP, et al. PIK3CA activating mutations in facial infiltrating lipomatosis. Plast Reconstr Surg 2014;133:12e.
910. Jansen AC, Oostra A, Desprechins B, et al. TUBA1A mutations: from isolated lissencephaly to familial polymicrogyria. Neurology 2011;76:988.
911. Pinto FO, Leblanc T, Chamousset D, et al. Diagnosis of Fanconi anemia in patients with bone marrow failure. Haematologica 2009;94:487.
912. Li X, Jiang M, Han W, et al. A novel TNNI2 mutation causes Freeman-Sheldon syndrome in a Chinese family with an affected adult with only facial contractures. Gene 2013;527:630.
913. Filipe B, Albuquerque Q, Bik E, et al. APC somatic mosaicism in a patient with Gardner syndrome carrying the E1573X mutation: report of a case. Dis Colon Rectum 2009;52:1516.
914. Lee JH, Huynh M, Silhavy JL, et al. De novo somatic mutations in components of the PI3K-AKT3-mTOR pathway cause of hemi-megalencephaly. Nat Genet 2012;44:941.
915. Eyries M, Coulet F, Girerd B, et al. ACVRL1 germinal mosaic with two mutant alleles in hereditary hemorrhagic telangiectasia associated with pulmonary arterial hypertension. Clin Genet 2012;82:173.
916. Pastrello C, Fornasarig M, Pin E, et al. Somatic mosaicism in a patient with Lynch syndrome. Am J Med Genet A 2009;149A:212.

917. Hsu AP, Sowerwine KJ, Lawrence MG, et al. Intermediate phenotypes in patients with autosomal dominant hyper-IgE syndrome caused by somatic mosaicism. J Allergy Clin Immunol 2013;131:1586.
918. Rabin R, Millan F, Cabrera-Luque J, et al. Intellectual disability due to monoallelic variant in GATAD2B and mosaicism in unaffected parent. Am J Med Genet A 2018;176(12):2907.
919. Tsubahara M, Hayashi Y, Niijima S, et al. Isolated growth hormone deficiency in two siblings because of paternal mosaicism for a mutation in the GH1 gene. Clin Endocrinol (Oxf) 2012;76:420.
920. Doisaki S, Muramatsu H, Shimada A, et al. Somatic mosaicism for oncogenic NRAS mutations in juvenile myelomonocytic leukemia. Blood 2012;120:1485.
921. Hafner C, Toll A, Gantner S, et al. Keratinocyte epidermal nevi are associated with mosaic RAS mutations. J Med Genet 2012;49:249.
922. Prochazkova K, Pavlikova K, Minarik M, et al. Somatic TP53 mosaicism in a patient with Li-Fraumeni syndrome. Am J Med Genet A 2009;149A:206.
923. Thibodeau IL, Xu J, Li Q, et al. Paradigm of genetic mosaicism and lone atrial fibrillation: physiological characterization of a connexin 43-deletion mutant identified from atrial tissue. Circulation 2010;122:236.
924. Amary MF, Damato S, Halai D, et al. Ollier disease and Maffucci syndrome are caused by somatic mosaic mutations of IDH1 and IDH2. Nat Genet 2011;43:1262.
925. Vissers LE, Fano V, Martinelli D, et al. Whole-exome sequencing detects somatic mutations of IDH1 in metaphyseal chondromatosis with D-2-hydroxyglutaric aciduria (MC-HGA). Am J Med Genet A 2011;155A:2609.
926. Odgerel Z, Sarkozy A, Lee HS, et al. Inheritance patterns and phenotypic features of myofibrillar myopathy associated with a BAG3 mutation. Neuromuscul Disord 2010;20:438.
927. Catalli C, Morgante A, Iraci R, et al. Validation of sensitivity and specificity of tetraplet-primed PCR (TP-PCR) in the molecular diagnosis of myotonic dystrophy type 2 (DM2). J Mol Diagn 2010;12:601.
928. Marini M, Bocciardi R, Gimelli S, et al. A spectrum of LMX1B mutations in Nail-Patella syndrome: new point mutations, deletion, and evidence of mosaicism in unaffected parents. Genet Med 2010;12:431.
929. Messiaen L, Vogt J, Bengesser K, et al. Mosaic type-1 NF1 microdeletions as a cause of both generalized and segmental neurofibromatosis type-1 (NF1). Hum Mutat 2011;32:213.
930. Goutagny S, Bah AB, Parfait B, et al. Neurofibromatosis type 2 in the elderly population: clinical and molecular features. Am J Med Genet A 2013;161A:667.
931. Saitsu H, Hoshino H, Kato M, et al. Paternal mosaicism of an STXBP1 mutation in OS. Clin Genet 2011;80:484.
932. Szuhai K, Jennes I, de Jong D, et al. Tiling resolution array-CGH shows that somatic mosaic deletion of the EXT gene is causative in EXT gene mutation negative multiple osteochondromas patients. Hum Mutat 2011;32:e2063.
933. Hague J, Delon I, Brugger K, et al. Male child with somatic mosaic Osteopathia Striata with Cranial Sclerosis caused by a novel pathogenic AMER1 frameshift mutation. Am J Med Genet A 2017;173(7):1931.
934. Kalish JM, Conlin LK, Mostoufi-Moab S, et al. Bilateral pheochromocytomas, hemihyperplasia, and subtle somatic mosaicism: the importance of detecting low-level uniparental disomy. Am J Med Genet A 2013;161A:993.
935. Steinbusch CV, van Roozendaal KE, Tserpelis D, et al. Somatic mosaicism in a mother of two children with Pitt-Hopkins syndrome. Clin Genet 2013;83:73.
936. Buffet A, Smati S, Mansuy L, et al. Mosaicism in HIF2A-related polycythemia-paraganglioma syndrome. J Clin Endocrinol Metab 2014;99:e369.
937. Doubaj Y, De Sandre-Giovannoli A, Vera EV, et al. An inherited LMNA gene mutation in atypical Progeria syndrome. Am J Med Genet A 2012;158A:2881.
938. Lindhurst MJ, Sapp JC, Teer JK, et al. A mosaic activating mutation in AKT1 associated with the Proteus syndrome. N Engl J Med 2011;365:611.
939. Ngai YF, Chijiwa C, Mercimek-Mahmutoglu S, et al. Pseudohypoparathyroidism type 1a and the GNAS p.R231H mutation: somatic mosaicism in a mother with two affected sons. Am J Med Genet A 2010;152A:2784.
940. Coughlin CR 2nd, Krantz ID, Schmitt ES, et al. Somatic mosaicism for PDHA1 mutation in a male with pyruvate dehydrogenase complex deficiency. Mol Genet Metab 2010;100:296.
941. Jin ZB, Gu F, Matsuda H, et al. Somatic and gonadal mosaicism in X-linked retinitis pigmentosa. Am J Med Genet A 2007;143A:2544.
942. Rushlow D, Piovesan B, Zhang K, et al. Detection of mosaic RB1 mutations in families with retinoblastoma. Hum Mutat 2009;30:842.
943. Psoni S, Sofocleous C, Traeger-Synodinos, et al. Phenotypic and genotypic variability in four males with MECP2 gene sequence aberrations including a novel deletion. Pediatr Res 2010;67:551.

944. Bartnik M, Derwińska K, Gos M, et al. Early-onset seizures due to mosaic exonic deletions of CDKL5 in a male and two females. Genet Med 2011;13:447.
945. Bartsch O, Kress W, Kempf O, et al. Inheritance and variable expression in Rubinstein-Taybi syndrome. Am J Med Genet A 2010;152A:2254.
946. Chiang PW, Lee NC, Chien N. Somatic and germ-line mosaicism in Rubinstein-Taybi syndrome. Am J Med Genet A 2009;149A:1463.
947. Carmignac V, Thevenon J, Adès L, et al. In-frame mutations in exon 1 of SKI cause of dominant Shprintzen-Goldberg syndrome. Am J Hum Genet 2012;91:950.
948. Castronovo C, Rusconi D, Crippa M, et al. A novel mosaic NSD1 intragenic deletion in a patient with an atypical phenotype. Am J Med Genet A 2013;161A:611.
949. Désir J, Cassart M, Donner C, et al. Spondyloperipheral dysplasia as the mosaic form of platyspondylic lethal skeletal dysplasia Torrance type in mother and fetus with the same COL2A1 mutation. Am J Med Genet A 2012;158A:1948.
950. Mineyko A, Doja A, Hurteau J, et al. A novel missense mutation in LIS1 in a child with subcortical band heterotopia and pachygyria inherited from his mildly affected mother with somatic mosaicism. J Child Neurol 2010;25:738.
951. Isodor B, Capito C, Paris F, et al. Familial frameshift SRY mutation inherited from a mosaic father with testicular dysgenesis syndrome. J Clin Endocrinol Metab 2009;94:3467.
952. Dufendach KA, Giudicessi JR, Boczek NJ, et al. Maternal mosaicism confounds the neonatal diagnosis of type 1 Timothy syndrome. Pediatrics 2013;131:e1991.
953. Inbar-Feigenberg M, Choufani S, Cytrynbaum C, et al. Mosaicism for genome-wide paternal uniparental disomy with features of multiple imprinting disorders: diagnostic and management issues. Am J Med Genet A 2013;161A:13.
954. Davis BR, Candotti F. Revertant somatic mosaicism in the Wiskott-Aldrich syndrome. Immunol Res 2009;44:127.
955. Kawai T, Nishikomori R, Izawa K, et al. Frequent somatic mosaicism of NEMO in T cells of patients with X-linked anhidrotic ectodermal dysplasia with immunodeficiency. Blood 2012;119:5458.
956. Yamada M, Okura Y, Suzuki, et al. Somatic mosaicism in two unrelated patients with X-linked chronic granulomatous disease characterized by the presence of a small population of normal cells. Gene 2012;497:110.
957. Twigg SR, Matsumoto K, Kidd AM, et al. The origin of EFNB1 mutations in craniofrontonasal syndrome: frequent somatic mosaicism and explanation of the paucity of carrier males. Am J Hum Genet 2006;78:999.
958. Cheillan D, Joncquel-Chevalier Curt M, Briand G, et al. Screening for primary creatine deficiencies in French patients with unexplained neurological symptoms. Orphanet J Rare Dis 2012;7:96.
959. Chen XL, Zhao Y, Ke HP, et al. Detection of somatic and germline mosaicism for the LAMP2 gene mutation c.808dupG in a Chinese family with Danon disease. Gene 2012;507:174.
960. Juan-Mateu J, Paradas C, Olivé M, et al. Isolated cardiomyopathy caused by a DMD nonsense mutation in somatic mosaicism: genetic normalization in skeletal muscle. Clin Genet 2012;82:574.
961. Vreeburg M, van Geel M, van den Heuij LG, et al. Focal dermal hypoplasia in a male patient due to mosaicism for a novel PORCN single nucleotide deletion. J Eur Acad Dermatol Venereol 2011;25:592.
962. Maas SM, Lombardi MP, van Essen AJ, et al. Phenotype and genotype in 17 patients with Goltz-Gorlin syndrome. J Med Genet 2009;46:716.
963. Margari L, Lamanna AL, Buttiglione M, et al. Long-term follow-up of neurological manifestations in a boy with incontinentia pigmenti. Eur J Pediatr 2013;172:1259.
964. Donsante A, Johnson P, Jansen LA, et al. Somatic mosaicism in Menkes disease suggests choroid plexus-mediated copper transport to the developing brain. Am J Med Genet A 2010;152A:2529.
965. Chénier S, Noor A, Dupuis L, et al. Osteopathia striata with cranial sclerosis and developmental delay in a male with mosaic deletion in chromosome region Xq11.2. Am J Med Genet A 2012;158A:2946.
966. Oegema R, Hulst JM, Theuns-Walks SD, et al. Novel no-stop FLNA mutation causes multi-organ involvement in males. Am J Med Genet A 2013;161:2376.
967. Ducamp S, Schneider-yin X, de Rooij F, et al. Molecular and functional analysis of the C-terminal region of human erythroid-specific 5-aminolevulinic synthase associated with X-linked dominant protoporphyria (XLDPP). Hum Mol Genet 2013;22:1280.
968. Quélin C, Saillour Y, Souville I, et al. Mosaic DCX deletion causes subcortical band heterotopia in males. Neurogenetics 2012;13:367.
969. Ptacek JT, Eberhardt TL. Breaking bad news. JAMA 1996;276:496.
970. Luz R, George A, Spitz E, et al. Breaking bad news in prenatal medicine: a literature review. J Reprod Infant Psychol 2017;35:14-31.

971. Bond CF, Anderson EL. The reluctance to transmit bad news: private discomfort or public display? J Eur Soc Psychol 1987;23:176.
972. Monaghan KG, Leach NT, Pekarek D, et al. The use of fetal exome sequencing in the prenatal diagnosis: a points to consider document of the American College of Medical Genetics and Genomics (ACMG). Genet Med 2020;22:675.
973. Horn R, Parker M. Opening Pandora's box?: ethical issues in prenatal whole genome and exome sequencing. Prenat Diagn 2018;38:20.
974. Parker M, Lucassen A. Using a genetic test result in the care of family members: How does the duty of confidentiality apply? Eur J Hum Genet 2018;26:955.
975. Robyr R, Bernard JP, Roume J, et al. Familial diseases revealed by a fetal anomaly. Prenat Diagn 2006;26:1224.
976. Donnelly JC, Platt LD, Rebarber, A, et al. Association of copy number variants with specific ultrasonographically detected fetal anomalies. Obstet Gynecol 2014;124:83.
977. Wapner RJ, Martin CL, Levy B, et al. Chromosomal microarray versus karyotyping for prenatal diagnosis. N Engl J Med 2012;367:2175.
978. Hawkins A, Stenzel A, Taylor J, et al. Variables influencing pregnancy termination following prenatal diagnosis of fetal chromosome abnormalities. J Genet Couns 2013;22:238.
979. Blakeley C, Smith DM, Johnstone ED, et al. Parental decision-making following a prenatal diagnosis that is lethal, life-limiting, or has long term implications for the future child and family: a meta-synthesis of qualitative literature. BMC Med Ethics 2019;20:56.
980. Supiano K, Vaughn-Cole B. The impact of personal loss on the experience of health professions: graduate students in end-of life and bereavement care. Death Stud 2011;35:73.
981. Silver J, Caleshu C, Casson-Parkin S, et al. Mindfulness among genetic counselors is associated with increased empathy and work engagement and decreased burnout and compassion fatigue. J Genet Couns 2018;27:1175.
982. Verp M, Bombard A, Simpson J, et al. Parental decision following prenatal diagnosis of fetal chromosome abnormality. Am J Med Genet 1988;29:613.
983. Meryash D, Abuelo D. Counselling needs and attitudes toward prenatal diagnosis and abortion in fragile X families. Clin Genet 1988;33:349.
984. Sandelowski M, Barroso J. The travesty of choosing after positive prenatal diagnosis. J Obstet Gynecol Neonatal Nurs 2005;34(3):307.
985. Lou S, Jensen LG, Peterson OB, et al. Parental response to severe or lethal prenatal diagnosis: a systematic review of qualitative studies. Prenat Diagn 2017;37(8):731.
986. Chow EWC, Watson M, Young DA, et al. Neurocognitive profile in 22q11 deletion syndrome and schizophrenia. Schizophr Res 2006;87:270.
987. Evers LJ, De Die-Smulders CE, Smeets EE, et al. The velo-cardio-facial syndrome: the spectrum of psychiatric problems and cognitive deterioration at adult age. Genet Couns 2009;20:307.
988. Baker K, Vorstman JAS. Is there a core neuropsychiatric phenotype in 22q11.2 deletion syndrome? Curr Opin Neurol 2012;25:131.
989. Murphy KC. Annotation: velo-cardio-facial syndrome. J Child Psychol Psychiat 2005;46:563.
990. Murphy KC. Schizophrenia and velo-cardio-facial syndrome. The Lancet 2002;359:426.
991. McDonald-McGinn DM, Hain HS, et al. 22q11.2 Deletion syndrome. In: Adam MP, Ardinger HH, Pagon RA, et al., eds. GeneReviews® [internet]. Seattle (WA): University of Washington, Seattle, 1993–2020, September 23, 1999.
992. White-van Mourik MCA, Connor JM, Ferguson-Smith MA. The psychosocial sequelae of a second-trimester termination of pregnancy for fetal abnormality. Prenat Diagn 1992;12:189.
993. Blumberg BD, Golbus MC, Hanson K. The psychological sequelae of abortion performed for a genetic indication. Am J Obstet Gynecol 1975;122:799.
994. Blumberg BD. The emotional implications of prenatal diagnosis. In: Emery, AEH, Pullen IM, eds. Psychological aspects of genetic counselling. London: Academic Press, 1984:202.
995. October T, Dryden-Palmer K, Copnell B, et al. Caring for parents after the death of a child. Pediatr Crit Care Med 2018;19(8S Suppl 2):S61.
996. Udipi S, Veach PM, Kao J, et al. The psychic costs of empathic engagement: personal and demographic predictors of genetic counselor compassion fatigue. J Genet Couns 2008:17;459.
997. Parkes CM. Bereavement. Studies of grief in adult life. London: Tavistock Publications, 1972.
998. Worden JW. Grief counseling and grief therapy, 2nd edn. New York: Springer, 1991.
999. Cacciatore J. Psychological effects of stillbirth. Semin Fetal Neonatal Med 2013;18:76.
1000. Appleton R, Gibson B, Hey E. The loss of a baby at birth: the role of the bereavement officer. Br J Obstet Gynaecol 1993;100:51.
1001. Seller M, Barnes C, Ross S, et al. Grief and midtrimester fetal loss. Prenat Diagn 1993;13:341.

1002. Fanos JH. Developmental tasks of childhood and adolescence: implications for genetic testing. Am J Med Genet 1997;71:22.
1003. Wertz DC, Fanos JH, Reilly PR. Genetic testing for children and adolescents: who decides? JAMA 1994;272:875.
1004. Clinical Genetics Society (UK). Report of a working party: the genetic testing of children. J Med Genet 1994;31:785.
1005. American Society of Human Genetics and American College of Medical Genetics. Points to consider: ethical, legal and psychosocial implications of genetic testing in children and adolescents. Am J Hum Genet 1995;57:1233.
1006. Green M, Solnit AJ. Reactions to the threatened loss of a child: a vulnerable child syndrome. Pediatrics 1964;034:58.
1007. McIntosh N, Eldrige C. Neonatal death: the neglected side of neonatal care? Arch Dis Child 1984;59:585.
1008. Bourne S. The psychological effects of a stillbirth on women and their doctors. J R Coll Gen Pract 1968;16:103.
1009. Crowther ME. Communication following a stillbirth or neonatal death: room for improvement. Br J Obstet Gynaecol 1995;102:952.
1010. American College of Obstetricians and Gynecologists, Society for Maternal-Fetal Medicine. Management of Stillbirth: Obstetric Care Consensus No, 10. Obstet Gynecol 2020;135:e110.
1011. Causes of death among stillbirths. Stillbirth Collaborative Research Network Writing Group. JAMA 2011;306:2459.
1012. Laury A, Sanchez-Lara PA, Pepkowitz S, et al. A study of 534 fetal pathology cases from prenatal diagnosis referrals analyzed from 1989 through 2000. Am J Med Genet A 2007;143A:3107.
1013. Korteweg FJ, Bouman K, Erwich JJ, et al. Cytogenetic analysis after evaluation of 750 fetal deaths: proposal for diagnostic workup. Obstet Gynecol 2008;111:865.
1014. Saleem S, Tikmani SS, McClure EM, et al. Trends and determinants from stillbirth in developing countries: results from the Global Network's Population-Based Birth Registry. Reprod Health 2018;15(Suppl 1):100.
1015. Stanley KE, Giordano J, Thorsten V, et al. Casual genetic variants in stillbirth. N Engl J Med 2020;383:1107.
1016. Barrett PM, McCarthy FP, Evans M, et al. Stillbirth is associated with increased risk of long-term maternal renal disease: a nationwide cohort study. Am J Obstet Gynecol 2020;223:427.e1.
1017. Brookes JAS, Hall-Craggs MA, Sams VR, et al. Non-invasive perinatal necropsy by magnetic resonance imaging. Lancet 1996;348:1139.
1018. Gagnon A, Wilson RD, Allen VM. Evaluation of prenatally diagnosed structural congenital anomalies. J Obstet Gynaecol Can 2009;31:875.
1019. Desilets V, Oligny LL. Fetal and perinatal autopsy in prenatally diagnosed fetal abnormalities with normal karyotype. J Obstet Gynaecol Can 2011;267:1047.
1020. Sethi N, Funamoto K, Ingbar C, et al. Noninvasive fetal electrocardiography in the diagnosis of Long QT syndrome: a case series. Fetal Daign Ther 2020;47(9):711.
1021. Shim SH, Ito M, Maher T, et al. Gene sequencing in neonates and infants with the long QT syndrome. Genet Test 2005;9:281.
1022. Cuneo BF, Kaizer AM, Clur SA, et al. Mothers with long QT syndrome are at increased risk for fetal death: findings from a multicenter international study. Am J Obstet Gynecol 2020;222:263.e1.
1023. Lewkowitz AK, Rosenbloom JI, López JD, et al. Association between stillbirth at 23 weeks of gestation or greater and severe maternal morbidity. Obstet Gynecol 2019;134:964.
1024. Nicholas AM, Lewin TJ. Grief reactions of parental couples: congenital handicap and cot death. Med J Aust 1986;144:292.
1025. Lafarge C, Mitchell K, Fox P. Perinatal grief following a termination of pregnancy for foetal abnormality: the impact of coping strategies. Prenat Diagn 2013;33:1173.
1026. Mashiach R, Anter D, Melamed N, et al. Psychological response to multifetal reduction and pregnancy termination due to fetal abnormality. J Matern Fetal Neonatal Med 2013,26:32.
1027. Lewis E, Bryan E. Management of perinatal loss of a twin. BMJ 1988;297:1321.
1028. Lewis E. Stillbirth: psychological consequences and strategies of management. In: Milunsky A, ed. Advances in perinatal medicine, vol. 3. New York: Plenum, 1983:205.
1029. McPhee SJ, Bottles K, Lo B, et al. To redeem them from death: reactions of family members to autopsy. Am J Med 1986;80:665.
1030. Irvin NA, Kennell JH, Klaus MH. Caring for the parents of an infant with a congenital malformation. In: Warkany J, ed. Congenital malformations: notes and comments. Chicago: Year Book Medical Publishers, 1971.
1031. Klaus MH, Kennell JH. Caring for parents of an infant who dies: maternal–infant bonding. St Louis, MO: CV Mosby, 1976.

1032. Blood C, Cacciatore J. Parental grief and memento mori photography: narrative, meaning, culture and context. Death Stud 2014;38:224.
1033. Flenady V, Boyle F, Koopmans L, et al. Meeting the needs of parents after a stillbirth or neonatal death. BJOG 2014;121(Suppl 4):137.
1034. Furlong RM, Hobbins JC. Grief in the perinatal period. Obstet Gynecol 1983;61:497.
1035. Shulman LP, Grevengood C, Phillips OP, et al. Family planning decisions after prenatal detection of fetal abnormalities. Am J Obstet Gynecol 1994;171:1373.
1036. Rowe J, Clyman R, Green C, et al. Follow-up of families who experience a perinatal death. Pediatrics 1978;62:166.
1037. Forrest GC, Standish E, Baum JD. Support after perinatal death: a study of support and counseling after bereavement. BMJ 1982;285:1475.
1038. Moldovan R, Pintea S, Austin J. The efficacy of genetic counseling for psychiatric disorders: a meta-analysis. J Genet Couns 2017;26:1341.
1039. Caldwell S, Wusik K, He H, et al. Development and Validation of the Genetic Counseling Self-Efficacy Scale (GCSES). J Genet Couns 2018;27:1248.
1040. Keller H, Wusik K, He H, et al. Further validation of the Genetic Counseling Self-Efficacy Scale (GCSES): its relationship with personality characteristics. J Genet Couns 2020;29(5):748.
1041. Borle K, Morris E, Inglis A, et al. Risk communication in genetic counseling: Exploring uptake and perception of recurrence numbers, and their impact on patient outcomes. Clin Genet 2018;94:239.
1042. Clarke A, Parsons E, Williams A. Outcomes and process in genetic counseling. Clin Genet 1996;50:462.
1043. Voorwinden JS, Plantinga M, Ausems M, et al. Cognitive and affective outcomes of genetic counseling in the Netherlands at group and individual level: a personalized approach seems necessary. Eur J Hum Genet 2020;28:1187.
1044. Montgomery SV, Barsevick AM, Egleston BL, et al. Preparing individuals to communicate genetic test results to their relatives: report of a randomized control trial. Fam Cancer 2013;12:537.
1045. Emery AEH, Raeburn JA, Skinner R. Prospective study of genetic counseling. BMJ 1979;1:253.
1046. Sibinga MS, Friedman CG. Complexities of parental understanding for phenylketonuria. Pediatrics 1971;48:216.
1047. Reynolds BD, Puck MH, Robinson A. Genetic counseling: an appraisal. Clin Genet 1974;5:177.
1048. American College of Medical Genetics and Genomics. ACMG policy statement: updated recommendations regarding analysis and reporting of secondary findings in clinical genome-scale sequencing. Genet Med 2015;17:68.
1049. Sorenson JR, Swazey JP, Scotch NA. Effective genetic counseling: more informed clients. In: Reproductive pasts, reproductive futures: genetic counseling and its effectiveness. New York: Alan R. Liss, 1981:79.
1050. Swerts A. Impact of genetic counseling and prenatal diagnosis for Down syndrome and neural tube defects. Birth Defects Orig Artic Ser 1987;23:61.
1051. Kessler S. Psychological aspects of genetic counseling. VI. A critical review of the literature dealing with education and reproduction. Am J Med Genet 1989;34:340.
1052. Davey A, Rostant K, Harrop K, et al. Evaluating genetic counseling: client expectations, psychological adjustment and satisfaction with service. J Genet Couns 2005;14:197.
1053. Milunsky A. Your genetic destiny: know your genes, secure your health, save your life. Cambridge, UK: Perseus Books, 2001.
1054. Baars MJH, Scherpbier AJJA, Schuwirth LW, et al. Deficient knowledge of genetics relevant for daily practice among medical students nearing graduation. Genet Med 2005;7:295.
1055. Marchant G, Barnes M, Evans JP, et al. From genetics to genomics: facing the liability implications in clinical care. J Law Med Ethics 2020;48:11.

2 Preimplantation Genetic Testing

Anver Kuliev and Svetlana Rechitsky

Herbert Wertheim College of Medicine, Florida International University, Miami, FL and Reproductive Genetic Innovations, Northbrook, IL, USA

Preimplantation genetic testing (PGT[1]) is a practical option for couples at risk of having offspring with serious/fatal chromosomal or monogenic diseases. It has been used for up to 600 monogenic disorders (PGT-M[1]). Moreover, it has been used for human leukocyte antigen (HLA) typing (PGT-HLA[1]), enabling the births of many children whose matched bone marrows have proved life-saving for siblings with congenital and acquired disorders requiring stem cell transplantation treatment.

Analysis of single cells or a few cells with a limited amount of available DNA has always presented a technical challenge, especially when PGT is faced with the need for accurate and rapid results from whole-genome amplification (WGA), followed by polymerase chain reaction (PCR) assays that are robust and sensitive. Next-generation sequencing (NGS) has allowed for accurate identification and transfer of euploid embryos (PGT for aneuploidies (PGT-A)[1]).

PGT-M was initially applied for the same indications as prenatal diagnosis,[2–4] but was then expanded to conditions that had never been considered, such as late-onset diseases with genetic predisposition and preimplantation HLA typing with or without testing for genetic disorders.[5–7]

PGT represents a natural evolution of the genetic disease prevention technology, from a period with limited genetic counseling and no prenatal diagnosis or treatment to a time when many options, including PGT, have become available.[8] Furthermore, PGT has been applied in order to improve access to the new treatment methods for some severe conditions by stem cell transplantation, for which no traditional treatment approaches are available. The impact of PGT and stem cell treatment on existing policies for the prevention of genetic disease (see Chapter 36) is clear from the increasing use of PGT to avoid unnecessary termination of many wanted pregnancies and for preimplantation HLA typing.

Approaches to preimplantation genetic testing

When prenatal genetic diagnosis was first considered in perspective, in 1984, the World Health Organization (WHO) emphasized the relevance of developing earlier approaches for genetic analysis with the possibility of diagnosis before implantation.[9, 10] The following possibilities for PGT were mentioned: genetic analysis of the first or second polar bodies and embryo biopsy at the cleavage or blastocyst stage.[10, 11] However, these approaches became possible only after introduction of the PCR assay[12] and success in micromanipulation and embryo biopsy.

First attempts at PGT were undertaken in mammalian embryos over 30 years ago,[13–18] when it was demonstrated that cells could be removed from mammalian preimplantation embryos and analyzed successfully without destroying the viability of the embryo in *in vitro* fertilization (IVF). PGT for human genetic disease was first demonstrated by Handyside et al.[19] for X-linked diseases

Genetic Disorders and the Fetus: Diagnosis, Prevention, and Treatment, Eighth Edition. Edited by Aubrey Milunsky and Jeff M. Milunsky.

and by Verlinsky et al.[20] for autosomal recessive disorders. Tens of thousands of children without detectable birth defects have been born following these procedures,[21–25] demonstrating that PGT can be performed safely in humans. Initially, PGT was based on polar body sampling and embryo biopsy at the cleavage stage, but the present standard shifted to blastocyst biopsy. The polar body approach is still, however, the only possibility for the ethnic groups where no embryos micromanipulation is allowed. The Preimplantation Genetic Diagnosis International Society (PGDIS) and the European Society of Human Reproduction and Embryology (ESHRE) Consortium have published an extensive set of best practice guidelines for PGT.[26, 27] These recommendations cover PGT organization, genetic and treatment-related counseling, psychologic evaluation, patient selection, all applicable technical issues, and quality control. The developments of preconception and PGT and the existing problems in the application of these early approaches to clinical practice are presented in this chapter, based on our 30 years' experience of over 22,000 PGT cycles, including 15,700 PGT-A, 491 PGT-HLA, and 6,778 PGT-M, involving a spectrum of, approximately, 600 different monogenic conditions (Table 2.1).

Polar body-based preimplantation genetic testing

The biopsy of gametes opened an intriguing possibility of preconception diagnosis of inherited diseases, because genetic analysis of biopsied gamete material made it realistic to select gametes containing an unaffected allele for fertilization and subsequent transfer.[28] In this way, not only was the selective abortion of an affected fetus avoided but also fertilization involving affected gametes, as an option for couples at risk of conceiving a genetically abnormal fetus.

Although preconception genetic testing could be achieved by genotyping either oocytes or sperm, the latter approach is still not realistic. Development of methods for culture of primary spermatocytes and spermatogonia followed by genetic analysis of matured spermatides is theoretically possible, but this still remains a subject for future research, such as in the framework of the current attempts at haploidization.[29, 30] The technique of sperm duplication has been introduced, which may allow testing of the sperm duplicate. However, errors may arise in the reduplication procedure, making the technique of sperm duplication inapplicable for clinical practice.[31, 32]

The only approach for preconception diagnosis at present, therefore, is genotyping oocytes by biopsy and subsequent genetic analysis of polar bodies. The first attempt to obtain oocyte karyotypes was undertaken in the mouse model by testing the second polar body in the early 1980s, but the technique required much improvement to be considered for clinical application.[33] Polar bodies were then used to test the possibility of amplification of β-globin sequences, again in the mouse model.[34] The first clinical application of the polar body approach was introduced in 1990.[20] It was demonstrated that, in the absence of crossover, the first polar body will be homozygous for the allele not contained in the oocyte and second polar body. However, the first polar body approach will not predict the eventual genotype of the oocytes if crossover occurs, because the primary oocyte in this case will be heterozygous for the abnormal gene. The frequency of crossover varies with the distance between the locus and the centromere, approaching as much as 50 percent for telomeric genes, for which the first polar body approach would be of only limited value, unless the oocytes can be tested further (Figure 2.1). Therefore, the second polar body analysis is required to detect hemizygous normal oocytes resulting after the second meiotic division. In fact, the accumulated experience shows that the most accurate diagnosis can be achieved in cases where the first polar body is heterozygous, so the detection of the normal or mutant gene in the second polar body predicts the opposite mutant or normal genotype of the resulting maternal contribution to the embryo after fertilization.[4]

To study a possible detrimental effect of the procedure, micromanipulated oocytes were followed and evaluated at different stages of development.[3, 4, 35] The absence of any deleterious effect of polar body removal on fertilization, preimplantation, and, possibly, postimplantation development made it possible to consider the polar body approach as a nondestructive test for genotyping the oocytes before fertilization and implantation. In another study, to assess the effect of the second polar body sampling on the viability and

Table 2.1 List of conditions for which preimplantation genetic testing (PGT) was performed and PGT-M outcome: 30 years of original experience.

Conditions	*Gene*	*Type of inheritance*	*No. patients*	*No. cycles*	*No. embryo transfers*	*No. embryos transferred*	*Pregnancy %*	*No. deliveries*
3-Hydroxyisobutyryl-CoA hydrolase deficiency (HIBCHD)	*HIBCH*	AR	1	1	1	2	0	0
3-Methylglutaconic aciduria with deafness, encephalopathy, and Leigh-like syndrome (MEGDEL)	*SERAC1*	AR	1	1	1	1	0	0
Achondroplasia (ACH)	*FGFR3*	AD	8	17	11	14	7	6
Achromatopsia 2 (ACHM2)	*CNGA3*	AR	1	1	1	1	1	1
Achromatopsia 3 (ACHM3)	*CNGB3*	AR	3	4	4	5	2	2
Acromesomelic dysplasia, Maroteaux type (AMDM)	*NPR2*	AR	1	1	2	2	1	1
Acyl-CoA dehydrogenase, medium-chain, deficiency	*ACADM*	AR	3	8	7	14	4	4
Acyl-CoA dehydrogenase, very long-chain; (ACADVL)	*ACADVL*	AR	5	6	6	11	2	2
Adrenal hyperplasia, congenital, due to 21-hydroxylase deficiency	*CYP21A2*	AR	23	34	26	42	17	17
Adrenoleukodystrophy (ALD)	*ABCD1*	XL	17	33	20	29	11	11
Agammaglobulinemia, X-linked (XLA)	*BTK*	XL	4	7	7	13	3	3
Aicardi–Goutieres syndrome 5 (AGS5 + CF)	*SAMHD1*	AR	1	2	2	2	1	1
Alagille syndrome 1 (ALGS1)	*JAG1*	AD	1	1	1	1	1	1
Albinism, ocular, type i (OA1)	*GPR143*	XL	1	12	5	9	4	3
Albinism, oculocutaneous, type ia (OCA1a)	*TYR*	AR	4	7	6	9	3	3
Albinism, oculocutaneous, type ii (OCA2)	*OCA2*	AR	3	6	5	9	3	3
Albinism, oculocutaneous, type iii (OCA3)	*TYRP1*	AR	1	1	0	0	0	0
Allan–Herndon–Dudley syndrome (AHDS)	*SLC16A2*	XL	1	2	2	2	1	1
Alopecia universalis congenita (ALUNC)	*HR*	AR	1	1	1	2	1	1
Alpha-1-antitrypsin deficiency (A1ATD)	*SERPINA1*	AR	9	16	14	18	9	8
Alport syndrome, autosomal dominant	*COL4A3*	AR	1	4	0	0	0	0
Alport syndrome, X-linked (ATS)	*COL4A5*	XL	8	16	15	22	10	9
Alzheimer disease 3	*PSEN1*	AD	2	3	3	6	3	3
Alzheimer disease 4	*PSEN2*	AD	1	1	1	2	0	0
Alzheimer disease (AD)	*APP*	AD	2	3	2	4	2	1
Amegakaryocytic thrombocytopenia, congenital (CAMT)	*MPL*	AR	1	1	0	0	0	0
Amyloidosis, hereditary, transthyretin-related	*TTR*	AD	3	7	5	6	3	2
Amyotrophic lateral sclerosis 1 (ALS1)	*SOD1*	XL	2	2	2	3	2	1
Amyotrophic lateral sclerosis 4, juvenile (ALS4)	*SETX*	AD	1	1	1	1	1	1
Anemia, nonspherocytic hemolytic, due to g6pd deficiency	*G6PD*	XL	9	12	12	15	6	6
Angelman syndrome (AS)	*UBE3A*	AD	2	2	2	3	1	1

Angioedema, hereditary, type i (HAE1)	*C1NH*	AD	3	4	3	4	1	1
Aniridia (AN)	*PAX6*	AD	4	7	5	6	4	4
Aortic valve disease 1 (AOVD1)	*NOTCH1*	AD	1	1	2	2	1	1
Argininosuccinic aciduria	*ASL*	AR	2	3	3	4	1	1
Arterial tortuosity syndrome (ATS)	*SLC2A10*	AR	1	2	2	2	1	1
Arthrogryposis, distal, type 2a (DA2a)	*MYH3*	AD	1	2	2	2	1	1
Arthrogryposis, distal, type 2b (DA2b)	*TNNI2*	AD	1	2	1	1	0	0
Arthrogryposis, distal, type 2b (DA2b)	*TNNT3*	AD	1	3	2	3	2	1
Arthrogryposis, distal, type 9 (DA9)	*FBN2*	AD	1	2	2	2	2	2
Ataxia-telangiectasia (AT)	*ATM*	AD	5	12	7	8	6	5
Auriculocondylar syndrome 2 (ARCND2)	*PLCB4*	AR	1	1	0	0	0	0
Axenfeld–rieger syndrome, type 1 (RIEG1)	*PITX2*	AD	3	13	13	15	5	4
Bardet–Biedl syndrome 10 (BBS10)	*BBS10*	AR	1	2	3	4	1	1
Bardet–Biedl syndrome 2 (BBS2)	*BBS2*	AR	1	1	2	2	2	1
Bardet–Biedl syndrome 4 (BBS4)	*BBS4*	AR	1	1	2	2	1	1
Bartter syndrome, type 3 (BARTS3)	*CLCNKB*	AR	1	1	2	2	1	1
Basal cell nevus syndrome (BCNS) (Gorlin)	*PTCH1*	AD	6	7	6	10	4	4
Benign chronic pemphigus (BCPM)	*ATP2C1*	AD	1	1	1	1	1	0
Beta-ureidopropionase deficiency (UPB1D)	*UPB1*	AR	1	1	2	2	2	1
Biotinidase deficiency	*BTD*	AR	3	5	2	3	2	2
Birt–Hogg–Dube syndrome (BHD)	*FLCN*	AD	1	2	1	1	1	1
Bleeding disorder, platelet-type, 16 (BDPLT16)	*ITGB3*	AD	1	1	0	0	0	0
Blepharophimosis, ptosis, and epicanthus inversus (BPES)	*FOXL2*	AD	3	7	5	7	3	3
Blood group – Kell–Cellano system	*KEL*	AR	14	32	19	32	5	5
Brachydactyly, type B1 (BDB1)	*ROR2*	AD	1	3	2	4	2	2
Branchiooculofacial syndrome (BOFS)	*TFAP2A*	AD	1	1	1	2	0	0
Breast cancer	*PALB2*	AD	2	4	2	2	1	1
Breast–ovarian cancer, familial, susceptibility to, 1 (BROVCA1)	*BRCA1*	AD	93	175	128	183	89	83
Breast–ovarian cancer, familial, susceptibility to, 2 (BROVCA2)	*BRCA2*	AD	64	123	87	122	55	51
Campomelic dysplasia with autosomal sex reversal	*SOX9*	AD	1	1	0	0	0	0
Camurati–Engelmann disease (CAEND)	*TGFB1*	AD	1	1	1	1	0	0
Canavan disease	*ASPA*	AR	4	6	5	7	5	5
Carbamoyl phosphate synthetase i deficiency	*CPS1*	AR	1	1	1	2	0	0
Cardioencephalomyopathy, fatal infantile, due to cytochrome *c* oxidase deficiency 1	*SCO2*	AR	2	5	5	10	3	3
Cardiomyopathy, dilated, 1A (CMD1A)	*LMNA*	AR	7	17	16	25	10	8
Cardiomyopathy, dilated, 1DD (CMD1DD)	*RBM20*	AD	1	2	2	2	2	2

(Continued)

Table 2.1 (Continued)

Conditions	*Gene*	*Type of inheritance*	*No. patients*	*No. cycles*	*No. embryo transfers*	*No. embryos transferred*	*Pregnancy %*	*No. deliveries*
Cardiomyopathy, dilated, 1E (CMD1E)	*SCN5A*	AD	1	2	2	2	1	1
Cardiomyopathy, dilated, 1G (CMD1G)	*TTN*	AD	2	2	3	3	1	1
Cardiomyopathy, dilated, 1S (CMD1S)	*MYH7*	AD	3	6	4	4	2	2
Cardiomyopathy, dilated, with woolly hair, keratoderma, and tooth agenesis (DCWHKTA)	*DSP*	AD	2	3	2	3	2	1
Cardiomyopathy, familial hypertrophic, 2 (CMH2)	*TNNT2*	AD	1	2	1	1	1	0
Cardiomyopathy, familial hypertrophic, 4 (CMH4)	*MYBPC3*	AD	14	22	16	23	11	9
Cardiomyopathy, familial hypertrophic, 7 (CMH7)	*TNNI3*	AD	1	1	1	1	0	0
Cardiomyopathy, familial hypertrophic, 8 (CMH8)	*MYL3*	AD	1	2	0	0	0	0
Carnitine deficiency, systemic primary (CDSP)	*SLC22A5*	AR	1	2	1	2	1	1
Carnitine palmitoyltransferase II deficiency, infantile	*CPT2*	AR	4	7	4	4	2	2
Cerebral arteriopathy, autosomal dominant	*NOTCH3*	AD	3	7	6	6	6	4
Cerebral creatine deficiency syndrome 1 (CCDS1)	*SLC6A8*	XL	1	1	1	2	1	1
Ceroid lipofuscinosis, neuronal 2, late infantile (CLN2)	*TPP1*	AR	2	3	2	2	2	1
Ceroid lipofuscinosis, neuronal, 10 (CLN10)	*CTSD*	AR	1	1	2	3	1	1
Ceroid lipofuscinosis, neuronal, 5 (CLN5)	*CLN5*	AR	1	1	2	3	0	0
Ceroid lipofuscinosis, neuronal, 6 (CLN6)	*CLN6*	AR	2	2	1	2	0	0
Charcot–Marie–Tooth disease, axonal, type 2A2 (CMT2A2)	*MFN2*	AD	2	9	6	7	2	2
Charcot–Marie–Tooth disease, axonal, type 2B (CMT2B)	*RAB7A*	AD	1	1	2	4	2	1
Charcot–Marie–Tooth disease, axonal, type 2E (CMT2E)	*NEFL*	AD	1	4	4	7	1	1
Charcot–Marie–Tooth disease, axonal, type 2F (CMT2F)	*HSPB1*	AD	1	1	1	1	0	0
Charcot–Marie–Tooth disease, demyelinating, type 1A (CMT1A)	*PMP22*	AD	28	56	38	51	25	21
Charcot–Marie–Tooth disease, demyelinating, type 1B (CMT1B)	*MPZ*	AD	2	5	2	5	0	0
Charcot–Marie–Tooth disease, X-linked, 1 (CMTX1)	*GJB1*	XL	6	9	9	14	5	5
Cholestasis, benign recurrent intrahepatic, 2 (BRIC2)	*ABCB11*	AR	1	2	2	4	1	1
Cholestasis, progressive familial intrahepatic, 3 (PFIC3)	*ABCB4*	AR	1	1	1	2	1	1
Chondrodysplasia punctata 1, X-linked recessive (CDPX1)	*ARSE*	XL	1	2	2	3	0	0
Choroideremia (CHM)	*CHM*	XL	3	5	5	9	3	3
Ciliary dyskinesia, primary, 15 (CILD15)	*CCDC40*	AR	1	1	1	1	1	1
Ciliary dyskinesia, primary, 3 (CILD3)	*DNAH5*	AR	2	2	1	2	1	1
Citrullinemia, classic	*ASS1*	AR	4	7	6	8	3	3

Cleidocranial dysplasia (CCD)	*RUNX2*	AD	1	3	5	5	2	2
Cockayne syndrome A (CSA)	*ERCC8*	AR	1	1	2	2	1	1
Coenzyme Q10 deficiency, primary, 7 (COQ10D7)	*COQ4*	AR	1	1	1	1	1	1
Cohen syndrome (COH1)	*VPS13B*	AR	2	2	2	4	2	2
Colorectal cancer, hereditary nonpolyposis, type 1 (HNPCC1)	*MSH2*	AD	11	21	14	17	7	6
Colorectal cancer, hereditary nonpolyposis, type 2 (HNPCC2)	*MLH1*	AD	10	18	15	25	9	9
Colorectal cancer, hereditary nonpolyposis, type 4 (HNPCC4)	*PMS2*	AD	1	2	1	1	0	0
Colorectal cancer, hereditary nonpolyposis, type 5 (HNPCC5)	*MSH6*	AD	5	10	8	11	5	5
Combined oxidative phosphorylation deficiency 13 (COXPD13)	*PNPT1*	AR	1	1	3	5	0	0
Cone–rod dystrophy 6 (CORD6)	*GUCY2D*	AD	1	1	1	0	0	0
Congenital disorder of deglycosylation (CDDG)	*NGLY1*	AR	1	1	2	2	1	1
Congenital disorder of glycosylation, type Ia (CDG1A)	*PMM2*	AR	5	5	4	4	3	3
Congenital disorder of glycosylation, type IIc (CDG2C)	*SLC35C1*	AR	1	1	2	3	0	0
Congenital disorder of glycosylation, type IIL (CDG2L)	*COG6*	AR	1	2	2	2	0	0
Congenital disorder of glycosylation, type In (CDG1N)	*RFT1*	AR	2	2	2	4	1	1
Cranioectodermal dysplasia 2 (CED2)	*WDR35*	AR	1	1	1	1	1	1
Craniofrontonasal syndrome (CFNS)	*EFNB1*	XL	1	1	1	1	0	0
Creutzfeldt–Jakob disease (CJD); Gerstmann–Straussler disease (GSD)	*PRNP*	AD	6	9	9	12	8	7
Crouzon syndrome	*FGFR2*	AD	8	16	14	23	9	8
Currarino syndrome	*MNX1*	AD	1	1	1	2	1	1
Cutis laxa, autosomal dominant 1 (ADCL1)	*ELN*	AD	1	4	3	4	2	2
Cutis laxa, autosomal recessive, type IIB (ARCL2B)	*PYCR1*	AR	1	1	2	2	1	1
Cutis laxa, autosomal recessive, type IIIA (ARCL3A)	*ALDH18A1*	AR	1	1	1	1	1	1
Cystic fibrosis (CF)	*CFTR*	AR	496	748	627	1072	354	314
Cystinosis, nephropathic (CTNS)	*CTNS*	AR	1	1	1	1	0	0
Danon disease	*LAMP2*	XL	1	2	2	2	2	2
Darier–White disease (DAR)	*ATP2A2*	AD	1	1	1	1	1	1
D-bifunctional protein deficiency	*H5D17B4*	AR	1	1	1	1	0	0
Deafness, autosomal dominant 3b (DFNA3b)	*GJB6*	AD	1	2	2	3	1	1
Deafness, neurosensory, autosomal recessive 1 (DFNB1)	*GJB2*	AR	51	68	56	80	33	30
Dentinogenesis imperfecta, shields type III	*DSPP*	AD	1	2	2	2	2	1
Developmental delay	*DHX35*	AR	1	1	2	2	1	1
Diabetes insipidus, nephrogenic, X-linked	*AVPR2*	XL	1	3	3	3	1	1
Diabetes mellitus, permanent neonatal (PNDM)	*INS*	AD	1	1	1	1	1	1

(Continued)

Table 2.1 (Continued)

Conditions	*Gene*	*Type of inheritance*	*No. patients*	*No. cycles*	*No. embryo transfers*	*No. embryos transferred*	*Pregnancy %*	*No. deliveries*
Diamond–Blackfan anemia 1 (DBA1)	*RPS19*	AD	1	1	1	2	1	1
Digeorge syndrome (DGS)	*TBX1*	AD	1	1	1	1	1	1
Dihydrolipoamide dehydrogenase deficiency (DLDD)	*DLD*	AR	1	1	1	1	1	1
Donnai–Barrow syndrome	*LRP2*	AR	1	1	0	0	0	0
Dyskeratosis congenita, autosomal dominant 3 (DKCA3)	*TINF2*	AD	1	2	2	3	1	1
Dyskeratosis congenita, autosomal dominant 2 (DKCA2)	*TERT*	AD	1	3	1	1	0	0
Dyskeratosis congenita, autosomal recessive 5 (DKCB5)	*RTEL1*	AR	1	1	2	2	1	1
Dyskeratosis congenita, X-linked (DKCX)	*DKC1*	XL	1	1	1	2	1	1
Dyskinesia, seizures, and intellectual developmental disorder (DYSEIDD)	*DEAF1*	AR	1	1	1	1	0	0
Dystonia 1, torsion, autosomal dominant (DYT1)	*TOR1A*	AD	16	36	35	63	18	18
Dystonia 28, childhood-onset (DYT28)	*KMT2B*	AD	1	1	1	1	0	0
Dystonia 3, torsion, X-linked (DYT3)	*TAF1*	XL	1	1	1	2	1	1
Ectodermal dysplasia 10b, hypohidrotic/hair/tooth type, autosomal recessive (ECTD10B)	*EDAR*	AR	1	1	1	2	1	1
Ectodermal dysplasia, hypohidrotic, X-linked (XHED)	*EDA*	XL	6	8	8	10	4	4
Ehlers–Danlos syndrome, classic type	*COL5A1*	AD	2	4	3	4	3	2
Ehlers–Danlos syndrome, type IV, autosomal dominant	*COL3A1*	AD	4	6	4	7	4	3
Ehlers–Danlos syndrome, type VI (EDS6)	*PLOD1*	AR	1	1	2	3	0	0
Emery–Dreifuss muscular dystrophy 1, X-linked (EDMD1)	*EMD*	XL	3	4	4	7	3	3
Epidermolysis bullosa dystrophica, autosomal dominant (DDEB)	*COL7A1*	AR	8	9	8	13	4	4
Epidermolysis bullosa simplex with pyloric atresia (EBSPA)	*PLEC1*	AR	1	2	1	3	1	1
Epidermolysis bullosa simplex, dowling-meara type (EBSDM)	*KRT5*	AD	1	2	1	2	1	1
Epidermolysis bullosa, junctional, Herlitz type	*LAMA3*	AR	4	9	7	13	7	7
Epidermolysis bullosa, junctional, non-herlitz type	*LAMB3*	AR	5	6	5	9	2	2
Epidermolytic hyperkeratosis (EHK)	*KRT10*	AD	2	3	2	2	2	2
Epileptic encephalopathy, early infantile, 2 (EIEE2)	*CDKL5*	XL	1	1	1	2	1	1
Epileptic encephalopathy, early infantile, 3 (EIEE3)	*SLC25A22*	AR	1	1	0	0	0	0
Epileptic encephalopathy, early infantile, 5 (EIEE5)	*SPTAN1*	AR	1	1	0	0	0	0
Epiphyseal dysplasia, multiple, 1 (EDM1)	*COMP*	AD	3	4	2	2	1	1
Exostoses, multiple, type I	*EXT1*	AD	11	21	17	29	12	10
Exostoses, multiple, type II	*EXT2*	AD	3	8	6	10	3	3
Fabry disease	*GLA*	XL	12	19	14	22	9	7

Facioscapulohumeral muscular dystrophy 1 (FSHD1)	*FRG1*	AD	25	51	42	71	23	20
Factor VII deficiency	*F7*	AR	1	1	1	1	0	0
Familial adenomatous polyposis 1 (FAP1)	*APC*	AD	23	44	36	57	17	15
Familial cold autoinflammatory syndrome 1 (FCAS1)	*NLPR3*	AD	1	1	1	1	1	1
Familial Mediterranean fever (FMF)	*MEFV*	AR	10	18	16	22	11	8
Fanconi anemia, complementation group A (FANCA)	*FANCA*	AR	2	5	2	3	2	2
Fanconi anemia, complementation group C (FANCC)	*FANCC*	AR	2	5	4	8	1	1
Fetal akinesia deformation sequence (FADS)	*NUP88*	AR	1	1	1	2	1	1
Fetal akinesia deformation sequence (FADS)	*RAPSN*	AR	1	1	1	2	1	0
Fragile-X mental retardation syndrome	*FMR1*	XL	312	608	450	662	243	214
Fraser syndrome 1 (FRASRS1)	*FRAS1*	AR	2	2	2	2	1	1
Friedreich ataxia 1 (FRDA)	*FXN*	AR	2	6	4	7	2	2
Frontotemporal dementia and/or amyotrophic lateral sclerosis 1 (FTDALS1)	*c9orf72*	AD	1	1	1	1	1	1
Fructose intolerance, hereditary	*ALDOB*	AR	2	7	6	7	3	3
Fumarase deficiency (FMRD)	*FH*	AR	1	1	0	0	0	0
Galactosemia	*GALT*	AR	3	7	5	6	2	2
Gastric cancer, hereditary diffuse (HDGC)	*CDH1*	AD	1	1	1	2	1	1
Gaucher disease, type I	*GBA*	XL	39	52	34	57	24	19
Geroderma osteodysplasticum (GO)	*GORAB*	AR	1	2	2	4	1	1
Gitelman syndrome (GTLMNS)	*SLC12A3*	AR	1	1	1	1	0	0
Glaucoma 3, primary congenital, A (GLC3A)	*CYP1B1*	AR	1	1	2	2	1	1
Glut1 deficiency syndrome 1 (GLUT1DS1)	*SLC2A1*	AD	1	2	1	2	0	0
Glutaric acidemia I	*GCDH*	AR	1	1	1	2	0	0
Glycine encephalopathy (GCE)	*GLDC*	AR	6	7	6	11	6	6
Glycogen storage disease Ia (GSD1A)	*G6PC*	AR	1	1	2	2	0	0
Glycogen storage disease II (GSD2)	*GAA*	AR	5	7	4	9	1	1
Glycogen storage disease IXa1 (GSD9A1)	*PHKA2*	XL	1	1	0	0	0	0
Glycogen storage disease VII (GSD7)	*PFKM*	AR	1	1	1	1	1	1
Gm1-gangliosidosis, type I	*GLB1*	AR	5	5	5	10	4	4
Granulomatous disease, chronic, X-linked (CDGX)	*CYBB*	XL	4	5	4	6	3	2
Greig cephalopolysyndactyly syndrome (GCPS)	*GLI3*	AD	1	1	2	2	0	0
Harel–Yoon syndrome (HAYOS)	*ATAD3A*	AR	1	3	3	3	1	1
Hemoglobin-alpha locus 1 (HBA1)	*HBA*	AR	14	23	21	38	10	10
Hemoglobin-beta locus (HBB)	*HBB*	AR	301	470	402	762	192	161
Hemophagocytic lymphohistiocytosis, familial, 2 (FHL2)	*PRF1*	AR	1	1	0	0	0	0

(Continued)

Table 2.1 (Continued)

Conditions	*Gene*	*Type of inheritance*	*No. patients*	*No. cycles*	*No. embryo transfers*	*No. embryos transferred*	*Pregnancy %*	*No. deliveries*
Hemophagocytic lymphohistiocytosis, familial, 3 (FHL3)	*UNC13D*	AR	3	4	4	5	4	3
Hemophilia A (HEMA)	*F8*	XL	62	103	88	145	50	42
Hemophilia B (HEMB)	*F9*	XL	5	6	6	9	6	6
Hereditary leiomyomatosis and renal cell cancer (HLRCC)	*FH*	AD	1	1	1	2	0	0
Hereditary motor and sensory neuropathy, type IIC (HMSN2C)	*TRPV4*	AD	1	1	2	2	1	1
Hermansky–Pudlak syndrome 1 (HPS1)	*HPS1*	AR	1	4	3	6	2	2
HLA + myelodysplastic syndrome (MDS)	*GATA2*	AD	1	2	1	1	1	1
HLA + Shwachman–Diamond syndrome (SDS)	*SBDS*	AR	4	10	3	4	2	2
HLA + adenosine deaminase deficiency (ADA)	*ADA*	AR	1	1	1	1	1	1
HLA + adrenoleukodystrophy	*ABCD1*	XL	3	7	2	2	1	1
HLA + Diamond–Blackfan anemia 1 (DBA1)	*RPS19,*	AD	6	13	10	15	5	5
HLA + Diamond–Blackfan anemia 2 (DBA2)	*RPS20*	AD	1	1	1	1	1	1
HLA + Diamond–Blackfan anemia 3 (DBA3)	*RPS 24*	AD	1	1	1	1	0	0
HLA + Diamond–Blackfan anemia 5 (DBA5)	*RPL35A*	AD	1	1	1	1	1	1
HLA + Diamond–Blackfan anemia 9 (DBA9)	*RPS10*	AD	1	1	2	2	1	1
HLA + ectodermal dysplasia, hypohidrotic, with immune deficiency	*IKBKG*	XL	2	9	6	8	2	2
HLA + Fanconi anemia, complementation group A (FANCA)	*FANCA*	AR	18	52	29	43	14	10
HLA + Fanconi anemia, complementation group C (FANCC)	*FANCC*	AR	2	5	5	8	1	1
HLA + Fanconi anemia, complementation group D2 (FANCD2)	*FANCD2*	AR	1	3	2	3	1	1
HLA + Fanconi anemia, complementation group F (FANCF)	*FANCF*	AR	2	5	2	3	0	0
HLA + Fanconi anemia, complementation group G (FANCG)	*FANCG*	AR	2	2	2	3	2	2
HLA + Fanconi anemia, complementation group I (FANCI)	*FANCI*	AR	1	2	2	3	0	0
HLA + Fanconi anemia, complementation group J (FANCJ)	*BRIP1*	AR	1	1	1	1	1	1
HLA + Fanconi anemia, complementation group JI (FANCJ)	*BRIP1*	AR	1	3	1	3	0	0
HLA + Glanzmann thrombasthenia (GT, +DMD)	*ITGA2B DMD*		1	2	2	4	1	0
HLA + granulomatous disease, chronic, autosomal recessive, cytochrome b-positive, type I (CDG1)	*NCF1*	AR	1	3	2	2	1	1
HLA + granulomatous disease, chronic, X-linked (CDGX)	*CYBB*	XL	6	16	13	17	7	6
HLA + hemoglobin-beta locus (HBB)	*HBB*	AR	92	188	119	177	41	31
HLA + hyper-IgE recurrent infection syndrome, autosomal recessive	*DOCK8*	AR	1	1	0	0	0	0
HLA + Krabbe disease	*GALC*	AR	1	1	1	2	1	1
HLA + myotonic dystrophy 1 (DM1)	*DMPK*	AD	1	2	1	2	1	1
HLA + neutropenia, severe congenital, 1, autosomal dominant (SCN1)	*ELANE*	AD	2	3	2	5	2	1

HLA + polycystic kidney disease 1 (PKD1)	*PKD1*	AD	1	1	1	2	1	1
HLA + sickle cell anemia	*HBB*	AR	18	29	18	27	12	8
HLA + thrombocythemia 1 (THCYT1)	*SH2B3*	AR	1	2	2	2	2	1
HLA + thrombotic thrombocytopenic purpura, congenital (TTP)	*ADAMTS13*	AR	1	2	2	4	1	1
HLA + Wiskott–Aldrich syndrome (WAS)	*WAS*	XL	1	1	0	0	0	0
HLA immunodeficiency with hyper-IgM, type 1 (HIGM1)	*CD40LG*	XL	8	15	9	13	5	4
HLA + pyruvate kinase deficiency of red cells	*PKLR*	AD	1	2	1	1	0	0
Holoprosencephaly 2 (HPE2)	*SIX3*	AD	1	1	1	2	0	0
Holt–Oram syndrome (HOS)	*TBX5*	AD	5	8	8	9	4	4
Homocystinuria due to cystathionine beta-synthase deficiency	*CBS*	AR	4	6	4	9	3	3
Homocystinuria due to deficiency of *n*(5,10)-methylenetetra-hydrofolate reductase activity	*MTHFR*	AR	1	1	1	2	0	0
Homocystinuria-megaloblastic anemia, cblG complementation type (HMAG)	*MTR*	AR	1	2	1	1	0	0
Human leukocyte antigens	*HLA*	AR	60	119	73	108	25	20
Huntington disease (HD)	*HTT*	AD	141	209	171	267	107	97
Hurler syndrome	*IDUA*	AR	7	10	8	13	3	3
Hyaline fibromatosis syndrome (HFS)	*ANTXR2*	AR	1	1	1	2	1	1
Hydrocephalus due to congenital stenosis of aqueduct of Sylvius (HSAS)	*L1CAM*	XL	11	16	16	34	8	6
Hydroxyacyl-CoA dehydrogenase/3-ketoacyl-CoA thiolase/enoyl-CoA hydratase, alpha subunit (HADHA)	*HADHA*	AR	4	4	4	13	3	3
Hyperinsulinemic hypoglycemia, familial, 1 (HHF1)	*ABCC8*	AR	2	11	8	19	4	2
Hyperuricemic nephropathy, familial juvenile, 1 (HNFJ1)	*UMOD*	AD	1	1	1	1	0	0
Hypogonadotropic hypogonadism 1 with or without anosmia (HH1)	*ANOS1*	XL	1	1	2	2	0	0
Hypogonadotropic hypogonadism 1 with or without anosmia (HH1)	*KAL1*	XL	1	2	1	1	1	1
Hypoparathyroidism–retardation–dysmorphism syndrome (HRDS)	*TBCE*	1R	1	1	1	2	0	0
Hypophosphatasia, infantile	*ALPL*	AR	6	7	6	9	4	4
Ichthyosis, congenital, autosomal recessive 1 (ARCI1)	*TGM1*	AD	2	9	7	10	1	1
Ichthyosis, lamellar, 2 (LI2)	*ABCA12*	AR	2	2	1	2	0	0
Ichthyosis, spastic quadriplegia, and mental retardation (ISQMR)	*ELOVL4*	AR	1	1	1	1	0	0
Ichthyosis, X-linked (XLI)	*STS*	XL	2	3	3	4	1	1
Ifap syndrome with or without Bresheck syndrome	*MBTPS2*	XL	2	3	2	5	2	1
Immunodeficiency with hyper-IgM, type 1 (HIGM1)	*CD40LG*	XL	4	14	14	22	6	6
Immunodysregulation, polyendocrinopathy, and enteropathy, X-linked (IPEX)	*FOXP3*	XL	2	3	3	3	1	1
Incontinentia pigmenti (IP)	*IKBKG*	XL	15	35	28	43	11	11

(Continued)

Table 2.1 (Continued)

Conditions	*Gene*	*Type of inheritance*	*No. patients*	*No. cycles*	*No. embryo transfers*	*No. embryos transferred*	*Pregnancy %*	*No. deliveries*
Infantile cerebellar-retinal degeneration (ICRD)	*ACO2*	AR	1	1	1	2	2	2
Infantile liver failure syndrome 1 (ILFS1)	*LARS*	AR	1	1	2	2	1	1
Isovaleric acidemia (IVA)	*IVD*	AR	1	1	1	2	0	0
Joubert syndrome 1 (JBTS1)	*INPP5E*	AR	1	1	2	2	1	1
Joubert syndrome 17 (JBTS17)	*CPLANE1*	AD	1	1	1	2	1	1
Joubert syndrome 2 (JBTS2)	*TMEM216*	AR	1	1	2	2	1	1
Joubert syndrome 21 (JBTS21)	*CSPP1*	AR	2	5	4	7	1	1
Joubert syndrome 23 (JBTS23)	*KIAA0586*	AR	1	1	1	2	1	1
Joubert syndrome 3 (JBTS3)	*AHI1*	AR	1	1	0	0	0	0
Joubert syndrome 6 (JBTS6)	*TMEM67*	AR	2	3	2	2	2	2
Krabbe disease	*GALC*	AR	11	12	11	19	7	5
Larsen syndrome (LRS)	*FLNB*	AD	2	2	1	1	1	1
Leber congenital amaurosis 2 (LCA2)	*RPE65*	AR	1	1	0	0	0	0
Leigh syndrome (LS)	*NDUFS8*	AR	1	1	0	0	0	0
Leigh syndrome (LS)	*SURF1*	AR	1	1	1	3	0	0
Lesch–Nyhan syndrome (LNS)	*HPRT1*	XL	1	4	3	3	2	2
Leukoencephalopathy with vanishing white matter (VWM)	*EIF2B2*	AR	1	1	1	2	1	0
Li–Fraumeni syndrome 1 (LFS1)	*TP53*	AD	16	22	17	24	13	11
Lipoid congenital adrenal hyperplasia (LCAH)	*STAR*	AR	1	2	2	3	1	1
Lissencephaly, X-linked, 2 (LISX2)	*ARX*	XL	1	1	1	2	0	0
Loeys–Dietz syndrome 1 (LDS1)	*TGFBR2*	AD	2	5	4	6	2	1
Long QT syndrome 1 (LQT1)	*KCNQ1*	AD	4	5	2	2	2	2
Long QT syndrome 2 (LQT2)	*KCNH2*	AD	3	3	2	2	1	1
Long QT syndrome 8 (LQT8)	*CACNA1C*	AD	1	1	1	1	1	1
Lymphedema, hereditary, III (LMPH3)	*PIEZO1*	AR	1	1	0	0	0	0
Lymphoproliferative syndrome, X-linked, 1 (XLP1)	*SH2D1A*	XL	1	1	2	3	2	2
Lysosomal acid lipase deficiency	*LIPA*	AR	2	2	2	4	2	2
Machado–Joseph disease (MJD)	*ATXN3*	AD	4	7	6	8	6	6
Macular dystrophy, vitelliform, 2 (VMD2)	*BEST1*	AD	1	1	1	1	1	1
Maple syrup urine disease (MSUD)	*BCKDHB*	AR	1	2	2	2	1	1
Marfan syndrome (MFS)	*FBN1*	AD	30	58	46	78	27	21
Marinesco–Sjogren syndrome (MSS)	*SIL1*	AR	1	3	3	5	1	1

Meckel syndrome, type 1 (MKS1)	*MKS1*	AR	2	5	5	9	2	2
Meckel syndrome, type 4 (MKS4)	*CEP290*		4	6	6	10	4	4
Meckel syndrome, type 6 (MKS6)	*CC2D2A*	AR	2	5	5	9	2	2
Meckel syndrome, type 6 (MKS6)	*CC2DA2*	AR	1	1	1	2	1	1
Meckel syndrome, type 8 (MKS8)	*TCTN2*	AR	1	1	2	2	1	1
Mental retardation, autosomal dominant 35 (MRD35)	*PPP2R5*	AD	1	1	2	2	1	1
Mental retardation, autosomal recessive 38 (MRT38)	*HERC2*	AR	1	2	2	3	1	1
Metachromatic leukodystrophy due to saposin B deficiency	*PSAP*	AR	1	1	0	0	0	0
Metachromatic leukodystrophy (MLD)	*ARSA*	AR	3	4	3	4	4	2
Metaphyseal chondrodysplasia, Schmid type (MCDS)	*COL10A1*	AD	2	7	3	4	2	2
Methylmalonic aciduria and homocystinuria, cblC type	*MMACHC*	AR	3	6	6	11	5	5
Methylmalonic aciduria due to methylmalonyl-CoA mutase deficiency	*MUT*	AR	2	4	4	4	2	2
Methylmalonic aciduria, cblB type	*MMAB*	AR	3	3	2	3	1	1
Microcephalic osteodysplastic primordial dwarfism, type I (MOPD1)	*RNU4ATAC*	AR	1	1	1	1	1	1
Microcephaly 2, primary, autosomal recessive (MCPH2)	*WDR62*	AR	1	1	1	1	0	0
Microcephaly 5, primary, autosomal recessive (MCPH5)	*ASPM*	AR	2	3	2	3	2	2
Microcephaly 6, primary, MCPH6)	*CENPJ*	AR	1	2	2	2	1	1
Microphthalmia, isolated, with coloboma 3 (MCOPCB3)	*VSX2*	AR	2	2	1	1	1	1
Midface hypoplasia, hearing impairment, elliptocytosis, and nephrocalcinosis (MFHIEN)	*AMMECR1*	XL	2	8	6	9	2	2
Migraine, familial hemiplegic, 1 (FHM1)	*CACNA1A*	AD	1	1	1	2	1	1
Mitochondrial complex i deficiency due to acad 9 deficiency	*ACAD9*	AR	1	1	1	2	1	1
Mitochondrial DNA depletion syndrome 13	*FBXL4*	AD	1	1	3	4	1	1
Mitochondrial DNA depletion syndrome 4a (Alpers type) (MTDPS4A)	*POLG*	AR	3	5	5	5	4	4
Molybdenum cofactor deficiency, complementation group B (MOCODB)	*MOCS2*	AR	1	1	3	4	0	0
Mosaic variegated aneuploidy syndrome 1 (MVA1)	*BUB1B*	AR	1	1	1	2	1	0
Mucolipidosis II alpha/beta	*GNPTAB*	AR	2	3	2	2	2	2
Mucopolysaccharidosis, type II (MPS2)	*IDS*	XL	9	20	15	29	10	6
Mucopolysaccharidosis, type IIIA (MPS3A)	*SGSH*	AR	2	2	2	3	0	0
Mucopolysaccharidosis, type IVA (MPS4A)	*GALNS*	AR	1	4	4	12	2	2
Multinucleated neurons, anhydramnios, renal dysplasia, cerebellar hypoplasia	*CEP55*	AR	1	1	1	2	1	1
Multiple congenital anomalies–hypotonia–seizures syndrome 2 (MCAHS2)	*PIGA*	XL	1	1	0	0	0	0
Multiple endocrine neoplasia, type I (MEN1)	*MEN1*	AD	8	21	16	23	7	4
Multiple endocrine neoplasia, type IIA (MEN2A)	*RET*	AD	6	11	11	17	8	8
Multiple endocrine neoplasia, type IV (MEN4)	*CDKN1B*	AD	1	3	1	1	1	1

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Table 2.1 (Continued)

Conditions	*Gene*	*Type of inheritance*	*No. patients*	*No. cycles*	*No. embryo transfers*	*No. embryos transferred*	*Pregnancy %*	*No. deliveries*
Muscular dystrophy, congenital merosin-deficient, 1A (MDC1A)	*LAMA2*	AR	6	7	7	14	7	6
Muscular dystrophy, Duchenne type (DMD)	*DMD*	XL	69	115	103	169	57	48
Muscular dystrophy, limb-girdle, type 2A (LGMD2A)	*CAPN3*	AR	1	1	0	0	0	0
Muscular dystrophy, limb-girdle, type 2S (LGMD2S)	*TRAPPC11*	AR	1	1	2	2	2	2
Muscular dystrophy–dystroglycanopathy (congenital with brain and eye anomalies), type A, 5 (MDDGA5)	*FKRP*	AR	1	3	3	3	1	1
Muscular dystrophy–dystroglycanopathy (congenital with brain and eye anomalies), type A, 4 (MDDGA4)	*FKTN*	AR	2	2	2	3	2	2
Myoglobinuria, acute recurrent, autosomal recessive	*LPIN1*	AR	1	1	1	1	1	1
Myopathy, areflexia, respiratory distress, and dysphagia, early-onset (EMARDD)	*MEGF10*	AR	1	1	1	1	1	1
Myopathy, centronuclear, X-linked (CNMX)	*MTM1*	XL	5	6	4	6	4	4
Myopathy, myofibrillar, 1 (MFM1)	*DES*	AD	1	1	1	1	1	1
Myotonia congenita, autosomal dominant	*CLCN1*	AD	1	1	1	2	1	1
Myotonic dystrophy 1 (DM1)	*DMPK*	AD	94	147	107	188	55	46
Myotonic dystrophy 2 (DM2)	*CNBP*	AD	1	2	2	4	2	2
Nail–patella syndrome (NPS)	*LMX1B*	AD	3	4	3	4	1	1
Nemaline myopathy 2 (NEM2)	*NEB*	AR	6	6	6	10	3	3
Nephrotic syndrome, type 1 (NPHS1)	*NPHS1*	AR	1	3	3	7	1	0
Nephrotic syndrome, type 2 (NPHS2)	*NPHS2*	AR	1	1	1	1	1	1
Nephrotic syndrome, type 5	*LAMB2*	AR	1	2	2	4	2	1
Neurofibromatosis, type I (NF1)	*NF1*	AD	51	90	80	123	46	41
Neurofibromatosis, type II (NF2)	*NF2*	AD	7	10	9	17	7	7
Neuropathy, hereditary sensory and autonomic, type III (HSAN3)	*IKBKAP*	AR	13	19	17	28	9	9
Neuropathy, hereditary sensory and autonomic, type VI (HSAN6)	*DST*	AD	1	2	2	2	2	2
Neutropenia, severe congenital, 1, autosomal dominant (SCN1)	*ELANE*	AD	1	1	1	1	1	1
Niemann–Pick disease, type A	*SMPD1*	AR	3	5	3	6	2	2
Nijmegen breakage syndrome (NBS)	*NBN*	AR	1	1	2	2	1	1
Noonan syndrome 1 (NS1)	*PTPN11*	AD	5	7	7	9	4	3
Norrie disease (ND)	*NDP*	XL	5	8	6	12	2	2
Omenn syndrome	*RAG1*	AD	2	6	5	12	1	1
Optic atrophy 1 (OPA1)	*OPA1*	AD	3	5	5	9	1	1
Ornithine transcarbamylase deficiency	*OTC*	XL	11	24	19	32	11	10

Osteogenesis imperfecta, type I (OI1)	*COL1A1*	AD	24	61	44	72	17	17
Osteogenesis imperfecta, type II (OI2)	*COL1A2*	AD	5	5	5	5	3	2
Osteogenesis imperfecta, type IX (OI9)	*PPIB*	AR	1	2	2	4	2	2
Osteopathia striata with cranial sclerosis (OSCS)	*AMER1*	XL	1	1	1	1	1	1
Osteopetrosis, autosomal recessive 1 (OPTB1)	*TCIRG1*	AR	5	7	7	13	3	3
Pachyonychia congenita 3 (PC3)	*KRT6A*	AD	1	2	2	2	2	1
Pancreatitis, hereditary (PCTT)	*PRSS1*	AD	1	1	1	2	1	1
Paraganglioma and gastric stromal sarcoma	*SDHB*	AD	1	1	0	0	0	0
Paramyotonia congenita of von Eulenburg (PMC)	*SCN4A*	AD	3	3	3	4	3	2
Pelizaeus–Merzbacher disease (PMD)	*PLP1*	XL	7	12	10	15	7	7
Periventricular nodular heterotopia 1 (PVNH1)	*FLNA*	XL	1	3	3	5	2	1
Peroxisome biogenesis disorder 1A (Zellweger) (PBD1A)	*PEX1*	AR	3	3	3	6	3	3
Peroxisome biogenesis disorder 2A (Zellweger) (PBD2A)	*PEX5*	AR	1	2	2	4	0	0
Peroxisome biogenesis disorder 3A (Zellweger) (PBD3A)	*PEX12*	AR	1	3	3	4	2	1
Peroxisome biogenesis disorder 5A (Zellweger) (PBD5A)	*PEX2*	AR	1	4	3	5	2	2
Peutz–Jeghers syndrome (PJS)	*STK11*	AD	4	9	7	9	6	4
Pfeiffer syndrome	*FGFR1*	AD	2	2	2	4	2	2
Phenylketonuria (PKU)	*PAH*	AR	15	20	14	16	8	7
Platelet disorder, familial, with associated myeloid malignancy (FPDMM)	*RUNX1*	AD	1	1	1	1	1	1
Pleuropulmonary blastoma (PPB)	*DICER1*	AD	1	1	1	1	1	1
Polycystic kidney disease 1 (PKD1)	*PKD1*	AD	48	84	64	98	37	34
Polycystic kidney disease 2 (PKD2)	*PKD2*	AD	7	10	9	15	3	3
Polycystic kidney disease, autosomal recessive (ARPKD)	*PKHD1*	AR	16	29	26	42	17	16
Polymicrogyria, bilateral frontoparietal (BFPP)	*ADGRG1*	AR	2	2	1	2	1	1
Polymicrogyria, bilateral frontoparietal (BFPP)	*GPR56*	AR	1	1	1	2	0	0
Pontocerebellar hypoplasia, type 1B (PCH1B)	*EXOSC3*	AR	1	1	2	2	1	1
Popliteal pterygium syndrome (PPS)	*IRF6*	AD	2	2	1	2	1	1
Porphyria, congenital erythropoietic	*UROS*	AR	1	1	1	1	1	1
Propionic acidemia	*PCCA*, *PCCB*	AR	3	3	3	5	2	2
Prothrombin deficiency, congenital; Factor V deficiency	*F2 F5*	AR	2	3	3	3	2	2
Pseudovaginal perineoscrotal hypospadias (PPSH)	*SRD5A2*	AR	1	2	2	4	1	1
Rap guanine nucleotide exchange factor 6 (RAPGEF6)	*RAPGEF6*	AD	1	2	3	4	3	1
Renal cell carcinoma, papillary, 1 (RCCP1)	*MET*	AD	1	1	2	2	1	1
Renal tubular acidosis, distal, autosomal recessive (RTADR)	*ATP6V0A4*	AR	1	1	2	3	2	1
Renal tubular dysgenesis (RTD)	*ACE*	AR	1	4	3	4	2	2

(Continued)

Table 2.1 (Continued)

Conditions	*Gene*	*Type of inheritance*	*No. patients*	*No. cycles*	*No. embryo transfers*	*No. embryos transferred*	*Pregnancy %*	*No. deliveries*
Restrictive dermopathy, lethal	*ZMPSTE24*	AR	2	2	2	3	1	1
Retinal dystrophy, early-onset, with or without pituitary dysfunction, included	*OTX2*	AD	1	1	0	0	0	0
Retinitis pigmentosa 2 (RP2)	*RP2*	XL	1	1	1	2	1	1
Retinitis pigmentosa 3 (RP3)	*RPGR*	XL	5	6	6	8	4	3
Retinitis pigmentosa 4 (RP4)	*RHO*	AD	3	5	2	4	1	0
Retinoblastoma (RB1)	*RB1*	AD	17	31	26	43	14	13
Retinoschisis 1, X-linked, juvenile (RS1)	*RS1*	XL	1	2	1	2	1	0
Rett syndrome (RTT)	*MECP2*	XL	3	5	4	4	3	1
Rhabdoid tumor predisposition syndrome 1 (RTPS1)	*SMARCB1*	AD	1	1	1	1	0	0
Rhesus blood group, D antigen (RHD)	*RHD*	AD	7	9	9	16	6	6
Sandhoff disease	*HEXB*	AR	4	6	5	8	4	4
Seckel syndrome 1 (SCKL1)	*ATR*	AR	1	1	2	2	0	0
Severe combined immunodeficiency, autosomal recessive	*IL7R*	AR	1	1	2	4	1	1
Severe combined immunodeficiency, autosomal recessive	*RAG2*	AR	2	5	4	5	3	3
Severe combined immunodeficiency, X-linked (SCIDX1)	*IL2RG*	XL	3	4	3	3	2	2
Short stature, idiopathic, X-linked (ISS)	*SHOX*	XL	2	2	2	3	2	2
Short-rib thoracic dysplasia 3 with or without polydactyly (SRTD3)	*DYNC2H1*	AR	1	1	1	1	1	1
Smith–Lemli–Opitz syndrome (SLOS)	*DHCR7*	AR	18	30	23	32	15	15
Sonic hedgehog (SHH)	*SHH*	AD	1	2	2	3	1	1
Sotos syndrome 1 (SOTOS1)	*NSD1*	AD	2	3	2	2	2	2
Spastic paraplegia 3, autosomal dominant (SPG3A)	*ATL1*	AD	1	1	1	1	1	1
Spastic paraplegia 4, autosomal dominant (SPG4)	*SPAST*	AD	6	10	8	12	7	5
Spherocytosis, type 2 (SPH2)	*SPTB*	AD	1	1	2	2	2	1
Spinal and bulbar muscular atrophy, X-linked 1 (SMAX1)	*AR*	XL	3	5	5	6	2	1
Spinal muscular atrophy, distal, autosomal recessive, 1 (DSMA1)	*IGHMBP2*	AR	2	3	2	4	1	1
Spinal muscular atrophy, type I (SMA1)	*SMN1*	AR	102	151	125	199	78	69
Spinocerebellar ataxia 1 (SCA1)	*ATXN1*	AD	4	7	6	8	4	4
Spinocerebellar ataxia 2 (SCA2)	*ATXN2*	AD	7	14	14	27	6	8
Spinocerebellar ataxia 6 (SCA6)	*CACNA1A*	AD	2	5	2	3	1	1
Spinocerebellar ataxia 7 (SCA7)	*ATXN7*	AD	2	3	3	7	2	1
Spinocerebellar ataxia 8 (SCA8)	*ATXN80S*	AD	1	1	1	1	1	1

Spondyloepiphyseal dysplasia tarda, X-linked (SEDT)	*TRAPPC2*	AD	1	1	2	2	1	1
Stargardt disease 1 (STGD1)	*ABCA4*	AR	4	10	5	6	2	2
Stickler syndrome, type I (STL1)	*Col2A1*	AD	4	4	3	5	2	2
Stickler syndrome, type II (STL2)	*COL11A1*	AD	2	7	6	15	1	1
Stickler syndrome, type II (STL2)	*COL18A1*	AR	1	1	1	1	1	1
Succinic semialdehyde dehydrogenase deficiency (SSADHD)	*ALDH5A1*	AR	3	4	4	9	2	2
Sulfocysteinuria	*SUOX*	AR	1	1	2	2	1	1
Supranuclear palsy, progressive, 1 (PSNP1)	*MAPT*	AD	2	3	3	5	1	1
Surfactant metabolism dysfunction, pulmonary, 3 (SMDP3)	*ABCA3*	AR	1	2	2	4	1	1
Symphalangism, proximal (SYM1)	*NOG*	AD	1	3	3	7	2	2
Tay–Sachs disease (TSD)	*HEXA*	AR	25	46	29	52	19	17
Telangiectasia, hereditary hemorrhagic, of Rendu, Osler, and Weber (HHT)	*ENG*	AD	4	11	6	7	3	3
Telangiectasia, hereditary hemorrhagic, type 2 (HHT2)	*ACVRL1*	AD	4	8	7	8	4	4
Temtamy syndrome (TEMTYS)	*C12orf57*	AR	1	1	1	2	0	0
Thrombocytopenia-absent radius syndrome (TAR)	*RBM8A*	AR	4	6	5	7	4	4
Treacher Collins syndrome 1 (TCS1)	*TCOF1*	AD	6	8	8	14	7	7
Treacher Collins syndrome 2 (TCS2)	*POLR1D*	AD	1	1	1	1	0	0
Tuberous sclerosis 1 (TSC1)	*TSC1*	AD	20	30	27	52	16	14
Tuberous sclerosis 2 (TSC2)	*TSC2*	AD	8	14	10	14	5	4
Tyrosinemia, type I (TYRSN1)	*FAH*	AR	1	7	7	13	5	3
Ulnar–Mammary syndrome (UMS)	*TBX3*	AD	1	3	3	4	1	1
Usher syndrome, type I (USH1)	*MYO7A*	AD	1	3	2	2	1	1
Usher syndrome, type IF (USH1F)	*PCDH15*	AR	2	4	4	6	4	2
Usher syndrome, type IIA (USH2A)	*USH2A*	AR	3	4	5	6	2	2
Usher syndrome, type IIC (USH2C)	*ADGRV1*	AR	1	1	1	2	1	1
Usher syndrome, type IIC (USH2C)	*GPR98*	AR	1	1	0	0	0	0
Van der Woude syndrome 1 (VWS1)	*IRF6*	AD	3	3	3	3	3	3
Von Hippel–Lindau syndrome (VHL)	*VHL*	AD	19	25	21	30	15	14
Waardenburg syndrome, type 2A (WS2A)	*MITF*	AD	2	6	6	6	4	4
Wilson disease	*ATP7B*	AR	3	3	3	5	3	2
Wiskott–Aldrich syndrome (WAS)	*WAS*	XL	6	15	13	20	9	8
Wolfram syndrome 1 (WFS1)	*WFS1*	AR	1	2	1	1	1	1
Xeroderma pigmentosum, complementation group g (XPG)	*ERCC5*	AR	1	1	0	0	0	0
TOTAL			3463	5869	4683	7443	2644	2332
						1.59	56.4%	

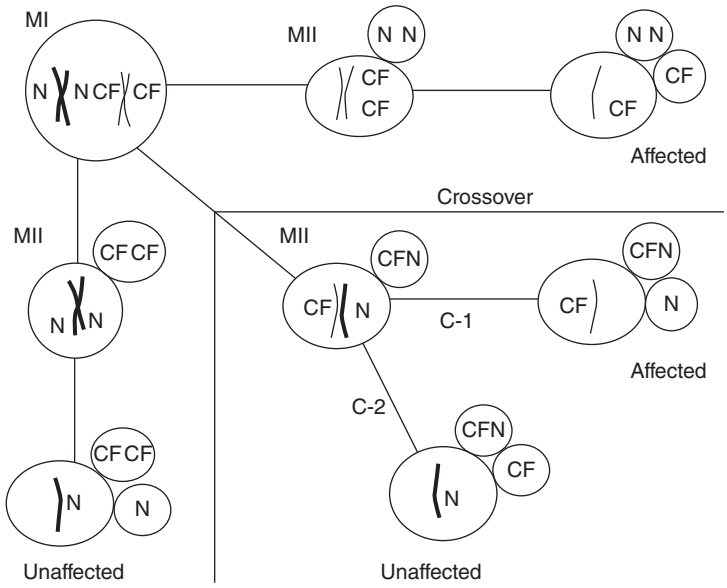

Figure 2.1 Scheme demonstrating the principle of preimplantation genetic analysis by sequential DNA analysis of the first and second polar body, using the cystic fibrosis (CF) locus as an example.
Source: Verlinsky Y, Kuliev AMA. Preimplantation genetic diagnosis. In: Milunsky A, Milunsky JM, eds. Genetic disorders and the fetus: diagnosis, prevention and treatment, 6th edn. Oxford, UK: John Wiley & Sons, 2010.

developmental potential of the resulting embryo, 343 biopsied and 445 nonbiopsied mouse embryos were compared for the percentage of embryos reaching the blastocyst stage.[36]

The results of PGT-M performed by polar body biopsy, representing the world's largest series, is shown in Table 2.2. A total of 1,016 PGT-M cycles were performed, for 538 autosomal recessive, 191 autosomal dominant, and 287 X-linked disorders. Of 1,016 cycles initiated, 838 (82.5 percent) resulted in transfer of 1,656 embryos (1.98 embryos per transfer on the average), 349 (41.6 percent) clinical pregnancies, and 385 babies born. Only two misdiagnoses were observed in the case of PGT for fragile-X syndrome and muscular dystrophy, which were due to consented transfer of additional embryo with insufficient marker analysis to exclude the probability of allele dropout (ADO) (see later). The example of PGT-M by polar body sampling is shown in Figure 2.2.

Table 2.2 Clinical outcome of PGT-M performed by polar body approach.

Conditions/mode of inheritance/ sampling type	*Patient*	*Cycles*	*Embryo transfer*	*No. embryos*	*Pregnancy*	*Spontaneous abortions*	*Baby*
Autosomal recessive							
Polar bodies	76	131	99	204	36	10	36
Polar bodies + blastomere/blastocyst	254	407	344	701	143	21	168
Subtotal	*330*	*538*	*443*	*905*	*179*	*31*	*204*
Autosomal dominant							
Polar bodies	29	52	40	84	22	4	21
Polar bodies + blastomere/blastocyst	79	139	122	233	49	7	61
Subtotal	*108*	*191*	*162*	*317*	*71*	*11*	*82*
X-linked							
Polar bodies	39	86	63	110	22	4	20
Polar bodies + blastomere/blastocyst	116	201	170	324	77	12	79
Subtotal	*155*	*287*	*233*	*434*	*99*	*16*	*99*
Total	593	1016	838	1656	349 (41.6%)	58 (17%)	385