Preventive management of children with congenital anomalies and syndromes

This unique source of reference and clinical guidance provides health professionals with an invaluable, structured approach to the preventive care of children with congenital anomalies. Over 120 disorders ranging from cerebral palsy to Down syndrome are discussed. For each disorder there is an introductory summary of key information, followed by more detailed listing of general pediatric and speciality concerns, all structured to provide an integrated approach to patient care. For 30 common disorders, preventive management checklists are provided: these checklists provide an ongoing record of the child’s medical complications and progress and they are designed to be copied or printed and placed in the medical record.

The text provides details of medical complications and preventive recommendations, supported by more than 500 references. The introductory chapters provide an overview of the approach to genetic/metabolic disease and developmental disabilities, and a useful glossary is also included.

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Preventive management of children with congenital anomalies and syndromes

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Suzanne LeBel Corrigan, M.D.

GNW

For my wife, Seddon Savage, who is, among other more important things, the best physician I know.

WCC
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Preface

How to use this book

This book is designed as a reference in which health professionals can access possible complications and design preventive management for common congenital anomalies or syndromes. Over 120 disorders are discussed, and 30 are described in detail with flow sheets that summarize preventive care considerations (see sample checklist). These preventive management checklists are intended for copying and placement in the medical record. By checking off the appropriate boxes as shown, the practitioner can assemble an ongoing record of screening, examination, and referral/counseling measures.

The standardized text entries for each disorder are organized by terminology, etiology, differential diagnosis, genetic/family counseling, complications, preventive management, validation of checklist guidelines, and, where available, specialized growth charts. Clinically oriented references are included to facilitate decisions about particular interventions. It is envisioned that most users will turn to the book with a specific disorder in mind and focus on the relevant management suggestions. A detailed table of contents and index are available for this purpose.

Another use of the book is to read more broadly about the approach to children with developmental disabilities and genetic disease. Because of rapid progress in the field of medical genetics, certain terms or concepts encountered in the chapters may be unfamiliar. For this reason, introductory chapters on the approach to genetic disease and developmental disabilities have been provided (Part I, Chapters 1 and 2). These sections review basic characteristics of the diseases and the specialized tests that are available for diagnosis. These facts allow pediatricians and family practitioners to be informed participants in the management of congenital disorders. A glossary is also appended to aid with specialized terminology. Other books include more extensive discussion of genetic/developmental principles and of particular birth defect/syndrome disorders (Jones, 1997; Gorlin et al., 1990).
xii Preface

Which disorders are included?

The more common congenital anomalies and syndromes were selected for detailed discussion, with emphasis on those requiring chronic management due to mental and physical disability. To qualify as a “more common” disorder, an estimated incidence above 1 in 25,000 births was required, since that number makes it probable that the disorder will come to the attention of the average pediatric practitioner. If the disorder is rarely encountered by practitioners or if there are limited strategies for preventive care, then the discussion is limited to a few paragraphs without the inclusion of a checklist. Sample, blank checklists are appended to this preface so that practitioners can tailor them for rarer disorders.

It should be noted that hydrocephalus and spina bifida are isolated anomalies rather than syndromes, and that cerebral palsy is a functional description of brain injury or developmental anomaly. However, their congenital origin and requirements for chronic management justify coverage in this book. It is expected that the developmental pediatrician will provide specialty expertise for the latter disorders, while the pediatric geneticist will be more actively involved with patients having malformation syndromes.

Some common metabolic disorders are also discussed in the book, although it is recommended that metabolic specialists be continuously involved in their care. The frequent laboratory measurements and dietary modifications required by acute metabolic disorders are not adequately conveyed by a checklist approach, but the occurrence of developmental disabilities in many of these children justifies attention to preventive management in other areas. Checklists are definitely useful for some chronic metabolic conditions, exemplified by the mucopolysaccharidoses discussed in Chapter 19.

Rationale for preventive guidelines

For those interested in the rationale for particular management guidelines, reading of Chapter 3 is recommended. The central rationale is that each syndrome or anomaly places the patient at higher risk for particular complications as compared to the general population; preventive screening or evaluation for these complications is then justified by criteria of efficiency (selection of high-risk patients) and ethics (improved quality of life). This strategy of ameliorating complications is one of secondary or tertiary rather than primary prevention, since few congenital disorders can be prevented or cured (see Chapter 3). A list of complications is the basis for preventive management guidelines, and is rendered in a standard format on part 1 of each checklist. General complications are listed first (e.g., increased mortality, feeding problems), followed by a standard sequence of organ systems and
Types of preventive guidelines

body regions. The Committee on Genetics, American Academy of Pediatrics (1994, 1995a, 1995b, 1995c, 1996a, 1996b) has published consensus recommendations for the health care supervision of children with Down syndrome, Turner syndrome, achondroplasia, neurofibromatosis-1, fragile X syndrome, and Marfan syndrome. These recommendations are certainly followed in this book, and their spirit is extrapolated to 25 other common disorders for which consensus guidelines are not yet formulated.

Although there is a clear rationale for alerting practitioners to the complications of a disorder, the nature and timing of intervention often requires clinical judgment. Some children with severe dysfunction may benefit more from palliative care than the inconveniences of medical intervention. Decisions about screening measures become particularly difficult when anesthesia is required (e.g., brain imaging), or when a positive result has controversial significance (e.g., cervical spine radiographs for atlantoaxial instability in Down syndrome). Such recommendations are often footnoted in the checklists, with the reminder that clinical judgment must always be used.

Types of preventive guidelines

The sample checklist, parts 2–4 includes general pediatric recommendations in the first column, drawn from the guidelines in Bright Futures (Greene, 1994) and updated with a current immunization schedule. The next three columns list recommendations for the specific anomaly or syndrome, grouped by screening (e.g., laboratory tests, imaging studies), evaluation (e.g., alertness for particular signs or symptoms), and referral/counseling (e.g., specialty evaluations, counseling services). The presence of general pediatric and disease-specific guidelines on the same flow sheet provides the practitioner with a comprehensive, on-going summary of patient care.

“Family Support” appears frequently in the referral/counseling column. This is a prompt to the primary care physician to inquire about the general impact of the child’s condition on family life. Questions should routinely be raised about specific family stresses, school issues, the status of siblings, access to information, contact with other families affected by the same condition, and financial pressures. Eligibility for benefits such as Medicaid, Supplemental Security Income (SSI), Title V, and respite care should be considered and followed with appropriate referrals. Some families may need to consider the financial planning issues related to income taxes, trusts, and estate planning when individuals with developmental disabilities are involved. Many states have family support programs for families of children with disabilities which may include the services of a family support coordinator. All eligible families should be referred to such programs. Birthdays, the anniversaries
of a diagnosis, and life transition (preschool to elementary school; school to work/adult life) are particularly difficult times for families during which extra support may be needed.

Included in family support are links to disease-specific family support groups that can be invaluable in sharing experience with social and medical concerns. Many of these are listed on the checklists, part 1. The Exceptional Parent Magazine annual guide (http://www.eparent.com) and the Alliance of Genetic Support Groups (http://www.medhelp.org/geneticalliance/), and the Association for Retarded Citizens (ARC, http://www.arc.org) provide good sources for American and Canadian groups, while the searchUK function (http://www.searchuk.com) can find links to many groups in the United Kingdom. The ARC and Family Village (http://familyvillage.wisc.edu/) websites are also excellent sources of information about disabilities.

**Validation of preventive management guidelines**

Having stated that the preventive management guidelines are based on disease complications, it must again be emphasized that the invasiveness and frequency of preventive screening may be subject to dispute. Decisions between recommended screening (e.g., echocardiography) versus evaluation of symptoms (e.g., auscultation for cardiac murmurs) are often difficult, and practitioners should bear in mind that guidelines promoted by professional organizations such as the American Academy of Pediatrics are available for only a few disorders. Certainly practitioners should feel free to modify the guidelines based on their experience and style.

To offer greater breadth of perspective, the recommendations have been reviewed by members of an editorial advisory board: Drs. John Carey and James Hanson in medical genetics, Dr. Michael Msall in developmental pediatrics, and Dr. Joel Steinberg in general pediatrics. Dr. Steinberg has the added perspective of being in a pediatric practice for many years before becoming Medical Director at Children’s Medical Center of Dallas. Clearly there is much work to do regarding disease natural history and outcome before these preventive recommendations acquire the force of scientific validation. Even the Down syndrome management guidelines, endorsed by several authorities (Rubin and Crocker, 1988; Cooley and Graham, 1991; Carey, 1992; Committee on Genetics of the American Academy of Pediatrics, 1994), remain to be justified by controlled studies.

In summary, this book should be used to enhance the health care of patients with congenital anomalies and syndromes by considering preventive management guidelines. It is certainly not intended to impose unwanted advice on experienced physicians or to add new burdens to the already busy routines of those involved in patient care. However, anyone observing the improved outcomes for patients with
Acknowledgments

Down syndrome over the past few decades must award some merit to preventive management. While congenital disorders are often incurable, preventive care offers a satisfying opportunity for health professionals to enhance the quality of life of children with developmental or genetic disorders.

Acknowledgments

The authors wish to thank the advisory board for their many suggestions regarding the format and content of preventive management checklists.
Preventive Management of

### Clinical diagnosis:

### Incidence:

### Laboratory diagnosis:

### Genetics:

### Key management issues:

### Growth charts:

### Parent groups:

### Basis for management recommendations:

#### Summary of clinical concerns

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RES, reticuloendothelial system, bold: frequency > 20%

### Key references
### Syndrome

**Preventive medical checklist (0–1yr)**

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**Neonatal**
- / /
  - Neonatal screen
  - HB

**1 month**
- / /
  - Family support

**2 months**
- / /
  - Early intervention

**4 months**
- / /
  - Early intervention

**6 months**
- / /
  - Family support

**9 months**
- / /
  - Hearing, vision

**1 year**
- / /
  - Family support
  - Early intervention

**Clinical concerns for syndrome, ages 0–1 year**

Guidelines for the neonatal period should be undertaken at whatever age the diagnosis is made; DTPaP, acellular DTP; IPV, inactivated poliovirus; RV, rotavirus; Var, varicella; alternative timing; by practitioner; as dictated by clinical findings; parent group, family/sib, financial, and behavioral issues as discussed in the preface; including developmental monitoring and motor/speech therapy.
### Syndrome

#### Preventive medical checklist (15m–6yrs)

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**Clinical concerns for**, ages 1–6 years

Guidelines for prior ages should be undertaken at the time of diagnosis; \(^1\)alternative timing; \(^2\)by practitioner; \(^3\)as dictated by clinical findings; \(^4\)parent group, family/sib, financial, and behavioral issues as discussed in the preface; \(^5\)including developmental monitoring and motor/speech therapy.
# Syndrome

## Preventive medical checklist (6+ yrs)

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**Clinical concerns for** syndrome, ages 6+ years

Guidelines for prior ages should be undertaken *at the time of diagnosis*; Td, tetanus/diphtheria; Var, varicella; *alternative timing*; ³by practitioner; ⁴as dictated by clinical findings; ⁵parent group, family/sib, financial, and behavioral issues as discussed in the preface; ⁶birth control, STD screening if sexually active; ⁷repeat every decade.
Glossary of genetic and molecular terms

These brief definitions should be supplemented by consulting the texts recommended in the Preface.

Acrocentric chromosome. Chromosome with small short (p) arms as opposed to metacentric chromosomes with approximately equal short and long (q) arms.

Allele. Alternative gene structure (e.g., S and A alleles of the β-globin gene).

Agenesis. Absence of a part of the body caused by an absent anlage.

Aneuploidy. Abnormal chromosome number that is not an even multiple of the haploid karyotype, i.e., 47,XX,+21 or 90,XX.

Anlage, primordium, blastema: Embryonic precursor to a tissue, organ or region.

Anomaly. Any deviation from the expected or average type in structure, form and/or function which is interpreted as abnormal.

Anticipation: Worsening of phenotype with subsequent generations.

Aplasia: The absence of a body part resulting from a failure of the anlage to develop.

ASO: Allele-specific oligonucleotides used for DNA diagnosis.

Association: Any non-random occurrence in one or more individuals of several morphologic defects not identified as a sequence or syndrome. Associations represent the idiopathic occurrence of multiple congenital anomalies.

Atavism: A developmental state that is normal in phylogenetic ancestors, but abnormal in their descendants.

Atrophy: Decrease in a normally developed mass of tissue(s) or organ(s) due to decrease in cell size and/or cell number.

Base pairs (bp): Adenine-Thymine (A-T) or Guanine-Cytosine (G-C) pairing in DNA; also the basic unit for DNA strand length.

Blastogenesis: Stages of development from karyogamy and the first cell division to the end of gastrulation (stage 12, days 27–28).

Candidate gene: A gene implicated in pathogenesis based on protein function, chromosomal location, or sequence homology.

Chromosomal rearrangements: Aberration where chromosomes are broken and rejoined as opposed to numerical excess or deficiency.
Glossary

Chromosome painting: Use of repetitive DNA FISH probes to fluoresce entire chromosomes or chromosome regions.

Contiguous gene deletions: Deletion encompassing neighboring genes to produce a composite phenotype.

Cross-over: Breakage and reunion of chromosomes that realign parental loci.

Cytogenetic notation: Formal nomenclature describing karyotypes and chromosome location, i.e.:

- 47,XY,+11: Extra chromosome 11 (Trisomy 11)
- 45,XY-11: Absent chromosome 11 (Monosomy 11)
- 46,XY,11q-: Terminal deletion of chromosome 11
- 46,XY,11q+: Extra material of unknown origin on 11q
- 46,XY,del(11p11p13): Interstitial deletion between bands p11 and p13 of chromosome 11
- 46,XY,dup(3q): Extra material derived from the long arm of chromosome 3.

Dysmorphogenesis: Abnormal development leading to abnormal shape of one or more body parts (dysmorphology).

DNA cloning: Isolation of a DNA segment by insertion into a simple genome (plasmid, bacteriophage) and production of multiple copies.

DNA diagnostic techniques: Use of DNA modifying enzymes, hybridization, and size separation technologies for diagnosis of identity, genetic disease, or predisposition.

DNA hybridization: Rejoining (reannealing) of complementary DNA or RNA stands.

DNA marker: DNA segment, often anonymous, that exhibits sufficient sequence variation to be useful in genetic linkage and DNA diagnosis.

DNA sequence: Order of nucleotides in a DNA segment, usually displayed from the 5′-triphosphate (5′ end) to the 3′-hydroxyl (3′ end) nucleotides.

Empiric risks: Recurrence risk based on epidemiologic survey of affected families.

Exon: Portion of gene that encodes protein.

First degree relative: Those with 50% of genes in common (child, parent, sibs).

FISH: Fluorescent in situ hybridization, a technique by which fluorochromes are attached to DNA probes and hybridized with cytogenetic or cell preparations.

Functional cloning: Isolation of gene segments based on gene function, i.e. using antibodies to a characterized protein or expression assays where traits are deleted or restored to cultured cells.

Gene map: Order of genes within a chromosome or entire genome.

Genetic heterogeneity: Multiple loci where mutations can produce a similar phenotype, such as autosomal dominant or X-linked Charcot–Marie–Tooth disease.

Genetic mapping: Use of genetic linkage to produce a relative gene order based on recombination distances (centimorgans = approximately 1 megabase).
Glossary

**Genome**: Complete set of genes (DNA) in an organism.

**Genomic DNA**: DNA isolated from an organism or tissue, containing transcription signals and introns that will be absent from cDNA.

**Genomics**: The study of function and disease based on gene structure and organization.

**Genotype**: Genetic constitution, often with reference to particular alleles at a locus.

**Germlinal mosaicism**: Mosaicism within the germ line, whereby a fraction of eggs or sperm may contain a particular mutation or chromosome aberration.

**Heteroplasm**: Different mitochondrial genomes in the same cell, a mechanism by which the proportions of altered mitochondria may increase in specific tissues to cause disease.

**Heterozygote**: Individual with different alleles at a locus.

**Homeobox**: A DNA sequence shared by several Drosophila segmentation genes.

**Homoetic mutations**: Mutations altering segment identity in Drosophila. In a broader sense, a developmental switch analogous to that replacing one homologous insect segment with another.

**HOX, hox**: Gene clusters in humans and mice that exhibit homology to the structure and expression of Drosophila homeotic loci.

**Hyperplasia**: Overdevelopment of an organism, organ or tissue resulting from a decreased or increased number of cells.

**Hypertrophy**: Increase in size of cells, tissue or organ.

**Hypoplasia**: Underdevelopment and overdevelopment of an organism, organ or tissue resulting from a decreased or increased number of cells.

**Hypotrophy**: Decrease in size of cells, tissue or organ.

**IGF**: Insulin-like growth factor.

**Incomplete penetrance**: Absence of phenotypic expression in a person known from a pedigree to have an abnormal genotype.

**Interstitial deletions**: Chromosomal deletion removing regions between termini.

**Isochromosomes**: Duplicate long or short chromosome arms that result in deficiency – i.e., Turner syndrome patients with i(Xq) are monosomic for Xp.

**Karyotype**: A standard number and arrangement of chromosomes as obtained from human blood or tissue specimens. A normal karyotype is 46,XX for females and 46,XY for males.

**Kilobases (kb)**: Unit of DNA/RNA length = 1000 bp; megabase = 1 million bp.

**L1CAM**: L1 cell adhesion molecule implicated in X-linked hydrocephalus.

**Linkage**: The tendency for neighboring genes to segregate together in families.

**Locus**: Unique location of a gene on a chromosome.

**Major anomaly**: Anomaly with cosmetic or surgical consequences.

**Malformation**: A morphologic defect of an organ, or larger region of the body, resulting from an intrinsically abnormal developmental process.
Glossary

Maternal inheritance: Inheritance mechanisms that exhibit maternal transmission based on abnormal mitochondria or maternal RNAs.

Meiosis: The process of germ cell division that randomly allots one chromosome of each pair to gametes.

Mendelian inheritance: The classical autosomal dominant, autosomal recessive, and X-linked inheritance mechanisms derived from Mendel's observations in peas.

Microdeletions: Chromosome deletions requiring prometaphase banding for visualization.

Minor anomaly: Anomaly of no medical but considerable diagnostic significance.

Mitosis: The process of somatic cell division that produces identical genomes in daughter cells.

Morphogenesis: A developmental process that includes the stages of blastogenesis and organogenesis.

Morphology: Discipline of zoology that concerns itself at once with the form, formation and transformation of living beings.

Mosaicism: Variation in DNA sequence or chromosome constitution among different cells of an organism.

Multifactorial determination: Dependence of traits on multiple genes plus the environment.

Multipoint linkage: Linkage analysis that examines multiple traits or markers in a pedigree and orders them relative to one another.

Normal variant: Deviation from expected or average type in structure, form or function that is more frequent (arbitrarily >4% of population) and more innocuous than an anomaly.

Obligate carrier: Carrier deduced by pedigree structure.

Oligonucleotide: Short nucleotide sequence often obtained by chemical synthesis.

Organogenesis: A developmental process that extends from late stage 13 (day 28) until the end of stage 23 (day 56) when the major organs and body parts are formed.

Paired box: A DNA sequence motif found in the paired gene of the fruit fly.

PAX: Genes in mice and humans containing paired boxes.

PCR: Polymerase chain reaction by which individual gene segments are amplified through sequential cycles of polymerization, heat denaturation, and reannealing.

Phenotype: Individual traits or characters.

Physical mapping: Gene order based on actual physical measurements in terms of chromosome bands or DNA base pairs.

Pleiotropy: Multiple traits determined by a single cause, often a gene mutation.

Point mutations: Nucleotide substitutions.

Polymorphism: Multiple alleles at a locus, producing amino acid or DNA sequence variation.
Glossary

**Polypeptide chains**: Proteins or, in the case of multiple subunits, components of proteins formed by peptide bonds between amino acids.

**Polyploidy**: Abnormal chromosome number that is a multiple of the haploid karyotype, e.g., 69,XXY or 92,XXXX.

**Positional cloning**: Isolation of gene segments based on chromosome location.

**Primary relative**: First degree relative, i.e. those sharing 50% of genes.

**Primer**: Oligonucleotide used to begin nucleic acid polymerization at a particular site on a DNA strand, e.g., with PCR or reverse transcriptase.

**Proband**: Individual bringing family to attention, indicated by arrow in pedigrees.

**Prometaphase analysis**: Karyotype prepared from synchronized cells arrested in early prophase; these studies require prior notice to the laboratory.

**Propositus**: Same as proband.

**Protein polymorphism**: Products of alternate alleles at a locus exemplified by the ABO or HLA systems.

**Quantitative traits**: Incremental phenotypes such as height or blood pressure.

**Recombinant DNA**: Chimeric DNA molecules produced by joining of segments from different species, often using the complementary “sticky ends” produced by restriction endonucleases.

**Recombination**: Breakage and reunion of DNA strands.

**Repetitive DNA**: DNA sequences that have multiple copies in a genome.

**Restriction endonuclease**: A bacterial enzyme designed for defense against bacteriophage that recognizes and cleaves at specific nucleotide sequences.

**Reverse genetics**: Genetic analysis proceeding from chromosomal location to cloned gene; positional cloning is now the preferred term.

**Robertsonian translocations**: Joining of two acrocentric chromosomes at their short arms to produce a single translocation chromosome.

**Sequence**: A cascade of primary and secondary events that are consequences of a single primary malformation or a disruption.

**Somatic mosaicism**: Variation in DNA sequence or karyotype among different somatic cells of an organism.

**Sporadic**: Isolated case, often implying lack of inheritance or genetic causation.

**Submicroscopic deletion**: Small chromosome deletions that can be visualized only by DNA analysis.

**Syndrome**: Multiple anomalies thought to be pathogenetically related and not representing a sequence.

**Syndrome variability**: Differing phenotypic manifestations among individuals with the same syndrome.

**Targeting sequences**: Amino acid regions that direct proteins to particular cellular locations.
Glossary

*Teratology*: The study of abnormal development, particularly with regard to the disruptive influence of drugs, chemicals, and physical agents.

*Threshold*: A theoretical barrier at which an individual’s combination of genes and environmental exposure crosses from predisposition to actual defect.

*Translocation breakpoint*: The region of recombination between two chromosomes.

*Translocation carriers*: Individuals with “balanced” translocations that have no extra or missing chromosome material.

*Triplet repeat amplification*: Increased number of tandemly repeating 3-bp units that can alter gene expression, as in fragile X syndrome or myotonic dystrophy.

*Trisomies/monosomies*: Karyotypes with extra or missing entire chromosomes.

*Uninformative*: Genetic linkage study where parental alleles and therefore the risk for disease transmission cannot be distinguished.

*Uniparental disomy*: Two copies of a chromosome pair derived from one parent.

*Variable expressivity*: Variable symptoms among affected individuals in a family.

*Zygotic expression*: Synthesis of gene products from zygotic DNA rather than maternal RNA molecules.